CARBOHYDRATES

- carbohydrates are the most abundant molecules found in nature

- these complex multifunctional compounds exhibit classic organic chemical behavior in the execution of myriad important biological applications

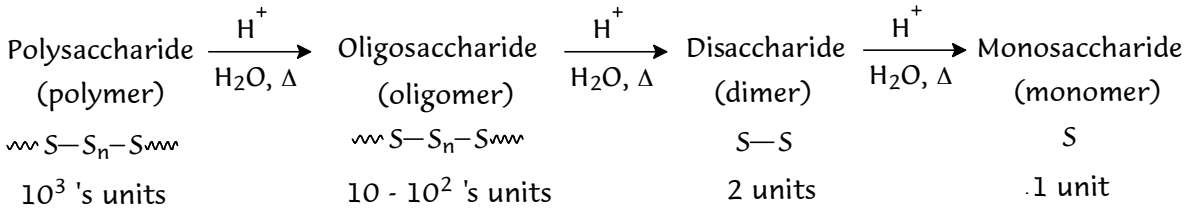
CLASSIFICATION –

Original Definition ➢ hydrate of carbon, $C_n(H_2O)_m$ (a common molecular formula)

Modern Definition ➢ a polyhydroxyaldehyde, a polyhydroxyketone or a compound which easily hydrolyzes to either of them

Saccharide, S ➢ a sugar unit (from Latin for *sweet*)

Carbohydrate Hierarchy –



Monosaccharides & Disaccharides are commonly referred to as "*simple sugars*"

I. MONOSACCHARIDES –

- the structural characteristics of monosaccharides are fundamental to all carbohydrates

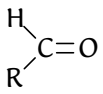
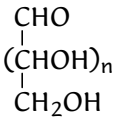
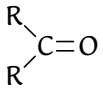
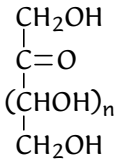
CLASSIFICATION –

- specific monosaccharides are usually referred to by their common names, but general classifications exist which are based on common structural features

A. Functional Group –

- every carbon in a monosaccharide is oxygenated (with a carbonyl =O or a hydroxyl -OH)

- monosaccharides can be classified according to the type of carbonyl group present:

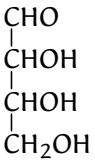
Functional Group	General Structural Formula	Name	Prefix	Suffix
 (Aldehyde)		Aldose	aldo-	-ose
 (Ketone)		Ketose	keto-	-ose

B. Number of Carbons –

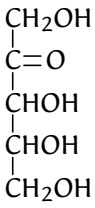
- monosaccharides can be classified according to the number of carbons present:

# C's =	3	4	5	6	7	.....
Name = (Suffix)	triose	tetrose	pentose	hexose	heptose	.....

EX. classify according to FG & #C's



an aldotetrose

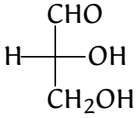


a 2-ketopentose

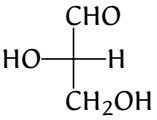
C. D & L Configuration –

- all CHOH group carbons in monosaccharides are stereocenters (C*)

- the D/L configuration of all carbohydrates is based on the stereocenter contained in the simple aldotriose, glyceraldehyde



D-(+)-glyceraldehyde
(R-configuration)



L-(-)-glyceraldehyde
(S-configuration)

- all D-series sugars can be degraded to D-(+)-glyceraldehyde

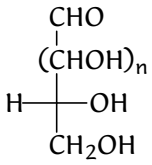
- all L-series sugars can be degraded to L-(-)-glyceraldehyde

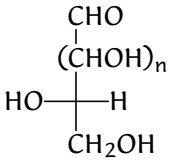
Assigning the D/L Series Configuration –

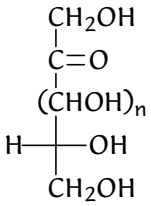
- place the most oxidized carbon (C=O) closest to the "top" in a Fischer projection (FP)

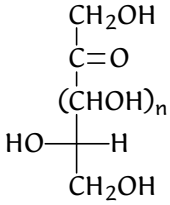
- examine the configuration of the CHOH closest to the "bottom" (2nd to "last" C in the FP)

-OH Right ➢ D-Series **-OH Left ➢ L-Series**

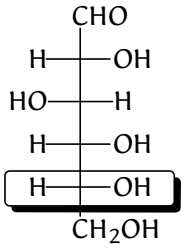

D-aldoses

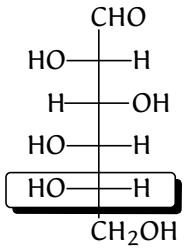

L-aldoses

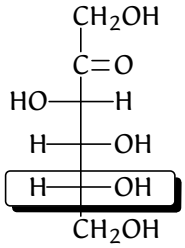

D-ketoses

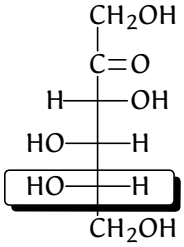

L-ketoses

EX 's


D-(+)-glucose

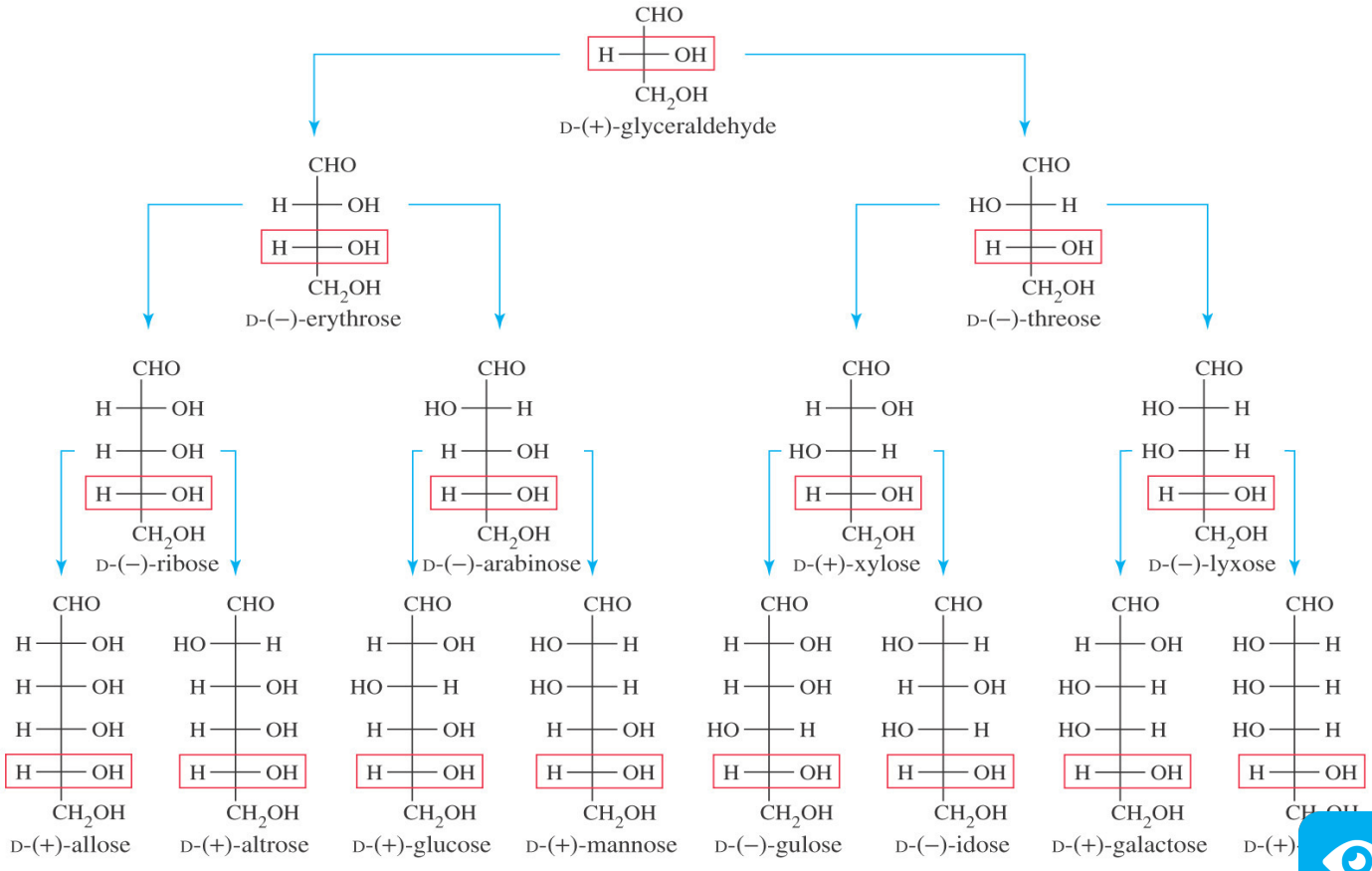

L-(-)-glucose


D-(-)-fructose


L-(+)-fructose

- most naturally occurring sugars are D-series

Family of D-Aldoses



EPIMERS –

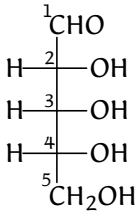
- a pair of sugars which differ in configuration at **one asymmetric carbon (C*) only**

- while the unique configuration can exist at *any* stereocenter, the most common class of epimers differ in configuration at C-2 (in which case the carbon's number may be understood & omitted)

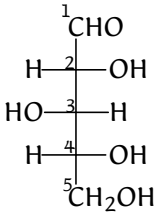
- epimers are a class of diastereomers (stereoisomers which are *not* mirror image enantiomers)

- the arrows in the family of D-aldoses (shown on previous page) relate pairs of C-2 epimers

Other EX 's

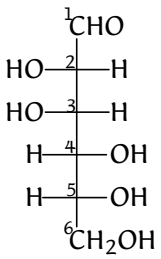


D-ribose

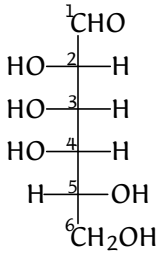


D-xylose

aldopentoses which are **C-3 epimers**



D-mannose

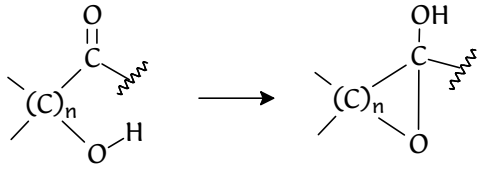


D-talose

aldohexoses which are **C-4 epimers**

CYCLIC STRUCTURES OF MONOSACCHARIDES –

- recall that the intramolecular addition reaction of a γ or δ-hydroxycarbonyl compound results in the formation of a cyclic hemiacetal



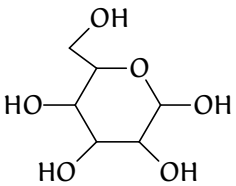
hydroxy aldehyde
or
hydroxy ketone

cyclic hemiacetal

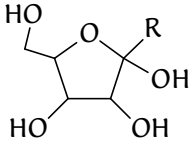
n = 3 or 4
ring = 5 or 6 member

- monosaccharides exist predominately (>99%) in this more stable cyclic hemiacetal form

- aldohexoses form six-membered ring hemiacetals, while aldopentoses & ketohexoses form five-membered ring hemiacetals



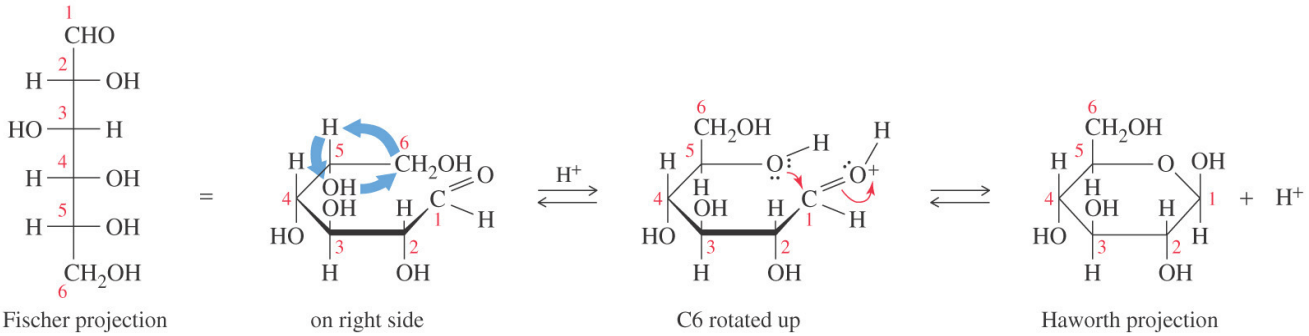
aldohexoses



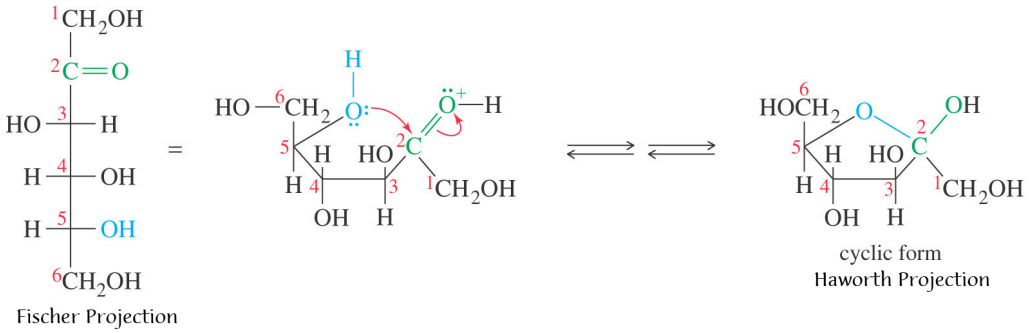
aldopentoses & ketohexoses

R = H or CH_2OH

EX. D-(+)-Glucose ➢ an aldohexose which forms a six-membered ring hemiacetal



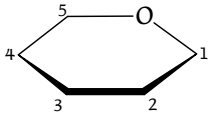
EX. D-(-)-Fructose ➢ an ketohexose which forms a five-membered ring hemiacetal



Drawing Haworth Projection Formulas –

Six-Membered Ring Hemiacetals –

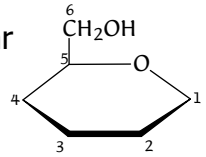
- draw a flat cyclohexane with hemiacetal ring oxygen in the upper right corner



- the hemiacetal carbon is on the right side of the ring @ C-1

- number the ring clockwise from C-1 to C-5

- C-6 is the -CH_2OH group which points up in a D-sugar & down in an L-sugar

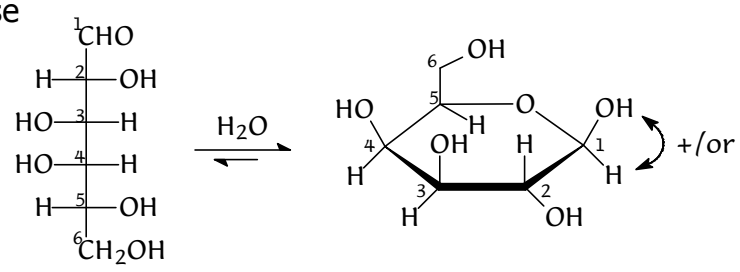


- the configurations @ C-2,C-3 & C-4 are determined from the following correlation:

Fischer Projection	Haworth Projection
-OH *Right*	-OH *Down*
-OH *Left*	-OH *Up*

- the configuration @ C-1 is indeterminate (-OH can be either up or down)

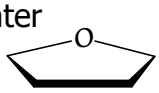
EX. D-(+)- Galactose



Fischer Projection Haworth Projection

Five-Membered Ring Hemiacetals –

- draw a flat cyclopentane (pointing "back") with hemiacetal ring oxygen in the center

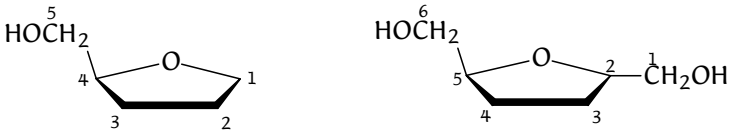


- the hemiacetal carbon is on the right side of the ring:

  @ C-1 in aldopentoses or @ C-2 in ketohexoses (C-1 is a -CH_2OH)

- number the ring clockwise from C-1 to C-4 (aldopentoses) or C-2 to C-5 (ketohexoses)

- C-5 or C-6 is the -CH_2OH group which points up in a D-sugar & down in an L-sugar



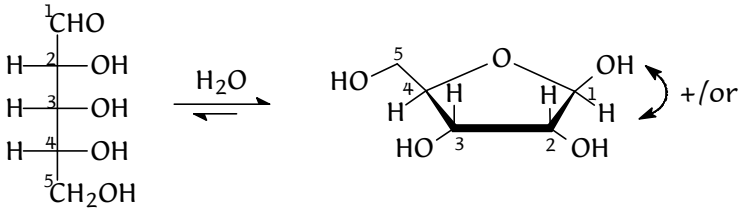
aldopentoses 2-ketohexoses

- the configurations @ C-2 & C-3 (aldopentoses) or @ C-3 & C-4 (ketohexoses) are determined from the following correlation:

Fischer Projection	Haworth Projection
-OH *Right*	-OH *Down*
-OH *Left*	-OH *Up*

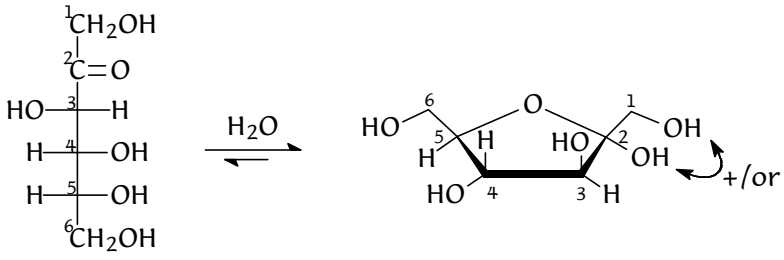
- the configuration @ C-1 (aldopentoses) or @ C-2 (ketohexoses) is indeterminate (-OH can be either up or down)

EX. D-(-)- Ribose ➢ an aldopentose



Fischer Projection Haworth Projection

EX. D-(-)- Fructose ➢ a 2-ketohexose



Fischer Projection Haworth Projection

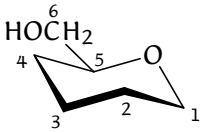
Conformations of Six-Membered Ring Hemiacetals –

- the most stable cyclic hemiacetal form for aldohexoses is the **chair** conformer

Drawing Chair Conformers for Aldohexoses –

- arrange a chair with the hemiacetal carbon (C-1) pointing down on the right

- place the hemiacetal oxygen in the upper right position



- number the ring clockwise from C-1 to C-5

- C-6 is the -CH_2OH group which points up in a D-sugar & down in an L-sugar

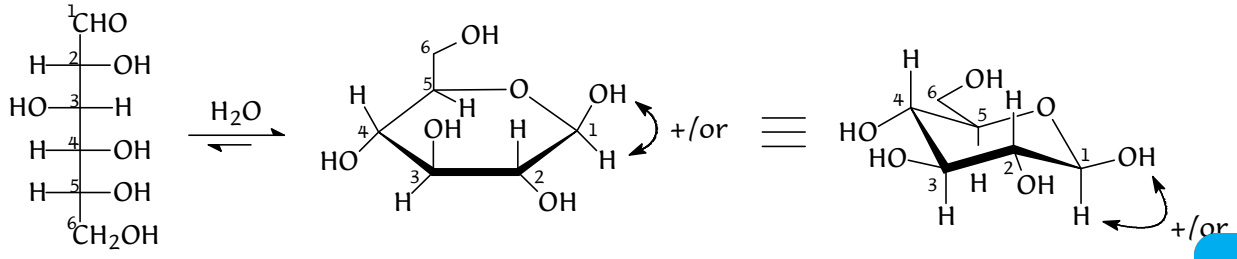
- the configurations @ C-2, C-3 & C-4 are determined from the following correlation:

Fischer Projection	Haworth Projection	Chair Conformer
-OH *Right*	-OH *Down*	-OH *Down*
-OH *Left*	-OH *Up*	-OH *Up*

- the configuration @ C-1 is indeterminate (-OH can be either up or down)

- the most stable aldohexose chair conformations will have the most equatorial -OH's

EX. D-(+)- Glucose



Fischer Projection Haworth Projection Chair Conformer

Anomers –

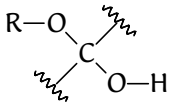
- diastereomers resulting from the indeterminate configuration at the hemiacetal carbon (C-1 or C-2) where the -OH can point either up or down

  Anomeric Carbon –

  - the original carbonyl carbon (C=O) which reacts & becomes the cyclic hemiacetal carbon

  - this position is C-1 in aldopentoses & aldohexoses and C-2 in ketohexoses

  - it is the only carbon in the ring with two oxygens attached



- anomers are also a class of **epimers** (diastereomeric sugars with identical configurations at every stereocenter except one)

- anomers are distinguished as follows:

Name	Configuration @ Anomeric Carbon
α-Anomer (Alpha)	-OH *Down*
β-Anomer (Beta)	-OH *Up*

Mutarotation –

- because anomers are diastereomers, they have unique physical properties

- therefore, the specific rotation [α] values for anomers will be different

- placing either the α-anomer or the β-anomer in solution results in a "drift" of the specific rotation value [α] to a **mutual** value between the values of the two anomers

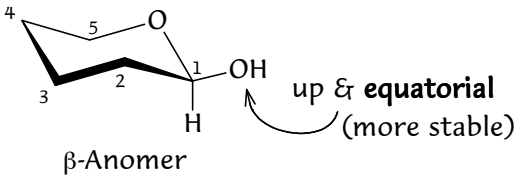
- the phenomenon of mutarotation is the result of an equilibrium which exists between the α-anomer & the β-anomer in solution:

  α-anomer ⇌ "open-chain" carbonyl ⇌ β-anomer

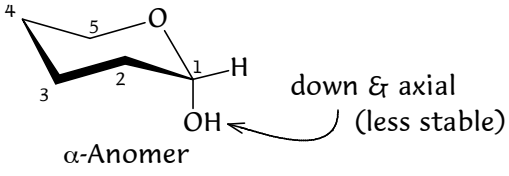
- for aldohexoses, the mutarotation value is always **closer** to the value for the **β**-anomer

- this indicates that the equilibrium mixture contains more of the **more stable β**-anomer

- the β-anomer is more stable because the -OH on the anomeric carbon (C-1) is up & **equatorial**

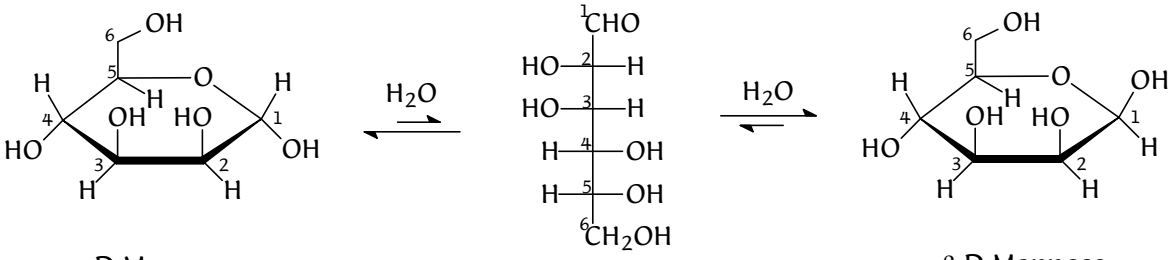


β-Anomer



α-Anomer

EX. D-(+)- Mannose



- after equilibrium has been established, the mutarotation value for D-(+)-mannose is:

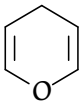
$[\alpha]_{eq}$ = +60° (closer to the specific rotation value for the β-anomer)

Naming Cyclic Monosaccharides –

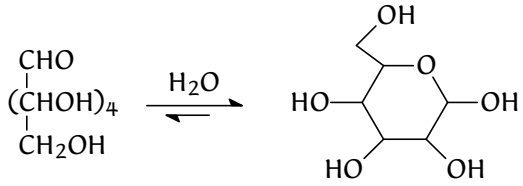
- sugars are classified and named according to hemiacetal ring size:

Pyranoses –

- six-membered ring hemiacetals (from *pyran*, a six-membered oxygen heterocycle)


Pyran

- pyranoses are the cyclic derivations of aldohexoses:

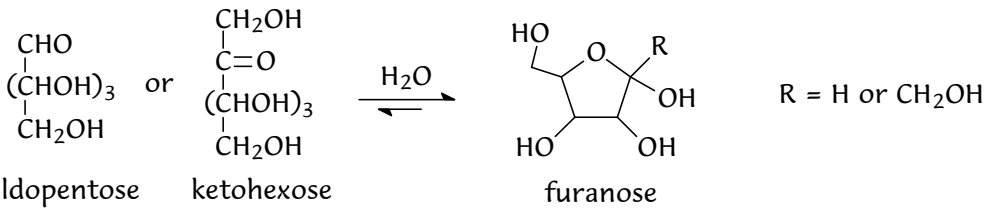


Furanoses –

- five-membered ring hemiacetals (from *furan*, a five-membered oxygen heterocycle)


Furan

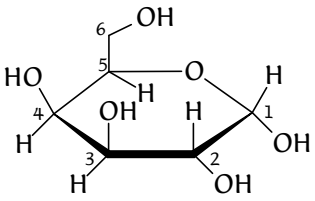
- furanoses are the cyclic derivations of aldopentoses & ketohexoses:



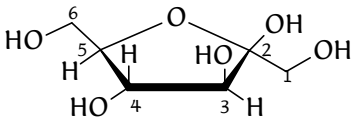
- the complete name of a specific monosaccharide in its cyclic hemiacetal form would include the prefix of that sugar's name:

<α or β> - <D or L> - <sugar name prefix> - <pyran or furan> - ose

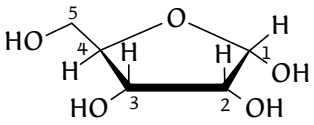
EX 's



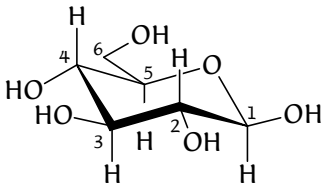
α-D-galactopyranose



β-D-fructofuranose



α-D-ribofuranose



β-D-glucopyranose

- students are responsible for knowing the structural formulas of the following monosaccharides:

  D-(+)-Glyceraldehyde (an aldotriose)

  D-(-)-Ribose (an aldopentose)

  D-(+)-Glucose (an aldohexose)

  D-(+)-Galactose (an aldohexose)

  D-(+)-Mannose (an aldohexose)

  D-(-)-Fructose (an ketohexose)

- only the Fischer projection formulas require memorization – the Haworth projection & chair conformer structural formulas are derived from the Fischer projection's pattern of -OH's

- note that there is no correlation between D/L (a drawing convention) & +/- (a physical property)

- students are only responsible for D & L structure (+ & - may be ignored)

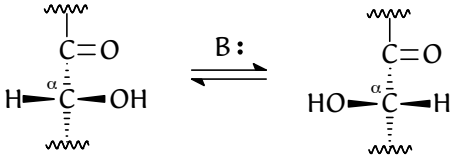
REACTIONS OF MONOSACCHARIDES –

- because they are multifunctional compounds, monosaccharides exhibit the chemical behavior of three unique functional groups – carbonyls, alcohols & hemiacetals

- the small amount of "open-chain" carbonyl form present in the equilibrium accounts for the aldehyde/ketone reactions of monosaccharides

A. Epimerization –

- a base-catalyzed process where the acidic alpha-hydrogen (α-H) is removed & replaced, causing the configuration at the alpha-carbon (α-C) to be racemized (creates epimers)



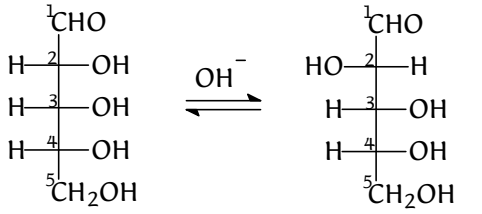
aldose or ketose

aldose or ketose

B: = OH^-, NH_3, RNH_2, R_2NH, R_3N,....

Mechanism –

EX.

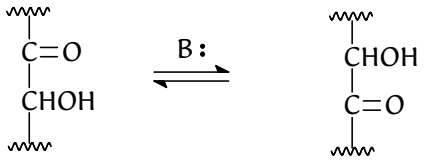


D-ribose D-arabinose

B. Enediol Rearrangement –

- a base-catalyzed process where the carbonyl group migrates along the carbon chain

- note that aldoses & ketoses can thus interconvert under basic conditions

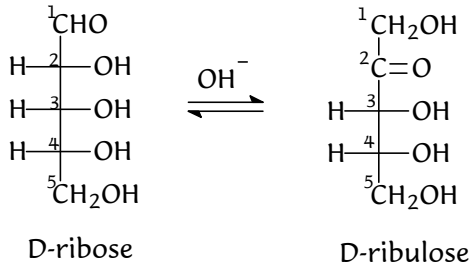


aldose or ketose ketose or aldose

B: = OH^-, NH_3, RNH_2, R_2NH, R_3N,....

Mechanism –

EX.



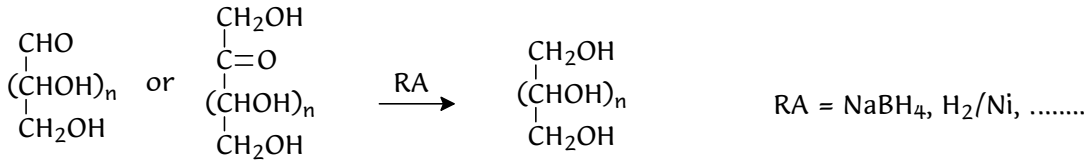
D-ribose D-ribulose

- under basic conditions, monosaccharides will undergo both epimerization & enediol rearrangement, resulting in complex product mixtures

- therefore, contact with alkaline reagents is mostly avoided

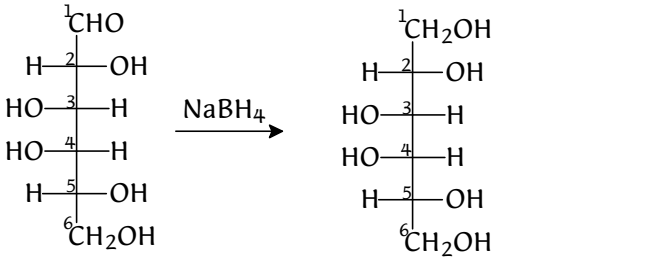
C. Reduction –

- the small amount of "open-chain" carbonyl form present in the equilibrium allows for conversion of the carbonyl to an alcohol



aldose ketose alditol

EX.



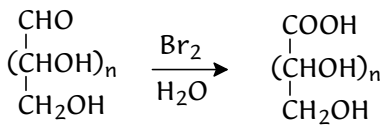
D-galactose D-galactitol (Dulcitol)

D. Oxidation –

- different oxidizing agents produce different sugar derivatives:

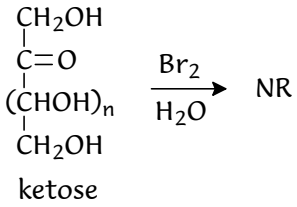
1) Bromine Water, Br_2/H_2O

- only the aldehyde group of an aldose reacts:



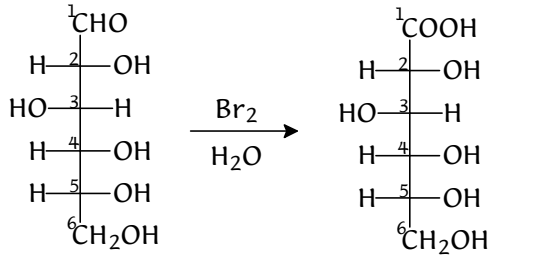
aldose aldonic acid

- ketoses do not react:



ketose

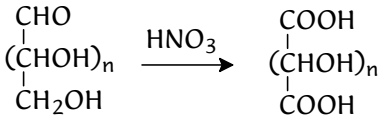
EX.



D-glucose D-gluconic acid

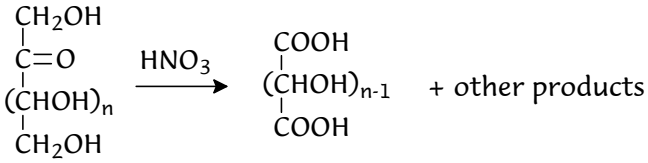
2) Nitric Acid, HNO_3

- both the aldehyde & primary alcohol groups of an aldose are oxidized:



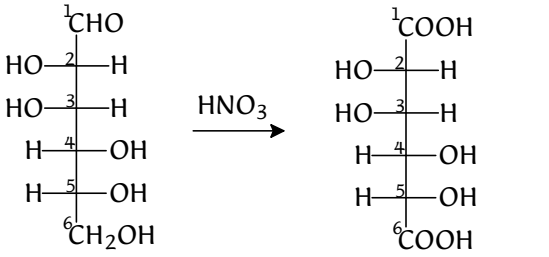
aldose aldaric acid

- ketoses also react, giving more complex product mixtures:



ketose aldaric acid

EX.



D-mannose D-mannaric acid

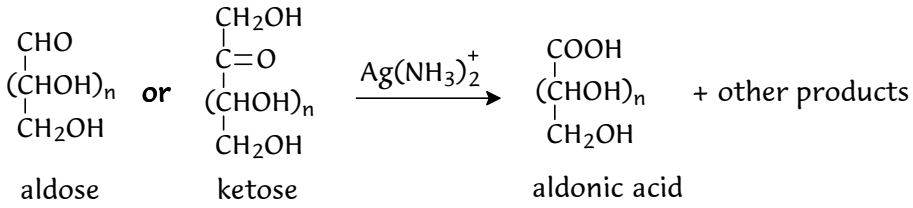
3) Tollen's Reagent, $Ag(NH_3)_2^+$

- Tollen's reagent provides a simple visible chemical test for aldehydes (a silver mirror is produced upon oxidation indicating a "positive test")

- other oxidizing agents, such as Fehling's & Benedict's solutions (copper(II) complexes) produce similar observable results with aldehydes (a red precipitate indicates a positive test)

- all of these reagents are strongly basic, and therefore cause epimerization & enediol rearrangement to occur with monosaccharides, resulting in complex product mixtures

- since enediol rearrangement converts ketoses to aldoses, ketoses are also ultimately oxidized & give positive tests, making them indistinguishable from aldoses:



- while Tollen's reagent may not be useful for distinguishing aldoses from ketoses, it is useful for identifying a certain class of carbohydrates:

  Reducing Sugars, RS –

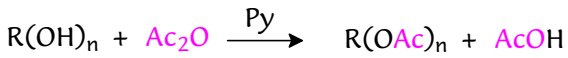
  - sugars which *reduce* Tollen's reagent (& related OA's), becoming oxidized themselves

  - include all aldoses & ketoses (which equilibrate in the cyclic hemiacetal form)

  - exist as anomers & exhibit mutarotation $\left(\alpha\text{-anomer} \rightleftharpoons \beta\text{-anomer}\right)$

E. Ester Formation –

- all hydroxy groups in the monosaccharide react (like alcohols) with acid derivatives to produce ester groups



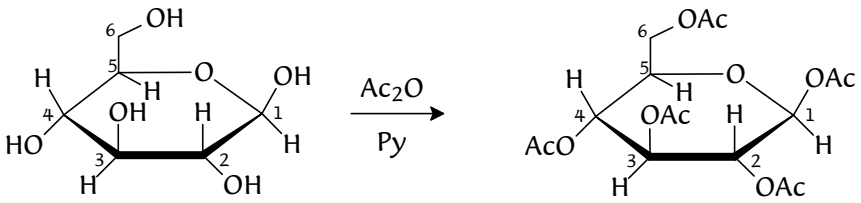
$R(OH)_n$ = sugar, **all** OH's react, including hemiacetal OH

Ac = $-\overset{O}{\overset{\|}{C}}-CH_3$ (acetyl group); other acyl groups possible

Ac_2O = $CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$ (acetic anhydride); other acid derivatives possible

Py =  (pyridine); other bases possible

EX.



E. Ether Formation –

- all hydroxy groups in the monosaccharide react (like alcohols) with alkyl halides to produce ether groups

$$R(OH)_n + CH_3I \xrightarrow{Ag_2O} R(OCH_3)_n + AgI$$

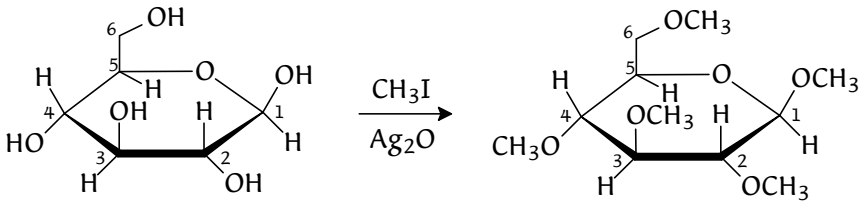
$R(OH)_n$ = sugar, **all** OH's react, including hemiacetal OH

CH_3 (Methyl) most common alkyl group; others possible

I (Iodo) most common leaving group; others possible

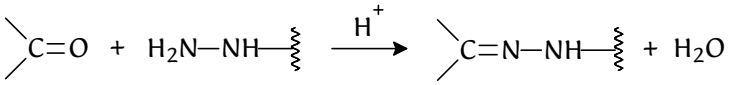
Ag_2O (Silver oxide) most common base; others possible

EX.



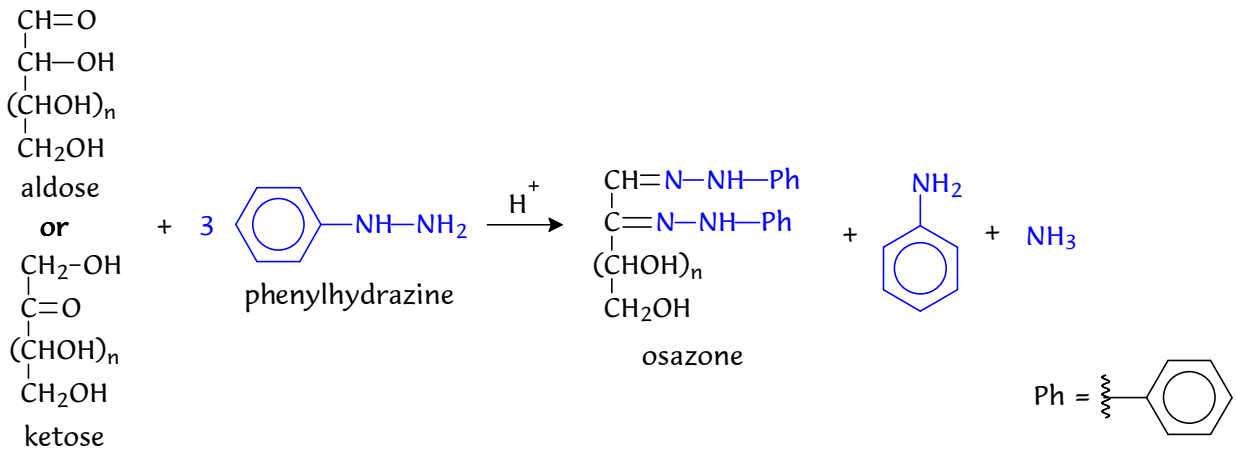
F. Osazone Formation –

- recall the reaction of carbonyls with hydrazines to produce hydrazones:



- the first <u>two</u> carbons of both aldoses & ketoses react with phenylhydrazine to form a bis-hydrazone known as an osazone

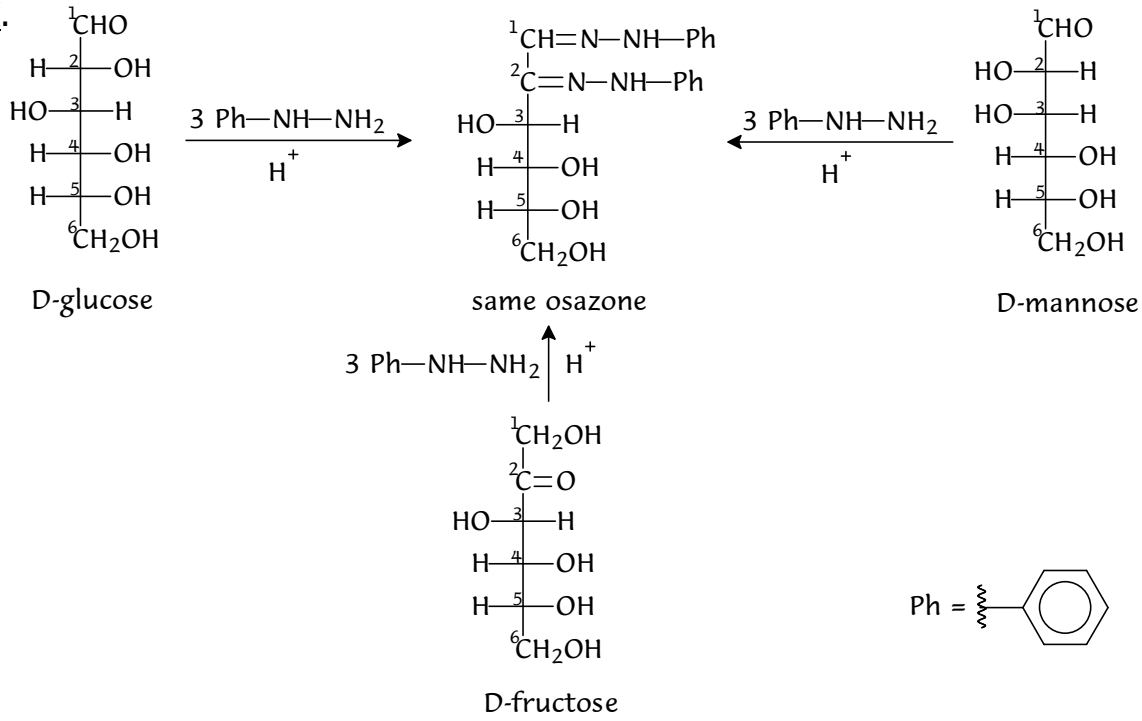
- hydrazone formation at the first carbonyl group is followed by oxidation of the α-carbon's hydroxyl group to a second carbonyl group which then forms the second hydrazone:



- any difference at C-1 or C-2 is lost in the formation of osazones

- thus, C-2 epimers will form the same osazones (as will related aldoses & ketoses)

EX.



G. Glycoside Formation –

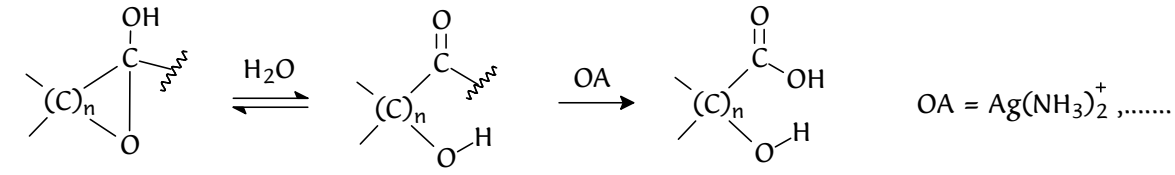
- recall that Tollen's reagent (& related OA's) identify *reducing sugars*

- this distinguishes them from *nonreducing sugars* which do <u>not</u> give positive Tollen's tests

- this distinction is the result of the different functional groups present in these two cyclic monosaccharide classes:

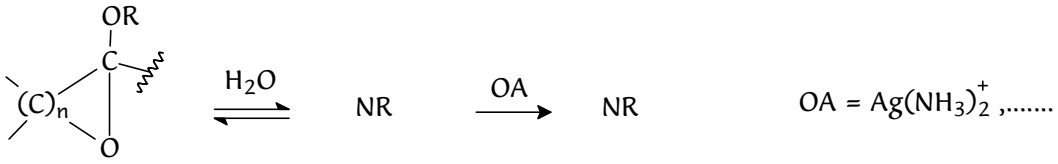
  - the reducing sugar has a <u>hemiacetal</u> group which opens in water

  - the nonreducing sugar has an <u>acetal</u> group which does <u>not</u> open in water:



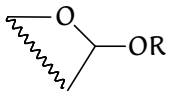
cyclic hemiacetal (aldose or ketose) | open-chain carbonyl | oxidizes (gives + test)

therefore; **reducing** sugars are **hemiacetals**



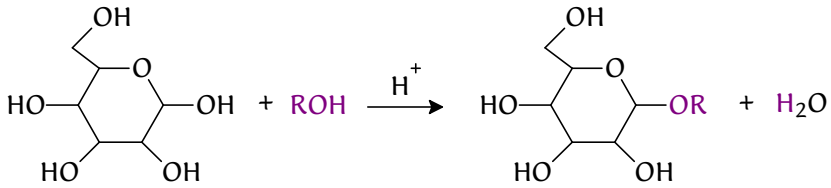
cyclic acetal (glycoside) | won't open in H_2O (requires H^+) | does not oxidize (does **not** give + test)

therefore; **nonreducing** sugars are **acetals** (glycosides)

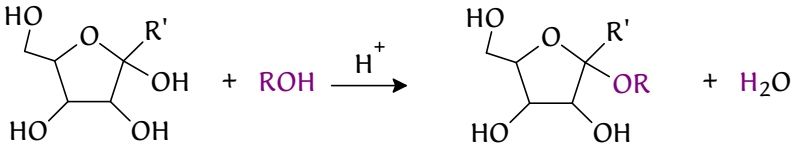
- **Glycosides** are cyclic **acetal** forms of sugars 

- they are prepared by the acid-catalyzed reaction of an alcohol with a pyranose or furanose

- note that <u>only</u> the anomeric (hemiacetal) carbon's hydroxyl group reacts under these conditions



pyranose | pyranoside



furanose | furanoside | R' = H or CH_2OH

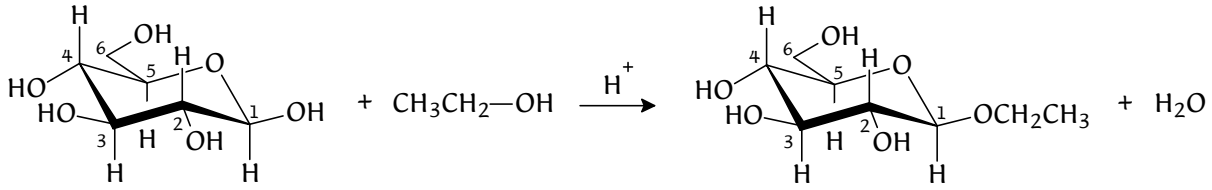
ROH = CH_3OH, CH_3CH_2OH, PhOH, another monosaccharide,.....

<u>Naming Glycosides</u> –

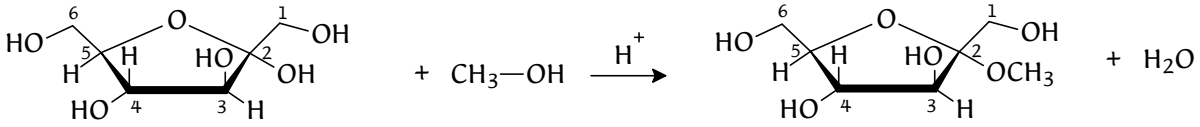
- place R group (alkyl or aryl) name in front (separate word)

- change ending from **e** ⇒ **ide**

EX 's Preparation & naming of glycosides



β-D-glucopyranose ethyl β-D-glucopyranoside



α-D-fructofuranose methyl α-D-fructofuranoside

- note the distinct contrast in chemical behavior between reducing & nonreducing sugars:

Nonreducing Sugars, NRS –

- sugars which *do not* reduce Tollen's reagent (& related OA's)
- are glycosides (cyclic acetals)
- *do not* equilibrate in water with the "open-chain" carbonyl form
- *do not* exhibit anomerism or mutarotation (α-anomer ⇄ β-anomer)

II. DISACCHARIDES –

- sugars composed of two monosaccharides connected in glycoside (acetal) linkages
- the glycosidic bond is formed between the anomeric carbon of the "first" monosaccharide unit & the hydroxyl group of the "second" monosaccharide unit
- disaccharides can be categorized according to the position of the hydroxyl group on the "second" monosaccharide unit making up the glycoside:

OH Position on 2nd MS Unit	Disaccharide Class
@ C-4	1→4' Glycoside
@ C-6	1→6' Glycoside
@ C-1	1→1' Glycoside
@ C-2	1→2' Glycoside

- disaccharides can be categorized according to the configuration at the anomeric carbon of the first monosaccharide unit:

"OR" Position on Anomeric C of 1st MS Unit	Disaccharide Class
Up	β-Glycoside (beta)
Down	α-Glycoside (alpha)

- typical monosaccharide units found in naturally occurring disaccharides are *glucose*, *galactose* & *fructose*

A. 1→4' Glycosides –

- these represent the most common naturally occurring disaccharides

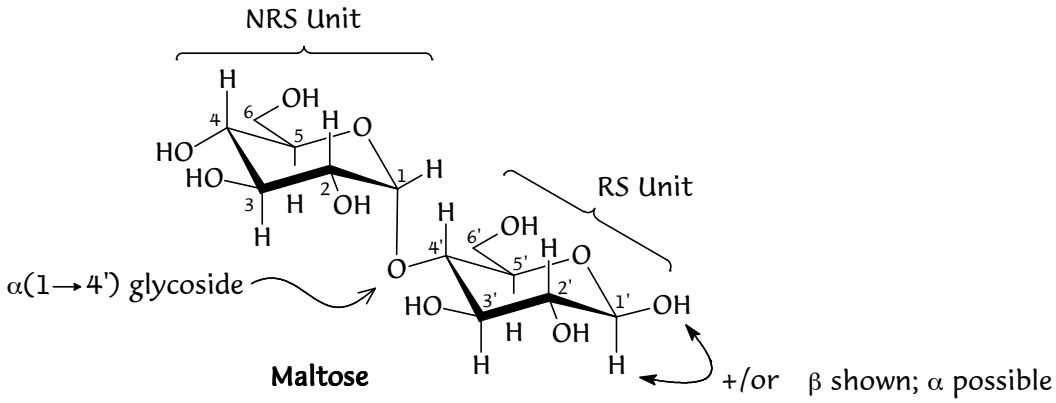
- the anomeric carbon (C-1) of the first MS unit is connected through the C-4 OH of the second MS unit

1) Maltose –

- this disaccharide is a hydrolysis product of starch:

$$\text{Starch} \xrightarrow[H_2O,\ \Delta]{H^+} \text{Maltose} \xrightarrow[H_2O,\ \Delta]{H^+} 2\ \text{Glucose}$$

- maltose can be described as: **two glucose units in an α(1→4') glycoside** (glucoside)



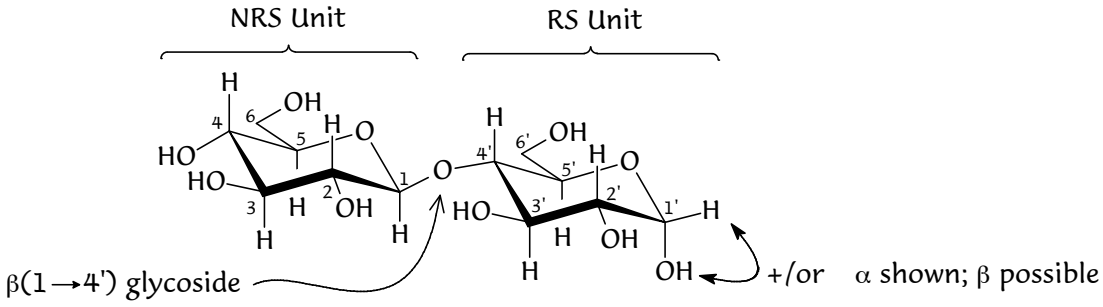
4-O-(α-D-glucopyranosyl)-β-D-glucopyranose

2) Cellobiose –

- this disaccharide is a hydrolysis product of cellulose:

$$\text{Cellulose} \xrightarrow[H_2O,\ \Delta]{H^+} \text{Cellobiose} \xrightarrow[H_2O,\ \Delta]{H^+} \text{2 Glucose}$$

- cellobiose can be described as: **two glucose units in a β(1→4') glycoside** (glucoside)



Cellobiose

4-O-(β-D-glucopyranosyl)-α-D-glucopyranose

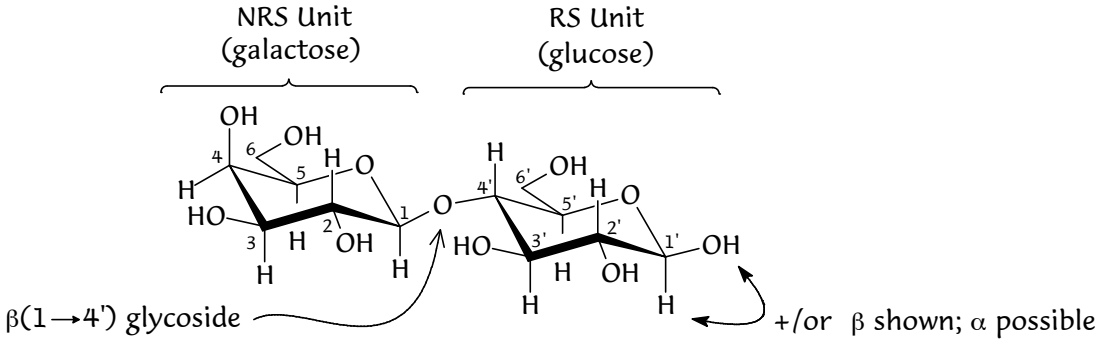
3) Lactose –

- a naturally occurring disaccharide found in the milk of mammals such as cows & humans

- lactose yields galactose & glucose upon hydrolysis:

$$\text{Lactose} \xrightarrow[H_2O,\ \Delta]{H^+} \text{Galactose + Glucose}$$

- lactose can be described as: **galactose** (nonreducing) **& glucose** (reducing) **units in a β(1→4') glycoside** (galactoside)



Lactose

4-O-(β-D-galactopyranosyl)-β-D-glucopyranose

B. 1→6' Glycosides –

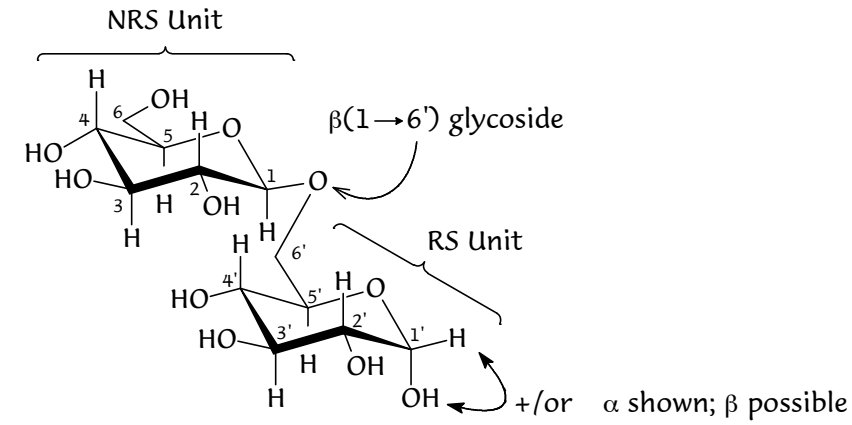
- the anomeric carbon (C-1) of the first MS unit is connected through the C-6 OH of the second MS unit

Gentiobiose –

- this disaccharide is incorporated into crocin, the principle component of saffron

$$\text{Gentiobiose} \xrightarrow[H_2O,\ \Delta]{H^+} 2\ \text{Glucose}$$

- gentiobiose can be described as: **two glucose units in a β(1→6') glycoside** (glucoside)



Gentiobiose

6-O-(β-D-glucopyranosyl)-α-D-glucopyranose

C. 1→2' Glycosides –

- these compounds & their related 1→1' glycosides represent the *nonreducing disaccharides*

- the glycosidic linkage involves the anomeric carbons from both monosaccharide units

Sucrose –

- a naturally occurring disaccharide found in sugar cane & sugar beets (table sugar)

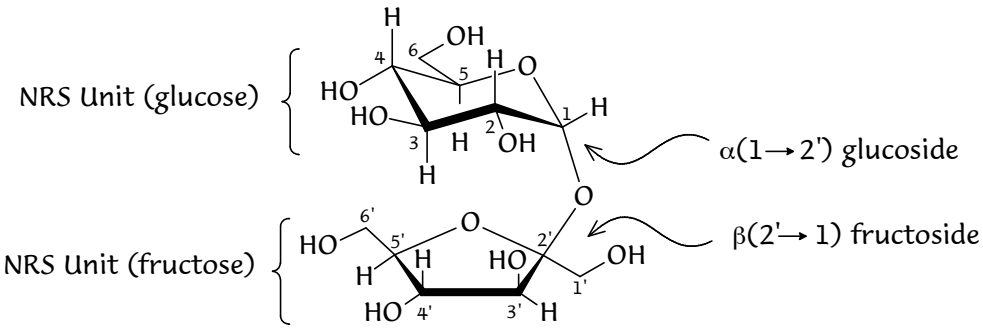
- hydrolysis of sucrose yields glucose & fructose

$$\text{Sucrose} \xrightarrow[H_2O,\ \Delta]{H^+} \text{Glucose} + \text{Fructose}$$

- sucrose can be described two ways:

glucose & fructose units in an α(1→2') glycoside (glucoside)

or; **fructose & glucose units in a β(2'→1) glycoside** (fructoside)



Sucrose

α-D-glucopyranosyl-β-D-fructofuranoside
or
β-D-fructofuranosyl-α-D-glucopyranoside

Naming Disaccharides –

- the following systematic nomenclature method is used for disaccharides:

1) identify the hydroxyl oxygen making the glycosidic bond as a number prefix followed by O

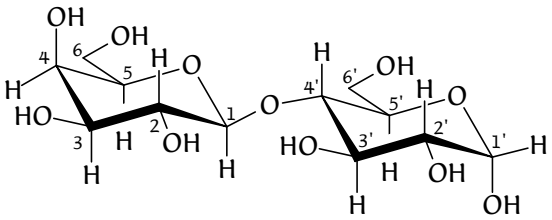
   EX. 4-O- prefix indicates the RS unit's C-4 OH makes the glycoside

2) name the NRS unit (left), changing the ending from ose → osyl

3) name the RS unit (right) as a normal cyclic monosaccharide & indicate the anomer present

- students are not responsible for common names of disaccharides

EX.



Lactose

4-O-(β-D-galactopyranosyl)-α-D-glucopyranose

III. POLYSACCHARIDES –

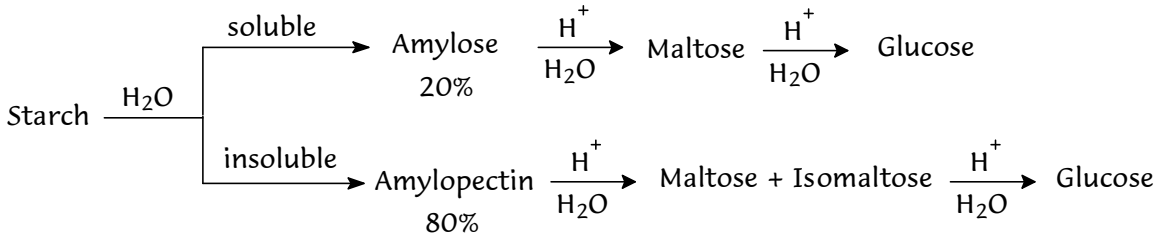
- macromolecules made up of long chains of monosaccharide units joined in glycosidic linkages

- the most common polysaccharides are polymers of glucose

A. Starch –

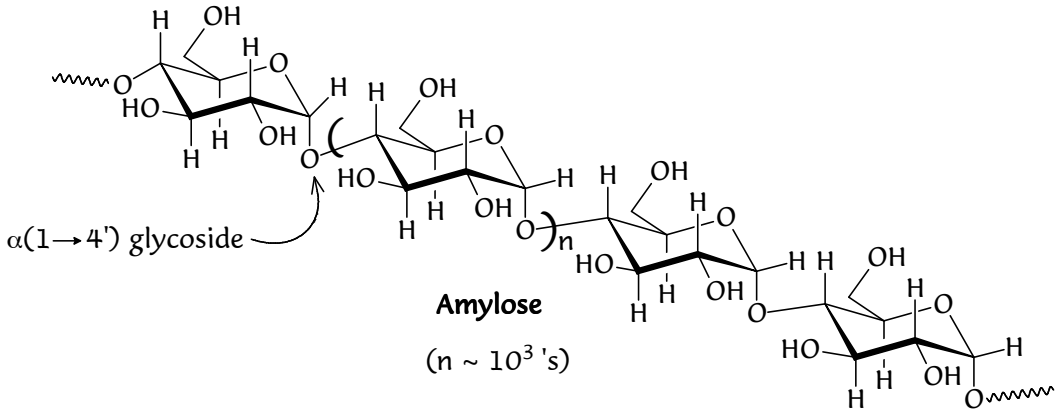
- the glucose (energy) storage form for plants

- starch contains two components, which are separable on the basis of water solubility



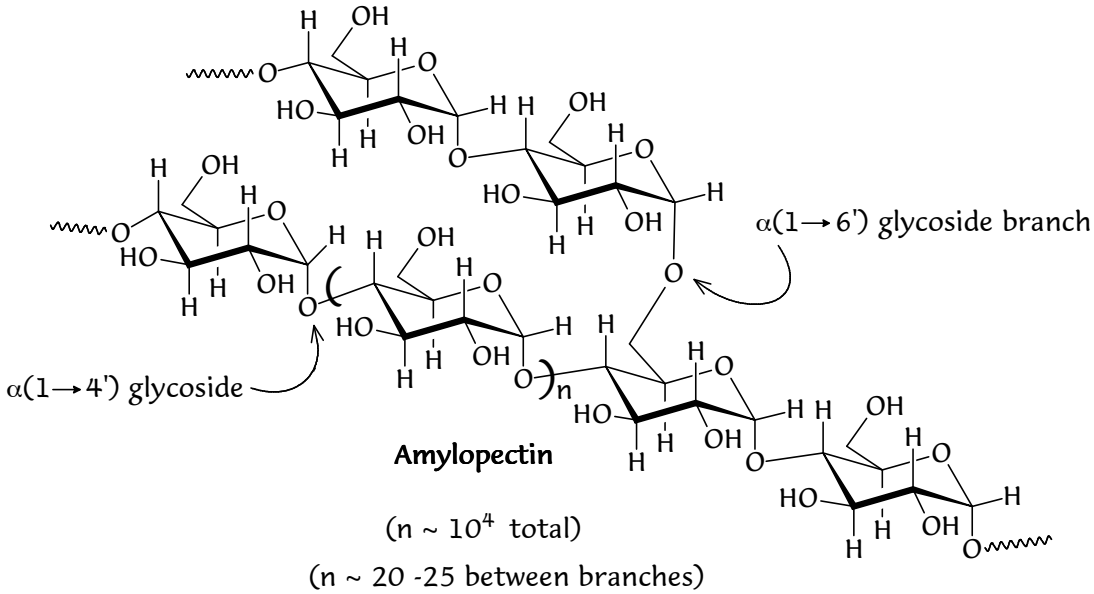
1) Amylose –

- a linear polymer of glucose units in α(1→4') glycosides (glucosides)



2) Amylopectin –

- a branched polymer of glucose units in α(1→4') glycosides with α(1→6') glycoside branches

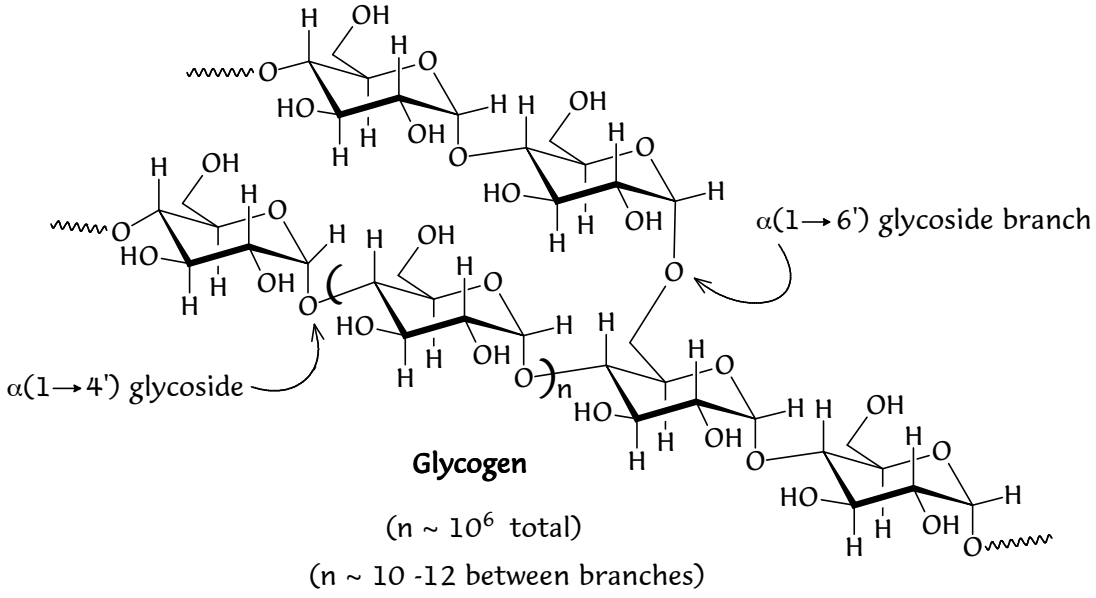


B. Glycogen –

- the glucose (energy) storage form for animals

- a branched polymer of glucose units in α(1→4') glycosides with α(1→6') glycoside branches

- so; same as amylopectin, but more highly branched

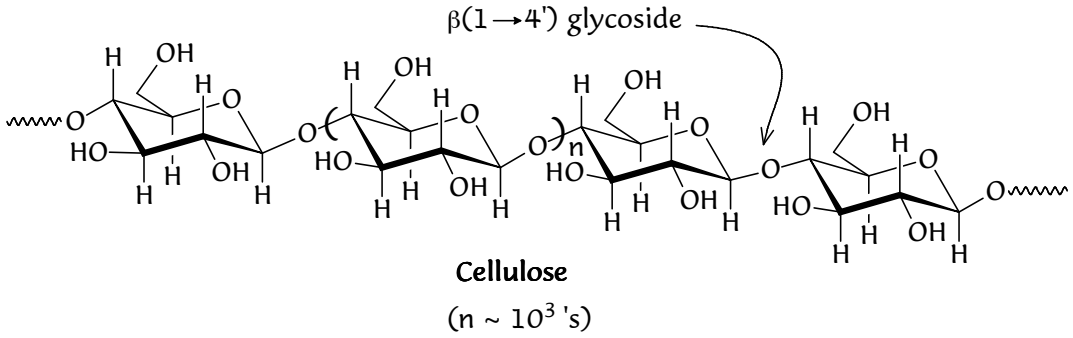


- the increased branching in glycogen provides more available glucose "ends" to satisfy the greater metabolic demand of motile organisms

C. Cellulose –

- the principal component of plant cell walls, providing the plant's structural strength & rigidity

- a linear polymer of glucose units in β(1→4') glycosides (glucosides)



- most organisms cannot digest cellulose because they lack the enzyme which catalyzes the hydrolysis of the β–glucoside