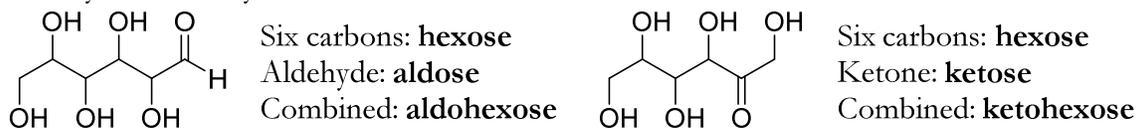


Loudon Chapter 24 Review: Carbohydrates

Jacque Richardson, CU Boulder – Last updated 5/23/2019

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). They can be described by how many carbons they have, and whether the carbonyl is an aldehyde or a ketone.

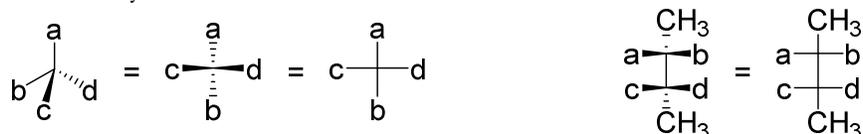


Every carbon in the chain, except the two end carbons and the carbonyl carbon, is a stereocenter. The number of possible stereoisomers gets big very fast – remember that a molecule with n stereocenters has 2^n possible stereoisomers.

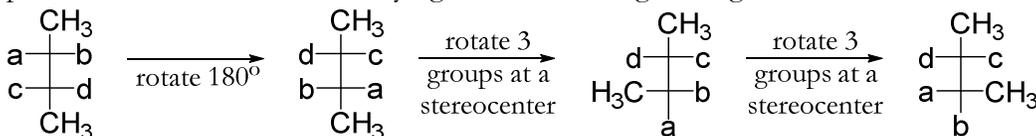


Fischer Projections

Fischer projections were invented to show stereochemistry in an organized way on carbohydrates. They were created by German carbohydrate chemist and 1902 Nobel Prize winner, Emil Fischer. To create a Fischer projection, arrange the tetrahedral carbon so that the vertical bonds at the chiral center point away from you and the horizontal bonds point towards you. If there are multiple stereocenters along the parent chain (the backbone), arrange them vertically.



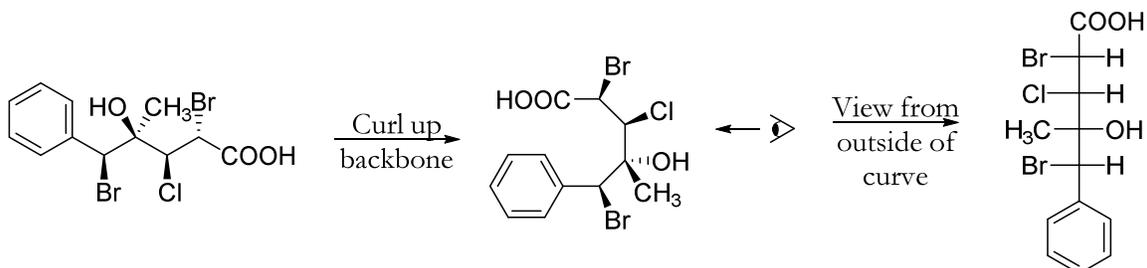
There are two valid ways to redraw a Fischer projection: rotate the entire projection 180° (but not 90° , since this would involve swapping bold and dashed bonds), or rotate three groups at the same stereocenter. Playing with a modeling kit might make this easier to see.



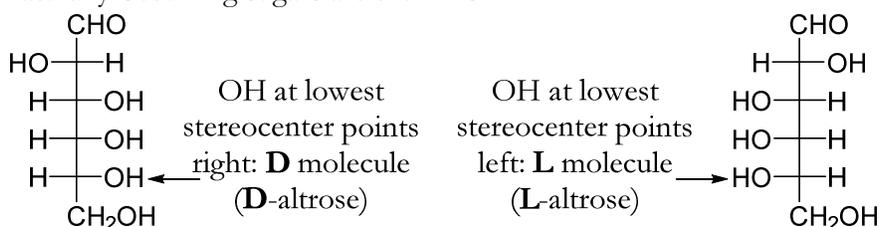
To convert a normal skeletal structure to a Fischer projection, arrange the molecule's backbone so that all the bends are curving around in the same direction, rather than alternating in a zigzag. (The molecule itself doesn't necessarily bend into this conformation in reality; this is just a standardized way of showing it.) You will probably have to rotate every alternating carbon around 180° to do this, which means that which means that the bold and dashed bonds will appear to interchange on these carbons, although the absolute configuration (R or S) should remain the same. Once the backbone is curled up, you can look down on the molecule from outside the curve. In this example, all the groups which are on bold bonds in the curled-up structure end up pointing to the left in the Fischer projection.

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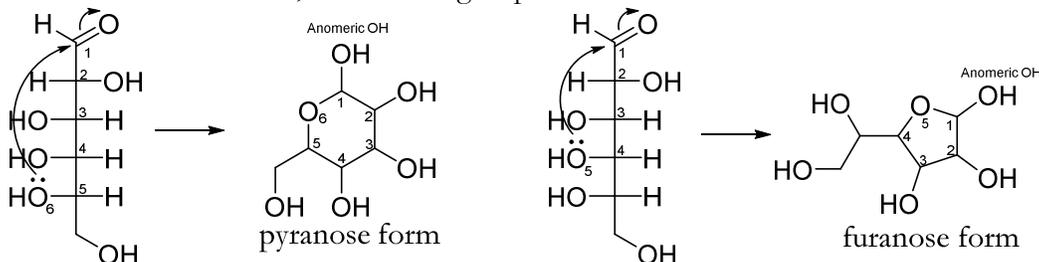
For carbohydrates, the carbonyl carbon is put at or near the top of the chain by convention. The lowest stereocenter, furthest from the carbonyl, determines whether the carbohydrate is **D** or **L**. If the OH points left, it's an **L** molecule. If the OH points right, it's **D**. The two molecules below are enantiomers, so they have the same name except for the **D** or **L** prefix. Almost all naturally-occurring sugars are the **D** form.



Remember that two **enantiomers** have every stereocenter flipped (R to S, or S to R) between the two molecules. Two **diastereomers** have some but not all stereocenters flipped. A subset of diastereomers are **epimers**: two structures that are identical except for a single stereocenter that's flipped.

Cyclization and Haworth Projections

Just because carbohydrates 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 can react with themselves to form a cyclic hemiacetal. Usually they make five-membered rings (called furanoses) or six-membered rings (called pyranoses), since these are the most stable ring sizes. The OH group that does the attack always becomes the oxygen in the ring. The carbon that used to be the carbonyl is identifiable because it's the only carbon in the ring with two bonds to oxygen. This carbon is called the **anomeric carbon**, and its OH group is the anomeric OH.



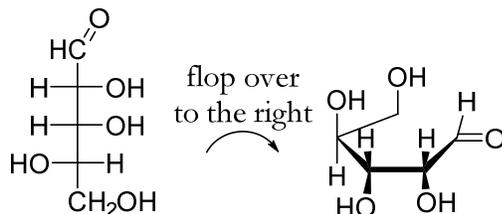
To help show what's going on with the stereocenters, Haworth projections are used. These show the cyclic form of the molecule in a flat ring, but viewed from the side rather than from above. To generate the Haworth projection, there are several steps to follow.

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

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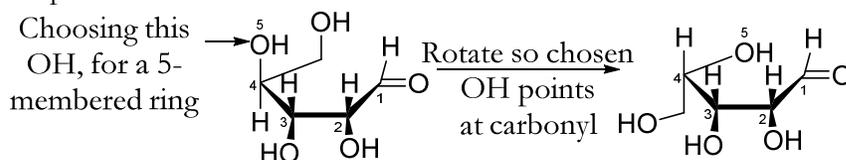
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anything on the right in the Fischer projection is down in the Haworth projection. The lowest carbon in the chain isn't a stereocenter, so it doesn't matter where its OH points.

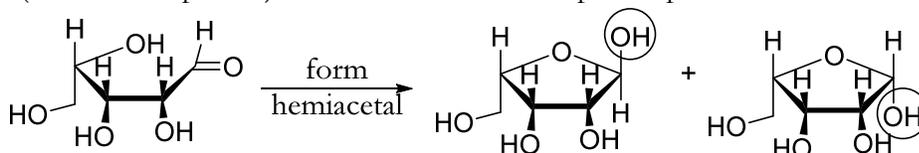


(Note that the part of the structure that's closer to you is shown here with bold/wedge bonds, to make it easier to visualize. You don't have to add that detail though.)

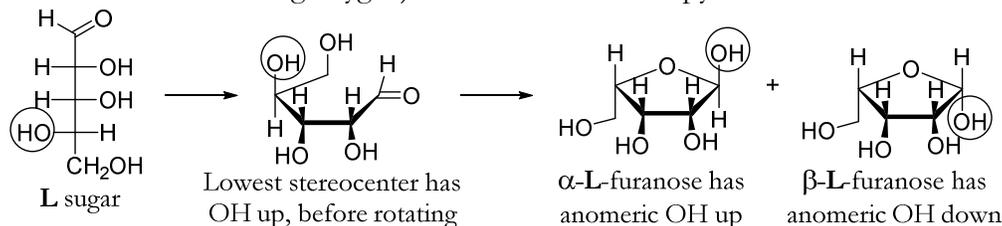
- Decide which OH group you're going to cyclize onto – this depends on whether you're asked to make the furanose (5-membered) or pyranose (6-membered) ring. Numbering is helpful here. If necessary, rotate the chosen OH into position so it's in the plane of the molecule, pointing towards the carbonyl. The rest of the chain after this gets rotated out to become an up or down substituent.



- Form the hemiacetal between the chosen OH and the carbonyl. The anomeric carbon becomes a new stereocenter. Because this stereocenter could be either R or S, there are two different forms of each ring which vary only at the anomeric carbon and are called **anomers** (a subset of epimers). The anomeric OH can point up or down.

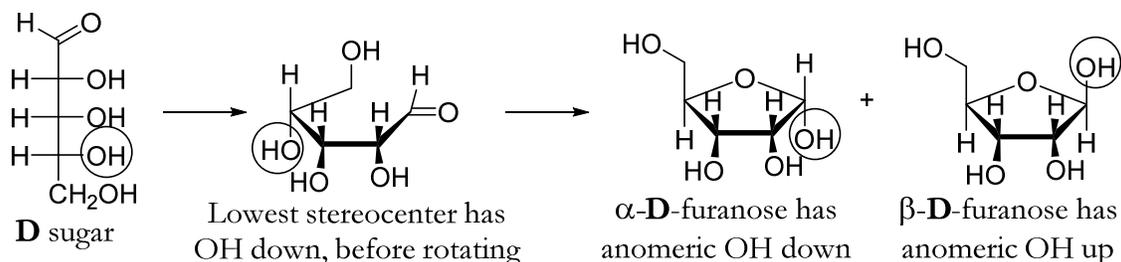


- To describe the two different anomers for each ring size, we use α and β . In the α anomer, the anomeric OH is pointing the same direction as the OH at the lowest stereocenter (the one that determines **D** or **L**) was pointing, before you rotated any OH groups into place in step 2. In the β anomer, it's pointing the opposite direction. This means that a **L** structure has the anomeric OH pointing up for α and down for β , and vice versa for **D** (assuming you followed the previous steps, so the anomeric carbon is clockwise from the in-ring oxygen). This is true for both pyranose and furanose forms.



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These descriptors can be combined with the rest of the name. For example, if the **D** enantiomer of talose makes a five-membered ring with β stereochemistry at the anomeric carbon, it would be named β -**D**-talofuranose.

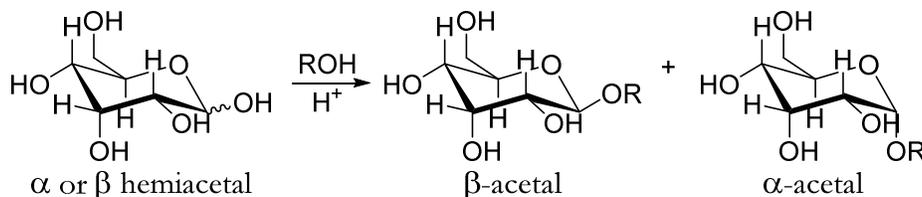
5. For pyranose forms, you might need to draw the six-membered ring in chair form. This follows the same rules as in Ch. 7 – up-pointing groups might be up axial or up equatorial, depending on which carbon you show them attached to. After a ring flip, though, they will switch between axial and equatorial.



All the forms of a molecule (α -pyranose, β -pyranose, α -furanose, β -furanose, and linear/acyclic) will interconvert, because hemiacetal formation is reversible. This is called **mutarotation**. It's catalyzed by either acid or base, but it can happen in neutral water too.

Glycosidic Bonds and Polysaccharides

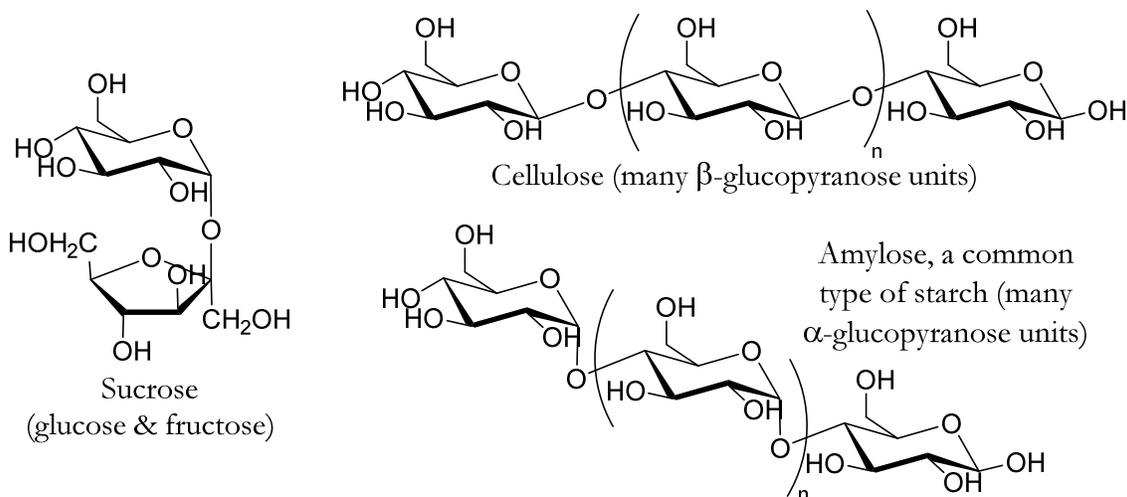
Since the cyclic forms of carbohydrates are hemiacetals, they can do the same things that other hemiacetals can do. For instance, they can convert to the full acetal if there's another molecule of alcohol and an acid catalyst. Just like in the cyclic hemiacetal, there are α and β form, and both will be formed from either hemiacetal.



The overall effect of this reaction is to convert the anomeric OH group into an 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^+ . What if the ROH molecule is actually another molecule of carbohydrate? In this case, you'll link together two carbohydrates (a.k.a. **monosaccharides**) into a **disaccharide**. You can also link more of them into a longer chain (a **polysaccharide**). Table sugar, sucrose, is a disaccharide – it consists of a molecule of glucose and a molecule of fructose. Many polysaccharides use attachments to multiple OHs around the ring to create branch points.

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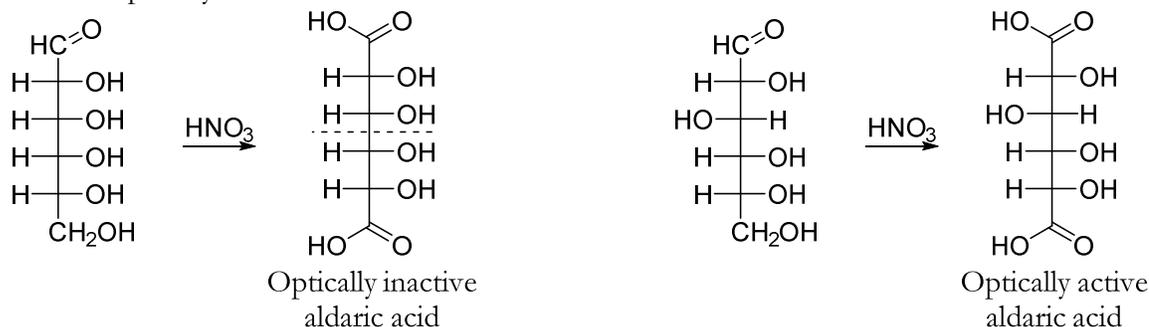
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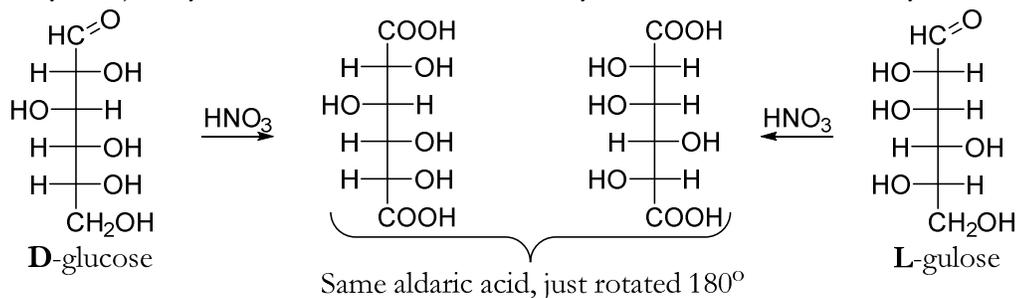
Reactions of Carbohydrates

There are a lot of reactions that can happen to carbohydrates, but we'll just focus on the two that will be useful for the Fischer Proof.

- Oxidation to the aldonic acid: this involves oxidizing both ends of the chain to carboxylic acids, while leaving the rest of the chain unaffected. This is useful because it gives us some information about the stereochemistry in the middle of the chain: if the carbohydrate's stereocenters are all symmetric across the center of the molecule, it will become optically inactive after this reaction.



This leads to one other interesting effect: two completely different carbohydrates can produce the same aldonic acid. Since both ends are symmetrical, it no longer matters which end is shown at the top (like it does for the aldehyde vs. alcohol ends of the carbohydrate). So you can rotate the aldonic acid by 180° and show it that way instead.

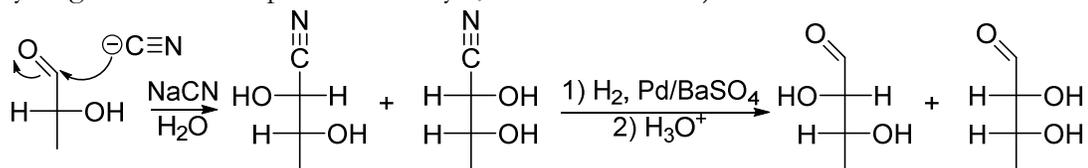


- The Kiliani-Fischer Synthesis: This involves lengthening the top end of the chain by one carbon, creating a new stereocenter. This is done in two steps: first, a cyanohydrin is formed by attacking the carbonyl with cyanide (we saw this in Ch. 19), and then the

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cyano group is reduced to an aldehyde (we haven't seen this before, but it looks a lot like hydrogenation with a poisoned catalyst, similar to Lindlar).

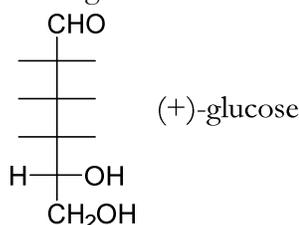


The net result of all this is that the chain gets lengthened by one carbon, and the product is a mixture of two epimers that differ only at the highest stereocenter. Every other part of the chain stays the same.

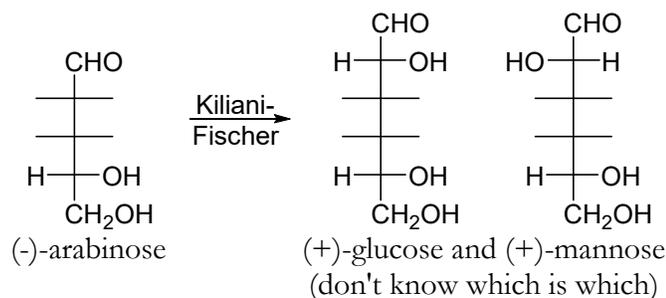
The Fischer Proof

This is how the structure of glucose was figured out originally. The only tools Fischer had at the time were melting point (to determine if two compounds were likely to be the same structure), polarimetry (to determine if a compound was optically active or not), and chemical reactions (mainly just the two listed above). All the steps of this proof refer to several different carbohydrates by name – arabinose, mannose, gulose and so forth. You don't need to know what the structures look like, because Fischer didn't know either at the time. He figured it out as he went along and so will we.

1. **Glucose is known to be an aldohexose**, so it has 4 stereocenters. 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. The absolute stereochemistry of (+)-glucose was not proven until 1950, but it turns out that Fischer's guess for the lowest stereocenter was correct!



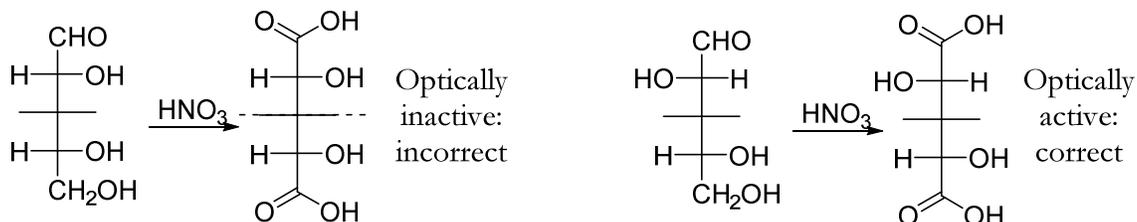
2. **(-)-Arabinose is converted to a mixture of (+)-glucose and (+)-mannose by the Kiliani-Fischer synthesis.** This means that (+)-glucose and (+)-mannose are almost the same structure, except for the top stereocenter, and they're both the same as (-)-arabinose everywhere else.



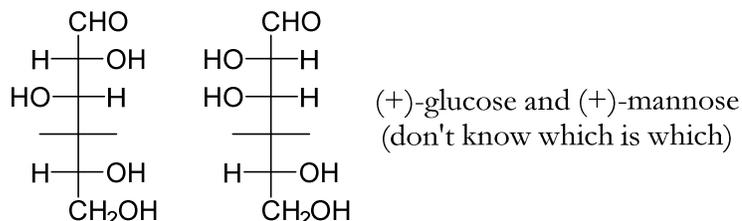
3. **(-)-Arabinose forms an optically active aldaric acid.** This means the topmost OH of (-)-arabinose must be on the left, to avoid mirroring the bottommost OH.

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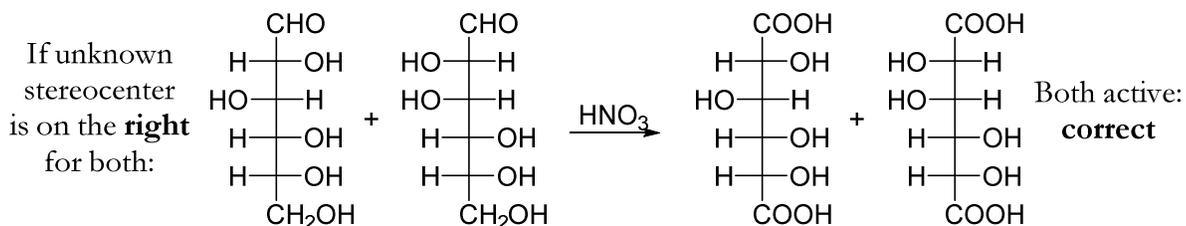
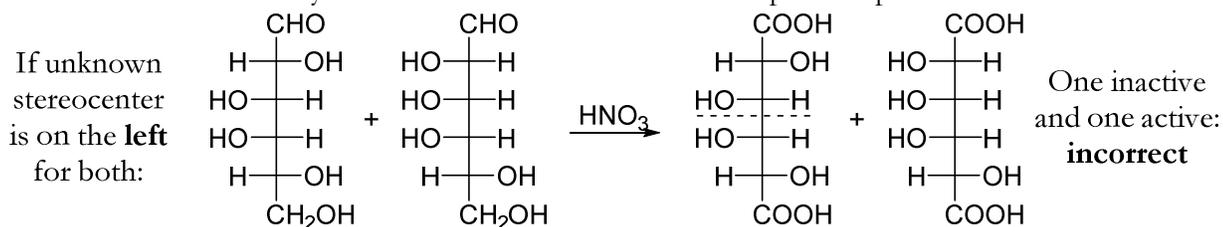
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Putting together what we have so far:



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



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

5. **(+)-Glucose forms the same aldaric acid as a different carbohydrate, (+)-gulose, but (+)-mannose doesn't have this relationship with any other carbohydrate.** This means that (+)-glucose and (+)-gulose have all the same stereocenters, just rotated 180°. Mannose doesn't have this same relationship with anything else, so if you rotate all its stereocenters by 180°, it should still look like mannose. This lets us determine which structure is which.

