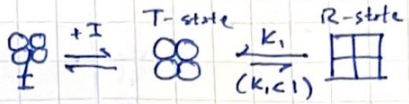
The Biological Significance of Allostery

→ The rate of reaction in a cell can change in response to changes in:

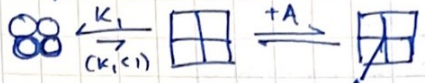
1) Substrate concentration
   - (e.g. Aspartate, for ATCase)
2) Concentration of other metabolites
   - (e.g. CTP & ATP, for ATCase)

→ Allosteric effectors may bind preferentially to either the T-state or the R-state, and would consequently shift the equilibrium in that direction.

Example diagram for a negative heterotropic effector:



- Shifts equilibrium to T-state (allosteric inhibition)



- Shifts equilibrium to R-state (allosteric activation)

(A for activator)

CARBOHYDRATES

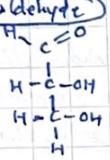
→ Carbohydrates have a general formula of $(C(H_2O))_n$, for hydrated carbons. (For this course $3 \leq n \leq 6$)

→ Monosaccharides are the simplest ~~monosaccharides~~ building block, or monomer, of carbohydrates.

- An example of a simple monosaccharide, glyceraldehyde:

Structural isomers form different carbohydrates:

Glyceraldehyde



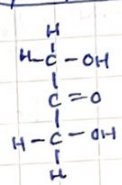
- This molecule is an aldotriose:
  - Aldo - aldehyde
  - Tri - 3 carbons
  - Ose - sugar

$C_3H_6O_3$

$(C(H_2O))_3$

- Example of an aldose

Dihydroxyacetone



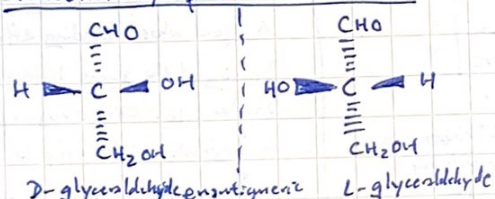
- This molecule is a dihydroxyacetone a ketotriose.

- Example of ketose

$C_3H_6O_3$

$(C(H_2O))_3$

Stereochemistry of Carbohydrates*

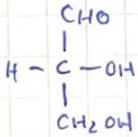


D-glyceraldehyde — enantiomeric set — L-glyceraldehyde

~~Glyceraldehyde~~

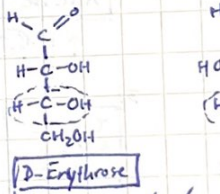
- In nature, D- enantiomers are the most commonly found form.

*Note: D-glyceraldehydes are usually drawn as a fischer projection:



D-glyceraldehyde.

D- Aldetetroses (Four carbons, $C_4H_8O_4$, or $(C(H_2O))_4$)



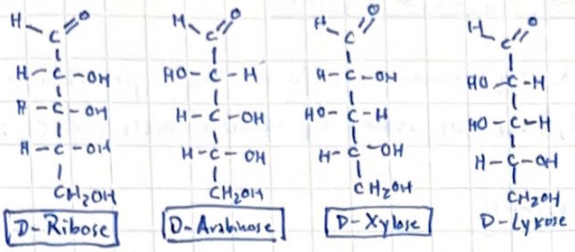
D-Erythrose
biologically significant

D - Threose

- Note that these two are diastereomers, and not enantiomers.
  - There for they are different molecules with different properties.

- To determine D or L, go to the furthest chiral carbon from the carboxyl carbon. Since the OH is on the right side (as marked by dotted circle), the molecule is in the D-orientation.

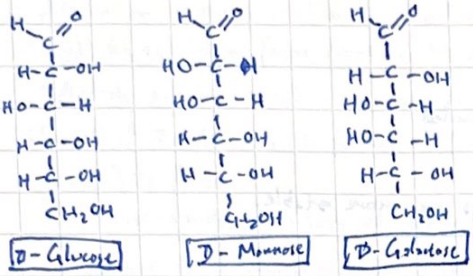
Adding another carbon, we get aldopentoses (5 carbons):



D-Ribose | D-Arabinose | D-Xylose | D-Lyxose

- All these carbons are in the D-configurations and are diastereomers of each other.
- The molecules boxed are functionally important in biological contexts. For example, D-Ribose forms the incredibly important backbone for DNA molecules.

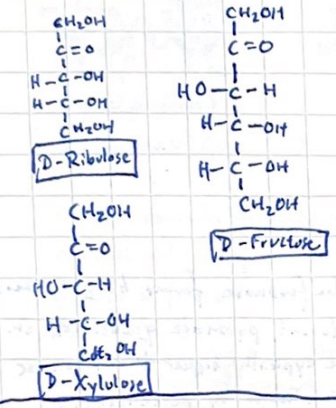
Adding another carbon, we get aldohexoses (6 carbons). The most important ones are shown:



D-Glucose | D-Mannose | D-Galactose

- Glucose and Mannose are epimers: that is, they are 2 monosaccharides which differ in stereochemistry at only 1 carbon.
- Glucose and galactose are also epimers.

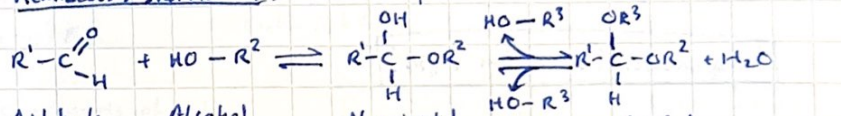
Important Ketoses:



D-Ribulose | D-Fructose | D-Xylulose

Sugar ~~Oxidation~~ Cyclization

Hemiacetals and Acetals: Recall the formation as:

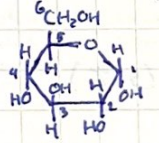


Aldehyde (Ketone works too) | Alcohol | Hemiacetal | Acetal

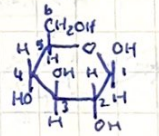
- Hemiacetals are unstable in aqueous solution at a pH of 7, though hemiacetal is favored in sugar form.

~~Epic~~ Cyclization of Glucose: Formation of α and β anomers

Glucose is commonly found in the forms:



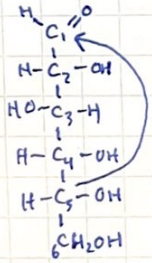
α-D-Glucopyranose "α-anomer"

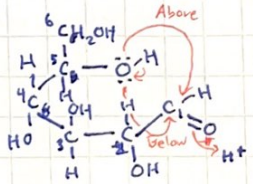


β-D-Glucopyranose "β-anomer"

- Note that the only difference in structure between α and β glucopyranose is the orientation of the OH on the first carbon.
- The first carbon in the pyranose ring is known as the anomeric carbon
- The anomer after cyclization is now a hemiacetal.

To cyclize, C_5 must react with C_1:



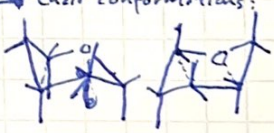


- The oxygen on the hydroxyl group may attack the first carbon above or below, contributing to the difference in structures between α and β glucopyranose:

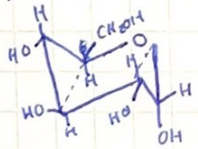
Results from an –OH attack from above

Results from an –OH attack from below.

- The pyranose rings may equilibrate with the linear form of glucose.
- Since pyranose rings are six membered rings, they take on ~~three~~ chair conformations:



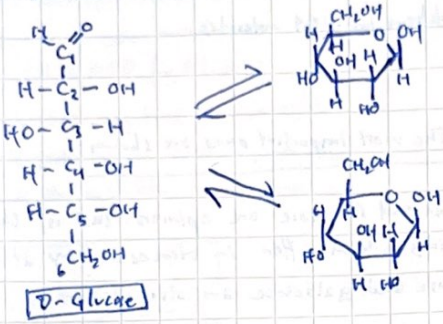
Looking at the chair conformation of α-D-glucopyranose:



- We notice that the heaviest groups are in the equatorial position mostly, contributing to the stability of glucose.
- Note that the configurations of 3 and 4 are fixed, as this is the structure of glucose [compare to mannose and galactose]. However, C_1 is in the axial position, which is less favorable compared to the OH in the equatorial position for β-anomers.

Cyclization of Glucose: Why does C_5-OH attack, but not C_4-OH or C_3-OH?

→ The stability of C_5-OH attacking's product (a six membered ring) contributes to its higher probability of formation compared with other carbons (such as C_4 or C_3). Let us assume C_4 attacks instead of C_5:

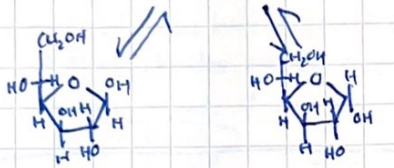


D-Glucose

β-pyranose 62% (rounded)

α-pyranose 38% (rounded)

Six membered rings are more stable.



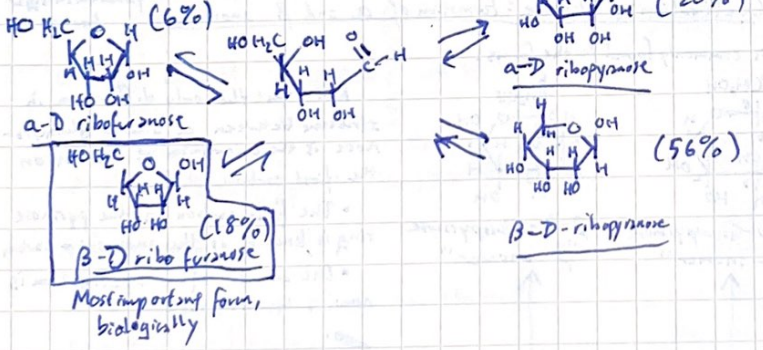
β-furanose

α-furanose

Together make up < 0.5% of product

Aldopentoses (5-carbon sugars)

Structures of D-Ribose:



(6%) α-D ribofuranose

(20%) α-D ribopyranose

(18%) β-D ribofuranose

Most important form, biologically

(56%) β-D-ribopyranose

- Despite the furanose forms being the most biologically relevant, pyranose quantities in the body are typically higher than furanose quantities, as shown by percentages.

"Reducing" Sugars

→ Glucose can act as a reducing agent in the open chain form due to the aldehyde at C_1.

- Benedict's Test involves using Cu(II) sulfate in sodium carbonate / sodium citrate to determine presence of glucose in open chain form. The Cu(II) sulfate acts as an oxidizing agent for the aldehyde.
  - In plain water and benedict solution, the color is blue
  - In a mixture of benedict solution and glucose, the tube becomes cloudy and reddish in color.

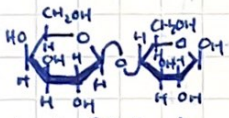
Disaccharides

→ Recall that hemiacetals in cyclic sugars are not stable in an aqueous solution at a pH of 7, even though the equilibrium favors sugars for hemiacetal forms.

→ Acetals are much stabler in aqueous solutions at a pH of 7. As such, the formation of disaccharides (pH ~7) is favored.

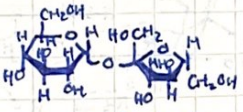
- Disaccharides are a type of acetal.

Two important disaccharides to consider: lactose & sucrose



Lactose (β-form)

Gal(β 1→4) Glc

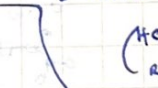


~~Sucrose~~ Sucrose

Glc(α1↔2β) Fru

- When considering the substituent components of each disaccharide (e.g. galactose & glucose for lactose and glucose & fructose for sucrose), we can predict the reductive properties of each.
  - Conducting a benedict's test shows that lactose results in the formation of precipitate and a reddish-brown color, whereas & sucrose retains the original blue color. Examining the structures, we can see why this is the case.

→ The reason is because a free hemiacetal group results in a sugar being able to ~~react~~ act as a reducing agent. Sucrose does not have a hemiacetal whereas lactose does.

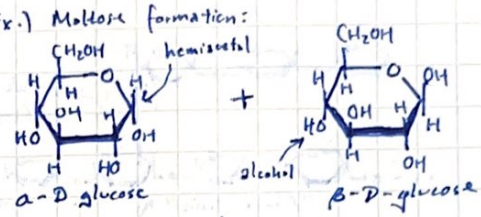


Hemiacetal

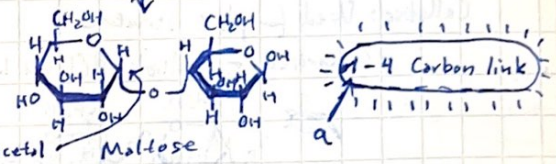
~~Sucrose's anomeric carbon is~~

→ Fructose has its anomeric carbon bound to glucose's anomeric carbon, resulting in no free hemiacetal to initiate reduction.

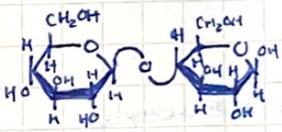
Ex.) Maltose formation:



Condensation reaction → H_2O



- The other formation (with two β-glucoses) is known as the formation of cellobiose, and contains instead a β1-4 carbon link instead of an α1-4 carbon link:

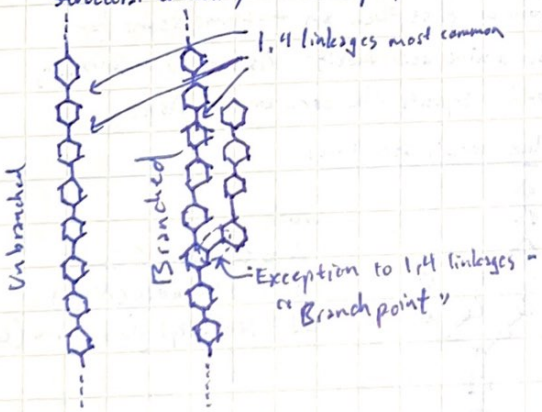


β 1-4 carbon link

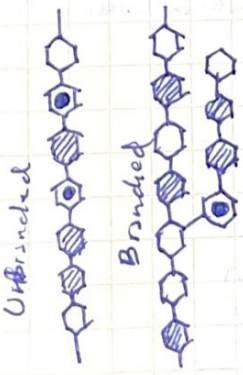
Cellobiose

Making Polysaccharides

Structural diversity in homopolysaccharides



Homopolysaccharides

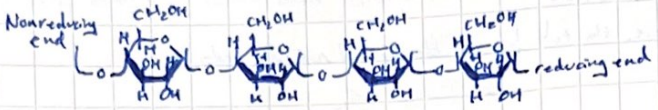


Heteropolysaccharides

Polysaccharide structure: Starch

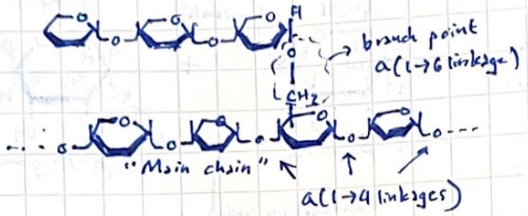
→ Starches have two components: amylose and amylopectin

- Amylose is an unbranched polysaccharide whereas amylopectin is branched.



Amylose

- Comprised of glucose polymers, α(1-4 linkages)
- When left to form polymers, created spiral shapes (each α-linkage is at an angle in space, so the chain bends)

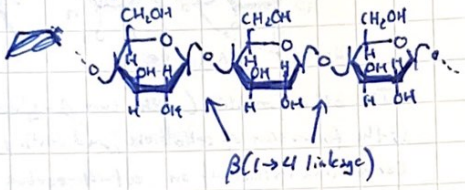


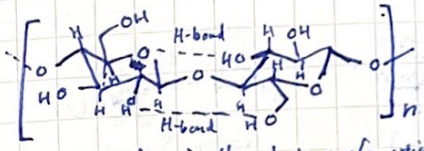
Amylopectin

- Comprised of branching glucose polymers made of a majority α(1→4 linkages) and some α(1→6 linkages) at the branch point.

Cellulose: Used for plant structure

- Comprised of multiple β(1→4 linkages) that are hard to break for the human body:

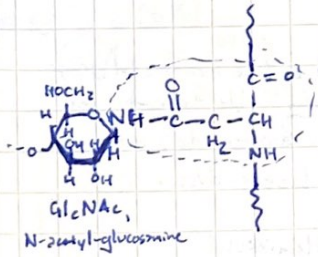




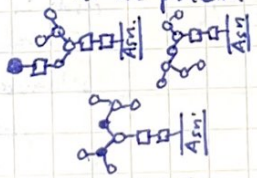
- Note how in the chair conformation diagram of cellulose, we can see how the β-link is very long. This is helpful for structural uses in plants.
- Additionally, the presence of hydrogen bonds further stabilizes the chain.
- Cellulose cannot branch, but may form hydrogen bonds between other cellulose chains.

Glycoproteins

N-linked glycoprotein an example:

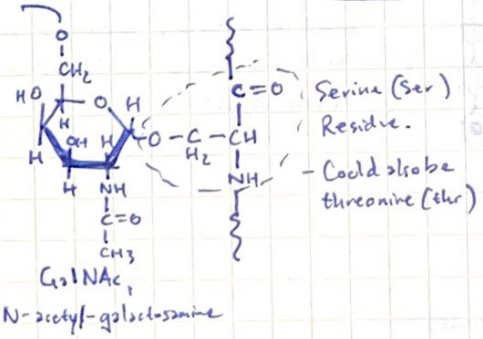


- Typically N-linked sugars contain many different sugars attached to the protein:



These can get pretty complicated.

O-linked glycoprotein example:

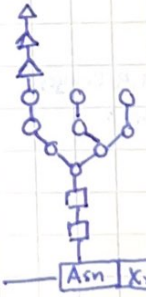


The Core N-linked Oligosaccharide

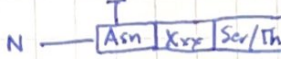
→ The core of the N-linked oligosaccharide always begins with two GlcNAcs, followed by chains of Mannose (Man).

→ The structure of the oligosaccharide is formed first, then an enzyme scans for an amino acid motif: Asn-Xxx-Ser/Thr, and deposits the core on the Asn.

The core's structure:



Where
- △ = Glucose (Glc)
- ○ = Mannose (Man)
- □ = N-acetyl glucosamine (GlcNAc)



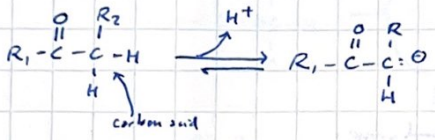
Purpose of protein glycosylation:

- The oligosaccharides are mainly used for cell to cell recognition in the body.
- Viruses may take advantage of the glycoproteins as well to enter the host cell
- Protein trafficking in the cell also relies on glycosylated proteins. The sugar acts as a tag for trafficking into the golgi apparatus.
  - Lectins are proteins which bind to oligosaccharides "tags" on proteins. (mannose-6-phosphate is an example)

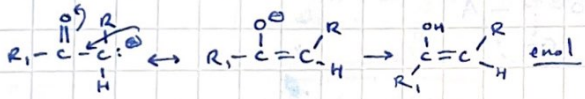
BCHM 462 - METABOLISM

Organic chem review:

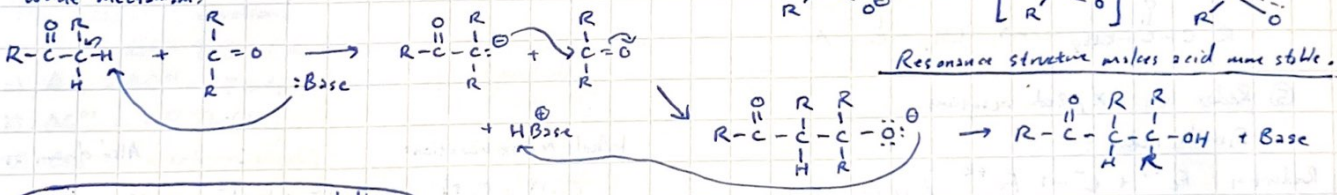
Aldol condensation



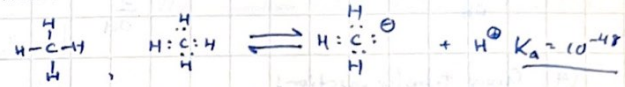
Formation of enol from aldol:



Whole mechanism:

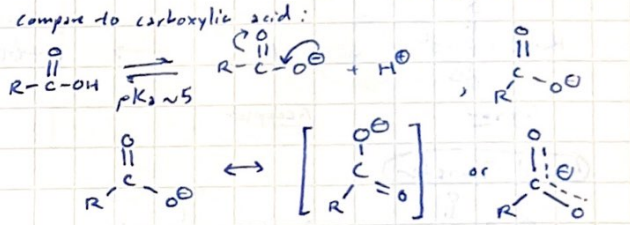


Acids:



Reaction highly favors reactants, therefore methane is considered an exceedingly weak acid.

compare to carboxylic acid:



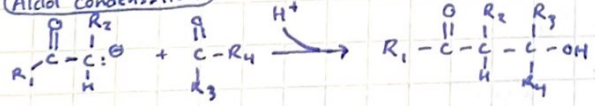
Resonance structure makes acid more stable.

Common reactions in metabolism:

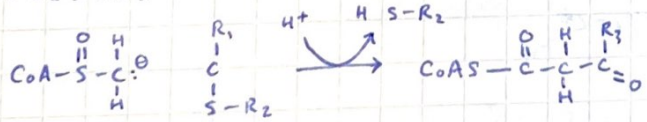
1) Making or breaking C-C bonds
2) Internal rearrangements, isomerizations, and eliminations
3) Free radical reactions ← We will not worry about this one
4) Group transfer reactions
5) Oxidation reduction reactions

① Making or breaking C-C bonds

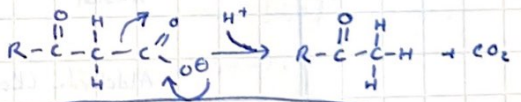
Aldol condensation



another example:



Claisen ester condensation - breaking C-C bonds



Decarboxylation of β-keto acid