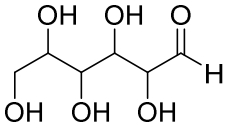
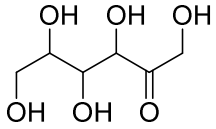
Loudon Chapter 24 Review: Carbohydrates

Jacquie Richardson, CU Boulder – Last updated 3/28/2019

This chapter is about carbohydrates – molecules with the general formula of $C_n(H_2O)_n$, or in other words $C_nH_{2n}O_n$. This is a very common formula for sugars and many other natural products. The structure is usually laid out so that the carbons are in a line and every carbon has an OH group, except for one which has a carbonyl (required to get the right degree of unsaturation). Many of them look like this:



Six carbons: **hexose**
Aldehyde: **aldose**
Combined: **aldohexose**



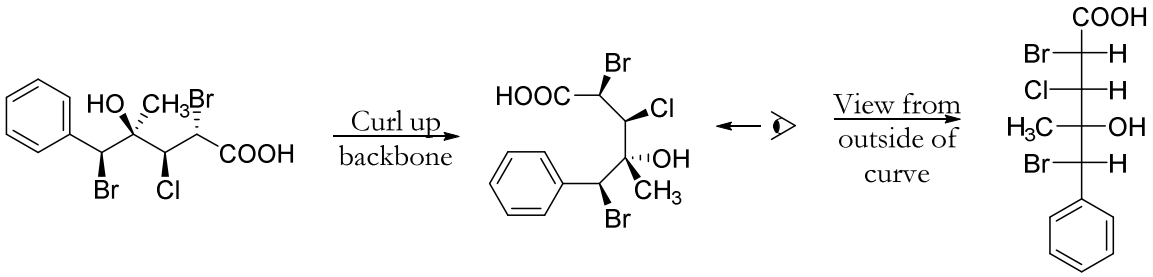
Six carbons: **hexose**
Ketone: **ketose**
Combined: **ketohexose**

The naming is subdivided based on how many carbons they have, and whether the carbonyl is an aldehyde or a ketone. These simple molecules (monosaccharides) can be joined into long chains (polysaccharides), in ways we'll see later.

Fischer Projections

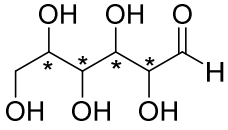
Since almost all the carbons in carbohydrates are stereocenters, there's a lot of chiral information that needs to be depicted. The standard way of doing this is with Fischer projections. This is done by putting the molecule's carbons into a vertical line, and having every junction follow the same pattern: the vertical lines are pointing into the page, and the horizontal lines are pointing out towards you.

This can get confusing with a long chain, but the easiest way to think of it is to push the entire molecule over to one side. When viewed in Fischer projection, the molecule shown above is arching out towards you like a bridge. But viewed from the side, every kink in the chain is bending in the same direction, rather than a zigzag formation like at the top of this page. The molecule itself doesn't necessarily bend into this shape in reality, but this is just a standardized way of showing it. There are standard ways of redrawing the molecule based on certain rules that are covered in the book. By convention, the carbonyl carbon is put as close to the top end of the drawing as possible.

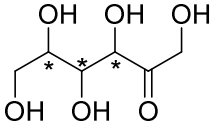


Stereochemistry

Every chiral center can be either R or S, and a molecule with *n* stereocenters has 2^n possible structures. For a molecule with three or four stereocenters, the number of possibilities gets pretty big.



4 stereocenters:
$2^4 = 16$ stereoisomers



3 stereocenters:
$2^3 = 8$ stereoisomers

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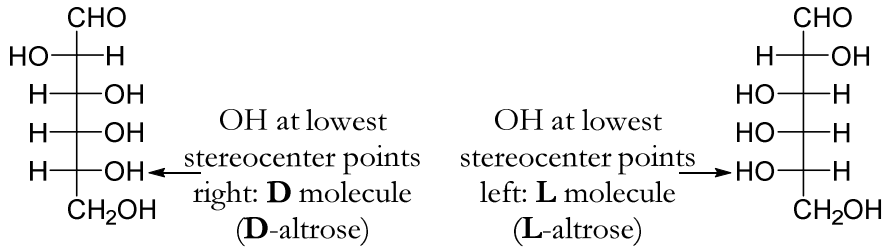
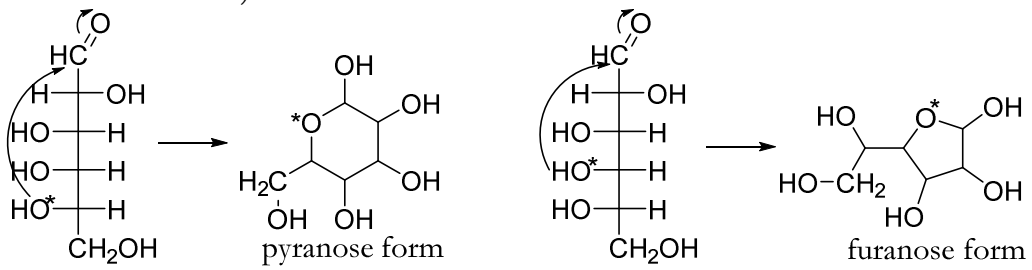
The possible structures come in pairs of enantiomers, where every stereocenter is flipped (R to S, or S to R) between the two molecules. The two enantiomers have the same common name, but are distinguished by having a **D** or **L** added to the name. This is based on the OH at the stereocenter furthest from the carbonyl, once all the carbons of the chain are placed in a vertical line for the Fischer projection (this may be something you need to arrange, if CH_2OH is hanging off to one side). If the OH at that stereocenter points left, it's an **L** molecule. If the OH points right, it's **D**. The two molecules below are enantiomers, so they have the same name except for the **D** or **L** part.



Any time you have two structures that are the same except for one stereocenter, they're called epimers, and converting between them is called epimerization.

Cyclization and Haworth Projections

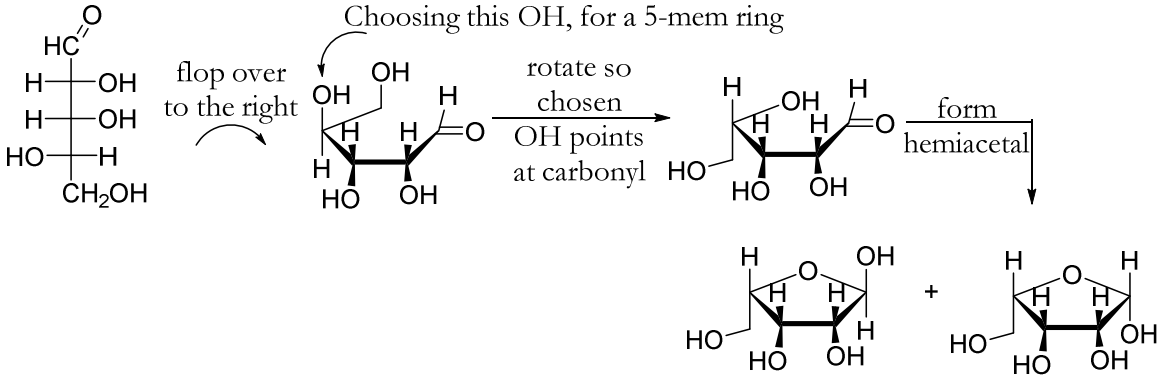
Just because monosaccharides are drawn as Fischer projections doesn't mean that they are in this linear form all the time. Since they have an aldehyde or ketone at one end, and at least one alcohol group at the other, they usually react with themselves to form a cyclic hemiacetal. Ideally they make five-membered rings (called furanoses) or six-membered rings (called pyranoses). Often they can make both, depending on which OH group is involved in the hemiacetal. The OH group that does the attack always becomes the oxygen in the ring (marked with an asterisk).

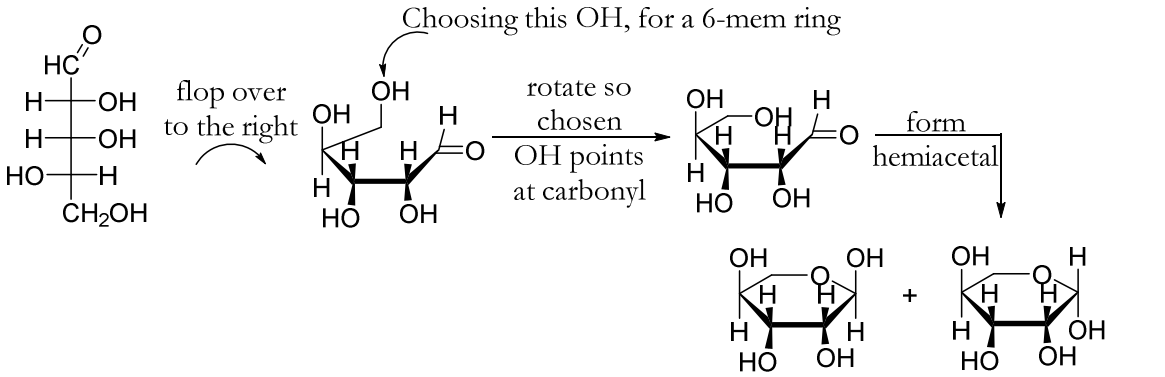


To help show what's going on with the stereocenters, Haworth projections are used. These show the cyclic form of the molecule in a flat ring, but viewed from the side rather than from above. To generate the Haworth projection, there are several steps to follow. See the example on the next page.

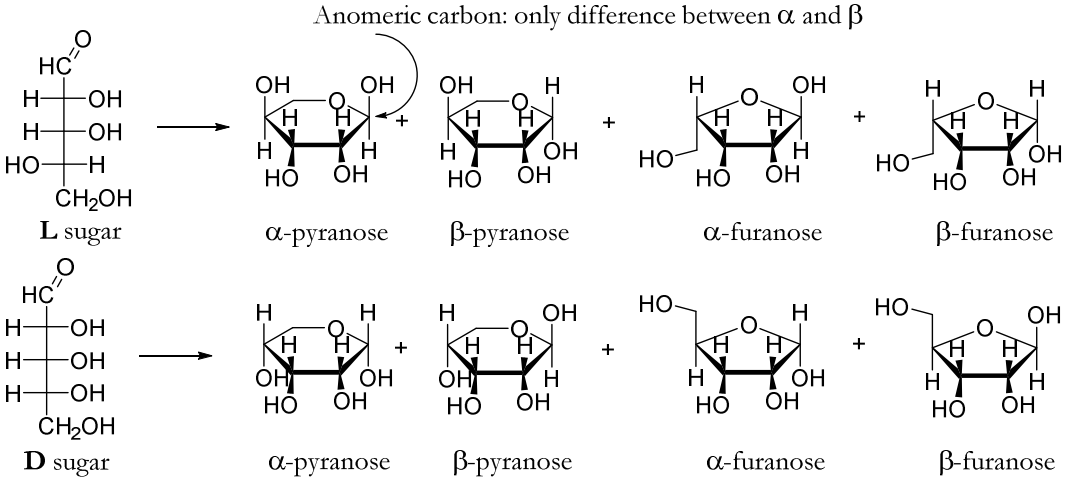
1. Take the Fischer projection and flop it over to the right, so that it's curled with the carbonyl at the right end and the terminal OH at the back. This means that any groups on the **left in the Fischer projection** are pointing **up in the Haworth projection** and anything on the right in the Fischer projection is down in the Haworth projection. The lowest carbon in the chain is usually achiral, so it doesn't matter which way its OH points.
2. Decide which OH group you're going to cyclize onto. For the five-membered ring, choose the OH on the third carbon after the carbonyl. For the six-membered ring choose the OH on the fourth carbon after the carbonyl.

3. If necessary, rotate the chosen OH into position so it's in the plane of the molecule, pointing towards the carbonyl. The rest of the chain after this gets rotated out to become an up or down substituent.
4. Form the hemiacetal between the chosen OH and the carbonyl.





As a result of these steps, the OH group that used to be the carbonyl is one step clockwise from the O in the ring. It's identifiable because it's on the only carbon in the ring with two bonds to oxygen, which is now a new stereocenter. This carbon is called the anomeric carbon. Because this stereocenter has free choice of being R or S, there are two different forms of each ring which vary only at the anomeric carbon and are called anomers.

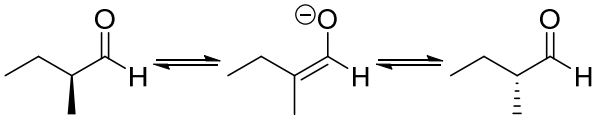


In the α anomer, the anomeric OH is pointing the same direction as the OH that determines **D** or **L**. In the β anomer, it's pointing the opposite direction. In effect, this means that a **L**

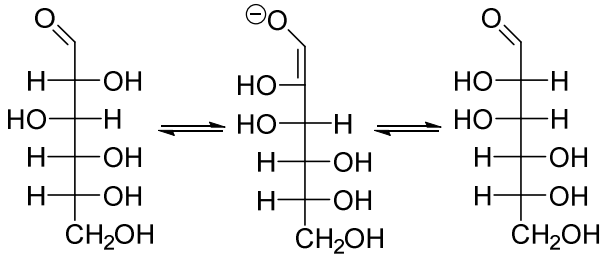
structure has the anomeric OH pointing up in the α form and down in the β form. The opposite is true for **D** structures. (If you make the six-membered ring, you may also have to draw out the chair cyclohexane conformation. Each product has two different chair forms, but one is usually more favored than the other.) Since the anomeric carbon isn't a permanent stereocenter (the hemiacetal formation can reverse itself at any time), these anomers do not count as epimers. All the possible cyclic forms of a molecule will interconvert if you give the hemiacetal a chance to reverse itself. This is called mutarotation. Just like hemiacetal formation, it's catalyzed by either acid or base, but it can happen in neutral water too.

Isomerization

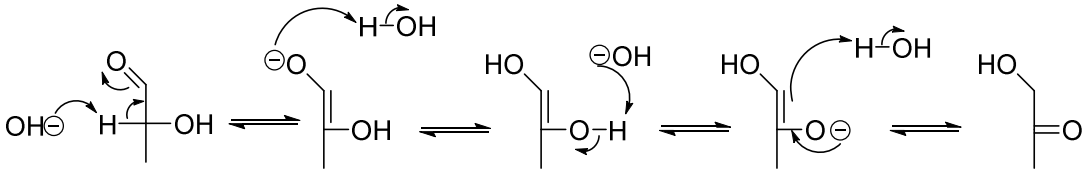
The structure of a carbohydrate can also change based on other chemistry that we've seen before. Remember that reaction in Ch. 22.2B where the stereocenters next to a carbonyl could change, by forming the enolate?



That happens here too. This means that any two structures which are different only at the alpha carbon can interconvert.

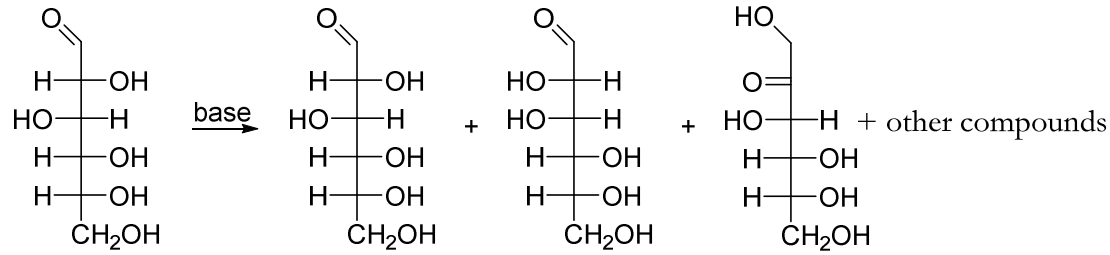


But there's something else that happens too, while the molecule is in the enolate form. It can convert into a different enolate, which allows it to move the carbonyl along the chain by one position.



aldose enolate enediol different enolate ketose

These two types of reaction occur together, when a carbohydrate is exposed to base. Together, they are called the Lobry de Bruyn-Alberda van Ekenstein reaction. The overall reaction is written as:



aldose carbohydrate | recovered starting material | epimer at alpha carbon | ketose form

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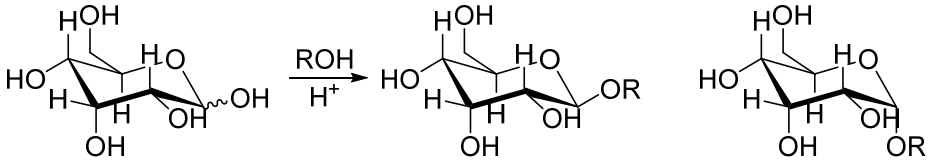
Glycosides

Since the cyclic forms of carbohydrates are hemiacetals, they can do things that other hemiacetals can do. For instance, they can covert to the full acetal if there's another molecule of alcohol (and an acid catalyst) for them to react with. Just like in the cyclic hemiacetal, there are α and β forms.

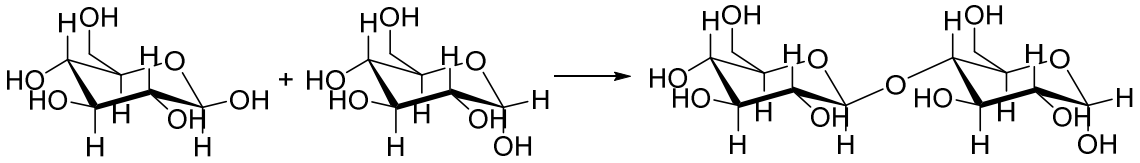


hemiacetal (alpha or beta form) | acetal (beta form) | acetal (alpha form)

The overall effect of this reaction is to convert the anomeric OH group into some kind of OR group. The mechanism is exactly the same as the mechanism for hemiacetals going to acetals. Once the acetal is formed it's stable in base, but can be hydrolyzed back to the hemiacetal in H_3O^+.

Disaccharides and Polysaccharides

Simple alcohols aren't the only kind that you can attach at the anomeric carbon. You can also attach an entire second molecule of carbohydrate. This links two saccharides together to make a disaccharide. Table sugar is an example of this.



Again, these can be either alpha or beta linkages. The chain can continue to a polysaccharide if you keep linking chains together at the anomeric OH of each ring.

A huge number of natural products follow this pattern, such as starch, cellulose, chitin, etc. Not all of them use the same kinds of linkages – some of them have beta linkages, and many of them use attachments to different OHs around the ring to create a branch in the polysaccharide.

Ether and Ester Derivatives

The anomeric OH isn't the only group that can have other things added to it. Any of the OHs around the ring can be put through reactions that regular OHs can do, but ether and ester formation is particularly common. For ethers, Williamson is still the default reaction. You don't need NaH though – the OHs on a carbohydrate are slightly more acidic, thanks to other nearby OHs, so you can get away with using a weaker base like NaOH. Then you bring in an alkyl halide to do S_N2.

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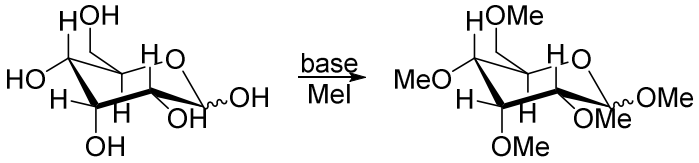
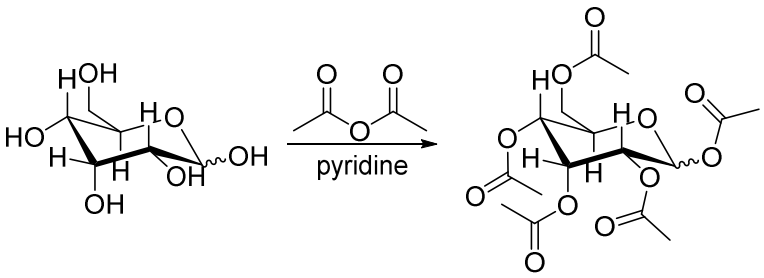


To remove these groups, you need to do ester hydrolysis: heat, water, and acid. The anomeric group comes off much more easily than the other groups.

To make esters, the most commonly used method is with either the acid chloride or the anhydride. Often, an acetyl group is attached to each OH.



Again, you need to hydrolyze these groups if you want them to come off. Heat, water, and either acid or base will do it.

Oxidation and Reduction

The aldehyde group in an aldose can be either reduced or oxidized, just like a regular aldehyde. There are several possible derivatives, just based on what happens to each end of the chain. All the secondary OHs along the chain remain the same, but the aldehyde at the top end and the primary alcohol at the bottom end can be turned into different combinations of things.

Top end	Bottom end	Name	How to make from aldose
Aldehyde	Primary alcohol	Aldose	N/A
Carboxylic acid	Primary alcohol	Aldonic acid	Oxidize with Br_2, H_2O, $CaCO_3$
Carboxylic acid	Carboxylic acid	Aldaric acid	Oxidize with dilute HNO_3
Primary alcohol	Primary alcohol	Alditol	Reduce with $NaBH_4$
Aldehyde	Carboxylic acid	Uronic acid	(not covered)

A reaction that *does* affect the secondary OHs in the chain is periodate cleavage. This is something we've seen before – it takes a vicinal diol and cuts it apart between the OH-bearing carbons. The same thing can happen in a carbohydrate, but since almost every carbon has an OH, this reaction can happen almost anywhere along the chain. A large number of oxidized fragments are possible.

The Kiliani-Fischer Synthesis

This reaction involves forming the cyanohydrin of the aldehyde. This adds a new carbon to the top of chain, and turns what used to be the top carbon into a new stereocenter. From there, you can turn the molecule into a new aldose by converting the cyano group to an aldehyde with catalytic hydrogenation using a poisoned catalyst.

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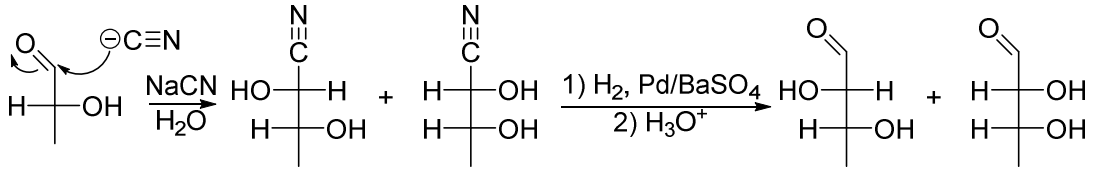
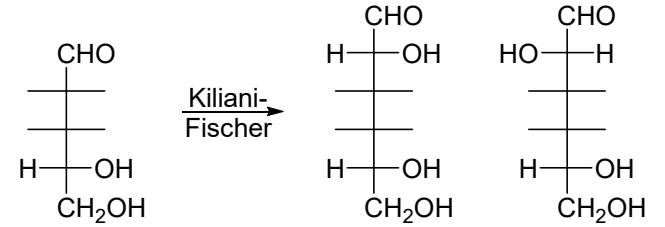


The net result of all this is that the chain gets lengthened by one carbon, and the product is a mixture of two epimers that are different at the second carbon of the chain. Every other part of the chain stays the same.

The Fischer Proof

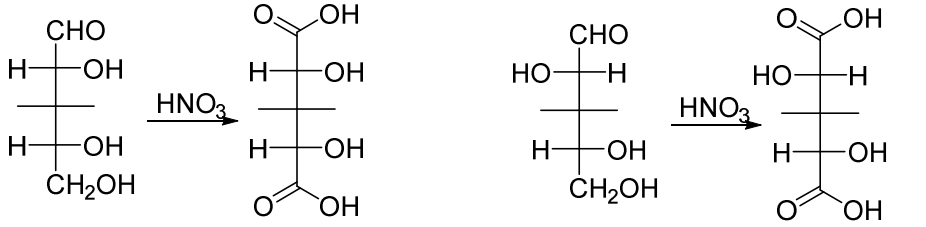
This is how the structure of glucose was figured out originally. Since there was no way to see the absolute stereochemistry of any of the stereocenters, Fischer had to guess for one stereocenter, and then figure out every other center relative to that. He decided to put the lowest OH on the right side for (+)-glucose - in other words, he assumed that (+) glucose is the **D** form. From there, he figured out the relative stereochemistry based on a few things he knew about optical activity and interconversions between different carbohydrates. (The absolute stereochemistry of (+)-glucose was not proven until 1950, but it turns out that Fischer's guess for the lowest stereocenter was correct!) Based on knowledge of the interconversions and derivatives of other carbohydrates, you can find their structures as well by similar reasoning.

1. <u>(–)-Arabinose is converted to a mixture of (+)-glucose and (+)-mannose by the Kiliani-Fischer synthesis</u>. This means that (+)-glucose and (+)-mannose are almost the same structure, except for the top stereocenter, and they're both the same as (–)-arabinose everywhere else.



(-)-arabinose (+)-glucose and (+)-mannose (don't know which is which)

2. <u>(–)-Arabinose forms an optically active aldaric acid when reacted with HNO_3</u>. This means that if you turn both ends of (–)-arabinose into the same carboxylic acid, it's chiral. The top OH of (–)-arabinose must be on the left.



Optically inactive: incorrect

Optically active: correct

Putting together what we have so far, this means that (+)-glucose and (+)-mannose look like this:

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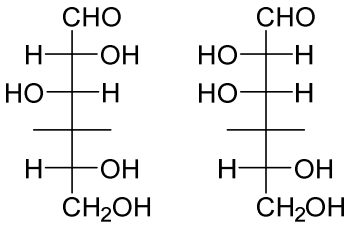
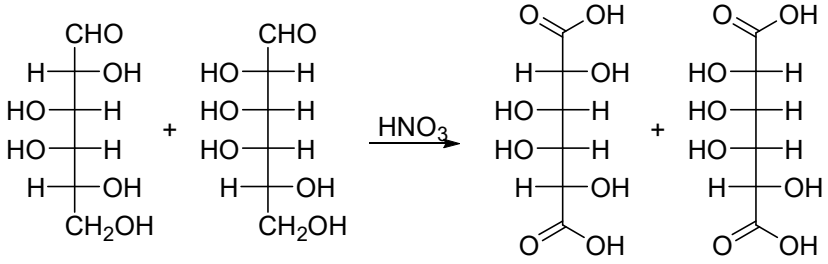


(+)-glucose and (+)-mannose
(don't know which is which)

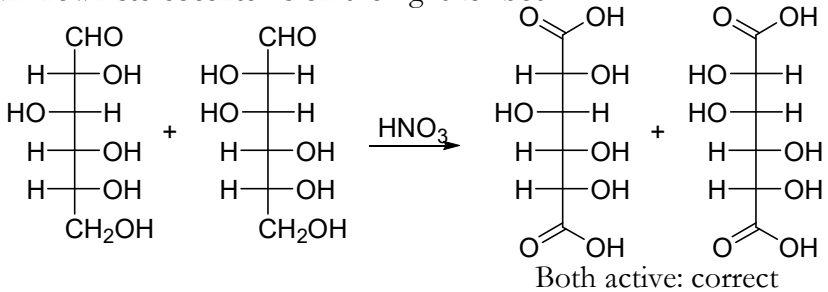
3. Both (+)-glucose and (+)-mannose form optically active aldaric acids when reacted with HNO_3. Again, this narrows it down because they're the same at all stereocenters except the top one.

   If unknown stereocenter is on the left for both:



One inactive and one active: incorrect

   If unknown stereocenter is on the right for both:



Both active: correct

   Of these two, we still don't know which is (+)-glucose and which is (+)-mannose.

4. (+)-Glucose forms the same aldaric acid as a different carbohydrate, (+)-gulose. Since aldaric acids have both ends identical (both carboxylic acids), this means that they have the same structure along most of the chain except for the ends. In other words, if you swap the end groups of (+)-glucose, you should get a different structure. This is not the case for (+)-mannose.