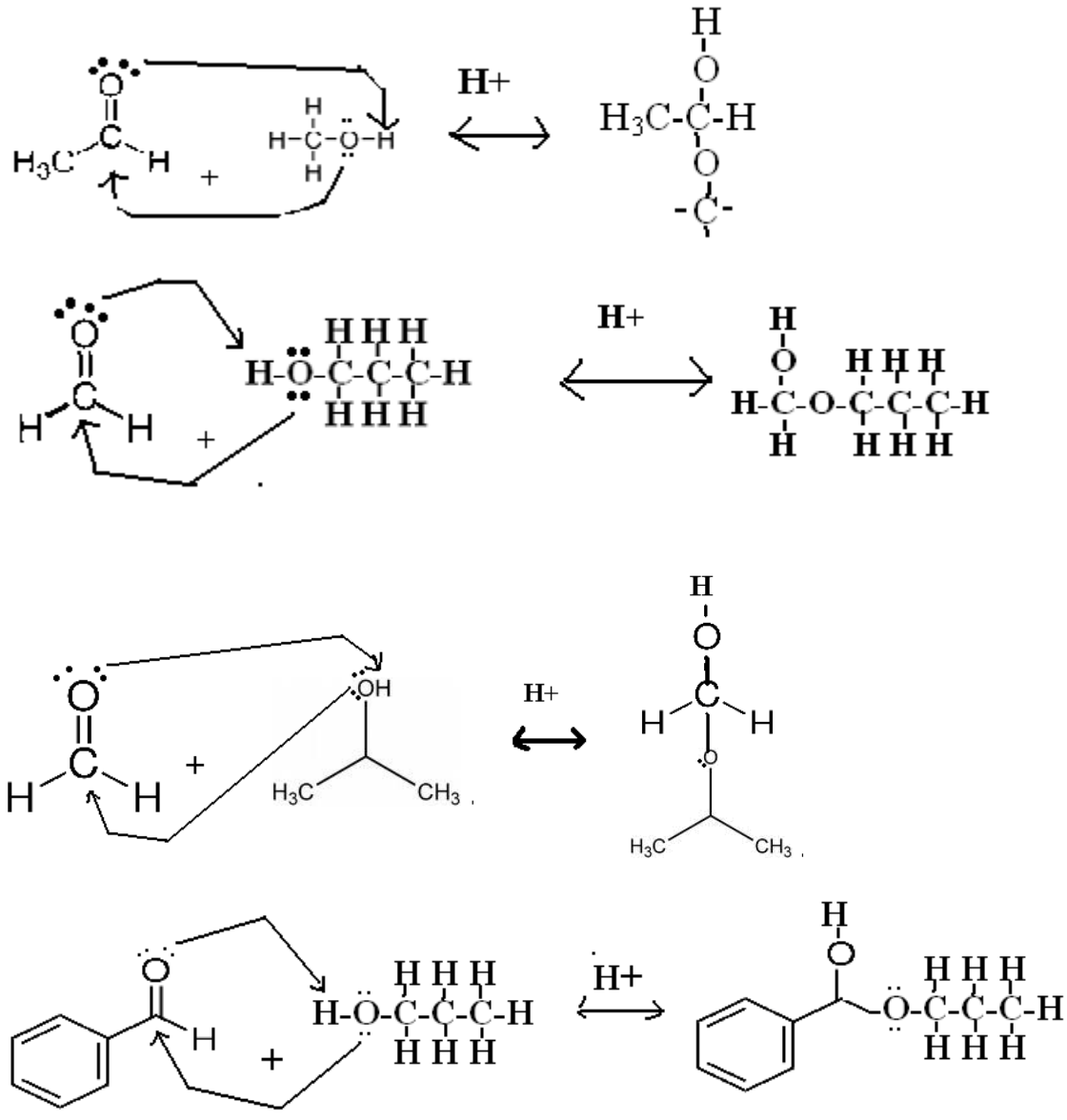
5.7 Hemiacetals and hemiketals

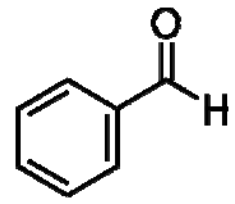
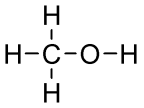
Aldehydes react with alcohols to produce hemiacetals in a manner very similar to the reaction of aldehydes with water to produce hydrates. (Ketones react in identical fashion, although the products are called hemiketals).

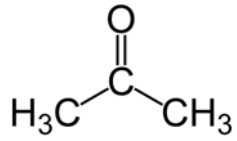
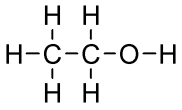
The reaction pathway is virtually identical to that of hydrate formation, with the alcohol substituting for the water molecule.

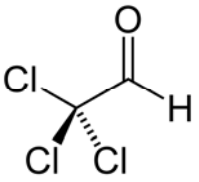
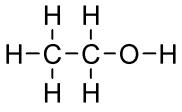


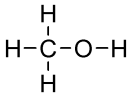
Note that we do NOT try to remove a water molecule from the reactive intermediates as we did with ester formation from carboxylic acids and alcohols. We are NOT forming an ester; we are forming a hemiacetal , which does not require the removal of a water molecule.

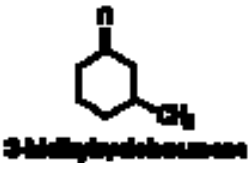
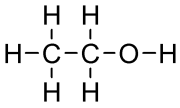
Try the following:

a)  +  $\xrightarrow{H^+}$

b)  +  $\xrightarrow{H^+}$

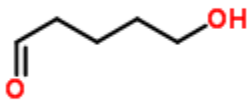
c)  +  $\xrightarrow{H^+}$

d)  +  $\xrightarrow{H^+}$

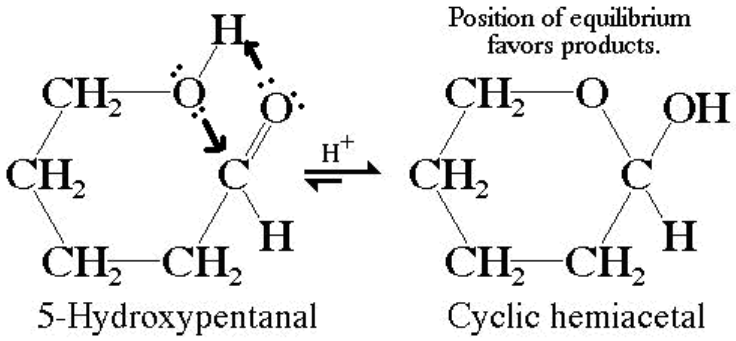
e)  +  $\xrightarrow{H^+}$

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

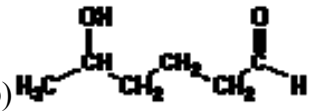
a)

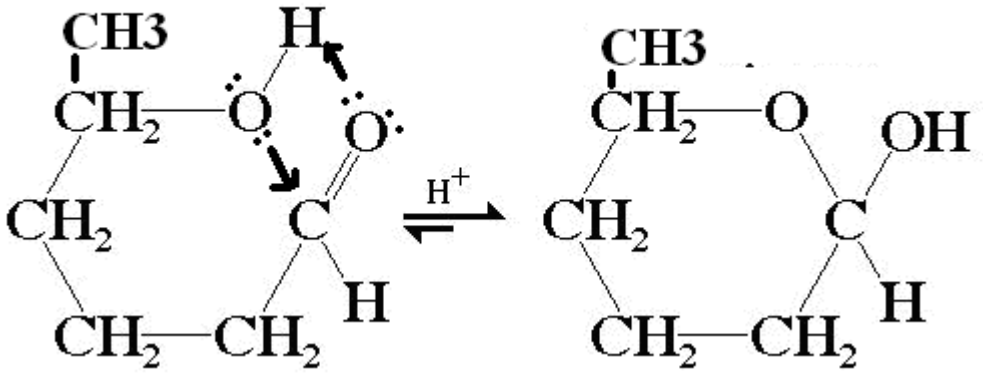


can curl around on itself so that the alcohol group can react with the aldehyde on the other end of the molecule.



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

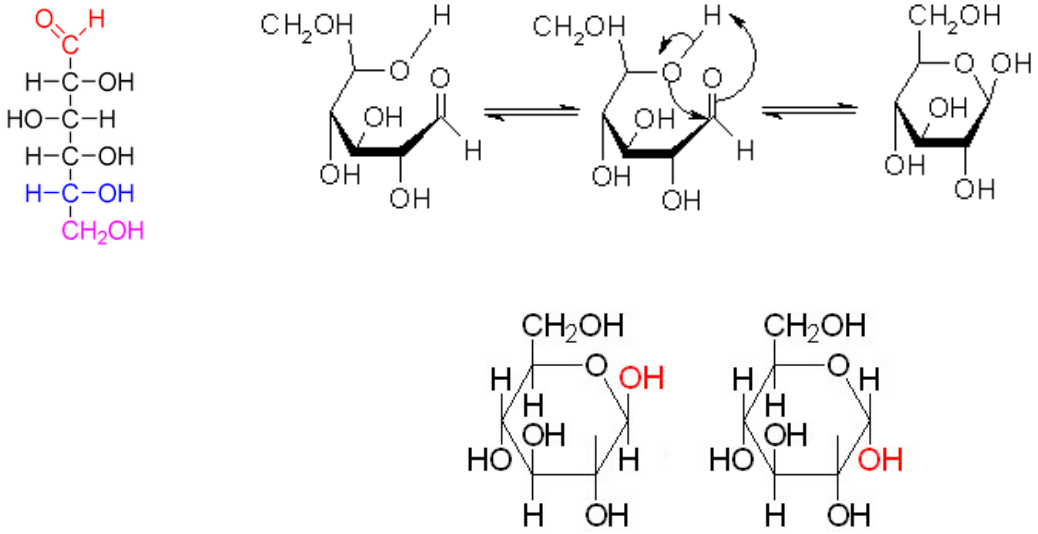
b)  _____H+____> Curl it around in a ring first



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.

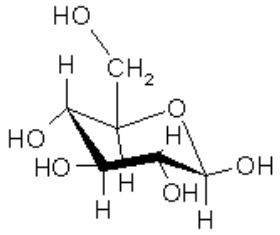
c) Glucose (structure shown earlier). The aldehyde group in glucose has a multitude of OH groups to choose from, but it prefers to react with an OH that allows it to form a stable ring; it reacts with the OH on C #5 to form a stable 6-membered hemi-acetal ring.



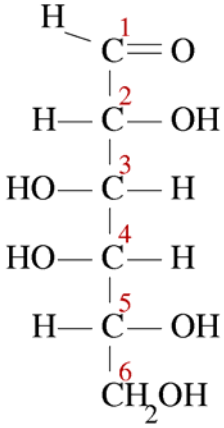
Beta glucose alpha- glucose

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.

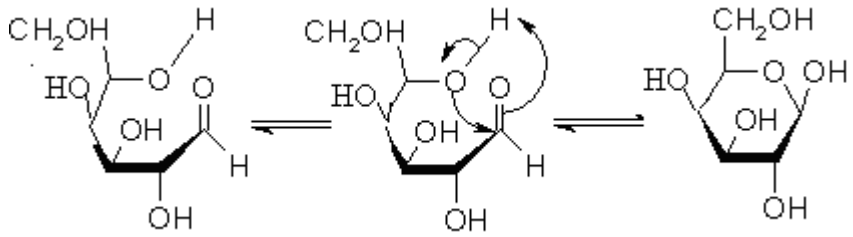


Try doing the same reaction pathway for making α-galactose, another sugar found in milk sugar. Note that it is the same as glucose except that the OH on #4 C is pointing in the opposite direction from that in glucose. As in the case of glucose, it might seem like we could rotate the chain any direction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



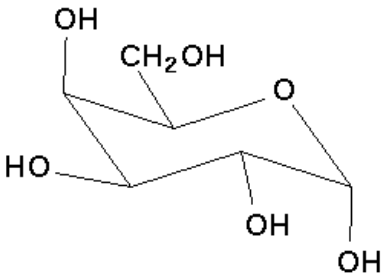
Galactose

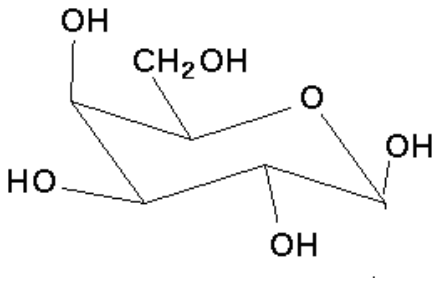
The structure of galactose is identical to glucose except that the OH group on C number 4 is pointing to the left instead of the right in glucose. When the galactose forms a cyclic hemiacetal, that results in the OH on C # 4 pointing upward (cis to C#6) rather than downward (trans to C # 6)



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

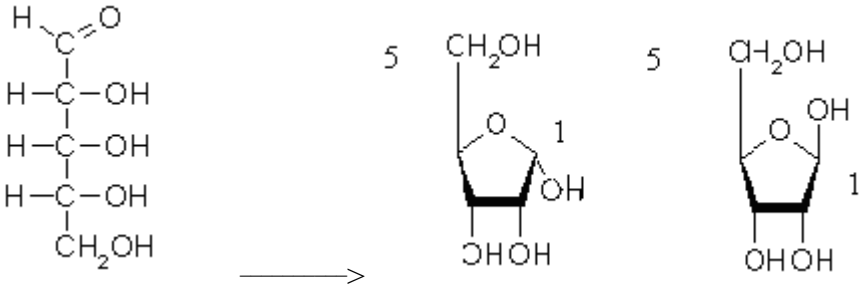
Real chair conformation of α galactose and β-galactose:





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