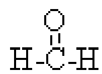
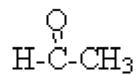
CHAPTER 5
ALDEHYDES AND KETONES

5.1 Introduction

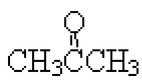
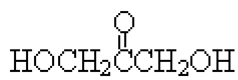
H
Aldehydes have a -C=O functional group. An aldehyde requires that at least one of the bonds on the C=O group is a hydrogen atom. When the carbonyl group (C=O) has two C atoms bonded to it is classified as a ketone.

5.2 Naming Aldehydes and Ketones

Systematic:	methanal	ethanal	propanal	butanal
Common:	**formaldehyde**	**acetaldehyde**		

You should know the common names! They are more commonly used than the systematic names.
Ketones:

Systematic:	propanone	1,3-dihydroxypropanone	3-heptanone
Common:	**acetone**	**dihydroxyacetone(DHA)**	

The ketone is assigned a number on the chain starting from whichever end gives the smaller number**.** It takes priority over branches off the chain.

Methanal (formaldehyde) is a commonly used preservative for biological specimens although concern about it being a mild carcinogen has prompted efforts to reduce its use and to provide very good ventilation when it is used to minimize exposure.

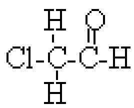
Propanone (acetone) is commonly used in nail polish remover. It is also a metabolic product sometimes formed by diabetics who are not controlling their blood sugar. It is readily detected, because it makes the breath smell like nail polish remover or “fruity”, not a normal situation! This condition is called **ketosis**, indicating the presence of ketones in the blood. This condition is also commonly associated with blood acidosis and the combined condition is referred to as **ketoacidosis.**

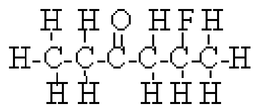
Dihydroxyacetone is the active ingredient in some sunless sun tanning lotions. It reacts with amino acids in the skin to form **melaninoids** which have a brown color. In its original formulation, it gave an orange tan but improvements in formulations have improved its esthetics considerably. It absorbs primarily in the UV-A range (320-400 nm) but only with a typical SPF of approximately 3 and hence can still leave an individual vulnerable to burning from UV radiation.

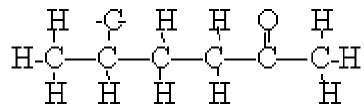
Numbering groups off the main chain.

Numbering should start from whichever end of the molecule gives the smaller # for the position of the C atom of the carbonyl (C=O) group. The aldehyde group will automatically be number one and it is not necessary to explicitly number it.

You should minimize the number of the C=O even if it produces a larger number for some other groups such as halogens or alkyl groups branching off the main chain.



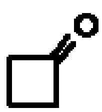


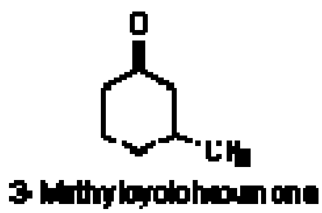


2-chloro(1)ethanal NOT
1-chloro (2)ethanal

5-fluoro-3-hexanone not
2-fluoro-4-hexanone

Ketone groups can occur in rings, for example:

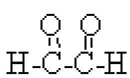


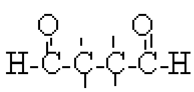


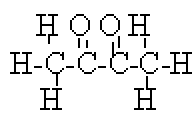
Cyclobutanone

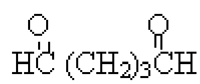
3-methyl (1-)cyclohexanone

We can have multiple aldehyde or ketone functional groups in a molecule:









(1,2)ethanedial

1,4 butanedial

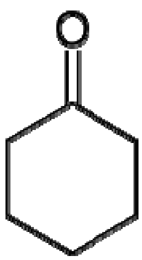
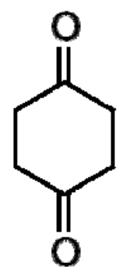
2,3 butanedione
diacetyl

1,5-pentanedial
(glutaraldehyde)

2,3 butanedione(diacetyl) is a natural product formed in very small amounts during yeast fermentation. It contributes to the taste of butter and to some Chardonnay wines. It has been added to artificial butter flavor for many years in margarine and popcorn flavoring. Several cases have come to medical attention where workers in poorly ventilated popcorn production facilities have developed a very rare disease called bronchiolitis obliterans. Although people eating the actual popcorn are exposed to orders of magnitude(~1,000,000) less diacetyl than workers in the popcorn plants, there are efforts underway to move away from widespread use of diacetyl as an artificial flavoring agent and several popcorn manufacturing companies have already switched to alternative flavoring agents. As in the case of mercury in amalgams, most toxicologists agree that the toxicity depends on the concentrations and that the amount of diacetyl in artificial butter flavor is not enough to cause health problems.

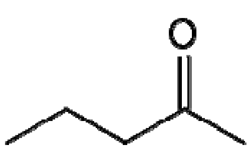
1,5-pentanedial (glutaraldehyde) was used for many years to "fix" microscope slides and as a high level disinfectant which can be used at room temperature for medical equipment which cannot tolerate autoclave temperatures. (What other molecule that we've discussed is used for this purpose?) Like formaldehyde, it probably kills bacteria and viruses by reacting (via its aldehyde groups) with cells walls and membranes. It is, however, extremely irritating to human lungs and skin and its use has decreased in recent years as less toxic sterilizing alternatives have been developed.

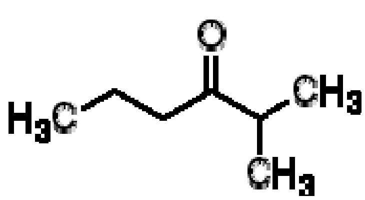
Ketones in rings

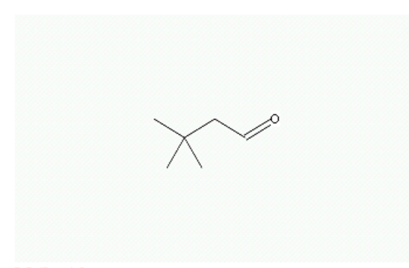
 has the real shape  

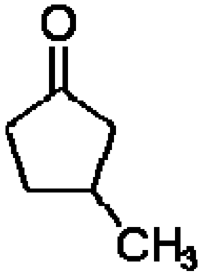
Cyclohexanone cyclohexanone(chair confirmation) 1,4-cyclohexanedione

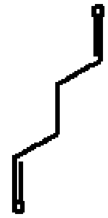
Naming practice:
Try naming these compounds:

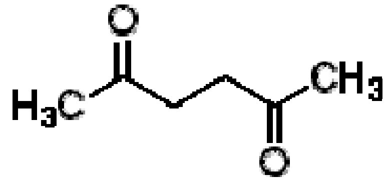


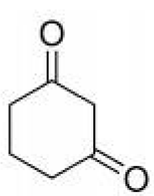


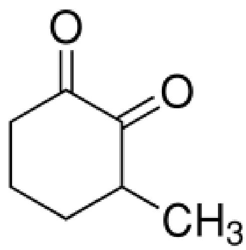


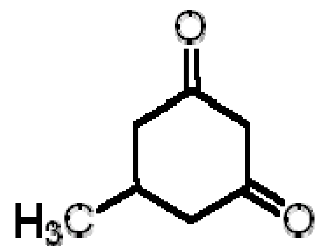






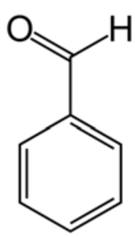






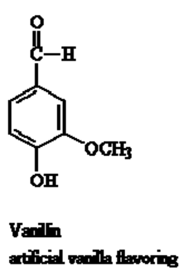
5.4 Some more aldehydes and ketones with practical uses.
Several flavoring agents are aldehydes or ketones.

Benzaldehyde



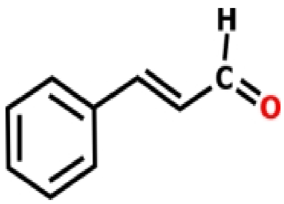
Benzaldehyde is used to make artificial almond flavor.

Vanillin



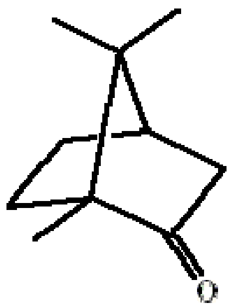
Vanillin is the primary ingredient in natural vanillin flavor as well as artificial vanillin flavor (which is made from petroleum).What other functional groups are in the vanillin molecule?

Cinnamaldehyde



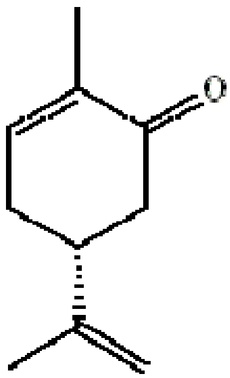
Cinnamaldehyde is the primary compound responsible for cinnamon odor and flavor. Are there cis and trans isomers? Which is the naturally occurring form shown above? Draw the other geometric isomer. Cinnamaldehyde made from petroleum can be used to make artificial cinnamon flavoring.

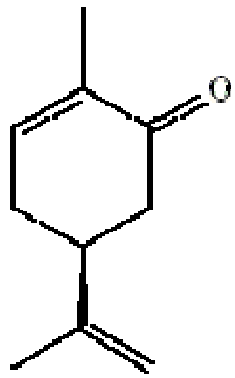
Camphor



Camphor is a natural oil obtained from several south east Asian trees, and can also be made from turpentine(a distillate of pine trees) as well as from oil! It provides a mild cooling and anesthetic sensation when applied to the skin and is used in products such as Vicks VapoRub. It is also found in some cough preparations.

Carvone



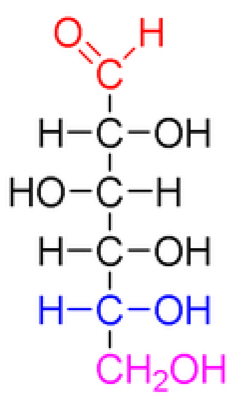


R-carvone (on the left) is the essential flavor of caraway seeds (used to flavor rye bread). S-carvone(on the right) is the primary flavor in spearmint.
How do these two molecules differ from each other? What sort of isomers are they?

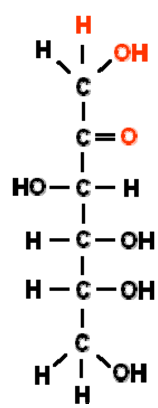
Mirror image molecules can have substantially different smells and flavors on your olfactory and taste receptors!!

Sugars

Sugars are polyhydroxy aldehydes or ketones:



Glucose
(an aldose)

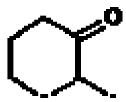


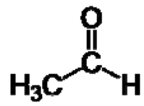
Fructose
(a ketose)

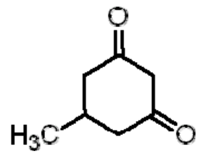
What functional groups are in glucose? Fructose?

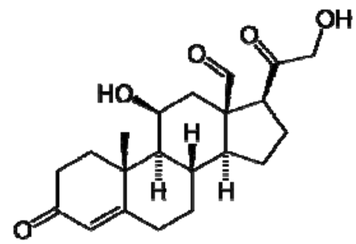
5.5 Solubility. The polar C=O group is not quite as polar as the polar O-H group, and so it is not quite as attracted to(and soluble in) water molecules, but we use the general rule of one polar carbonyl (C=O) group being able to solubilize up to 4 CH_2 units into water rather than making more complicated rules.

Predict whether the following will be soluble in water:



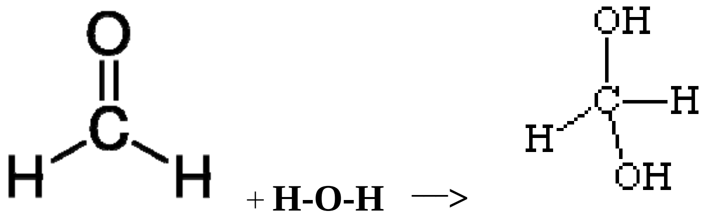






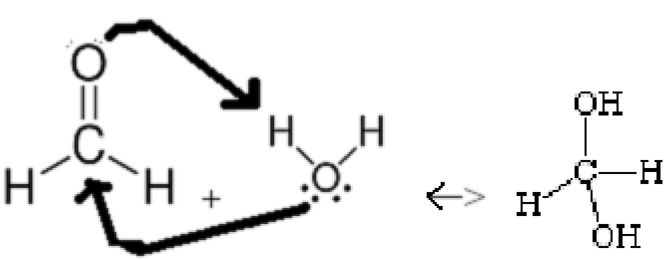
Aldosterone

5.6 Reactions of aldehydes and ketones with water to produce hydrates



Formaldehyde reacts with water to form a hydrated formaldehyde solution (1,1, methanediol) that is referred to as **formalin**. Formalin is used to preserve cadavers. Although the reaction is an equilibrium one, it lies far to the right with about 99.9% of the formaldehyde in the hydrate product form.

Although it isn't the real reaction pathway, we can regard the pi electrons of the C=O as picking up the H on the water, and pair of electrons on the O of the water then coming in and bonding to the C of the (former)carbonyl.

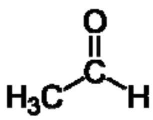


Reaction pathway:
A pair of electrons on the electronegative O atom of the C=O react with the hydrogen ion which is out looking for a pair of electrons to fill its outer shell. Note that, as before, we draw the arrow going from the electrons to what the electrons react with. This produces a positive oxonium ion since the O atom is sharing 3 pairs of electrons, while it prefers only to share 2 pairs. The O atom will pull the 2 pairs of electrons it shares with C even closer to itself, thus intensifying the partial positive charge of the C of the carbonyl. The electronegative O of the water molecule is then attracted to the C of the carbonyl group and a concerted electron rearrangement occurs with the O of the C=O pulling away the second pair of electrons from the C while the O of the water molecule shares a pair of its non-bonding electrons. This results in the O of the C=O once again only sharing 2 pairs of electrons. At the same time the O of the water molecule is sharing its pair of electrons with the C of the C=O, so that the C continues to have a total of 4 bonds. However, as the O of water shares a pair of electrons with the C, it is now sharing 3 pairs of electrons, so it has a

positive charge! In order to regain neutrality the O atom of the (former) water molecule kicks out one of the hydrogen ions (protons) with which it is sharing a pair of electrons. We indicate this with an arrow pointing from the shared electrons back to the O atom, indicating that the O regains full possession of the electrons. This allows it to regain neutrality and it also regenerates the proton that was used up in the beginning of the reaction pathway. This regeneration of the proton is necessary if the proton is really a catalyst.

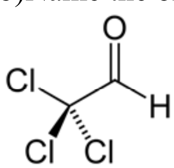
Although we will be sloppy and draw the arrows only in the forward direction, in fact all the above steps are reversible and we will end up with an equilibrium of both original reacts and the hydrate product.

a)Name the original reactant and show the product for the following: (At equilibrium 42% of the reactant remains and 58% is converted to the hydrate)



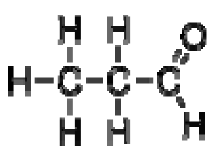
+ H-O-H <– H^+ ——>

b)Name the original reactant and show the reaction pathway:



+ H-O-H <— H^+ ——>

The common name for the product above is chloral hydrate and it was a sedative that was used in hospitals for many years although its use has decreased greatly. It was the active ingredient of “Mick Finns” and “knockout” drops.

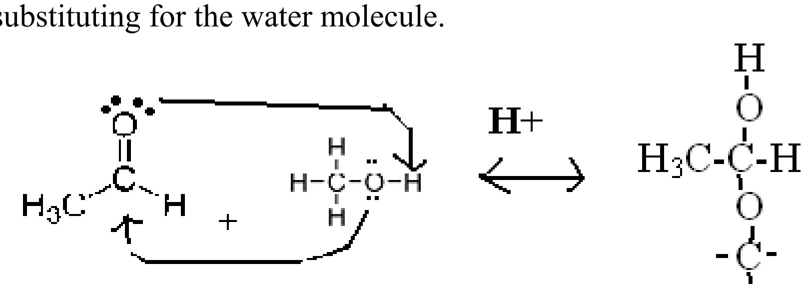


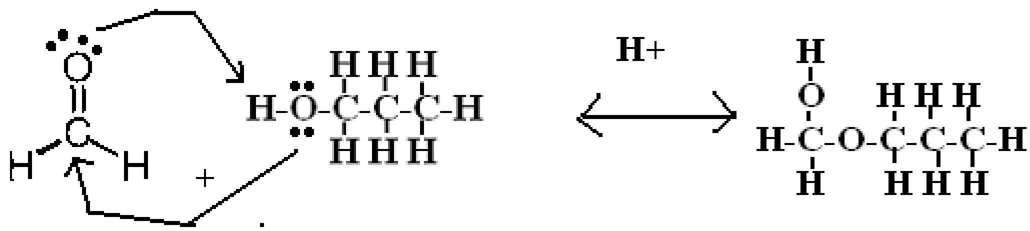
+ + **H-O-H** —>

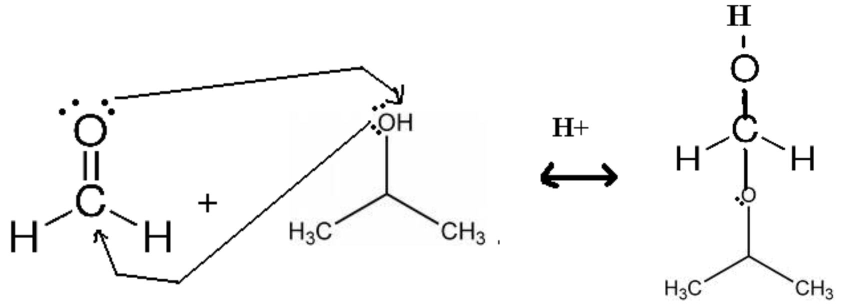
5.7 Hemiacetals and hemiketals

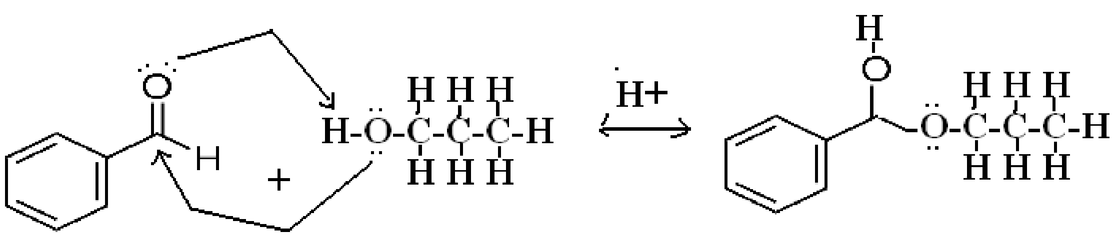
Aldehydes react with alcohols to produce hemiacetals in a manner very similar to the reaction of aldehydes with water to produce hydrates. (Ketones react in identical fashion, although the products are called hemiketals).

The reaction pathway is virtually identical to that of hydrate formation, with the alcohol substituting for the water molecule.



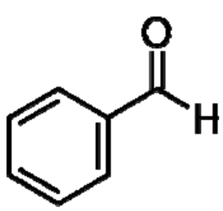
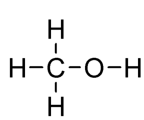


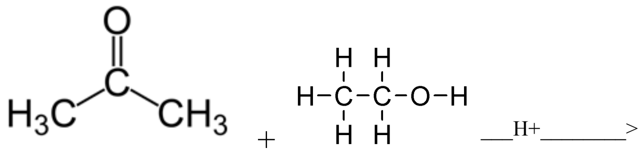


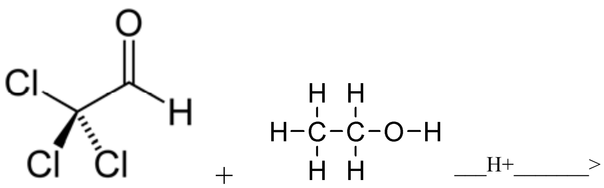


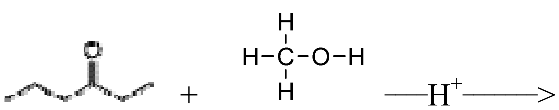
Note that we do NOT try to remove a water molecule from the reactive intermediates as we did with ester formation from carboxylic acids and alcohols. We are NOT forming an ester; we are forming a hemiacetal , which does not require the removal of a water molecule.

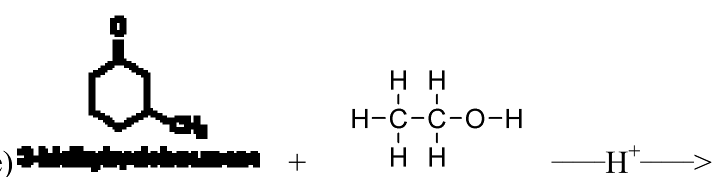
Try the following:

a)  +  _H+—>

b) 

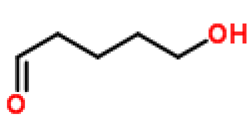
c) 

d) 

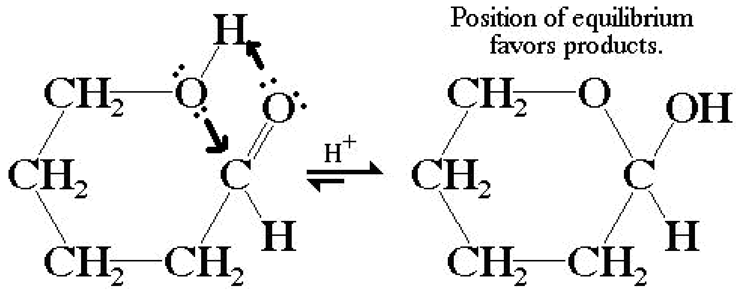
e) 

Like the ester formation, hemiacetal formation can produce a ring when the aldehyde and the alcohol are in the same molecule.

a)

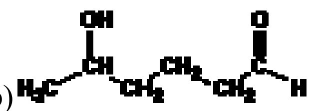


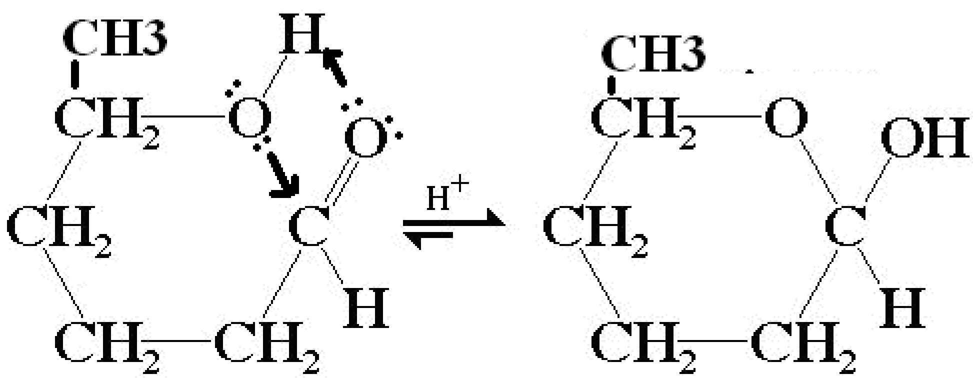
can curl around on itself so that the alcohol group can react with the aldehyde on the other end of the molecule.



5-Hydroxypentanal   Cyclic hemiacetal

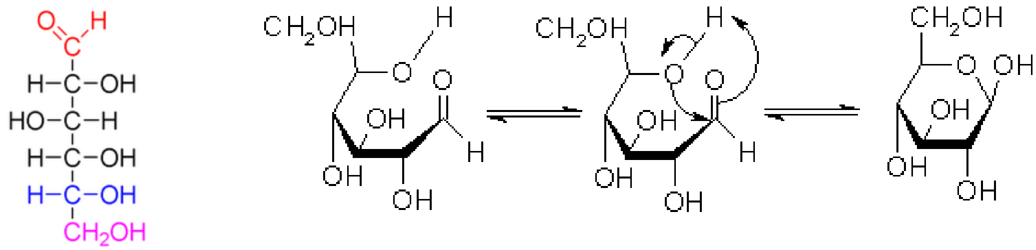
This forms a 6-membered ring which is quite stable. What is the real shape of this ring? What is the bond angle?

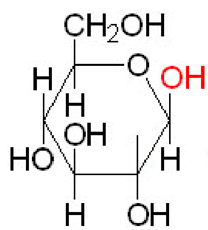
b)  _____H+____> Curl it around in a ring first

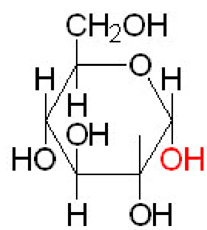


Note that in the above molecule the sixth C from the aldehyde end does NOT get incorporated into the ring and "hangs out" outside the ring as a methyl group. This introduces an additional complication which we have not dealt with before. When the ring closes, OH on the #1 C atom can be either cis or trans to the CH_3 group outside the ring. The formation of a ring can produce either of two different geometric isomers on a random basis. The production of two geometric isomers when the ring closes has important consequences when we deal with glucose and other monosaccharides.

c) Glucose (structure shown earlier). The aldehyde group in glucose has a multitude of OH groups to choose from, but it prefers to react with an OH that allows it to form a stable ring; it reacts with the OH on C #5 to form a stable 6-membered hemi-acetal ring.



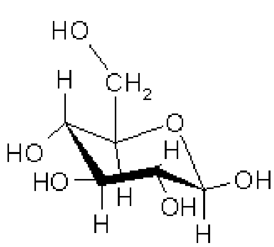




Beta glucose alpha- glucose

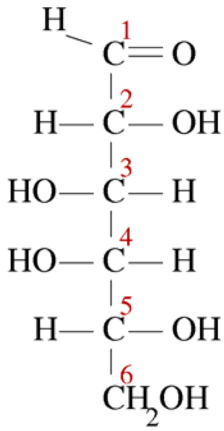
Although it might seem like free rotation would allow the OH groups to point in any direction, the necessity of twisting the ring in such a way as to position the OH group on the #5 C in such a way as to react with the partially positively charged carbon atom locks the other OH groups in the configuration shown above. The OH group ON the #1 carbon DOES have 2 possible configurations that it can form. It can be pointing either cis to the #6 C outside the ring or trans to the #6 C outside the ring. These two forms are of great importance in carbohydrate chemistry. The trans form is called α-glucose and the cis form is called β-glucose. As with all hemiacetals, this is an equilibrium reaction, although the equilibrium lies very far towards the product. In aqueous solution, 36% of the glucose in the α form, 64% in the β form and only about 0.02% is in the aldehyde form. Study this reaction pathway so you can do it on a quiz from memory. Make sure you can draw the structure exactly as it is shown in the example above.

Although the hemiacetal structure is drawn as if the 6-membered ring is flat (called the Haworth notation), remember that 6-membered rings with single bonds are most stable in the chair conformation and glucose is no exception. So the real geometry of *beta* glucose is shown below.



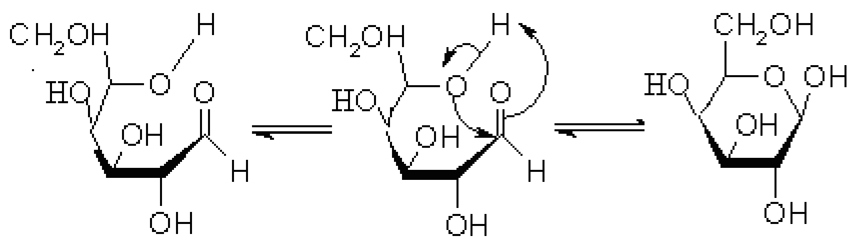
Try doing the same reaction pathway for making α-galactose, another sugar found in milk sugar. Note that it is the same as glucose except that the OH on #4 C is pointing in the opposite direction from that in glucose. As in the case of glucose, it might seem like we could rotate the chain any direction we want, but in fact it does make a difference.

Follow the reaction pathway that you saw for glucose exactly, except that the direction of the OH on C#4 will point in the opposite direction.



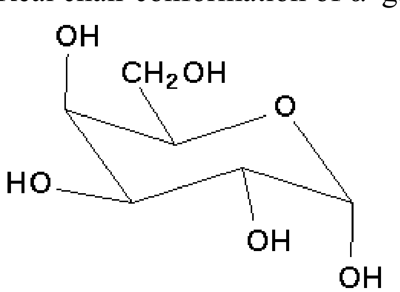
Galactose

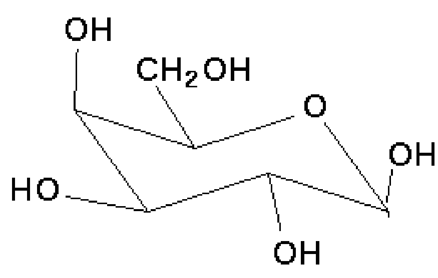
The structure of galactose is identical to glucose except that the OH group on C number 4 is pointing to the left instead of the right in glucose. When the galactose forms a cyclic hemiacetal, that results in the OH on C # 4 pointing upward (cis to C#6) rather than downward (trans to C # 6)



Is the above structure α or β? Draw the other form of galactose.

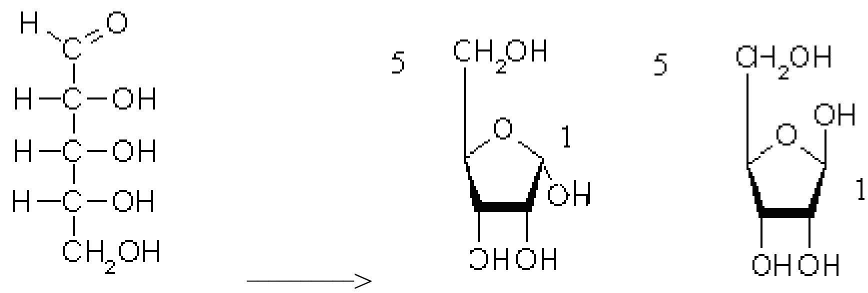
Real chair conformation of α galactose and β-galactose:





α galactose β-galactose

The 5 C sugar ribose is used to make nucleic acids (ribonucleic acid and deoxyribonucleic acid). Like glucose and galactose, the aldehyde form of the molecule has a strong tendency to form a cyclic hemiacetal. Like glucose it can exist in either the alpha or beta form based on the geometry of the OH group on C #1.



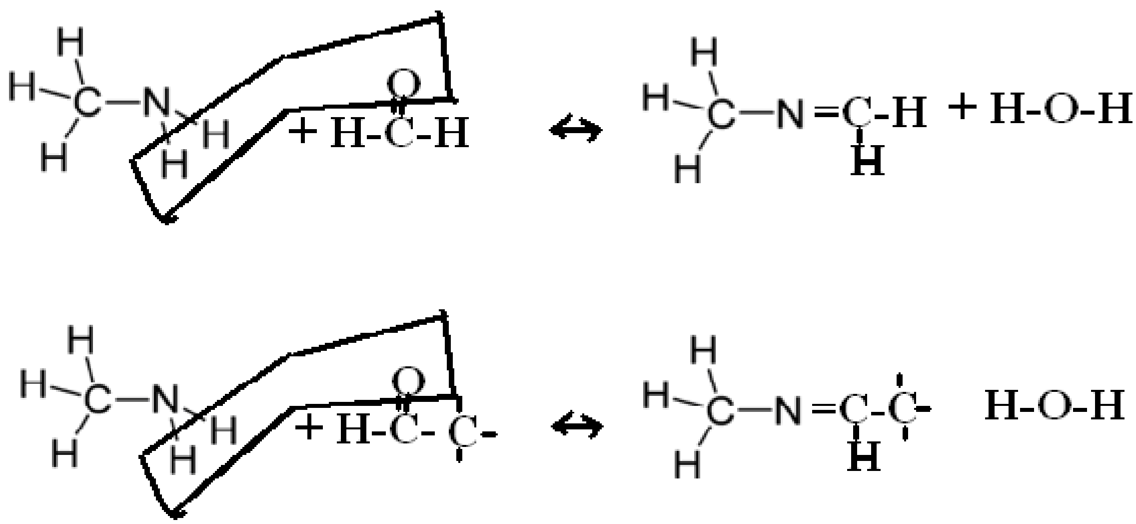
alpha ribose beta ribose

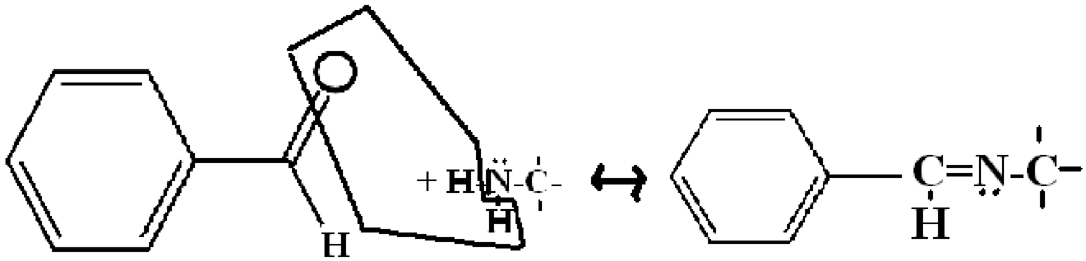
Although the 5-membered ring makes the structure look significantly different, the alpha ribose is the form in which the OH on C #1 is trans to the C outside the ring (C#5 in this case) and the beta ribose is the form in which the OH on C #1 is cis to the C outside the ring (C#5 in this case).

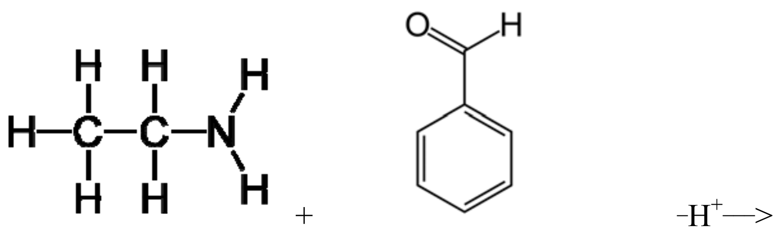
The numbering of the ring starts from the C which was originally an aldehyde (C=O) in the noncyclic form of the ribose molecule

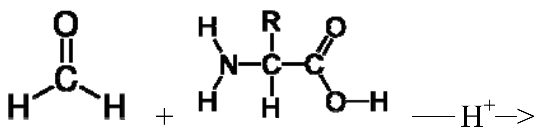
5.8 Imine formation

When aldehydes are combined with amines a reaction occurs that produces an **imine** and a water molecule. This reaction pathway starts is somewhat analogous to ester formation. Several examples of the reaction are shown below.



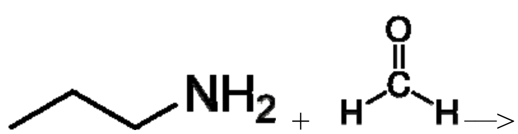


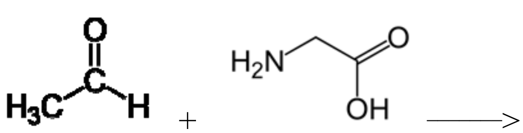




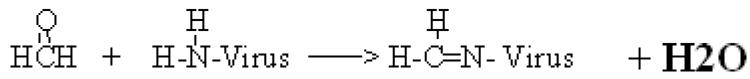
(This is a reaction that occurs with formaldehyde and amino acids.)

Try the following:





Formaldehyde is used to inactivate several different types of viruses for use in vaccines. Formaldehyde probably reacts with many different functional groups on the virus, but reaction with amine groups in proteins to form imines is an important one.



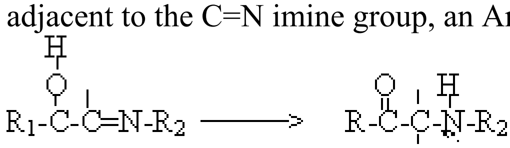
The goal is to prevent the virus from being active while still allowing the body's immune system to make antibodies against the virus. Vaccinations that may include formaldehyde include vaccines for flu, DPT (diphtheria, pertussis, tetanus), hepatitis A and B, and polio. The use of formaldehyde in these vaccines and concern over formaldehyde toxicity has led to substantial controversy.

Formaldehyde is used as a "fixative" in histological slides (slides of tissue prepared for microscopic examination) and it appears to work by reacting and crosslinking the amine groups of proteins. Formaldehyde is also used to preserve biological specimens, including cadavers and its reaction with the proteins of any living bacteria or mold probably are a major contributor to preventing the decomposition of the preserved specimen.

Formaldehyde is also used in a variety of glues used in the wood product industry and formaldehyde exposure of workers in these plants is monitored by OSHA because formaldehyde is suspected human carcinogen, albeit a weak one.

5.9 Further Reactions of Imines

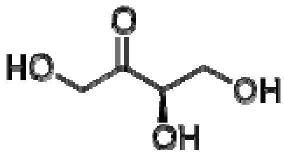
If an imine is formed on a molecule with additional OH groups, particular on the C adjacent to the C=N imine group, an Amadori rearrangement can occur as shown below:



This produces a product molecule with both a ketone and amine group which can undergo a wide variety of further complicated reactions which are collectively referred as the **Maillard reaction**, after the French organic chemist who first published a paper about them in 1912. Some of the products of the Maillard reaction are responsible for the smell of baked products (such as fresh baked bread) where amines in proteins can react with sugars. The Maillard reaction can also produce colored molecules that are responsible for the brown color of roasted coffee, bread crust, toast, other baked products, dark beers, and some types of caramel coloring.

Dihydroxyacetone, the active molecule used in sunless tan lotions, reacts with amine in the outermost dead layers of epidermis (the stratum corneum) to produce colored imine **melanoidins** which simulate a real tan. (The term melanoidins is based on melanin, the natural brown pigment; melanoidins have similar absorption patterns to melanin, but do not have the same structure).

Another small alcohol ketone, erythulose, is sometimes added to DHA for sunless tanning. What functional groups make the erythulose capable of similar reactions to DHA?



Erythulose

5.10 Glycated proteins

Glucose in the body (particularly the bloodstream) can react slowly and non-enzymatically with amine groups of proteins to form imines. These imines can rearrange further by the Amadori rearrangement and undergo further complicated Maillard reactions as discussed in **5.9.**

The resulting proteins are called **glycated proteins**. Sometimes the glycated protein is still fully functional and sometimes it is not. The amount of glycated protein present is typically proportional to the concentration of blood glucose. Poorly controlled diabetics who have frequent high levels of blood glucose also have higher than normal levels of glycated proteins. These glycated proteins appear to be responsible for some of the health problems frequently experienced by diabetics.

$$\text{Glucose-}\overset{\text{H}}{\text{C}}\text{=O} + \text{H-}\overset{\text{H}}{\text{N}}\text{-protein} \xrightarrow{H^+} \text{Glucose-}\overset{|}{\text{C}}\text{=N-protein} + H_2O$$

(Some sources refer to these products as glycosylated proteins, but the official recommendation is that that term be reserved for specific enzymatic addition of a sugar to a protein and that the term glycated protein refer to the non-enzymatic, non-specific addition of sugars to proteins.)

(Imine formation can occur in mitochondrial metabolism and may contribute to aging.)

5.10 Review

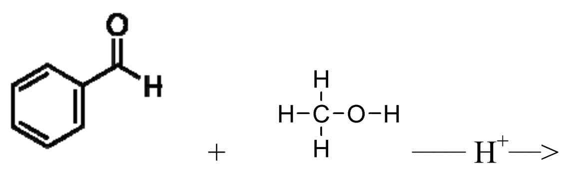
When we do these reaction pathways, you need to ask yourself what are the reactant molecules and what products are we trying to form.

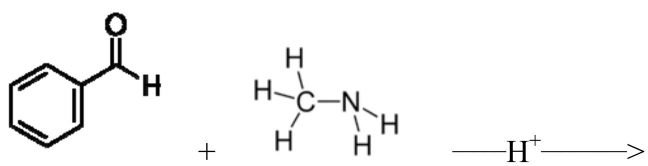
Reactants	Products
Carboxylic acid + alcohol	
Ester + water	
Aldehyde(ketone) + water	

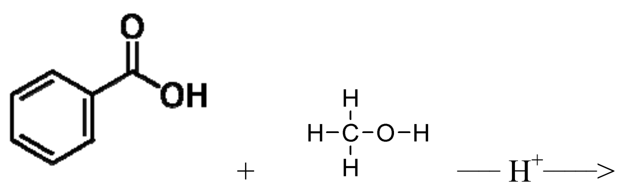
Aldehyde(ketone) + alcohol

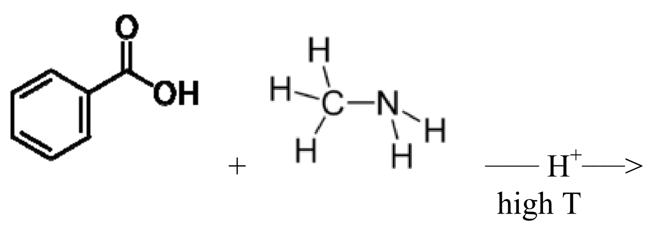
Aldehyde(ketone) + amine

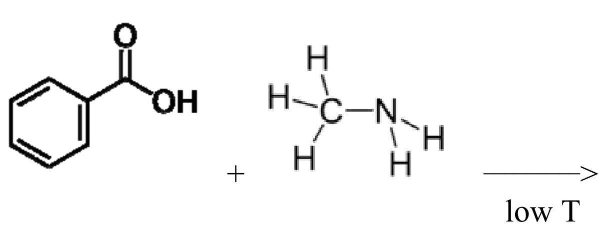
Try doing the following reaction pathways. Note that different reactions are mixed altogether, so think about what functional groups you're starting with and what you should end up with!

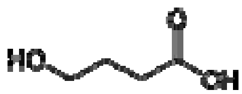
a) 

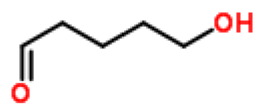
b) 

c) 

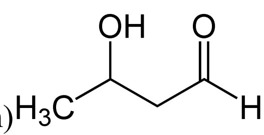
d) 

e) 

f)  —H⁺—>

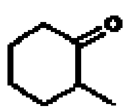


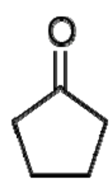
g) —H⁺—>

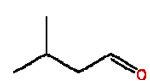
h)  —H⁺—>

ALDEHYDES AND KETONES STUDY GUIDE

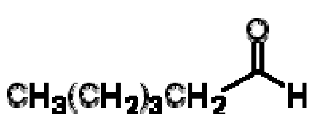
1. Name the following aldehydes and ketones according to systematic nomenclature:

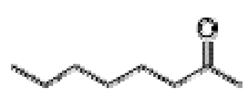
a) 

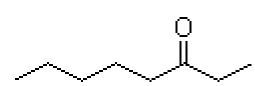
b) 

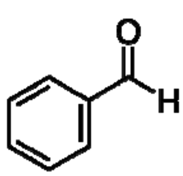
c) 

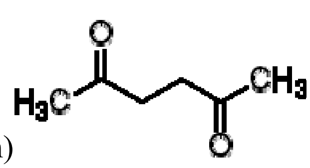
Cl

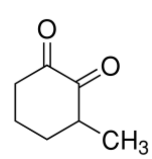
d) 

e) 

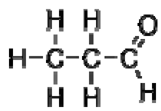
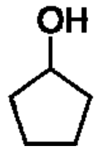
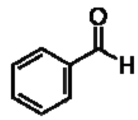
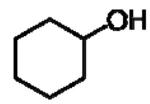
f) 

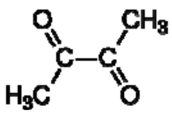
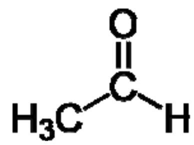
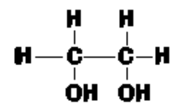
g) 

h) 

i) 

2. Show the structure of the product formed from the following molecules

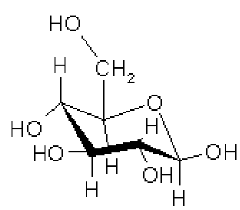
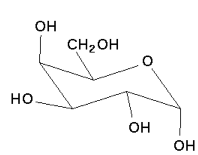
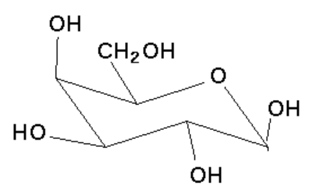
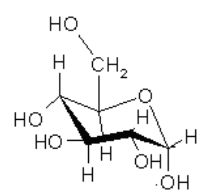
a)  +  —H^+—> b)  +  —>

c)  2 $HOCH_3$ —> d) **2**  + Ethylene glycol  —>

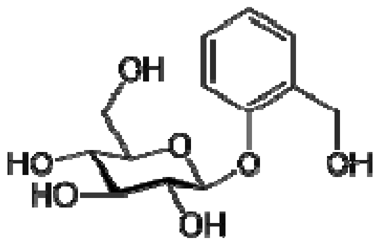
e) $HOCH_2CH_2CH_2CH_2C(H)=O$ —H+—> f) $HOCH_2CH_2CH_2C(H)=O$ —H+—>

3. Show the product of the formation of the hydrate of acetaldehyde.
4. Given the aldehyde form of the structure of glucose, show how glucose forms a hemi-acetal ring. Show the difference between α and β glucose.
5. Given the aldehyde form of galactose, show how galactose forms a hemi-acetal ring. Show the difference between α and β galactose.

6. Identify whether the following structures are glucose or galactose and whether they are in the alpha or beta form.

6. Salicin is the analgesic compound isolated from willow bark that gets metabolized into salicylic acid. Identify the sugar in salicin and determine whether it is in α or β form.

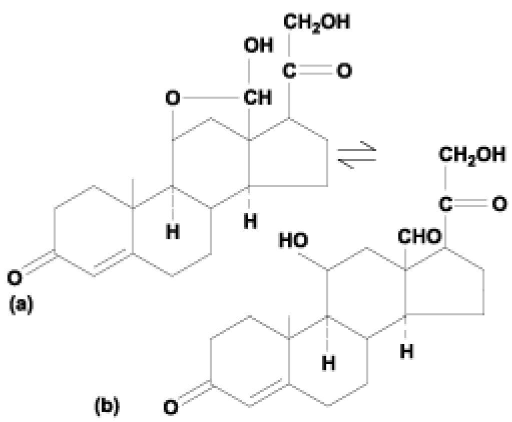


Salicin
(Salicin was first isolated from willow bark by Johann Buchner, inventor of the Buchner funnel!)

Digging deeper. Do an internet search on the controversy about the use of formaldehyde in vaccines and the various claims. Evaluate those concerns to the best of your ability and summarize what data is available to support or contradict those concerns.

Aldosterone is an important steroid hormone that helps retain sodium (and hence water). Water retention helps maintain blood pressure. It contains both an aldehyde and an alcohol group and these two functional groups can react reversibly to form a hemi-acetal ring as shown below. In fact most (~99%) of the aldosterone exists in the hemiacetal form

Hemiacetal form



aldehyde/alcohol form of aldosterone