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Grammatical Correction: Hanan Alsheikh

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Modified Sugars

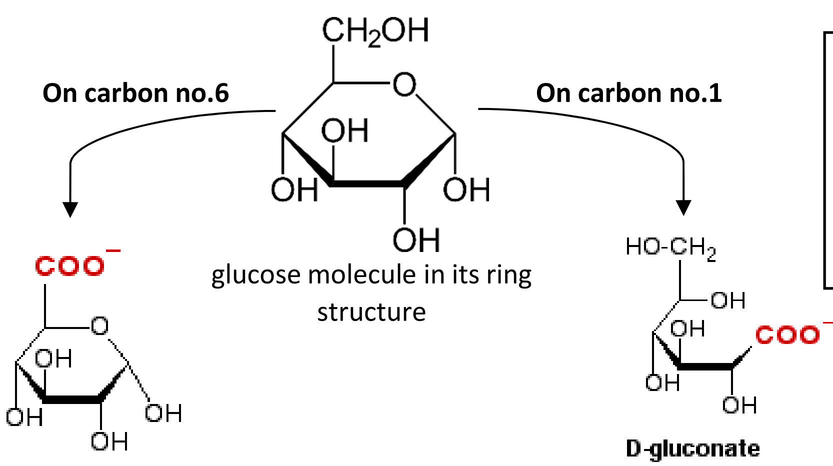
1.sugar **acids (oxidized sugars)**. 2.sugar **alcohols(reduced sugars)**. 3.sugar **esters**.
4. **Glycosides.** 5. **Amino** sugars.

different reactions such as: oxidation, reduction, esterification, and acetylation that can happen to sugars producing different types of sugar molecules with different functional groups.

Sugar Acids are products of sugar-oxidation reactions.

Example: a glucose can be oxidized into **carboxylic acid** through the OH group at **different** sites on its' sugar structure:

carbon no.6 is excluded outside the glucoses' ring structure. oxidation product on this site is **glucuronic acid** which turns into (glucuronate) once it donates its proton.



α-D-glucuronate
(D-glucuronic acid, **GlcUA**)
from **oxidation of glucose C6 OH**

D-gluconate
(D-gluconic acid, **GlcA**)
from **oxidation of glucose C1 aldehyde)**

the produced sugar acid is called gluconate or **gluconic acid**

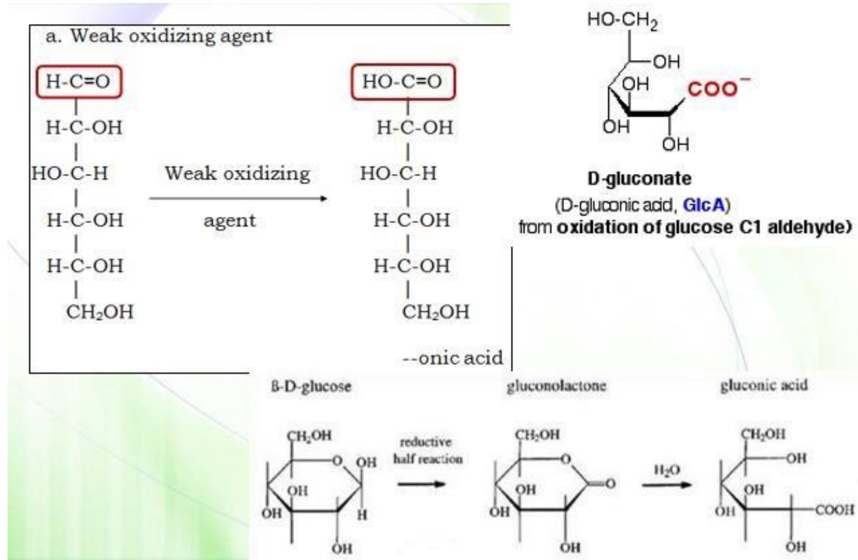
same idea applies to other monosaccharides such as galactose since it's a hexose as well, it can be oxidized into galacturonate (oxidation at C6) OR galactonate (oxidation at C1).

***Anomeric carbon**: the carbon that is present in the carbonyl group (carbon no.1 here), has the highest chance to be oxidized.

Oxidation is done by oxidizing agents that can be:
1. weak. 2. strong. 3.enzymes.

-**weak oxidizing agents** preferably oxidize the carbonyl carbon (anomeric carbon) that is attached to a hydroxyl group (OH), because oxidizing an aldehyde to carboxylic acid is a one-step reaction that can be achieved by a weak oxidizing agent.

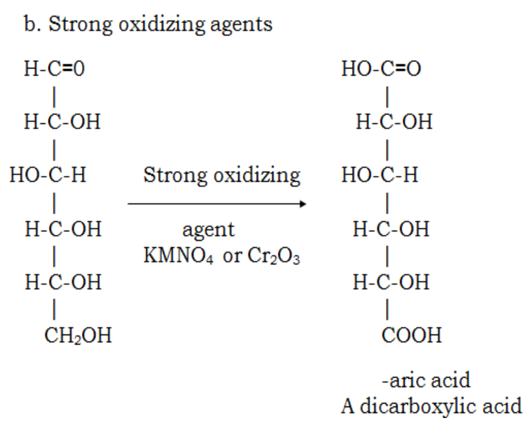
-when you look at the structure of glucose, you can see that **Carbon no.1** is the carbonyl carbon so oxidation by a weak agent is most likely to happen at that site rather than **Carbon no.6** because a primary alcohol is two steps away from becoming a carboxylic acid. and the final product is gluconate not glucuronate.

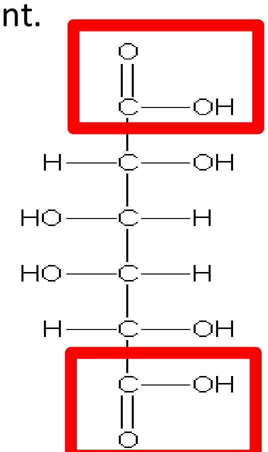


Strong oxidizing agents such as $KMNO_4$, Cr_2O_3

would both oxidize carbon no.1 and no.6 in a glucose or a galactose molecule producing a dicarboxylic acid (sugar acid with two oxidized sites, named by adding the suffix -aric + acid).

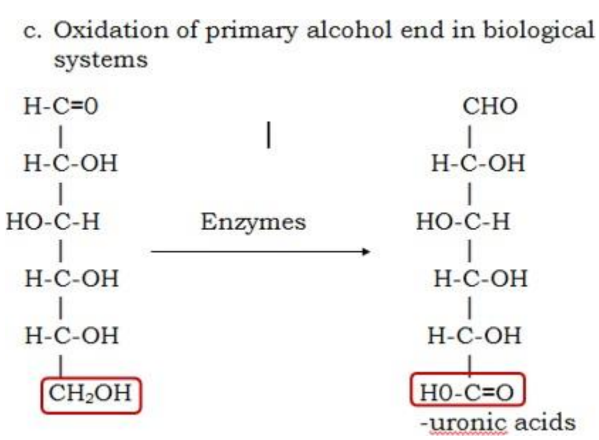
- galacteric acid → oxidized galactose by a strong oxidizing agent.

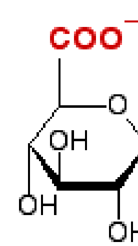




galactaric acid

Enzymes specifically oxidize carbon no.6 without oxidizing carbon no.1 to produce a sugar acid with the added suffix **-uronic** + acid.





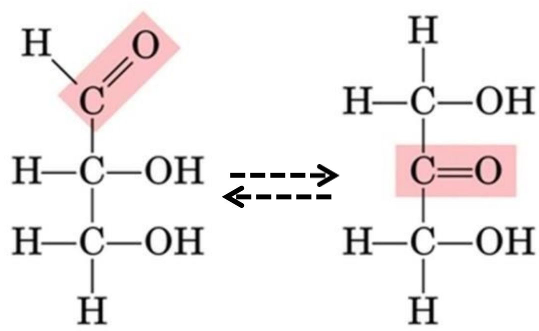
α-D-glucuronate
(D-glucuronic acid, GlcUA)
from oxidation of glucose C6 OH

Summary

Sugar acid	Oxidation site	Oxidation agent	examples
-uronic acid	Carbon no.6	Enzymes	Glucuronic acid (glucuronate) Galacturonate
-aric acid	Carbon no.1 + no.6	Strong oxidizing agent	Galactaric acid
-onic acid	Carbon no.1	Weak oxidizing agent	Galactonic acid (Galactonate) Gluconic acid (gluconate)

Note:

Recall that glucose and galactose **are aldoses**, their ability to oxidize to carboxylic acids is due to the presence of a hydrogen atom in the aldehyde group that can be easily removed and replaced by an oxygen, electrons are removed to get the molecule oxidized. Whereas **ketoses** (e.g. fructose) cannot get oxidized directly because the carbonyl carbon is connected to two carbons which makes it hard to add more oxygens or to even reduce hydrogen content and remove electrons from the molecule.

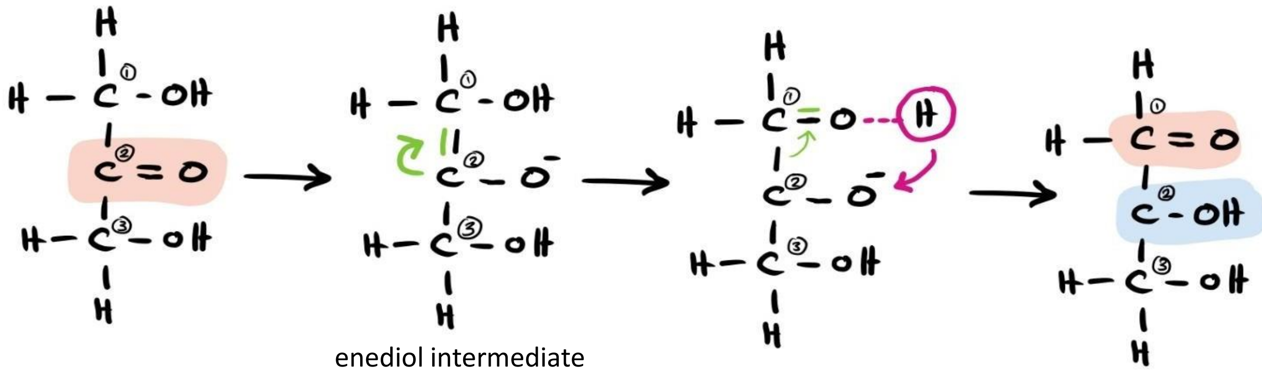


Aldose **Ketose**

-**indirect oxidation of ketoses:**
ketoses can be oxidized when they isomerize to aldoses, in which they're converted into **aldoses** throughout bonds + electrons rearrangement causing **the transfer of the carbonyl group from carbon.2 to carbon no.1.**

-The process; electrons of the double bond in the carbonyl group would shift causing the carbonyl carbon to form a double bond with an adjacent carbon (carbon no.1 in the picture below), then electrons would shift again from the two carbons causing carbon no.1 to form a double bond with the oxygen in its hydroxyl group removing the hydrogen of the hydroxyl group so it would bind with the oxygen of the 2nd carbon, and oxidation can finally take place.

electrons shift in this order: carbon no.2 → carbon no.1 and no.2 → carbon no.1

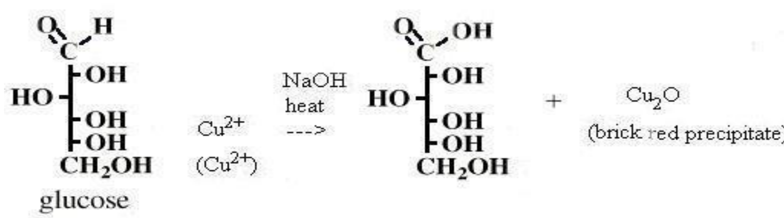


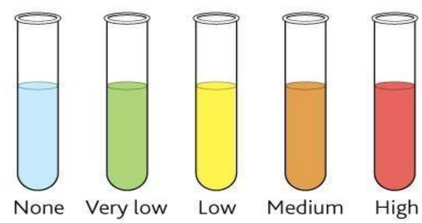
Biochemical tests that are used to distinguish aldehydes from ketones:

1.Benedict's test. 2.Tollen's test.

Benedict's test

a blue reagent that contains copper ion(Cu^{+2}) is going to be added to an aldehyde such as glucose, copper oxidizes it forming carboxylic acid

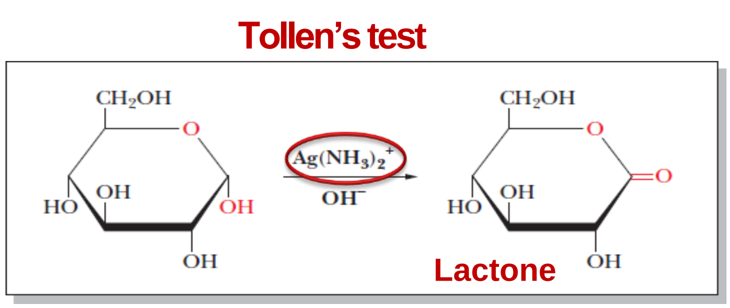




and a brick red precipitate (راسب) Cu_2O that is used as an indication for aldehyde presence in solutions, if a ketone was added to the copper reagent no reaction would take place and the color would stay as it is rather than becoming brick red colored.

Tollen's test Oxidation of cyclic sugars (lactone)

Tollen's test reagent $Ag(NH_3)_2^+$ contains silver (Ag), as it reacts with the ring structure of the sugar causing it to oxidize into **lactone**, leaving behind silver mirror. (Ag precipitate)



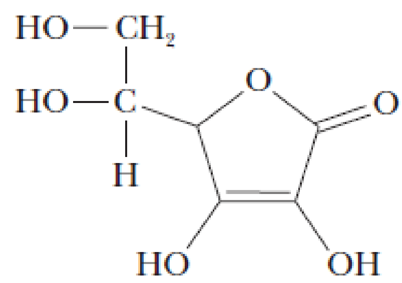
silver mirror

<u>Side Note</u>: A recent method for glucose detection only (no other reducing sugars) is based on the use of the enzyme glucose oxidase.

lactone: is produced from aldose oxidation, a cyclic ester that has carboxyl and alcohol functional groups.

Clinical Application on Tollen's Test ~ Lactone

- Vitamin C (ascorbic acid) is an unsaturated **lactone** that has an oxygen atom, a carbonyl group C=O, and a double bond in its ring structure.
  Vitamin C is important for uplifting and improving our immune system where it acts as antioxidant, and collagen synthesis.



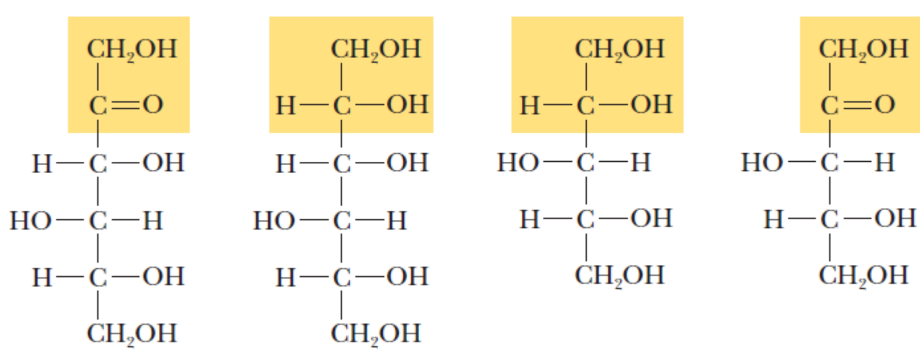
Ascorbic acid (Vitamin C)

- Air oxidation of ascorbic acid, followed by hydrolysis of the ester bond, leads to loss of activity as a vitamin, so whenever ascorbic acid-containing food gets exposed to Air, the Vitamin C gets oxidized, causing it to deactivate because a new molecule is formed.

- A lack of fresh food can cause vitamin C deficiencies which leads to scurvy.
  For example: sailors spend a lot of time in the sea sailing, their food wouldn't be fresh, the vitamin C in it is inactive, which in turn leads to vitamin C deficiency.

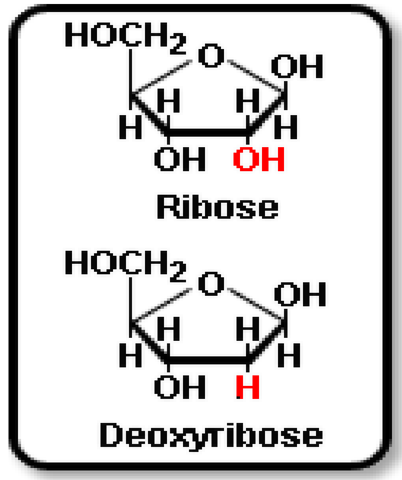
  vitamin C is important collagen synthesis, and collagen is important for gums, skin, and other tissues in our body, so when vitamin C is compromised, the quality of collagen is going to be reduced, causing lacerations and tears in the tissues.

Sugar Alcohols are products of ketose reduction, where the ketone group gets reduced back into a secondary alcohol.
Examples: Sorbose is reduced to Sorbitol and Xylulose → Xylitol.
-sorbitol, mannitol, and xylitol are used to sweeten food products. (e.g. sugar free gum contains reduced sugars such as sorbitol or xylitol)



D-Sorbose D-Sorbitol D-Xylitol D-Xylulose

Deoxy-sugars an example on reduced sugars



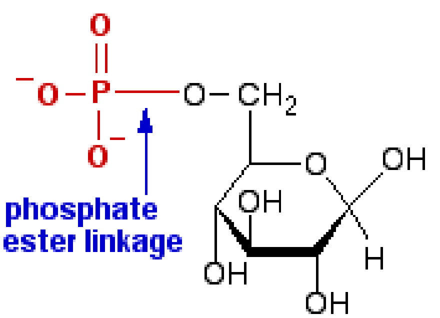
-reduced sugars have one or more hydroxyl groups that get replaced by hydrogens.

2-Deoxyribose a constituent of DNA structure is an example on reduced sugars, originally derived from ribose (an aldopentose) but lacks oxygen on carbon no.2 hence the name 2-deoxyribose.

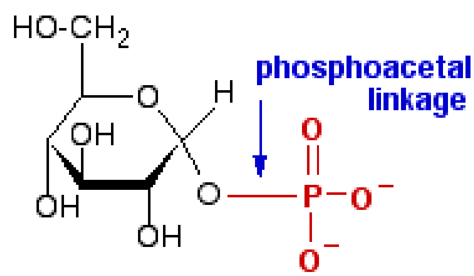
Ribose is present in the RNA structure whereas 2-deoxyribose is present in DNA which is the reason behind naming it deoxyribonucleic acid.

Sugar Esters are products of sugar esterification; addition of phosphate groups to hydroxyl groups by phosphorylation.

it's called esterification because the formula of the final product P=OOR is similar to esters' formula RC=OOR.



β-D-glucose-6-phosphate
(an ordinary **phosphate ester**)

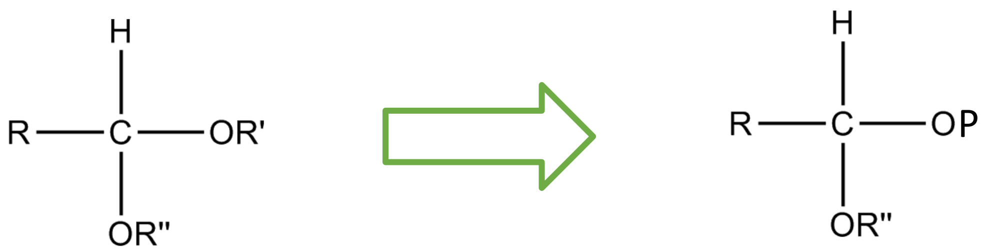


α-D-glucose-1-phosphate
(a **phosphoacetal**)

two different phosphorylation reactions can happen:

Reaction site	carbon no.6	carbon no.1
Sugar molecule	glucose-6-phosphate	glucose-1-phosphate
Type of linkage	Phosphate **ester** linkage	Phospho**acetal** linkage
Resulting molecule	Phosphate ester	phosphoacetal

when the reaction takes place at carbon no.6 in a glucose molecule, a phosphate ester is formed. however, adding the phosphate group to carbon no.1 would produce phosphoacetal which follows the formula of an acetal and has one O---P instead of O---R of a regular acetal.



Formula of Acetal

Formula of Phosphoacetal

Insight

Phosphorylation is a key reaction in sugar metabolism.
Recall what we took in the biology course: the first step in glucose metabolism is to convert it to a pyruvate which is achieved by multiple phosphorylation reactions.

both phosphorylation reactions are significant in metabolism, phosphorylation on carbon no.6 is important to mark glucose molecules (glucose-6-phosphate) for degradation in the reactions of glycolysis.
glucose-1-phosphate is important in other series of metabolism reactions.

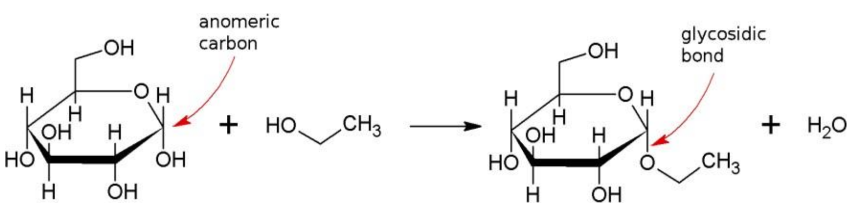
Glycosides:

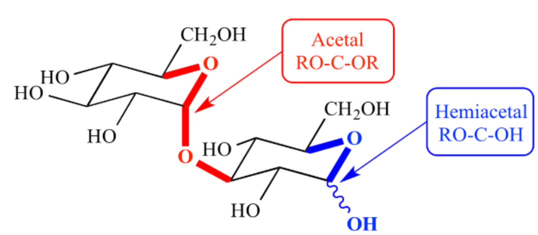
1.O-Glycosides.

2. N-Glycosides.

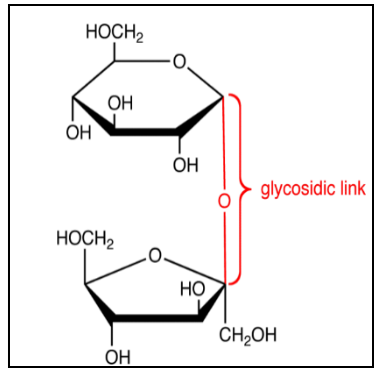
O-Glycosides: result from an interaction between the anomeric carbon (carbon no.1) in a sugar molecule with an alcohol group (from another sugar or an alcohol molecule) via a glycosidic bond.

-because the bonding occurred via oxygen atom the resulting molecule is called O-glycoside, which is a disaccharide.

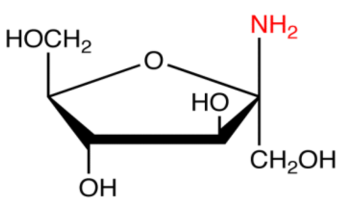




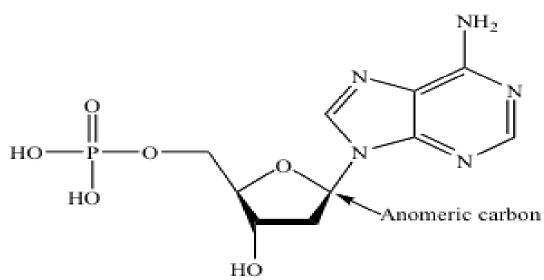
-this interaction is important in producing more complex sugars like disaccharide, oligosaccharides, and polysaccharides.
as well as glycoproteins formation via glycosylation of proteins, in which the interaction is also done through oxygen or nitrogen atoms.



N-Glycosides are generated when a monosaccharide is attached to another sugar or a functional group through a nitrogen atom.
Example: sugar molecules in DNA and RNA are connected to nitrogenous bases via the bases' nitrogen atom and the sugars' anomeric carbon, which makes the sugar molecule N-glycoside.

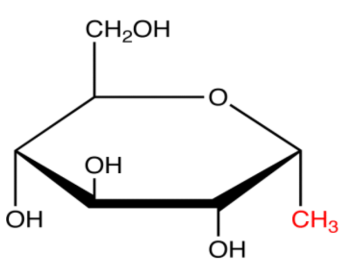


N-glycoside

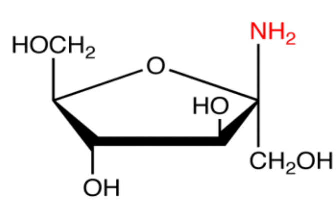


Note:
Glycosides are classified to 1.furanosides and 2.pyranosides depending on the sugar the make up their structure and regardless if they are N- or O-linked.

- Glycosides derived from furanose (a five-membered ring structure) are called furanoside, and those derived from pyranoses (six-membered ring structure) are called pyranosides.



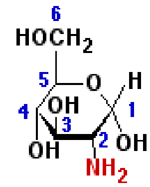
C-glycoside



N-glycoside

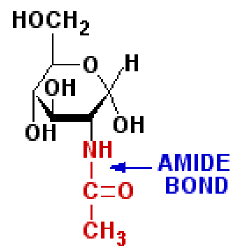
Amino Sugars

carbon no.2 of a sugar molecule gets modified by replacing the OH group by an amino group NH_2, the modified product is known as
2-glucosamine if the sugar is glucose



α-D-2-glucosamine
(GlcN)

-another modification: glucosamine would form an amide bond with a two-carbon unit C=OCH_3 (an acetyl group), the resulting product is N-acetyl-2-glucosamine.

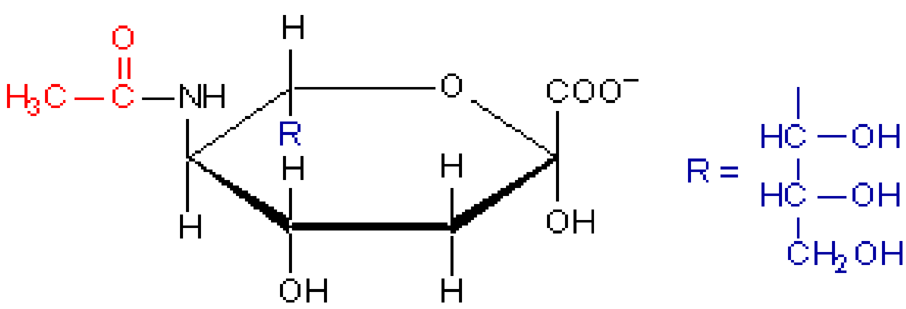


N-acetyl-α-D-2-glucosamine
(GlcNAc)

-galactose can be modified in the same principle as glucose here. (2-galactosamine, N-acetyl-2- galactosamine)

Sialic acid also known as N-acetyneuraminate, a modified sugar with carboxyl group on carbon no.1 and amino group on carbon no.4 that's forming an amide linkage with an acetyl group.

-the precursor of sialic acid is neuraminic acid which is an amino sugar, in which an acetyl group is added to neuraminic acid in order to form N-acetyneuraminate.



N-acetylneuraminate (sialic acid)

-sialic acid is an important sugar terminal residue present in the oligosaccharide chain of glycoproteins and glycolipids.

Let us now move to more complex sugars which are **disaccharides** and **oligosaccharides**.

Disaccharides

Disaccharides are sugars that are made from **two** monosaccharides joined by glycosidic linkage, they could be made from the same type of monosaccharides, and called **homo-disaccharides,** or they could be made from different types of monosaccharides, and called **hetero-disaccharides**.

These disaccharides are synthesized by an enzyme called "***glycosyltransferase"*** , this enzyme is responsible for the interaction between the first monosaccharide through the anomeric carbon and the second monosaccharide through another carbon that has an alcohol group attached to it.

❖ Distinctions of disaccharides

There are several factors that can affect the type and the structure of disaccharides that can be formed, such as:

1. The two specific sugar monomers involved and their stereo-configurations (they could have the same or different type of sugar, and they could also be in same configuration: either both in D-configuration or in L-configuration, OR a combination of D and L configurations.)

2. we may have different carbons that make the linkage between disaccharides, so it could be between C1 from the first sugar and C4 from the second sugar, or C1 and C6 and so on.

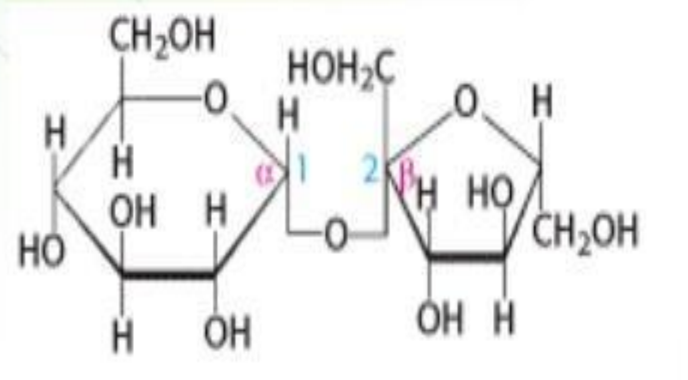
3. The order of the two monomer units (which one is first, and which one is second), example; galactose followed by glucose or the opposite of that.

4. The orientation of the OH group of the anomeric carbon whether it is upwards or downwards (α or β).
So, all these factors make different types of disaccharides as we will see next.

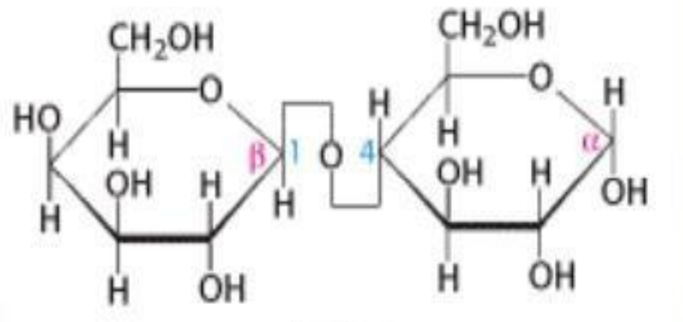
Examples on different types of abundant disaccharides

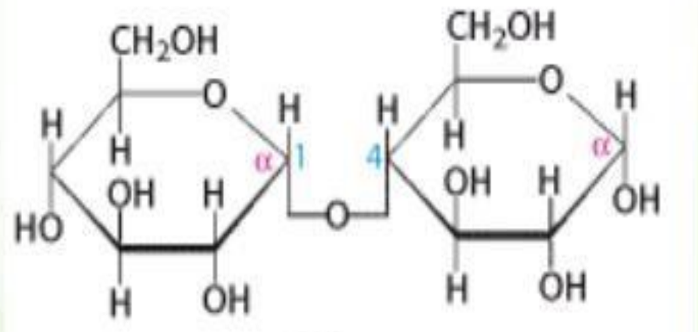
Sucrose (table sugar)

Sucrose is made from **glucose** (left) and **fructose** (right), the linkage is between the two anomeric carbons in each sugar (the carbon number 1 in glucose and carbon number 2 in fructose). α (1—2) linkage .
*You can easily distinguish between the carbon number 2 and carbon number 5 in **fructose**, carbon number 2 has a hydroxyl group and CH_2OH, while carbon number 5 has only a hydrogen atom and CH_2OH.



Sucrose
(α-D-Glucopyranosyl-(1→2)-β-D-fructofuranose





Lactose (milk sugar)

It is made of **galactose** (left) and **glucose** (right), look at carbon number 1 in each sugar, The OH in galactose is upwards so β, and the OH in glucose is downwards so α.The linkage is between carbon number 1 in galactose and carbon number 4 in glucose, and remember that OH on C4 in glucose is directed downward, so the shape of the bond between them will be like the letter N in English. The bond is called **β (1--- 4) linkage**.

Maltose (malt sugar)

Maltose is a **homo-disaccharide** which is made of two glucose residues. The two residues are α glucoses.

Recall that carbon number 1 in the first glucose has the α configuration, so the OH is directed downwards. However, carbon number 4 in the other glucose is also directed downwards, which makes the bond looks like the letter V in English.
The bond is called **α (1--- 4) linkage**.

- we mentioned earlier that these monosaccharides were able to get oxidized and act as **reducing sugars** (reduce oxidizing agents) like glucose or galactose or even fructose (although it is a ketose, it can be converted first to aldose and be oxidized), so all the monosaccharides can be reducing sugars.

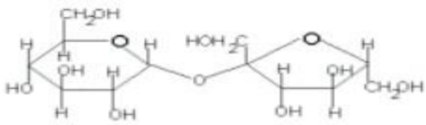
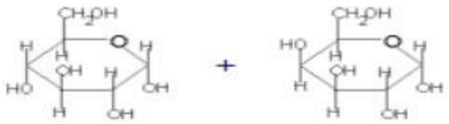
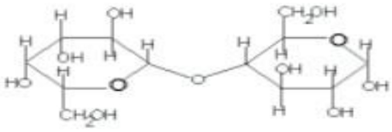
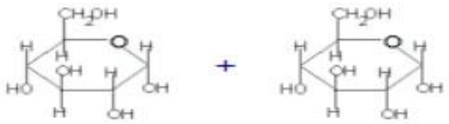
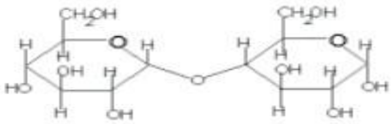
☒ Now, the question is, can disaccharides also act as reducing sugars?

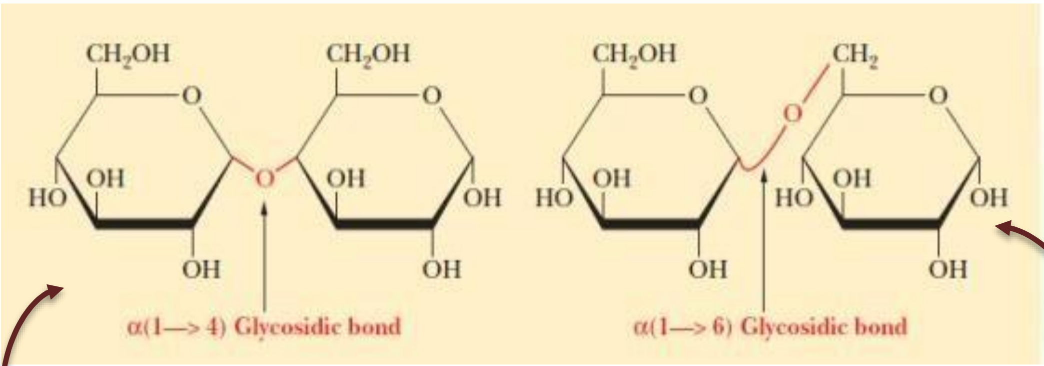
it depends on **the structure** of the disaccharide. A Disaccharide will act as a reducing agent if it still has a free (unbound) anomeric carbon, for example, the structure of the sucrose has two positions of **easy oxidation** (carbon number 1 in glucose and number 2 in fructose), notice that these carbons are connected via a linkage here, so they are unable to get oxidized (The OH groups are not available for oxidation), that's why this disaccharide is a non-reducing sugar. While in lactose, the OH in galactose is consumed in forming the linkage but the OH group in the glucose on carbon number 1 can be oxidized, so it is considered as reducing sugar.(maltose is the same as lactose).

Note: there are also some positions that can be oxidized but they are not oxidized easily (like carbon #6), so we take the easy oxidized positions as a reference for considering these sugar as reducing sugars or not .

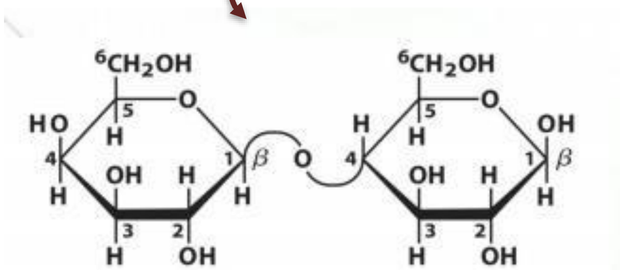
The picture below summarizes the formation of the three disaccharides that we have taken so far. (notice that OH leaves one sugar and H from the other sugar forming H_2O).

"Dehydration reaction"

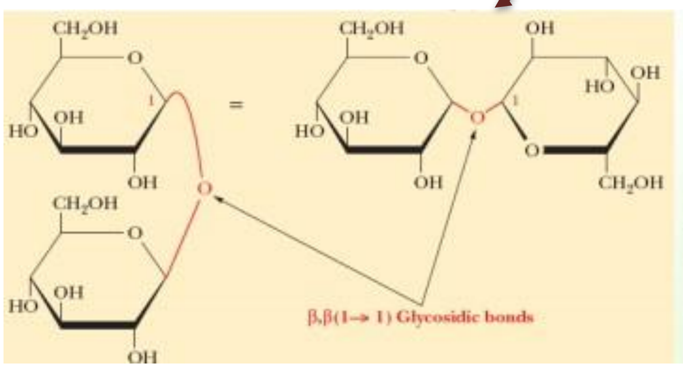
Name	Formula	Formed from	Structure
sucrose	$C_{12}H_{22}O_{11}$	glucose + fructose 	---> sucrose + H_2O 
lactose	$C_{12}H_{22}O_{11}$	glucose + galactose 	---> lactose + H_2O 
maltose	$C_{12}H_{22}O_{11}$	glucose + glucose 	---> maltose + H_2O 



So we have talked about different types of disaccharides like the α (1--- 4) linkage in the maltose sugar, or the α (1--- 6) linkage as we will learn later on. We have seen also the linkage in lactose, the β (1--- 4) linkage which is the only linkage in Beta form. There are also other examples where we have Beta linkage, β (1--- 1) between two glucose residues.

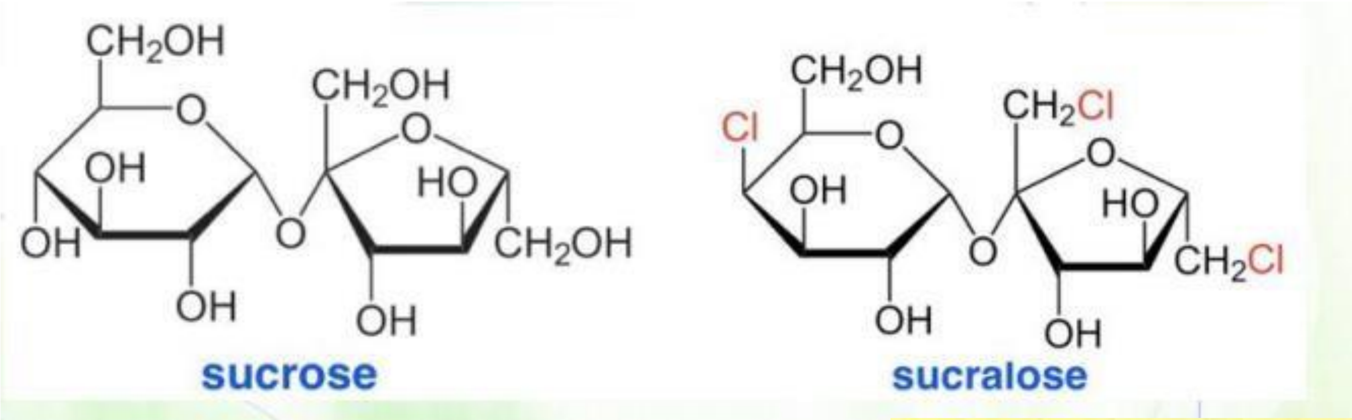


Lactose (β form)
β-D-galactopyranosyl-(1→4)-β-D-glucopyranose
Gal(β1→4)Glc



Sucralose (artificial sweetener)

A molecule that is synthesized in terms of structure of **sucrose**, but in sucralose, some OH groups are replaced by CL.



This molecule still has a sweet taste and it is considered as artificial sweetener (محلَي صناعي) such as ***Splenda*** (a brand of artificial sweetener), recall that all the sugars that we talked about previously are **naturally occurring**.

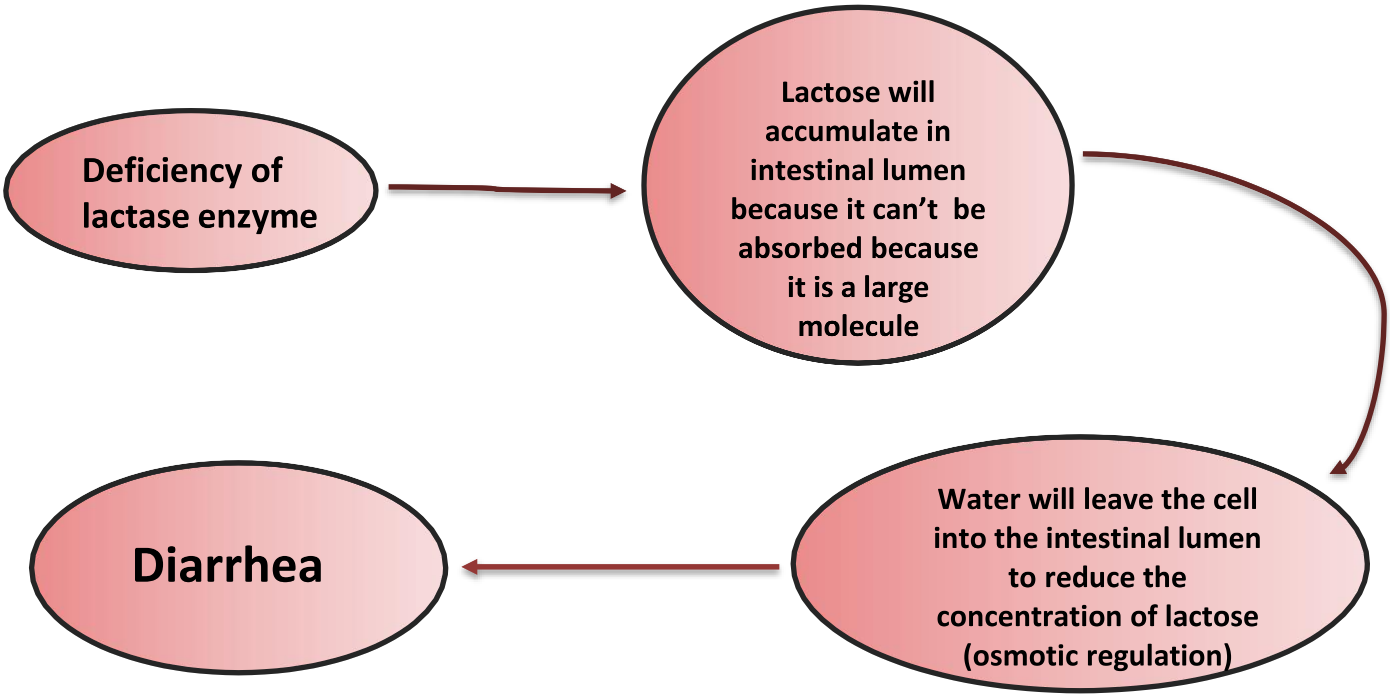
There has been some debate and controversy about the use of these molecules as alternatives of natural sugars, specially that it became a trend between females and males who are trying to lose weight. However, there are some reports talking about how harmful these sweeteners are for animals, but nothing has been proven on humans so far, but we have to be careful using them.

Milk problems

There are some problems or clinical applications related to disaccharides, we will talk about two of them.

1. **Lactose intolerance:** some people don't like to drink milk and they don't feel well after drinking it (specially older people), this is actually became the natural situation where most people can't drink milk without problems after drinking it, this is mainly due to the deficiency of an enzyme called "***lactase (B-galacatosidase)***" which is protruded from the **intestinal cells**. This enzyme is responsible for breaking the **β (1--- 4)** between the galactose and glucose in lactose, so the body can absorb them. So, whenever we have lactose accumulating in intestinal lumen, this is due to the deficiency in "***lactase***"enzyme (some textbooks say that the enzyme is present but its activity is reduced.

The whole process is summarized in the figure below:



❖ The accumulating lactose will be used by the normal bacteria in metabolic reactions that produce side products, such as CO_2, methane gas,etc. This will result in bloating (انتفاخ) as we see in this patient.

☒ So, what is the solution for this problem?

People at older age don't have to drink milk, the calcium in the milk can be obtained from other products like **yogurt** and **cheese** (the process in making yogurt and cheese reduces the amount of lactose inside them, that's why people don't face any problems after eating them but they do after drinking milk). The Vitamin D that is present in milk is at low amounts (to get the amount that is needed to the body daily, you have to drink 10 liters of milk), so you can get your daily need of Vitamin D by getting exposed to sun rather than obtaining it from milk.

Another solution is to drink milk that contain the enzyme "***lactase***", or to drink a milk that is **free from lactose**.

2. **Galactosemia:** a **genetic problem** in which galactose-metabolizing enzyme is missing due to genetic mutation. This will result in accumulation of **galactose**, because it can't get metabolized.

Accumulation of galactose will activate the transformation of galactose to an alcohol sugar called "***galactitol***", this sugar can't exit the cell and will disturb the **osmotic pressure** inside the cell and attract water molecules towards the cell and damaging them at the end.

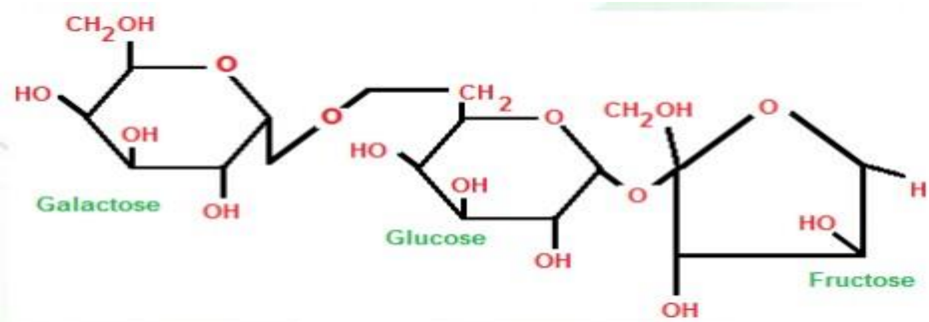
Since we talk about genetic problem, this will happen in an early age and damaging vital tissues particularly the brain, resulting in severe and irreversible **retardation** (اعاقة عقلية).It also affects the lenses of the eyes which causes **cataract** (اعتام عدسة العين).

Oligosaccharides (3-10 sugar molecules)

Raffinose:

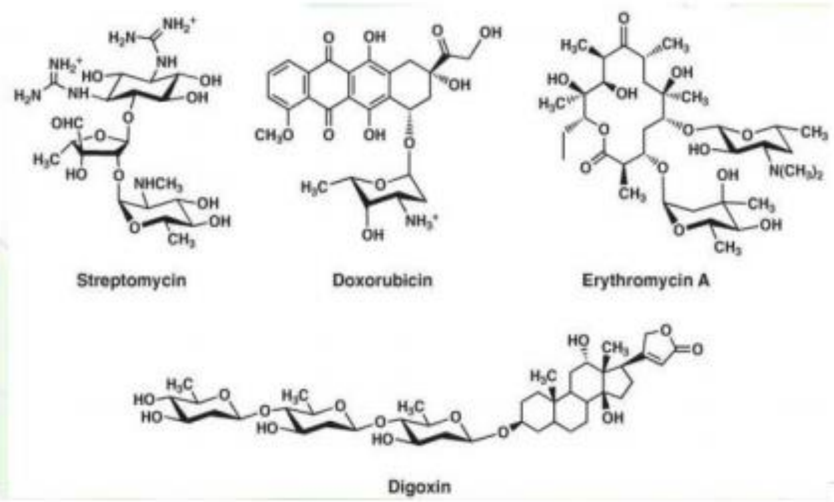
Raffinose: an oligosaccharide that is made of three sugars; galactose, glucose and fructose joined together by different bonds 1,6- and 1,2-. This oligosaccharide is present in beans and vegetables like cabbage, Brussel, sprouts, broccoli, asparagus, This sugar causes bloating, so why this happens?

That's because Humans lack the **alpha -galactosidase** enzyme that is needed to break down raffinose, but intestinal bacteria can ferment it into hydrogen, methane, and other gases



Oligosaccharides as drugs

Oligosaccharides can be synthesized and used as drugs such as antibiotics like (Streptomycin and erythromycin), cancer chemotherapy like (Doxorubicin) and as cardiovascular disease drug like (Digoxin).



`The End `

Self-assessment Questions

1) Deoxy sugars are produced via :

A. Reduction of a monosaccharide
B. Engaging anomeric carbons in a glycosidic bond
C. Conversion of sugar chain into cyclic form
D. Oxidation of a sugar acid
E. Hydrolysis of a disaccharide

Answer: A

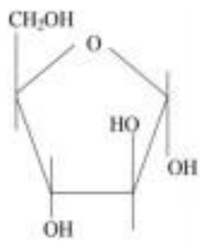
2) oxidation of carbon #6 of cyclic glucose results in :

A. Conversion to fructose
B. Production of glucoronate
C. Stabilizing the anomeric carbon
D. Production of a deoxy sugar
E. Opening of the ring sugar

Answer: B

3) The following structure is a ring form of D-arabinose.The name of this structure is :

A. α-D-arabinofuranose
B. β-D-arabinofuranose
C. α-D-arabinopyranose
D. β-D-arabinopyranose



D-arabinose

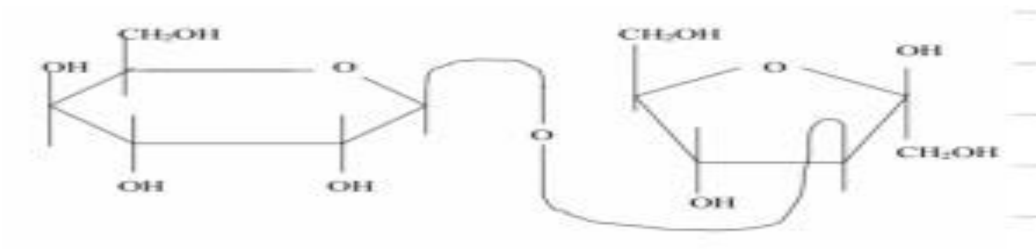
Answer: A

4) In the congenital disease galactosemia, high concentrations of galactose and galactitol accumulate in the blood. On the basis of their names, you would expect which one of the following statement to be correct ?

A. galactitol is an aldehyde formed from the keto sugar galactose
B. galactitol is the oxidized form of galactose
C. galactitol is the sugar alcohol of galactose
D. both galactitol and galactose are sugars
E. both galactose and galactitol would give a positive reducing sugar test

Answer: C

The following disaccharide is named D-avatose, answer the following two questions ;



5) What monosaccharides will be produced upon acid hydrolysis of D- avatose?

A. D-galactose and D-fructose
B. D-galactose and an epimer of D-fructose
C. an epimer of D-galactose and an epimer of D-fructose
D. D-fructose and an epimer of D-galactose

Answer: D

6) This structure

A. is α-D-avatose which contains a β 1,3 glycosidic bond.
B. is α-D-avatose which contains a β 1,2 glycosidic bond.
C. is β-D-avatose which contains a β 1,3 glycosidic bond.
D. is β-D-avatose which contains a β 1,2 glycosidic bond

Answer: C

Note: the disaccharide is named α or β according to the orientation of the anomeric carbon that is a part of the linkage. (mostly the first monosaccharide).

7)A patient was diagnosed with a deficiency of the lysosomal enzyme alpha-galactosidase. The name of the deficient enzyme suggest that it hydrolyzes a glycosidic bond, which best describes the bond that can't be broken ?

A. multiple hydrogen bonds between two sugar molecules
B. Between the anomeric carbon of a sugar and an OH (or N) of another molecule
C. Between two anomeric carbons in polysaccharides
D. Internal bond formation between the anomeric carbon of a monosaccharide and its own fifth carbon hydroxyl group.
E. Between the carbon containing the aldol or keto group and the α-carbon of the sugar.

Answer: B

BEST OF LUCK <3