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Lehninger Principles of Biochemistry

Fourth Edition

Chapter 7:

Carbohydrates and Glycobiology

[1] Carbohydrates – Introduction

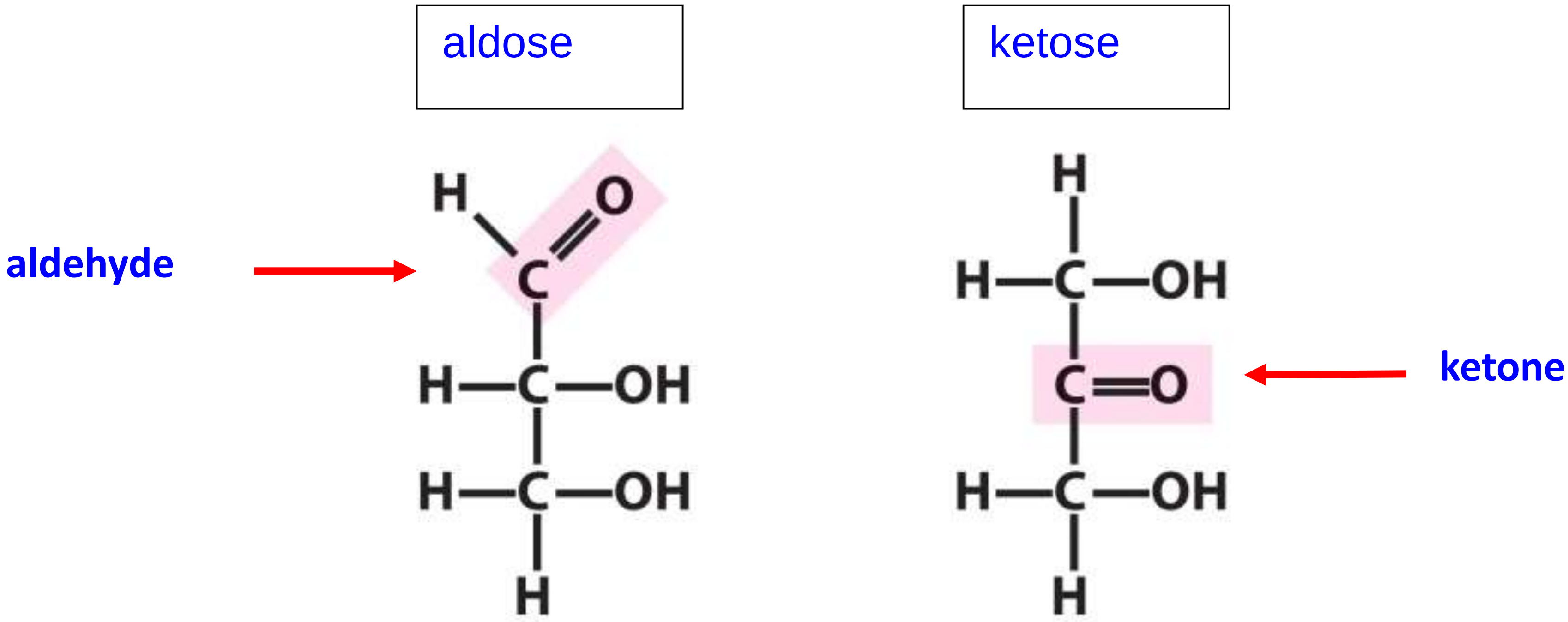
- Carbohydrates are essential to all living organisms and are the most abundant class of biological molecules.
- They are the end products of photosynthesis (100 billion tons of CO_2 + H_2O/year $\rightarrow$ cellulose and other plant products.
- The metabolic breakdown of monosaccharides provides most of the energy used to power biological processes.
- In structural material (cell walls, connective tissue)
- Important for cell signalling, cell-cell interactions
- Chemically, they are polyhydroxyl aldehydes or ketones.
- Contain three elements - C, H, O, many according to the formula $(CH_2O)_n$; where $n \geq 3$.
- Greek *saccharon* means sugar …

[2] Mono- and Disaccharides:

Monosaccharides:
Simple sugars – polyhydroxyl aldehyde or ketone (D-glucose)
Mono- with >4 carbons tend to have *cyclic* structures

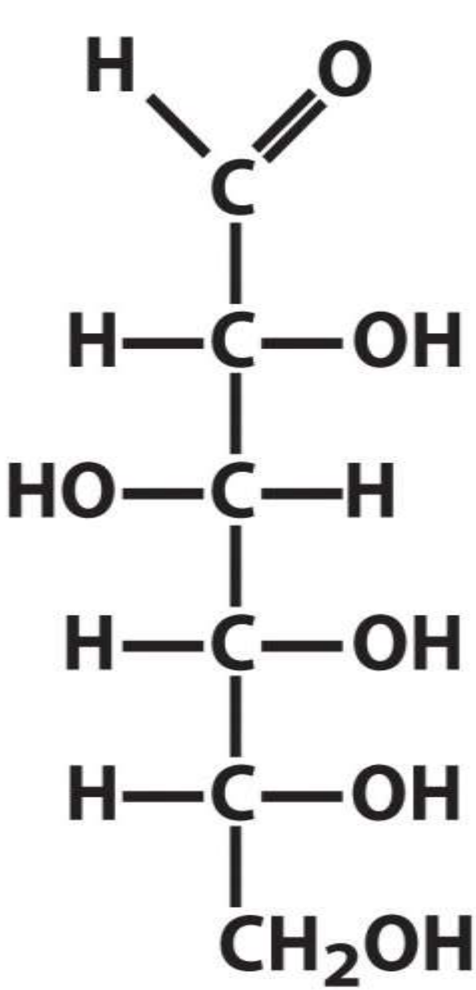
(2.1) The Anatomy of a Monosaccharide

- Poly hydroxyl aldehydes or ketones
- The smallest contain three carbons
- Freely soluble in water.
- Most have a sweet taste.
- C3 – triose, C4 – tetrose, C5 – pentose, C6 – hexose, C7 – heptose.

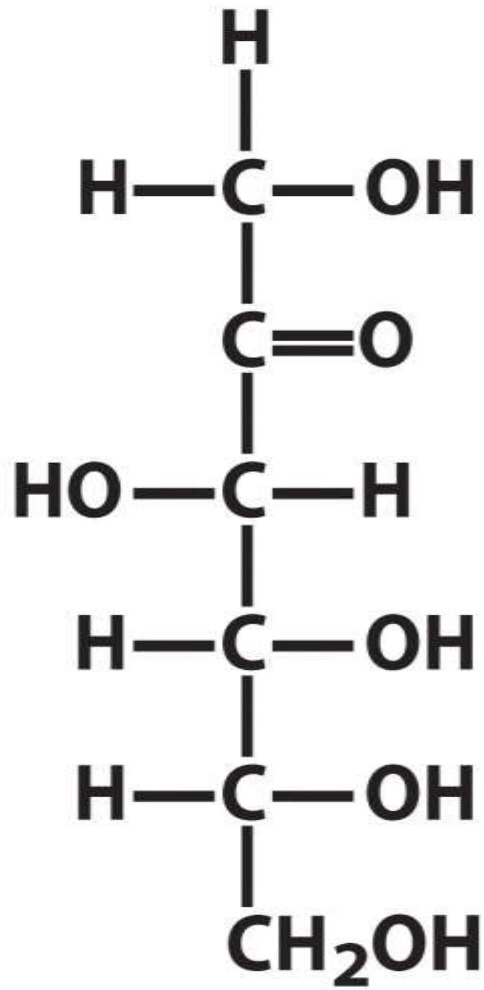


Glyceraldehyde, an aldotriose

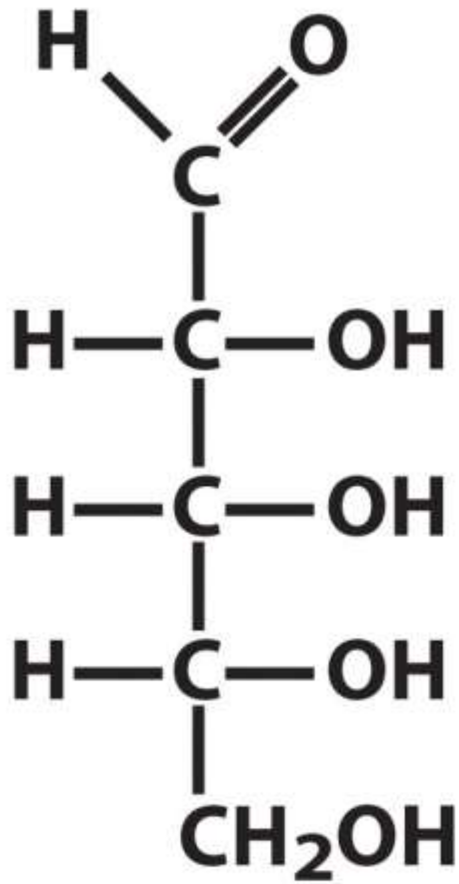
Dihydroxyacetone, a ketotriose



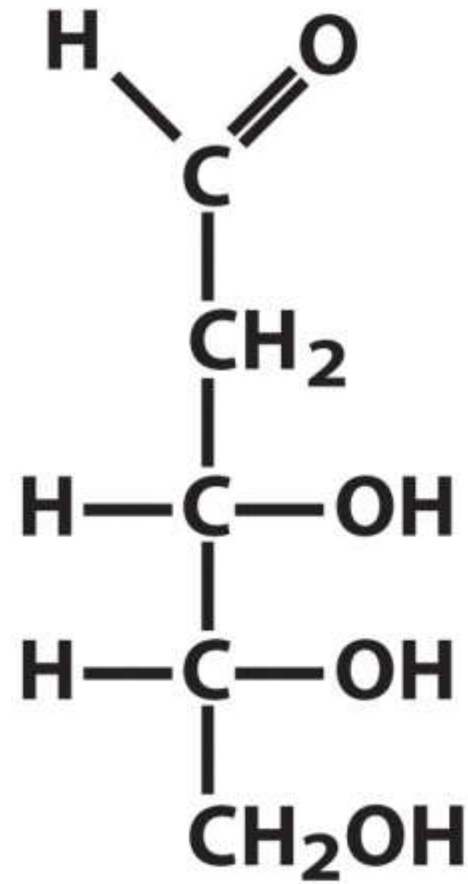
D-Glucose,
an aldohexose



D-Fructose,
a ketohexose



D-Ribose,
an aldopentose



2-Deoxy-D-ribose,
an aldopentose

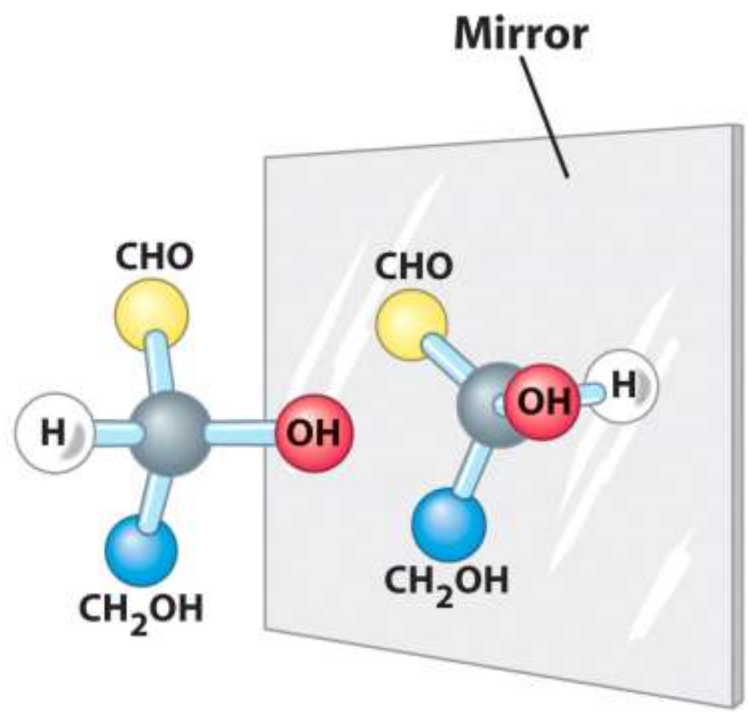
(2.2) Associated Stereochemistry

Recall: we will follow the same convention for sugars as we do for amino acids and glyceraldehyde –

Same as D-glyceraldehyde = D-isomers

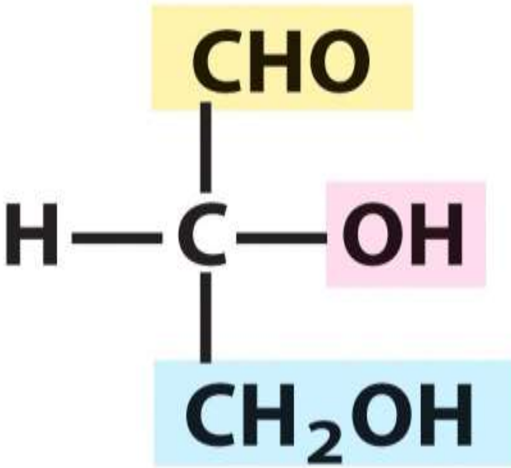
Same as L-glyceraldehyde = L-isomers

- L-sugars are much less abundant in nature.

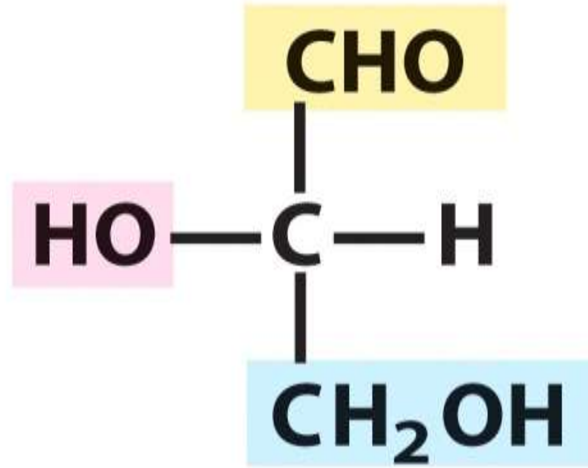


Ball-and-stick models

enantiomers



D-Glyceraldehyde



L-Glyceraldehyde

Fischer projection formulas

enantiomers

D-Glyceraldehyde

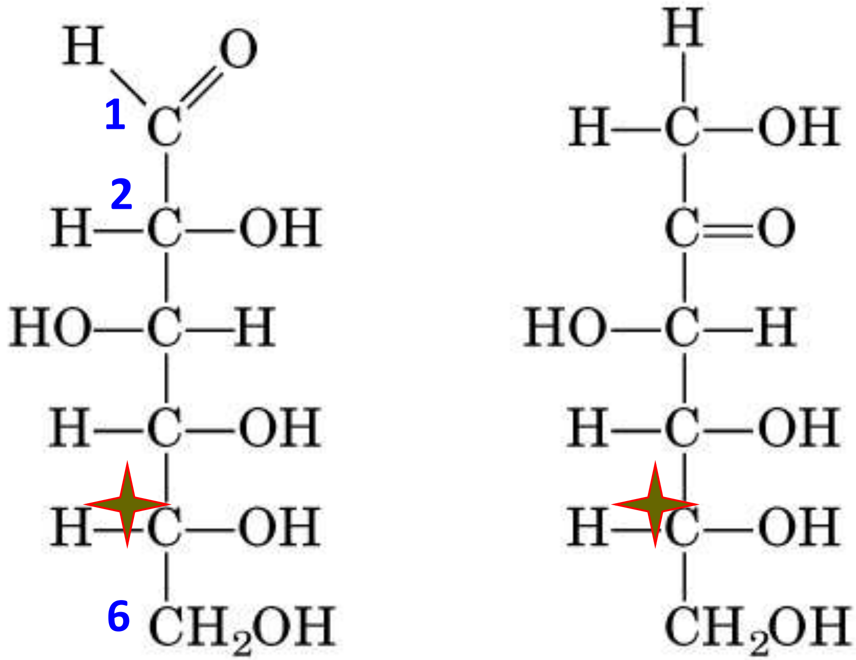
L-Glyceraldehyde

Perspective formulas

- Monosaccharides have many stereoisomers.
- *n* chiral centers ⇒ $\mathbf{2^{n}}$ stereoisomers.
- Aldose have $2^{\mathbf{n-2}}$, ketose have $2^{\mathbf{n-3}}$
  where n is the number of C.
  (half will be L- and half will be D-).

  Aldose has two achiral carbons (C1 and C6).
  Ketose has three achiral carbons (C1, C2, and C6)

• D-sugars have the same chiral configuration as D-glyceraldehyde at the chiral center farthest from the carbonyl carbon (Figure 7-3)



D-Glucose, an aldohexose

D-Fructose, a ketohexose

(b)

- There are 16 (= 2^4 for 4 chiral centers) aldohexoses, and D-glucose is one of them.

How many stereoisomers are associated with:

a) For a ketose: # stereoisomers = 2^{n-3}

For a hexose: n (# C) = 6

For ketohexoses: # stereoisomers = $2^{n-3} = 2^{6-3} = 2^3 = 8$

b) For an aldose: # stereoisomers = 2^{n-2}

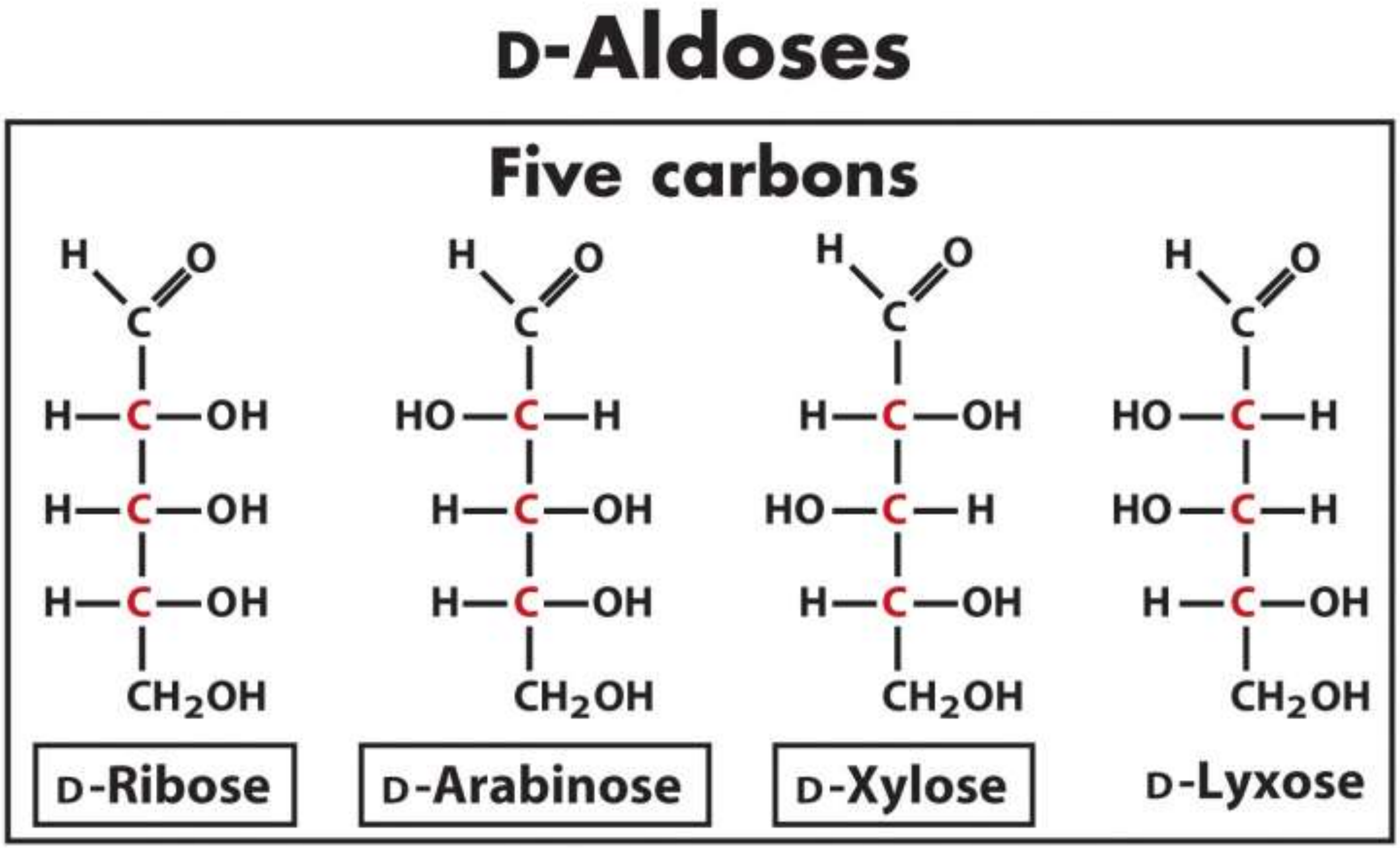
For a pentose: n (# C) = 5

For aldopentoses: # stereoisomers = $2^{n-2} = 2^{5-2} = 2^3 = 8$

There are also four L-aldopentoses.

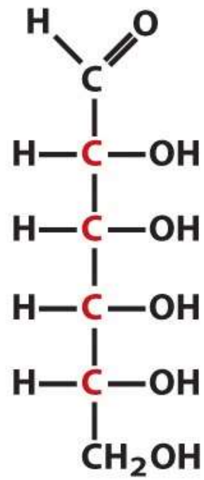
L-Ribose, L-Arabinose, L-Xylose, L-Lyxose.

Total 8 (2^{5-2}) aldopentoses.

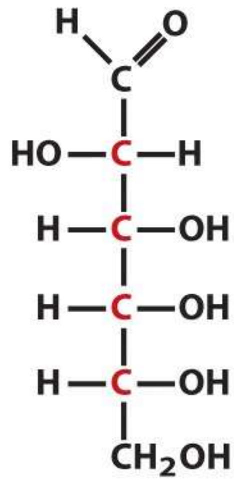


D-Aldoses

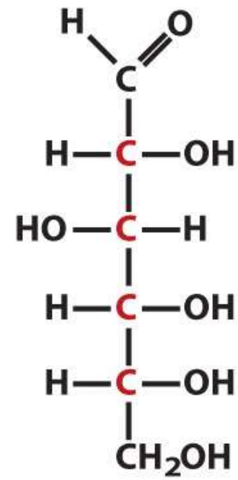
Six carbons



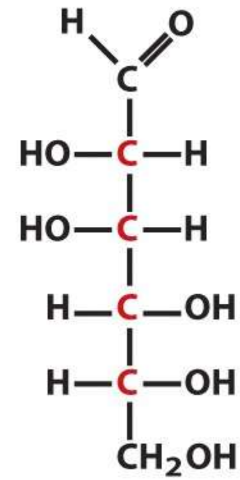
D-Allose



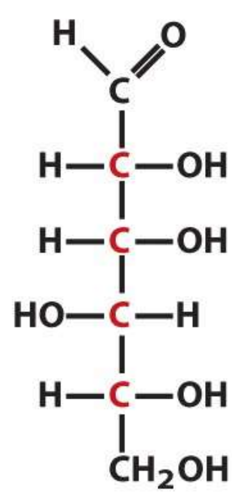
D-Altrose



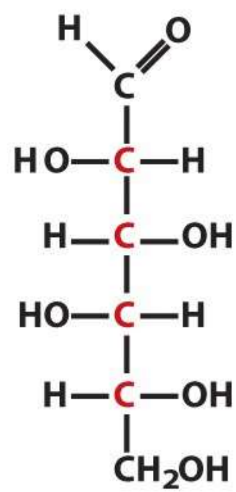
D-Glucose



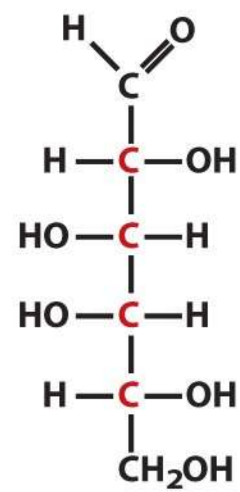
D-Mannose



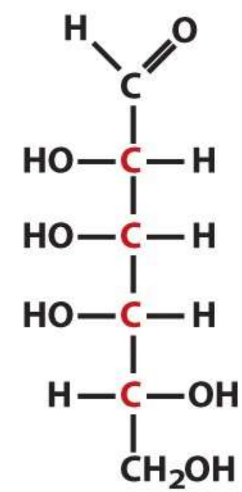
D-Gulose



D-Idose



D-Galactose



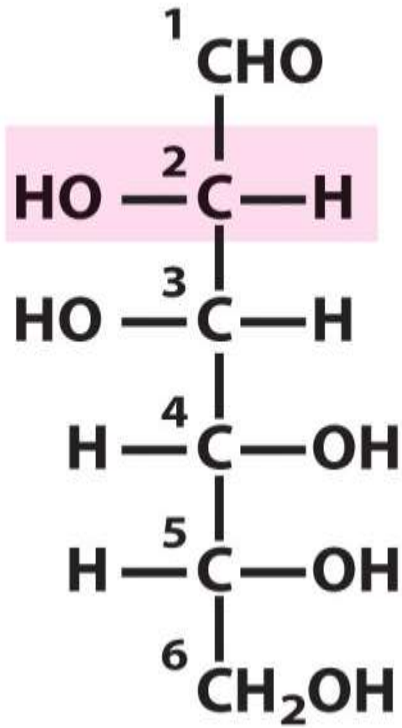
D-Talose

Epimers: sugars that differ only in the configuration around one carbon atom

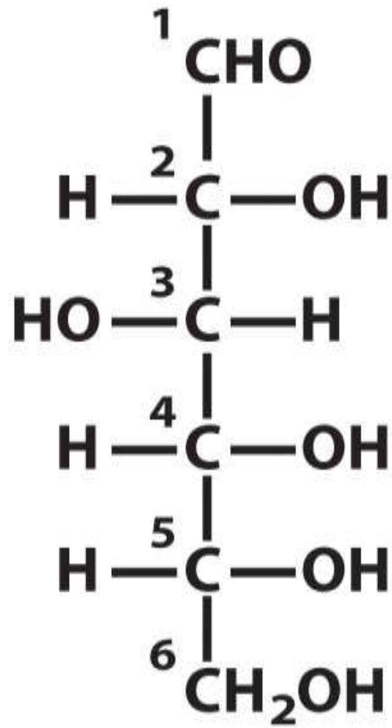
D-glucose and D-Mannose

D-Glucose and D-Galactose

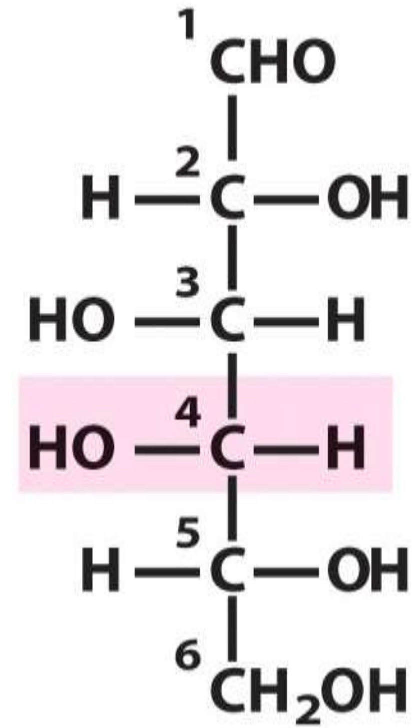
(D-Mannose and D-Galactose are not epimers.)



D-Mannose (epimer at C-2)



D-Glucose

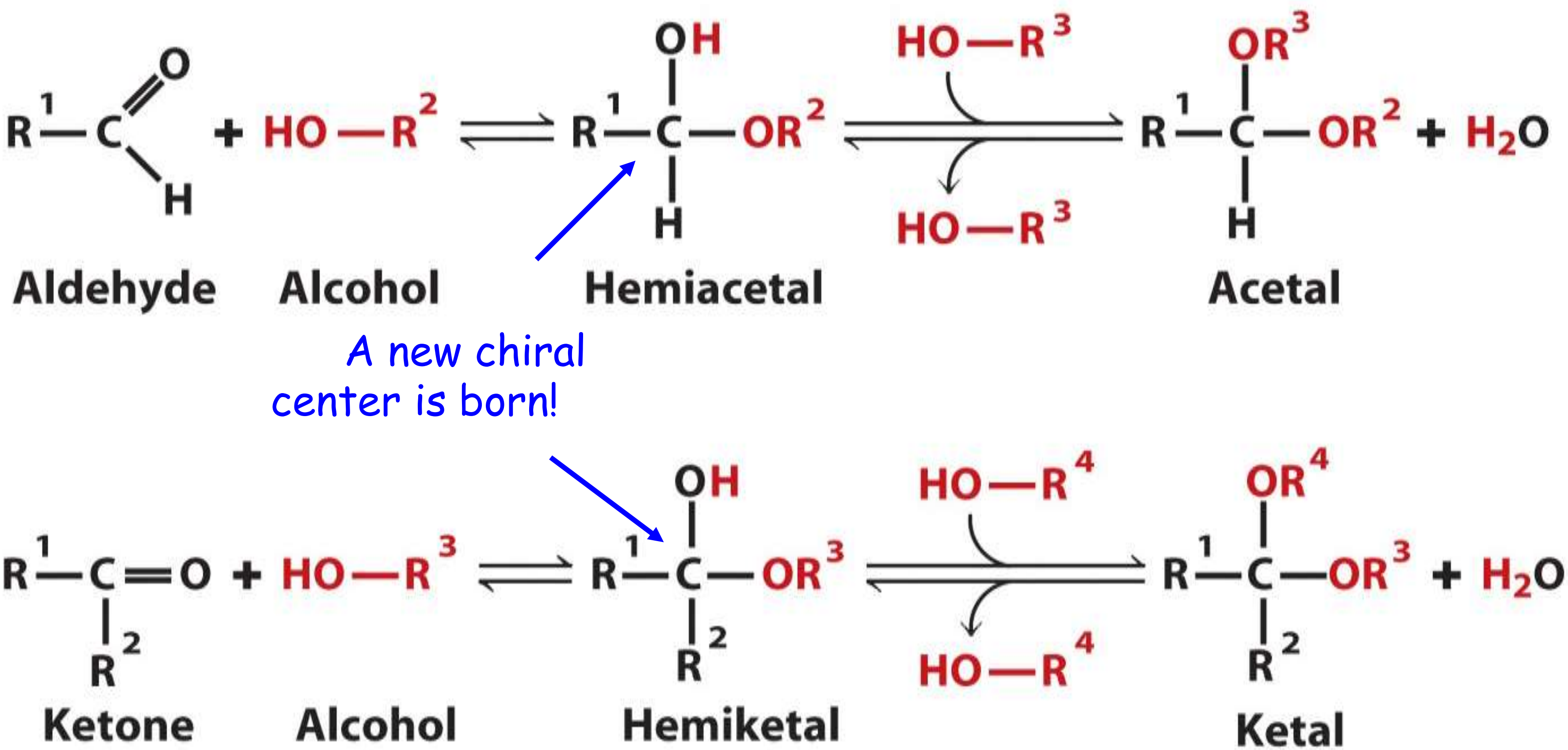


D-Galactose (epimer at C-4)

[3] Monosaccharide Ring Structures

In solution, aldotetroses and all monosaccharides with $n \geq 5$ occur predominantly as cyclic structures, because:

- Alcohol groups can react with the aldehydes or ketones to form hemiacetals and hemiketals.

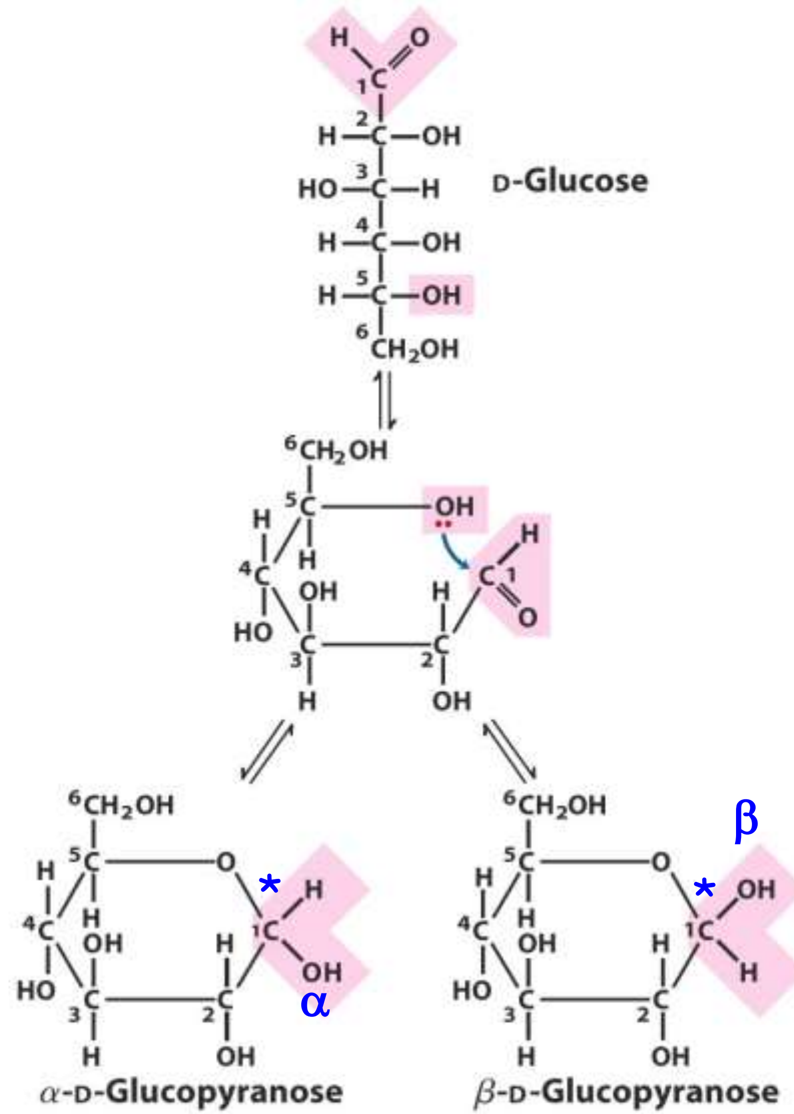


Sugars with ≥ 5 C mostly exist in their cyclized form (*intra*molecular hemiacetal formation):

- Since C1 becomes a chiral center, there are two new possible stereoisomers that are named **α** and **β**.

- Anomers: Isomeric forms that differ only in their configuration about the hemiacetal or hemiketal carbon atom. ⇒ α,β anomers

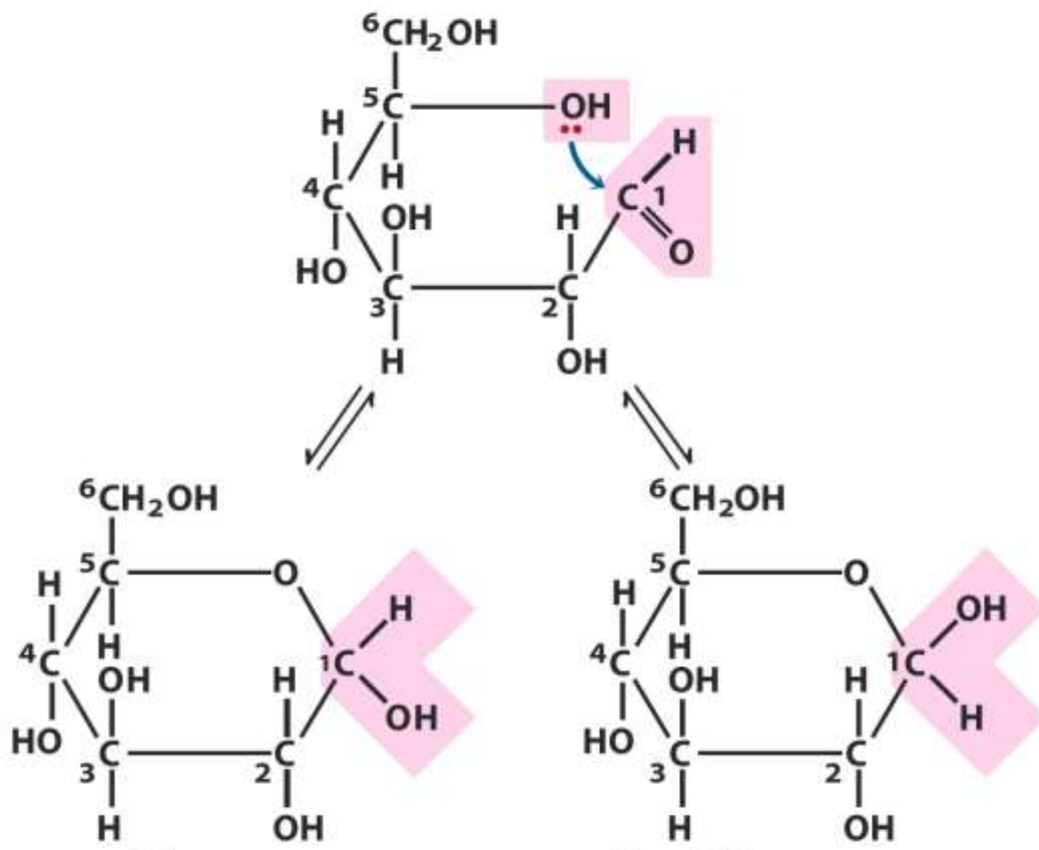
- anomeric carbon – the hemiacetal carbon atom.



Sugars with ≥ 5 C mostly exist in their cyclized form (*intra*molecular hemiacetal formation):

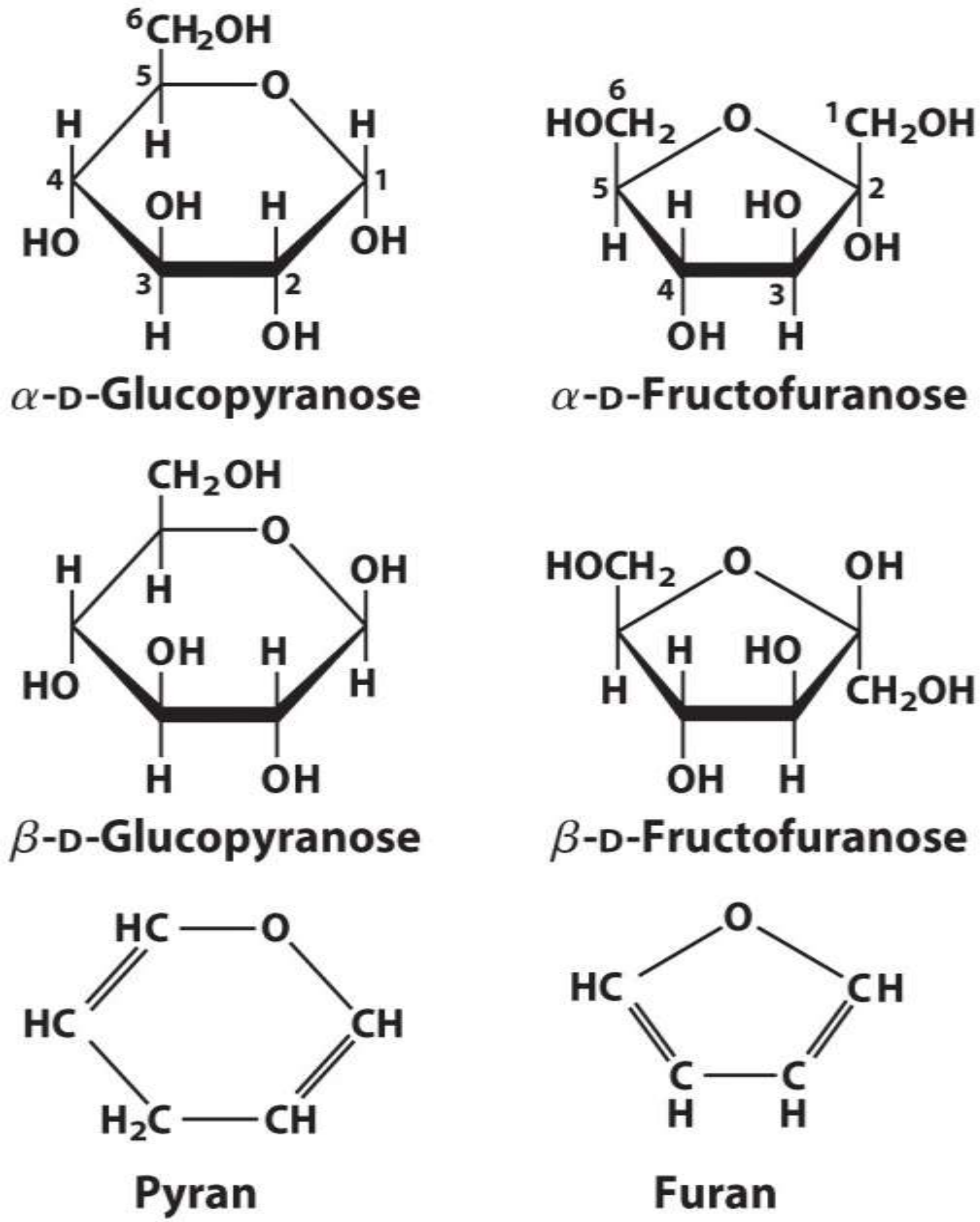
- The α,β anomers interconvert in solution by mutarotation.

- An equilibrium mixture of glucose will contain 1/3 α-anomer and 2/3 β-anomer in the D-configuration and very, very small amounts of the linear and five membered ring forms.

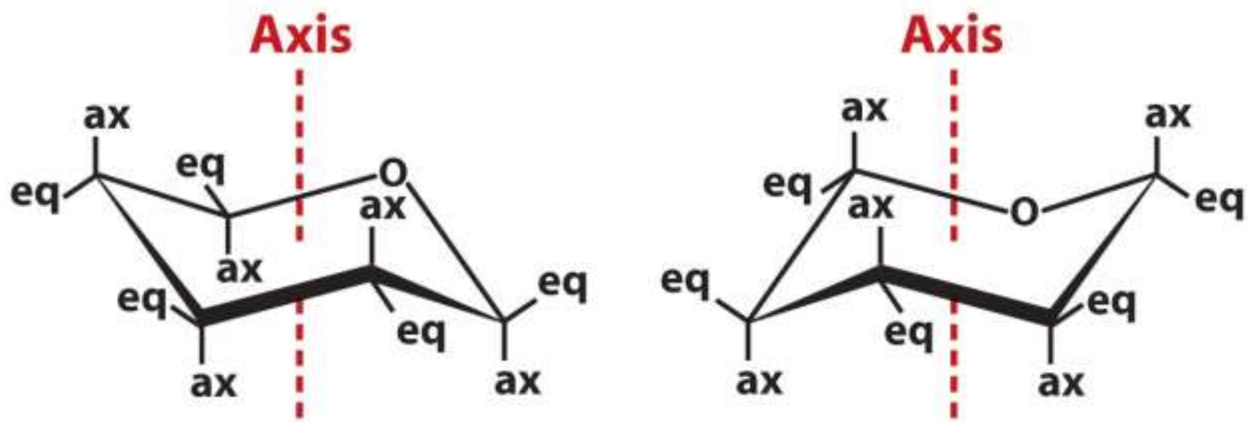


α-D-Glucopyranose β-D-Glucopyranose

- Since they resemble the six-membered ring, pyran, they are now called *pyranoses*.
- Likewise, aldoses (5C) and ketoses (6C) form five-membered rings and are called *furanoses* after furan.
- D−Fructose readily forms the furanose ring.
- β−D−fructofuranose is more common (stable).
- Haworth perspective formulas are used to depict the stereochemistry.

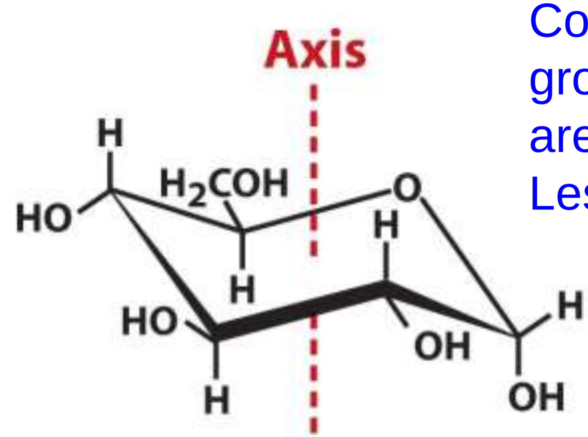


• Pyranose ring is not planar.
⇒ Two “chair” conformations (conformers).
• 3-D conformations can determine function and biological properties of polysaccharides.



Two possible chair forms

Not readily interconvertible.



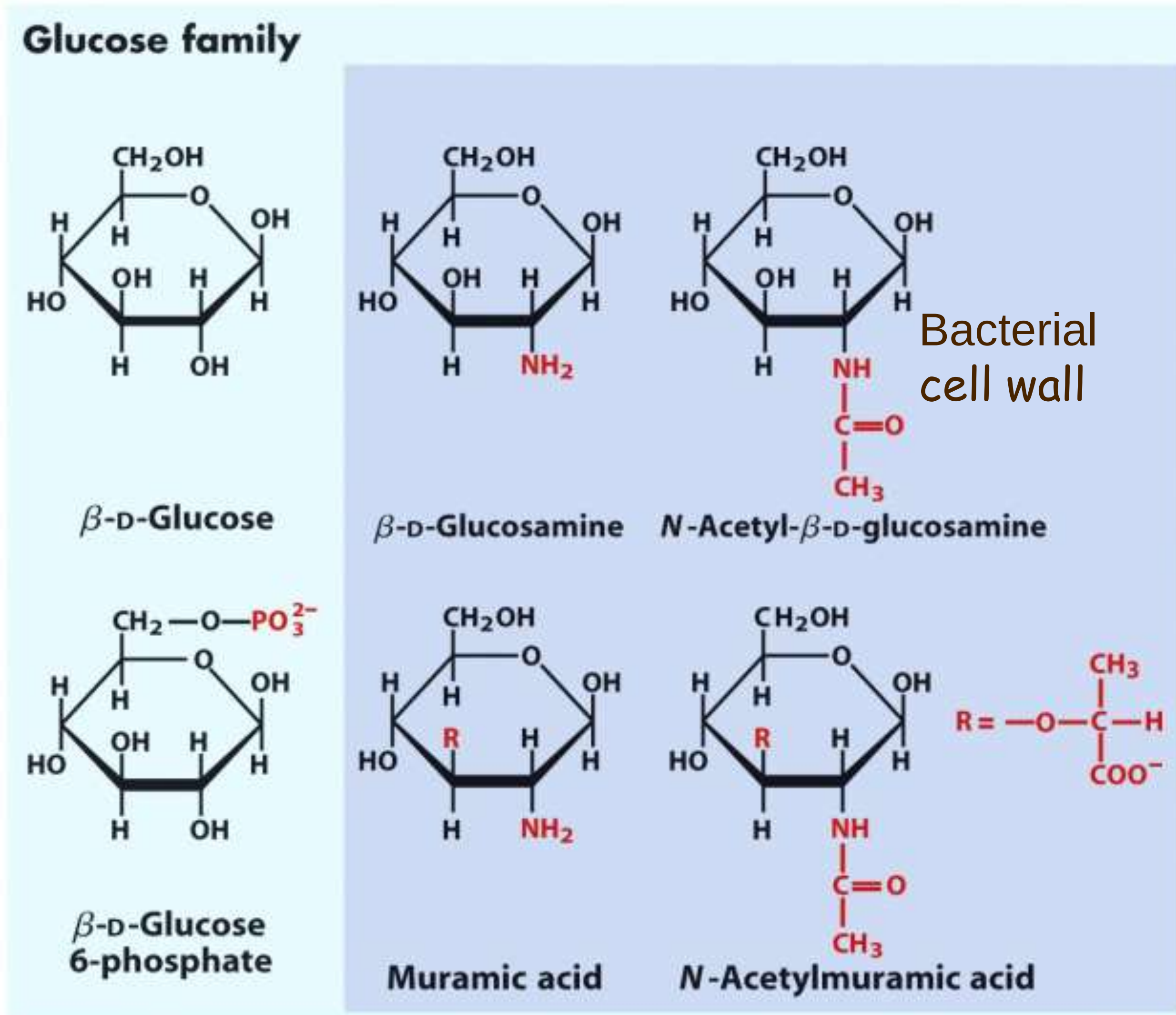
α-D-Glucopyranose

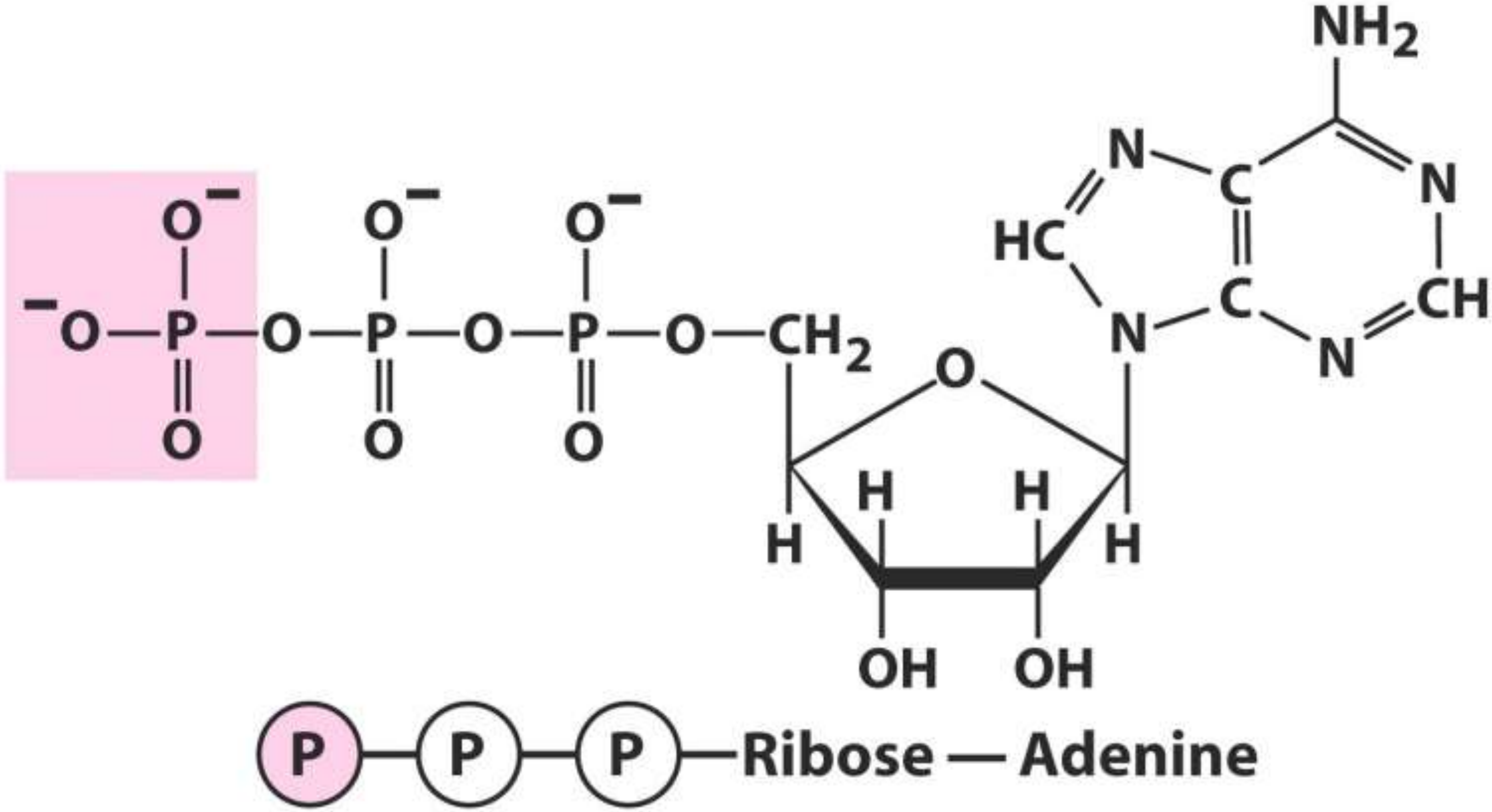
Conformers with bulky groups in eq positions are favored.
Less steric hindrance.
(Fewest repulsive interactions)

[4] Monosaccharide Derivatives

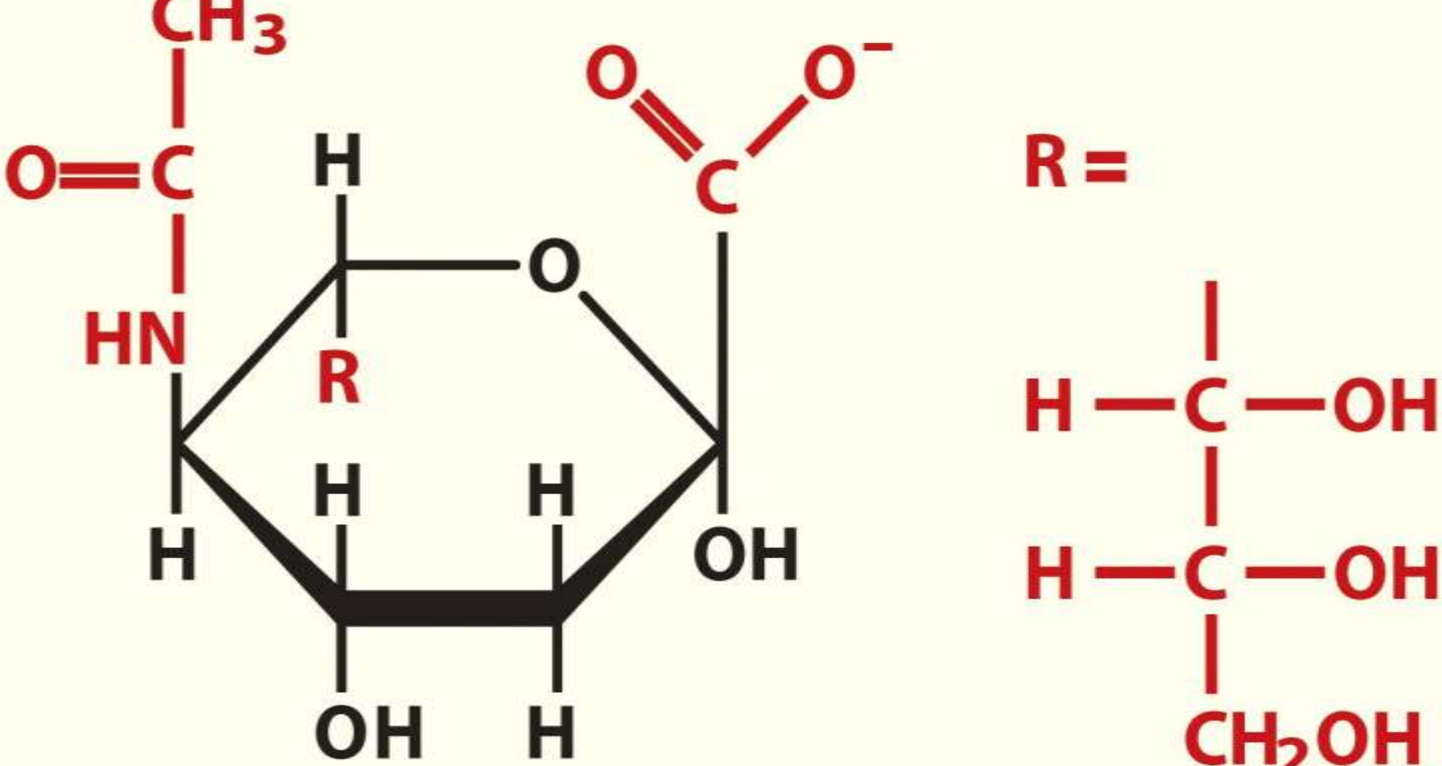
- Derivatives are formed by replacing the hydroxyl groups with other groups

–NH-(C=O)-CH_3,
–NH_2,
–(C=O)H → –COO^-,
–O-H → –O-PO_3^{2-}



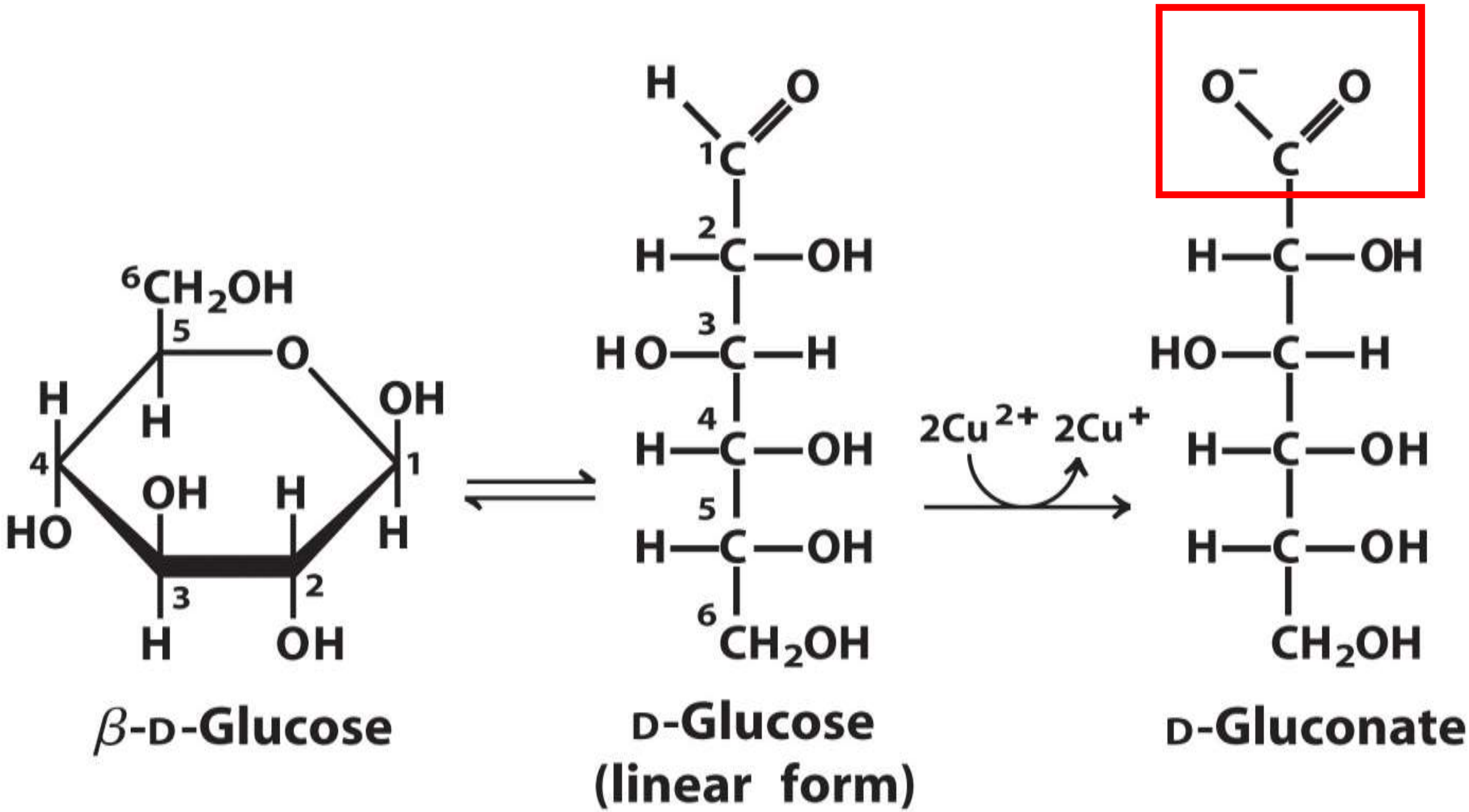

NH2
N
N
HC
C
C
CH
N
N
O−
O−
O−
−O
P
O
P
O
P
O
CH2
O
O
O
O
H
H
H
H
OH
OH
P
P
P
Ribose — Adenine

Acidic sugars

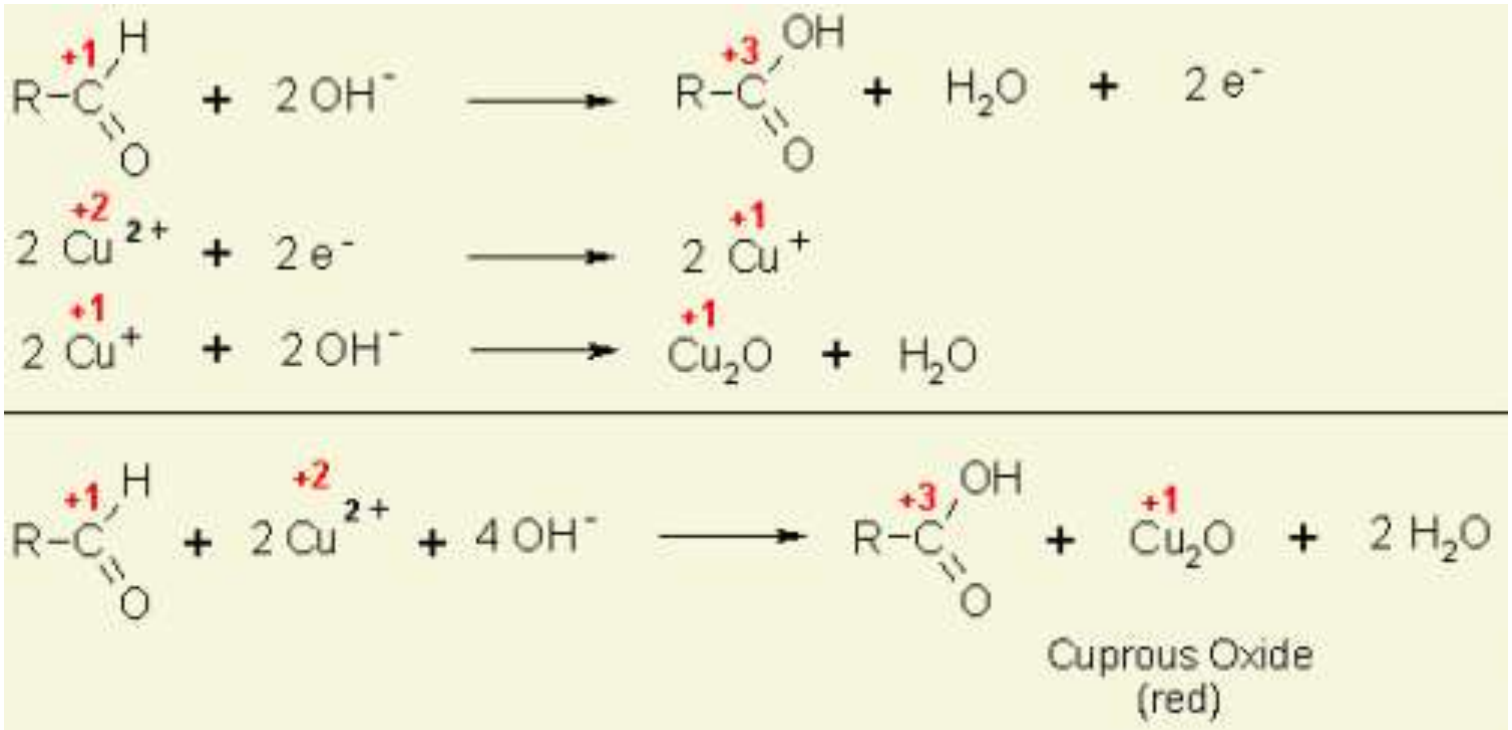


N-Acetylneuraminic acid
(a sialic acid)

• Monosaccharides can be oxidized by oxidizing agents such as Fe^{3+} or Cu^{2+} ions.



Fehling's reaction was used to measure blood glucose level.



(http://www.uni-regensburg.de/Fakultaeten/nat_Fak_IV/Organische_Chemie/Didaktik/Keusch/D-Fehling-e.htm)

Modern methods for blood glucose determination
(Glucose oxidase method)

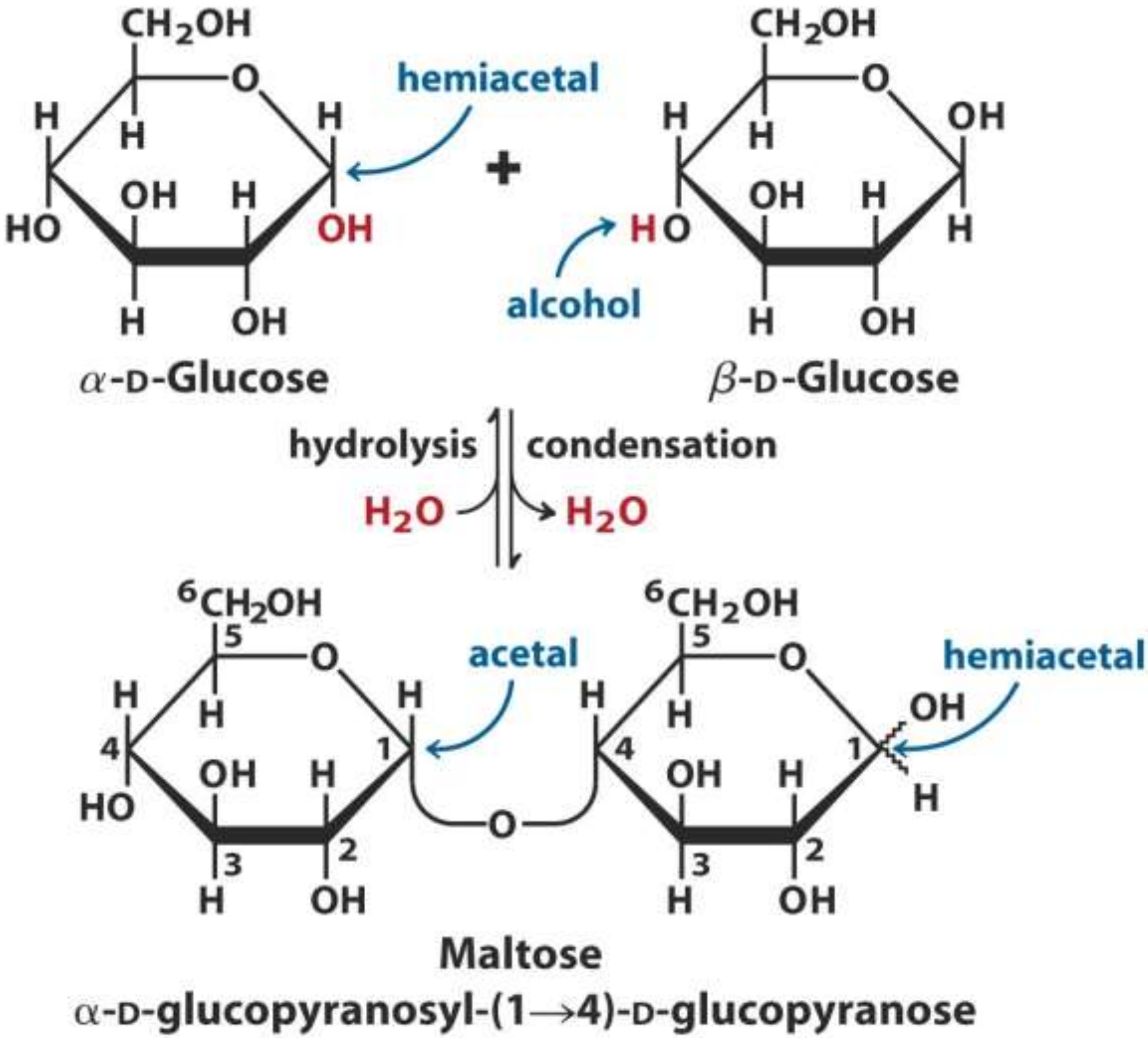
$$\text{D-Glucose} + O_2 \xrightarrow{\text{glucose oxidase}} \text{D-Glucono-}\delta\text{-lactone} + H_2O_2$$

H_2O_2 thus formed can be measured by several methods.

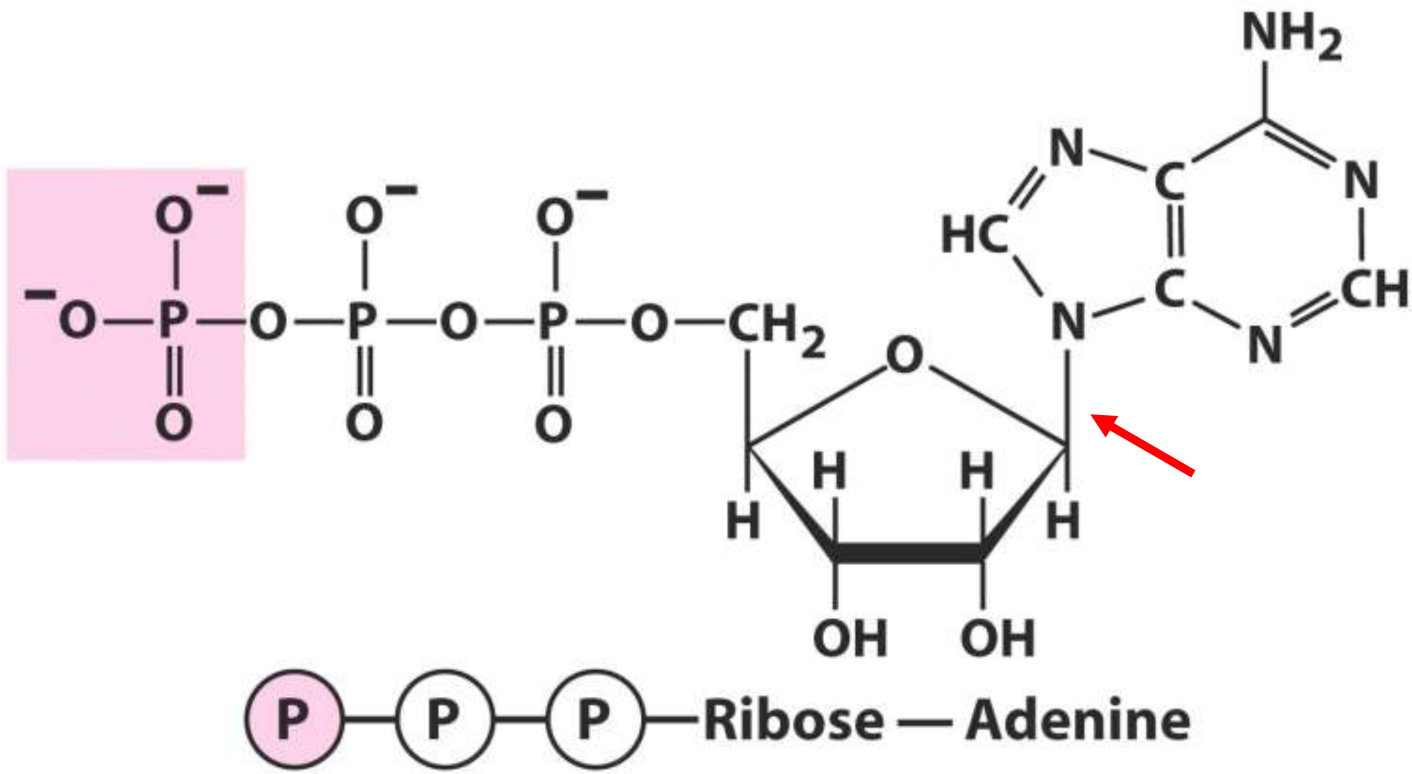
- H_2O_2 reacts with Fe(CN) in the presence of luminol to produce luminescence proportional to the initial glucose concentration.
- H_2O_2 is first converted to water and oxygen by the enzyme peroxidase (POD). Then, 4-aminophenazone, an oxygen acceptor, takes up the oxygen and together with phenol forms a pink coloured chromogen which can be measured at 515mm.

[5-1] Glycosidic Bonds

- Disaccharides arise through the formation of *O*-glycosidic bonds: condensation of anomeric carbon hydroxyl group with an alcohol.



- *N*-glycosidic bonds: anomeric carbon bound to an amine (ATP)



- There are two types of glycosidic bonds between
- the C1 of one sugar and the C4 of another:

  (α1→4) and (β1→4) linkages
- Naming oligosaccharides

  1. The name begins at the non-reducing end to the left.
  2. Give configuration (α or β) at anomeric C of the first monosaccharide.
  3. Name the non-reducing sugar (on left) → furano and pyrano distinguish 5 and 6 membered rings.
  4. Name linkage in parentheses i.e. (1→4) from first to second sugar.

     (use a double arrow if both are non-reducing).

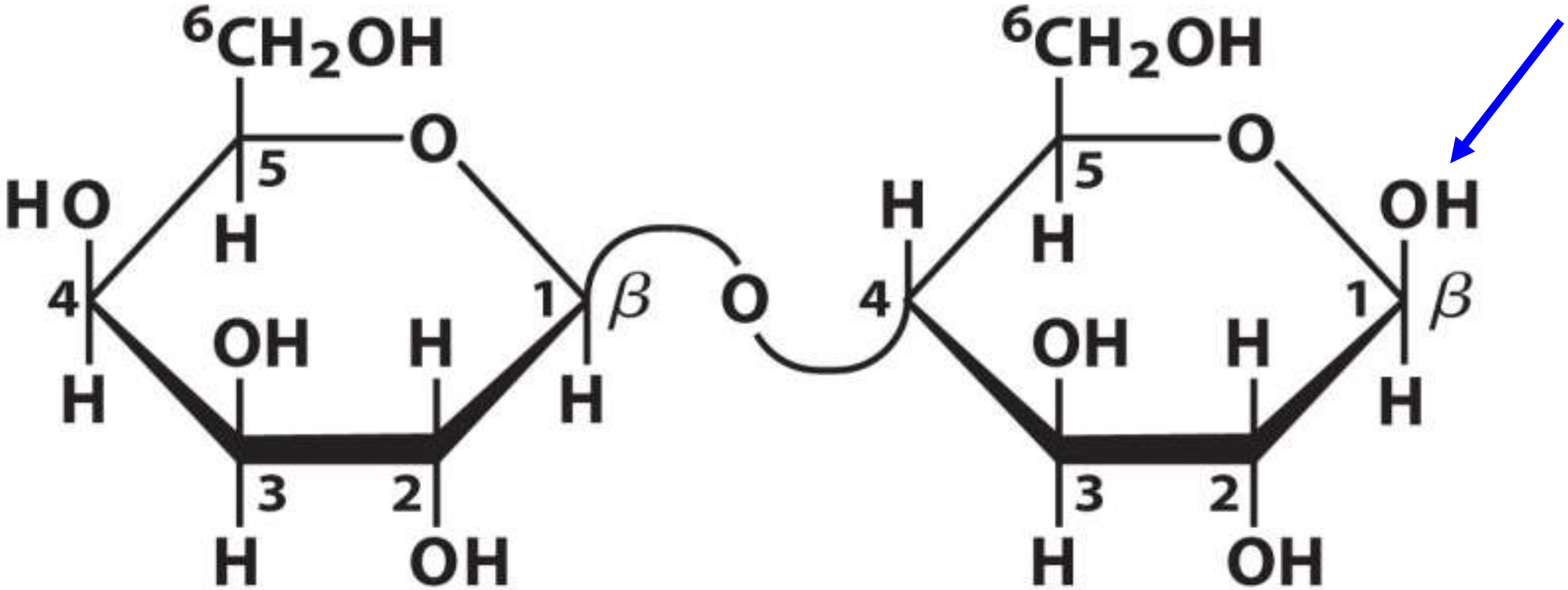
5. Name the second residue.
6. Non-reducing sugars are named as glycosides.

* In most cases, you are dealing with D-sugars and therefore the abbreviated version can be used …Maltose = Glc(α1→4)Glc

- The reducing end: the sugar with the *free* anomeric carbon that can be oxidized.

Oxidation occurs only w/ the linear form.

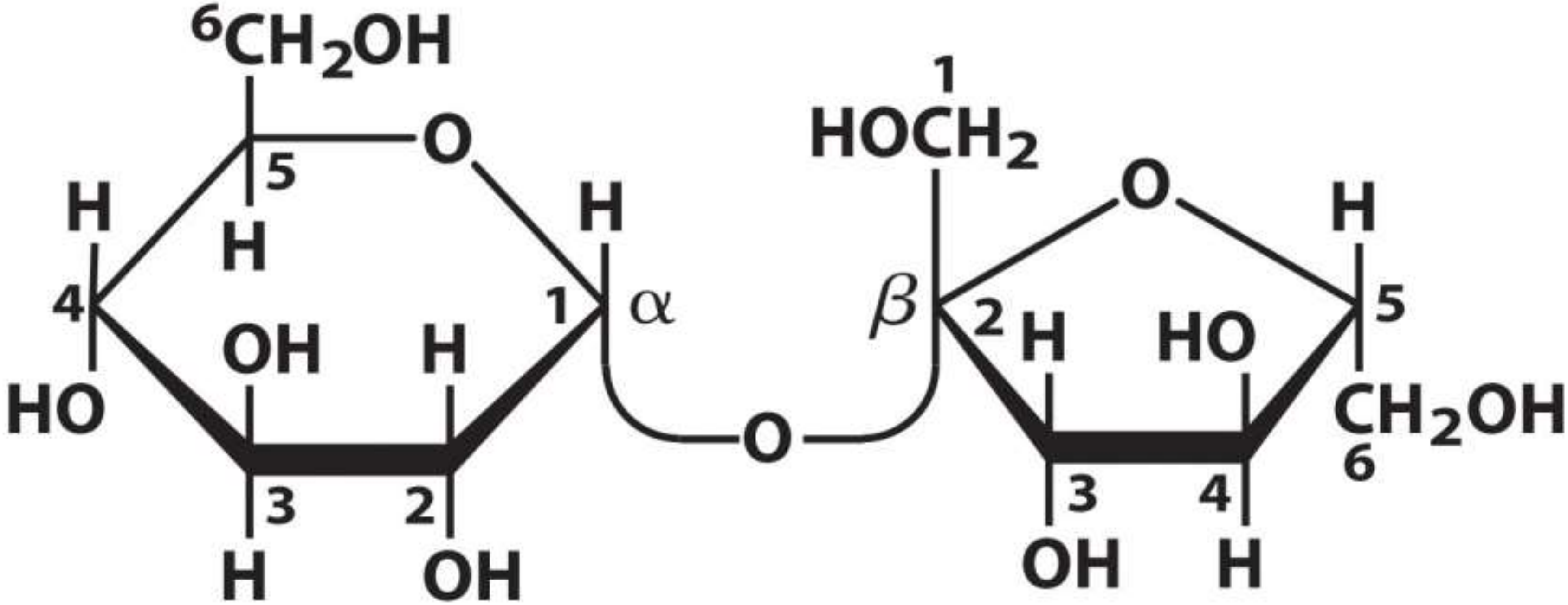
Maltose and lactose are reducing sugars, while sucrose is not.



Lactose (β form)

β-D-galactopyranosyl-(1→4)-β-D-glucopyranose

Gal(β1→4)Glc



Sucrose

α-D-glucopyranosyl β-D-fructofuranoside

Glc(α1$\leftrightarrow$2β)Fru

Bond between two anomeric carbons

TABLE 7–1 Abbreviations for Common Monosaccharides and Some of Their Derivatives

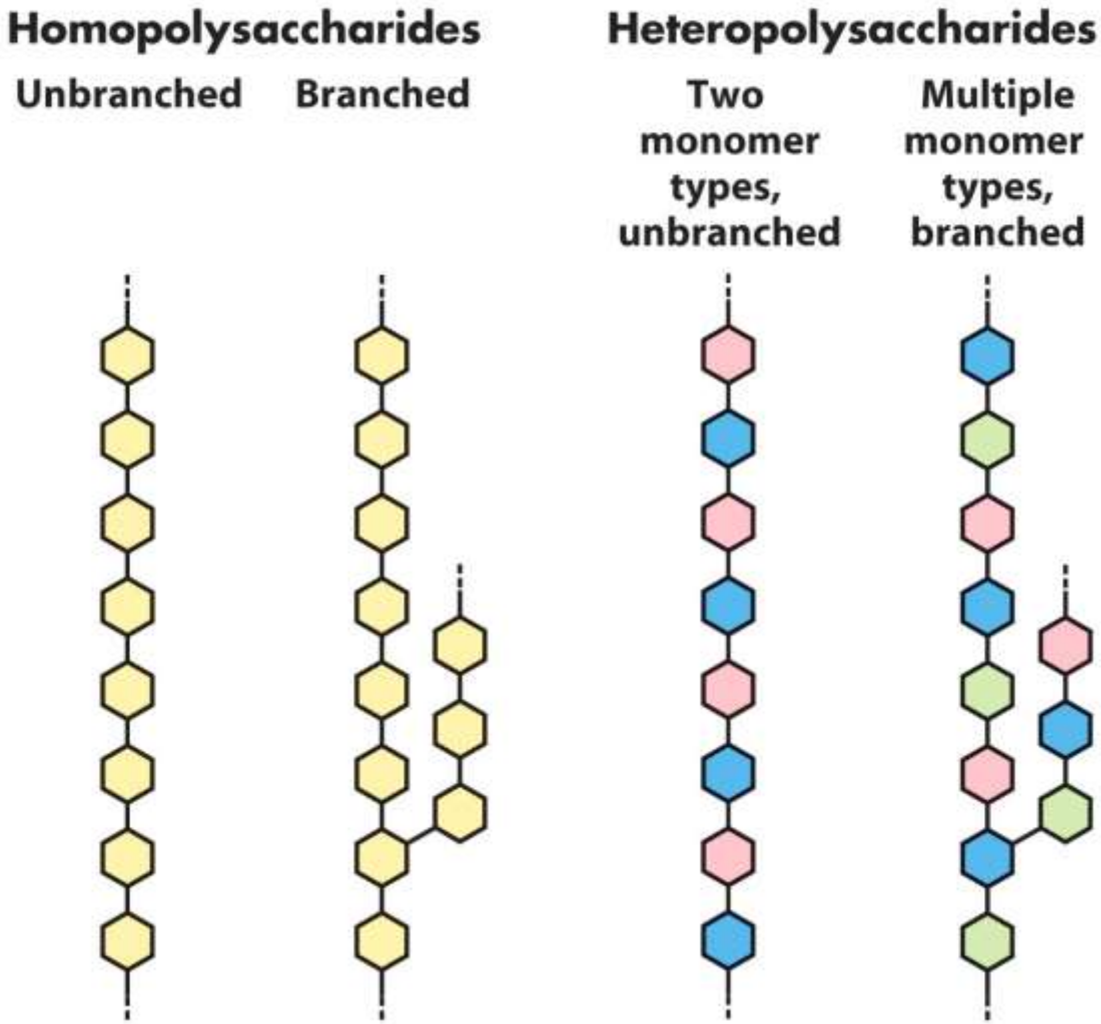
Abequose	Abe	Glucuronic acid	GlcA
Arabinose	Ara	Galactosamine	GalN
Fructose	Fru	Glucosamine	GlcN
Fucose	Fuc	*N*-Acetylgalactosamine	GalNAc
Galactose	Gal	*N*-Acetylglucosamine	GlcNAc
Glucose	Glc	Iduronic acid	IdoA
Mannose	Man	Muramic acid	Mur
Rhamnose	Rha	*N*-Acetylmuramic acid	Mur2Ac
Ribose	Rib	*N*-Acetylneuraminic acid (a sialic acid)	Neu5Ac
Xylose	Xyl		

[5-2] Polysaccharides (Glycans)

Diversity –
Monomeric units
Chain length
Type of linkage
Degree of branching
Do not have definite MW.

Homopolysaccharides:
made from only one sugar type

Heteropolysaccharides:
made from more than
one sugar type

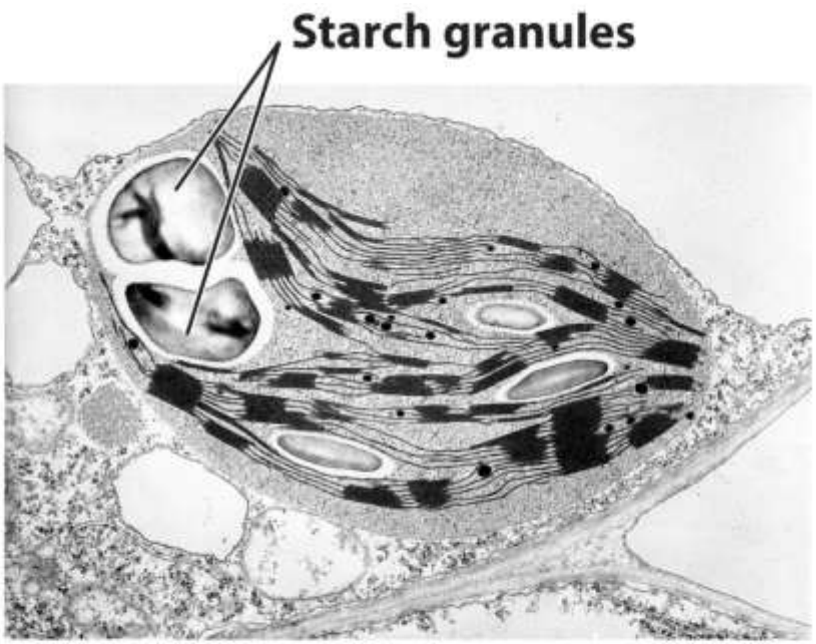


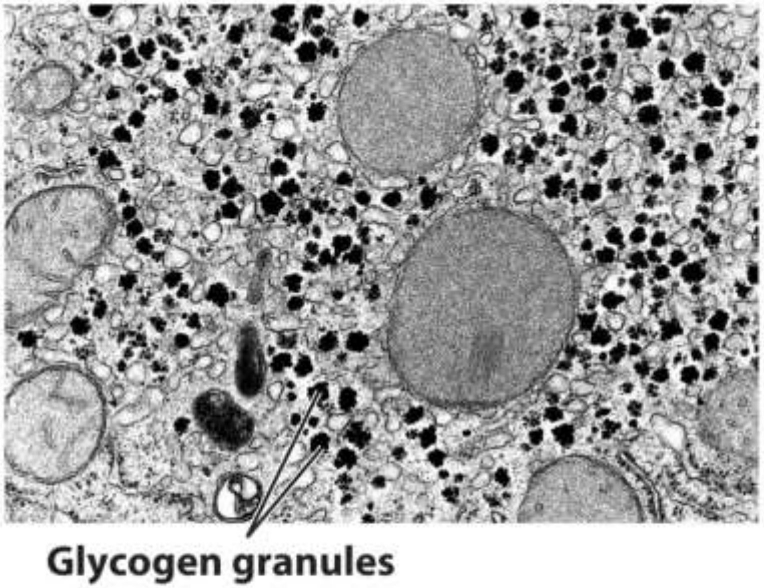
Homopolysaccharides:

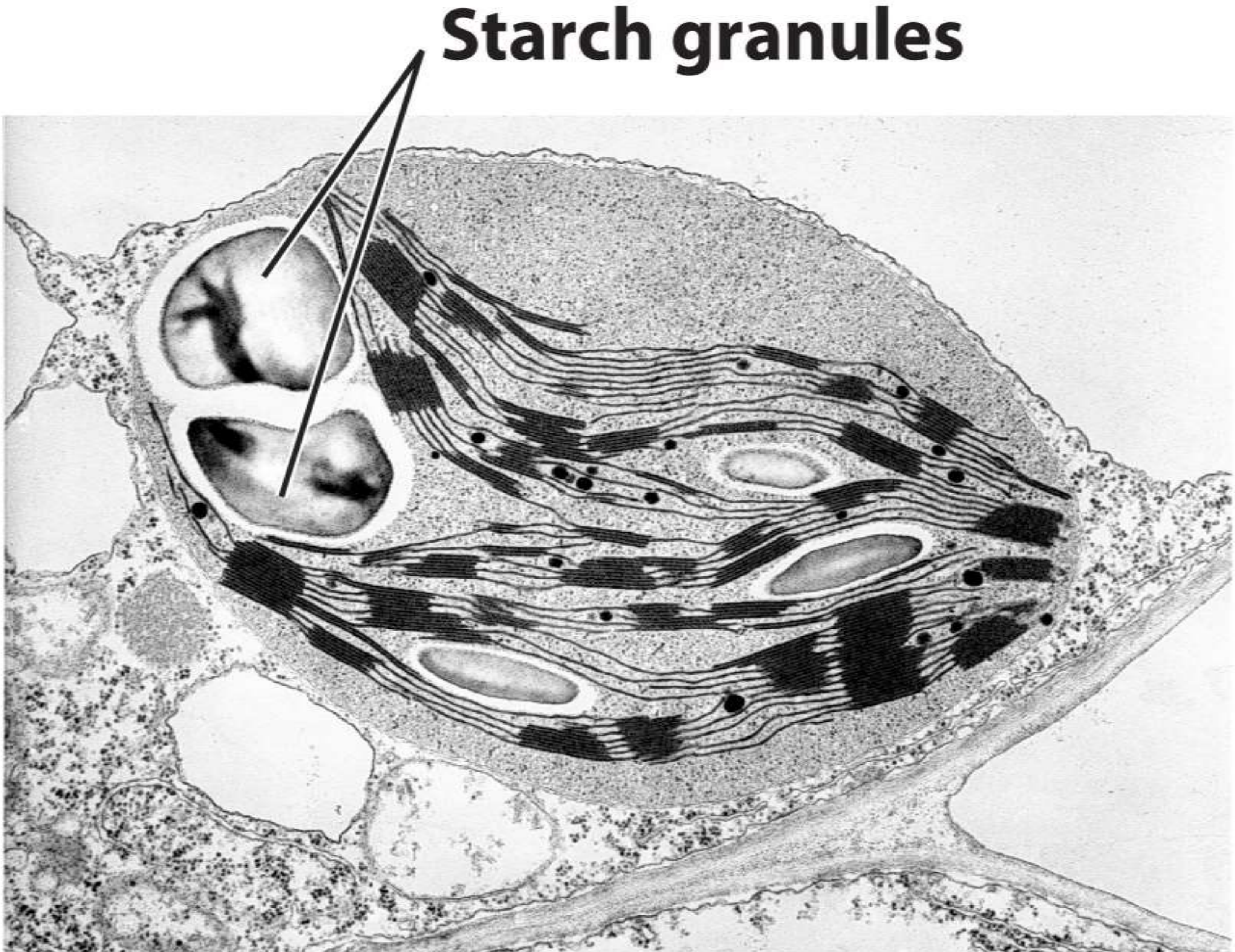
- Storage – Starch (storage in plants),
  Glycogen (storage in animals).
- Structural elements – Cellulose (plants cell wall),
  Chitin (animal exoskeleton).

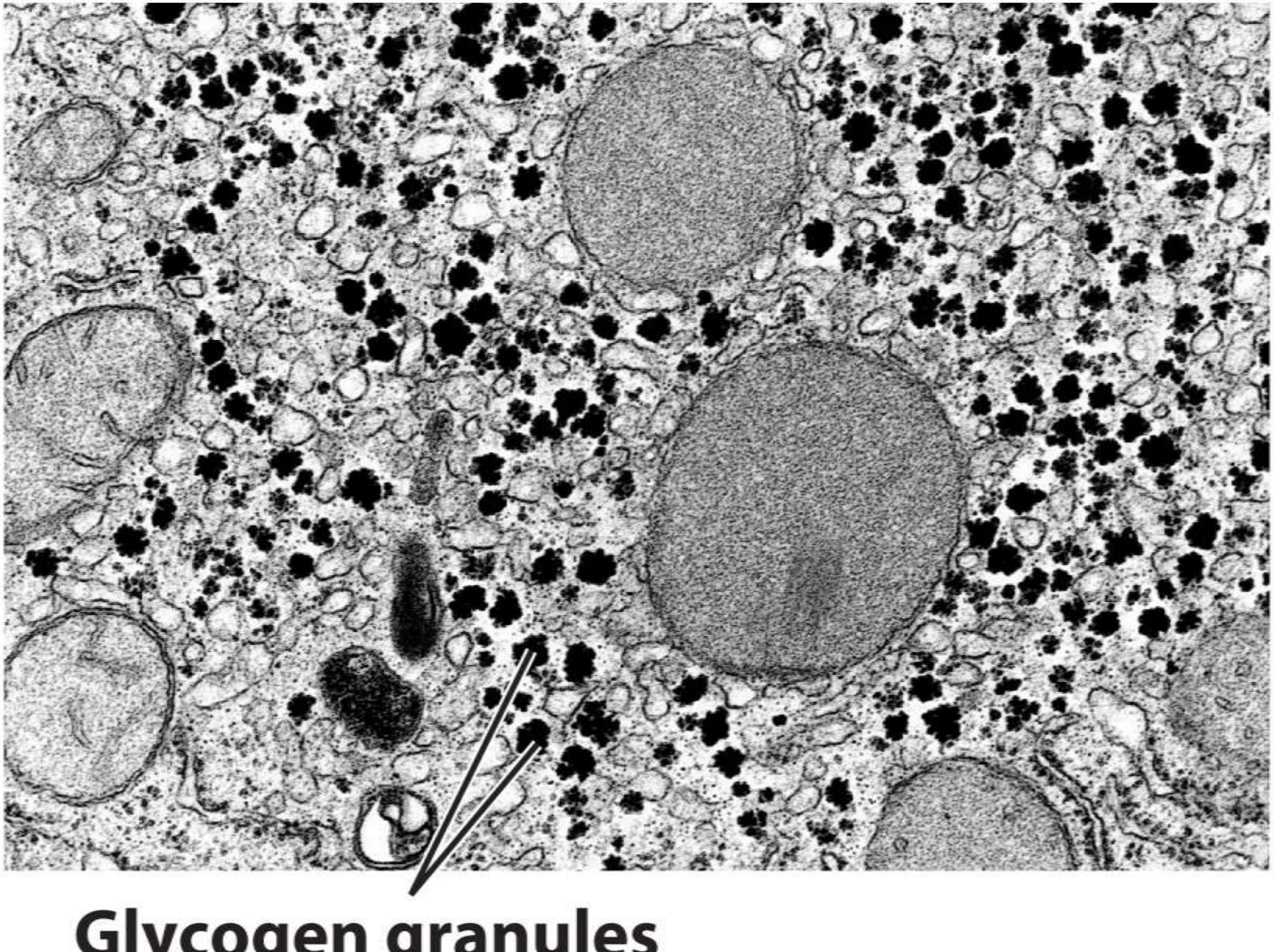
Heteropolysaccharides:

- Extracellular support – peptidoglycan (bacteria cell envelope),
  extracellular matrix in animal tissues.

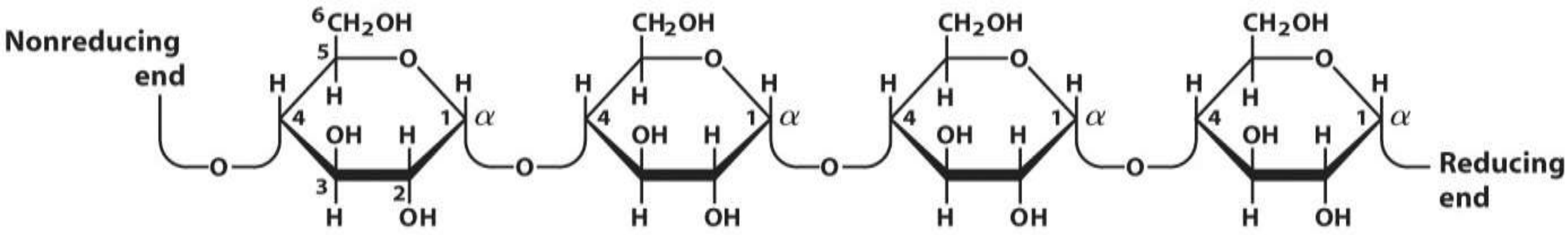





Starch granules

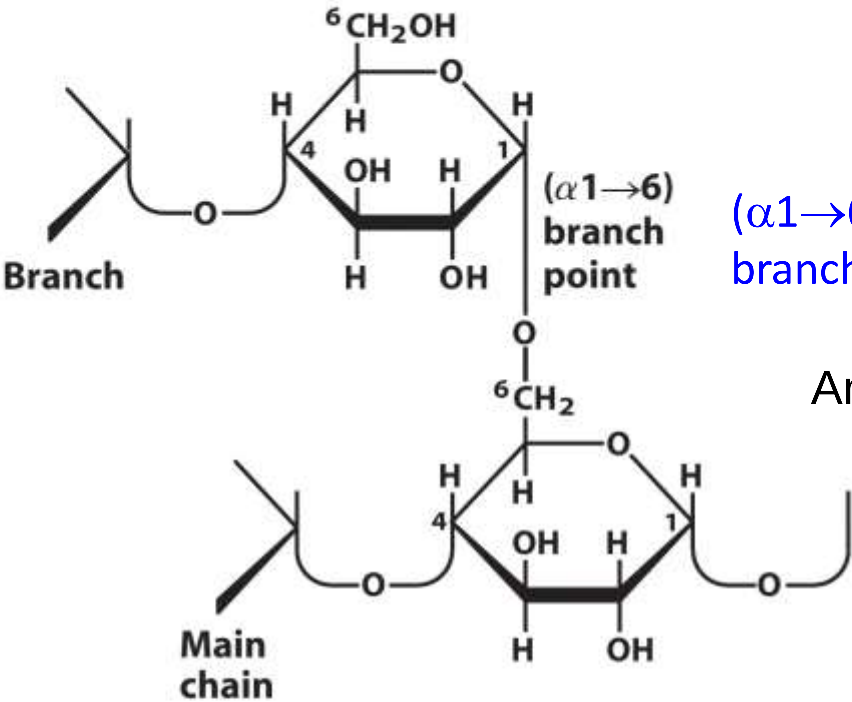

Glycogen granules

① Starch: Amylose (linear, M_r 10^3~10^6 Da)
vs Amylopectin (branched, M_r up to 10^8 Da)



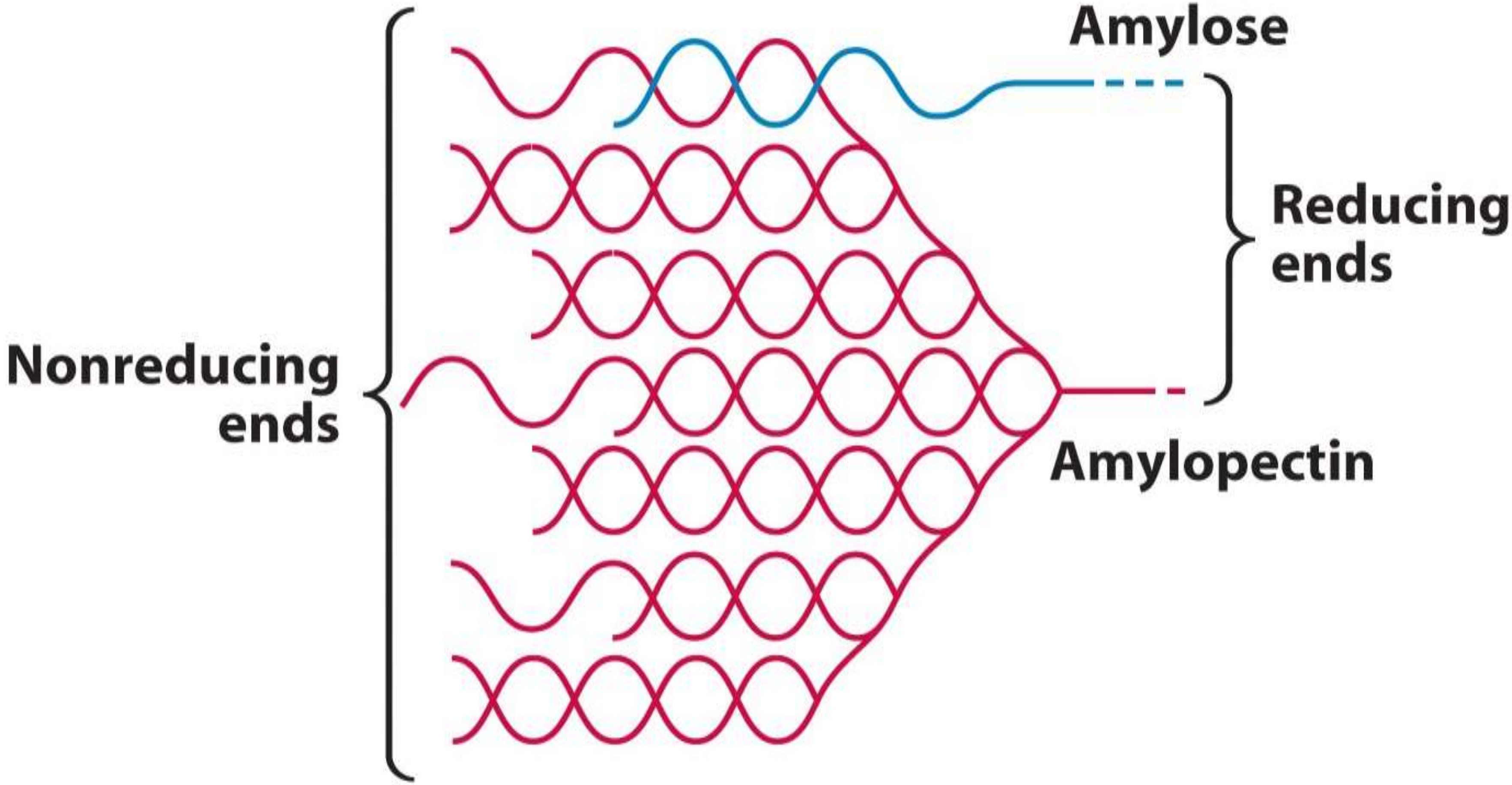
amylose

(α1→4)



(α1→6)
branching

Amylopectin


Amylose
Reducing ends
Nonreducing ends
Amylopectin

② Glycogen –

Storage polysaccharides in animals (liver and skeletal muscle).

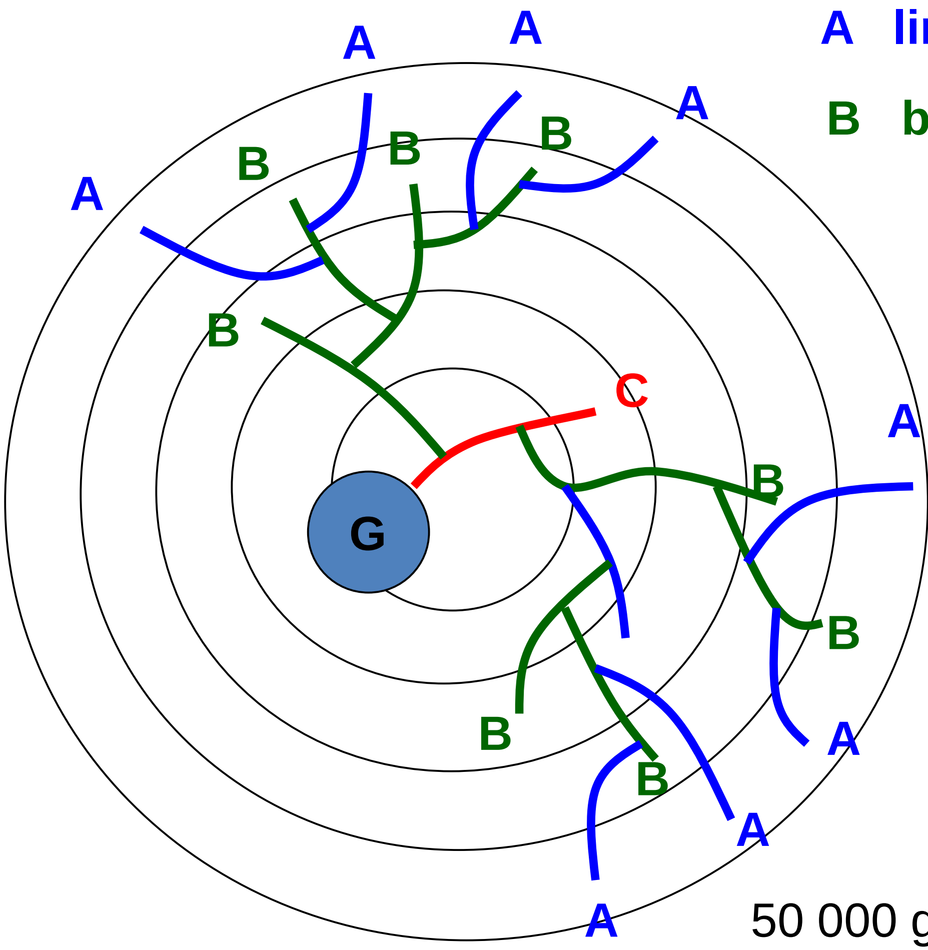
(α1$\rightarrow$4)-linked glucose with (α1-6)-linked branches-

(Like amylopectin)

Extensively branched and compact than starch.

Why branched? Degrading enzymes work on the nonreducing ends. More branches $\rightarrow$ more nonreducing ends $\rightarrow$ faster degradation.
Why polymer? In hepatocytes, [glycogen] = 0.01 μM, but equivalent to 0.4 M glucose. If 0.4 M glucose is stored, $\Rightarrow$ high osmolarity causing cell rupture. Energy costs to import glucose from the blood where [glucose] is only 5 mM.

Glycogen: The Perfect Molecule



A linear

B branched

All chains of same length (11~15 Glc/chain)
2 branching points/B chain
12 layers

Optimized !!
Thank you,
Natural Selection!

50 000 glucose units
2 000 non-reducing ends

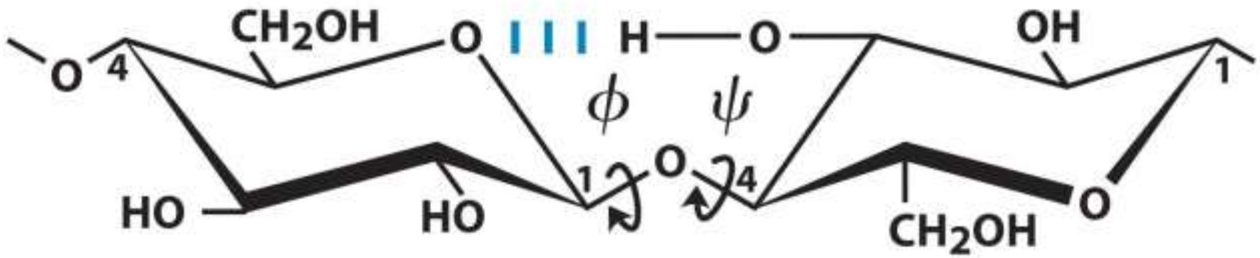
The Pursuit of Perfection by A. Cornish-Bowden

③ Cellulose – plant cell wall, wood, cotton.
Linear, unbranched, ~15,000 Glc units.
(β1$\rightarrow$4) linkage.

Animals do not have cellulase that cleaves the β(1$\rightarrow$4) linkage.

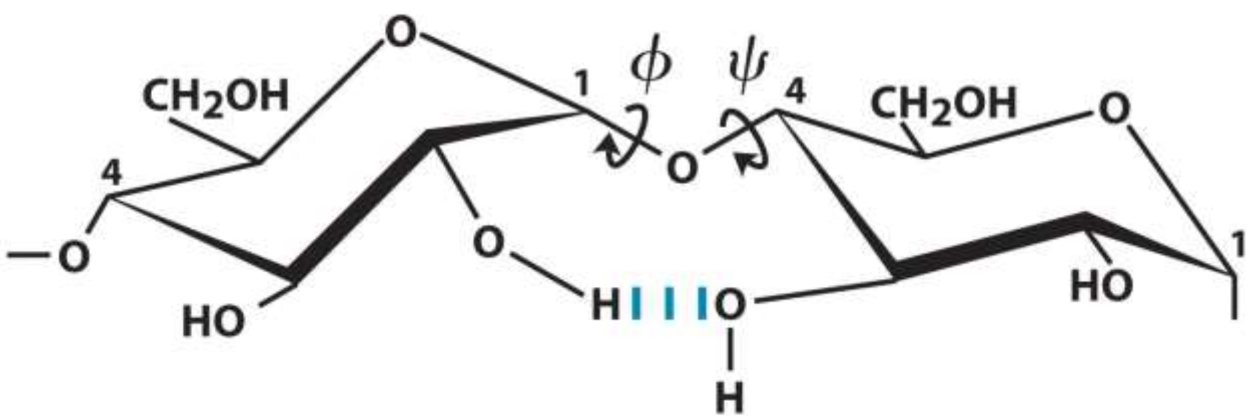
cf) α-amylase in saliva and intestines digests starch and glycogen.

Most abundant polysaccharides in nature.



Cellulose

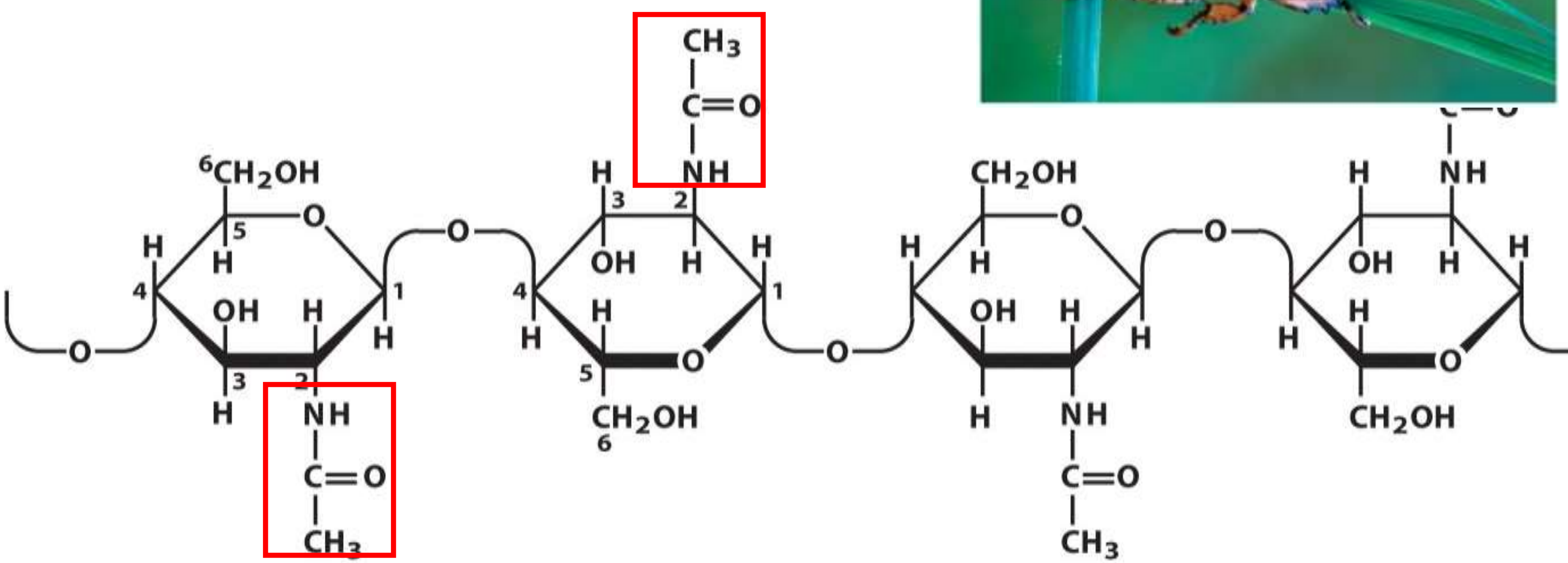
(β1→4)Glc repeats



Amylose

(α1→4)Glc repeats

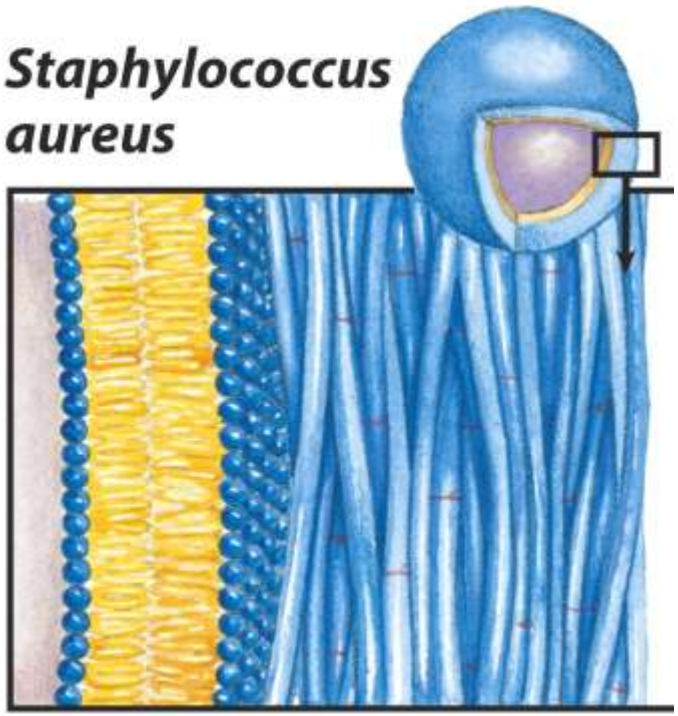
④ Chitin – exoskeleton of anthropods.
Linear, unbranched homopolymer.
N-acetylglucosamine units in (β1→4) linkage.
Only difference from cellulose is the acetylated amino group instead of –OH at C-2.

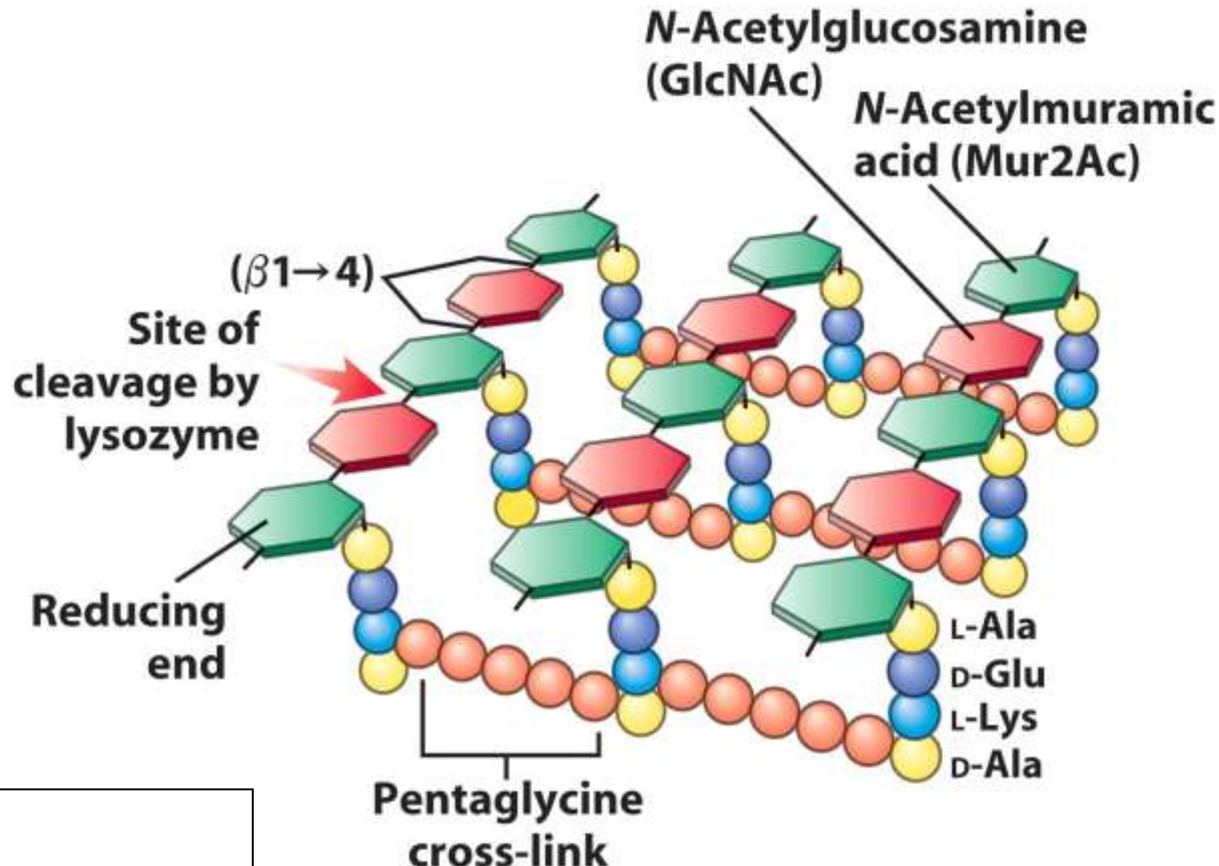


⑤ Bacterial cell walls

Alternating (β1→4) linked GlcNAc and Mur2Ac residues.

Lysozyme in tears and saliva cleaves the linkage.

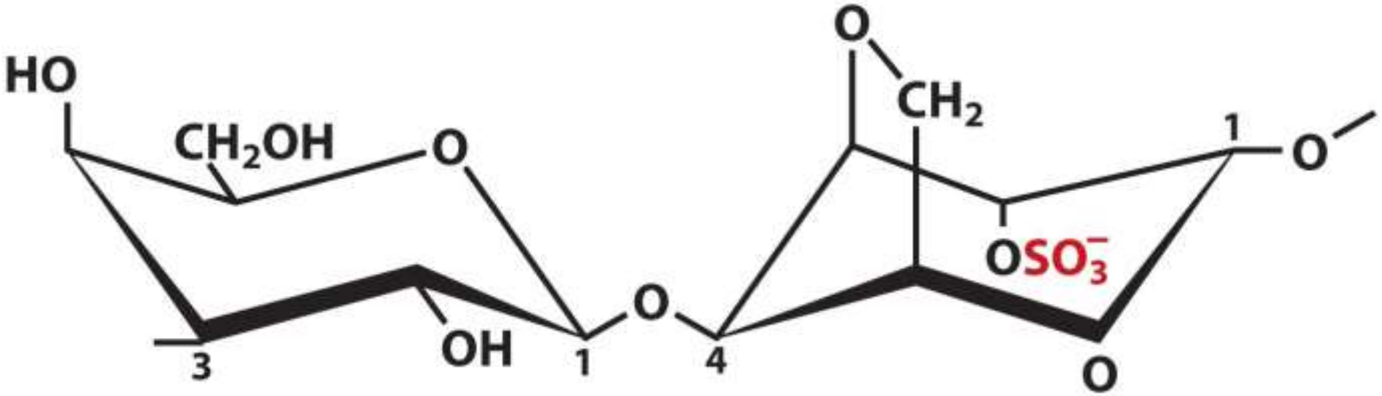




Penicillin and β-lactamase

⑥ Agar and Agarose in seaweeds

Agarose gel electrophoresis
& nucleic acids separation



Agarose

3)D-Gal(β1→4)3,6-anhydro-L-Gal2S(α1 repeats

TABLE 7–2 Structures and Roles of Some Polysaccharides

Polymer	*Type**	*Repeating unit*†	*Size (number of monosaccharide units)*	*Roles/significance*
Starch				Energy storage: in plants
Amylose	Homo-	(α1→4)Glc, linear	50–5,000	
Amylopectin	Homo-	(α1→4)Glc, with (α1→6)Glc branches every 24–30 residues	Up to 10^6	
Glycogen	Homo-	(α1→4)Glc, with (α1→6)Glc branches every 8–12 residues	Up to 50,000	Energy storage: in bacteria and animal cells
Cellulose	Homo-	(β1→4)Glc	Up to 15,000	Structural: in plants, gives rigidity and strength to cell walls
Chitin	Homo-	(β1→4)GlcNAc	Very large	Structural: in insects, spiders, crustaceans, gives rigidity and strength to exoskeletons
Dextran	Homo-	(α1→6)Glc, with (α1→3) branches	Wide range	Structural: in bacteria, extracellular adhesive
Peptidoglycan	Hetero-; peptides attached	4)Mur2Ac(β1→4) GlcNAc(β1	Very large	Structural: in bacteria, gives rigidity and strength to cell envelope
Agarose	Hetero-	3)D-Gal(β1→4)3,6-anhydro-L-Gal(α1	1,000	Structural: in algae, cell wall material
Hyaluronate (a glycosaminoglycan)	Hetero-; acidic	4)GlcA(β1→3) GlcNAc(β1	Up to 100,000	Structural: in vertebrates, extracellular matrix of skin and connective tissue; viscosity and lubrication in joints

*Each polymer is classified as a homopolysaccharide (homo-) or heteropolysaccharide (hetero-).

†The abbreviated names for the peptidoglycan, agarose, and hyaluronate repeating units indicate that the polymer contains repeats of this disaccharide unit. For example, in peptidoglycan, the GlcNAc of one disaccharide unit is (β1→4)-linked to the first residue of the next disaccharide unit.

[6] Glycoconjugates

Glycoconjugate: Biologically active molecule made from a carbohydrate covalently linked to a protein or lipid (glycoprotein or glycolipid) -- found at cell surfaces

Both glycoproteins and glycolipids are important in:

Cell-cell recognition and adhesion,

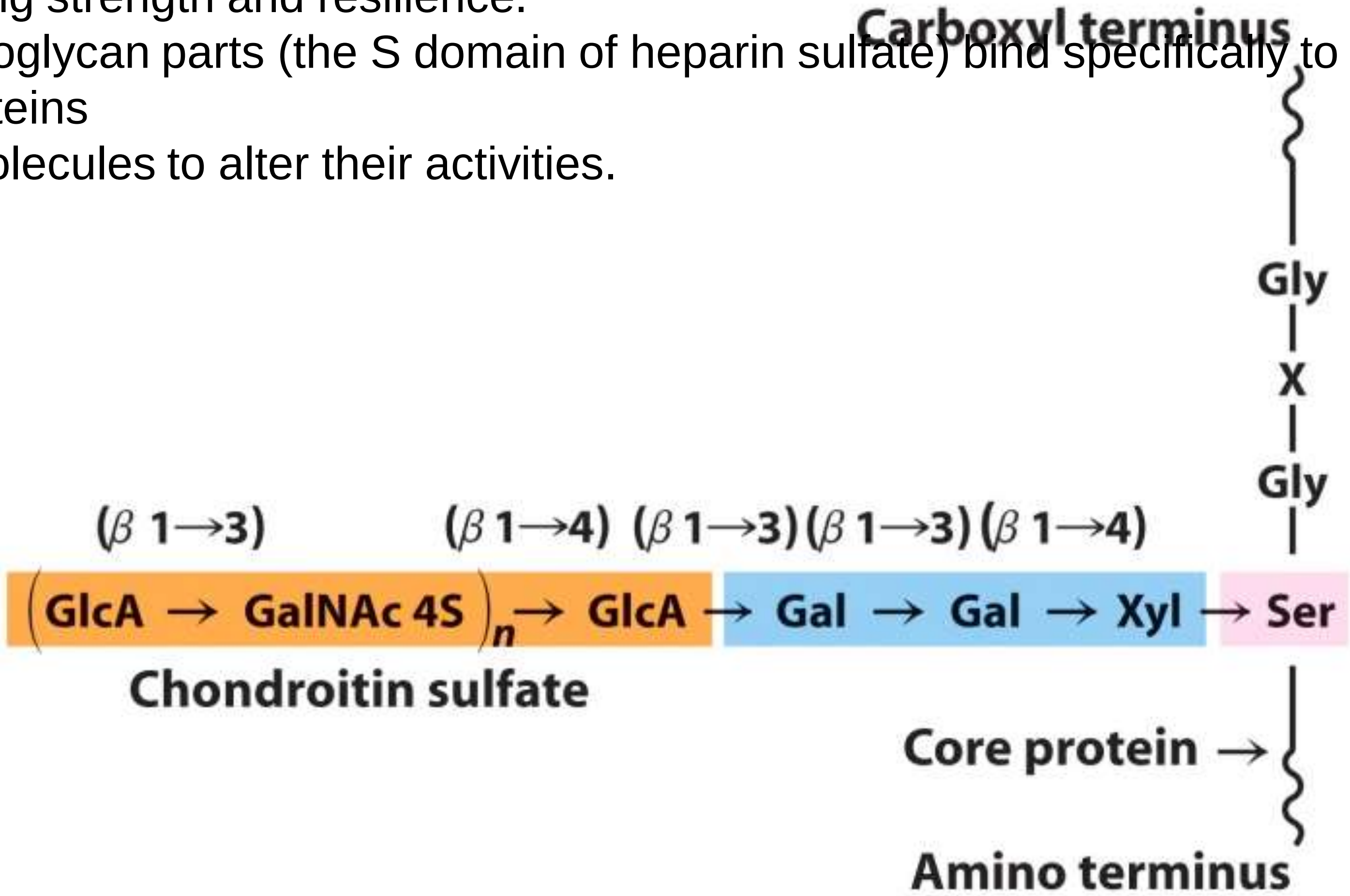
Cell migration during development

Blood clotting, The immune response, Wound healing, etc.

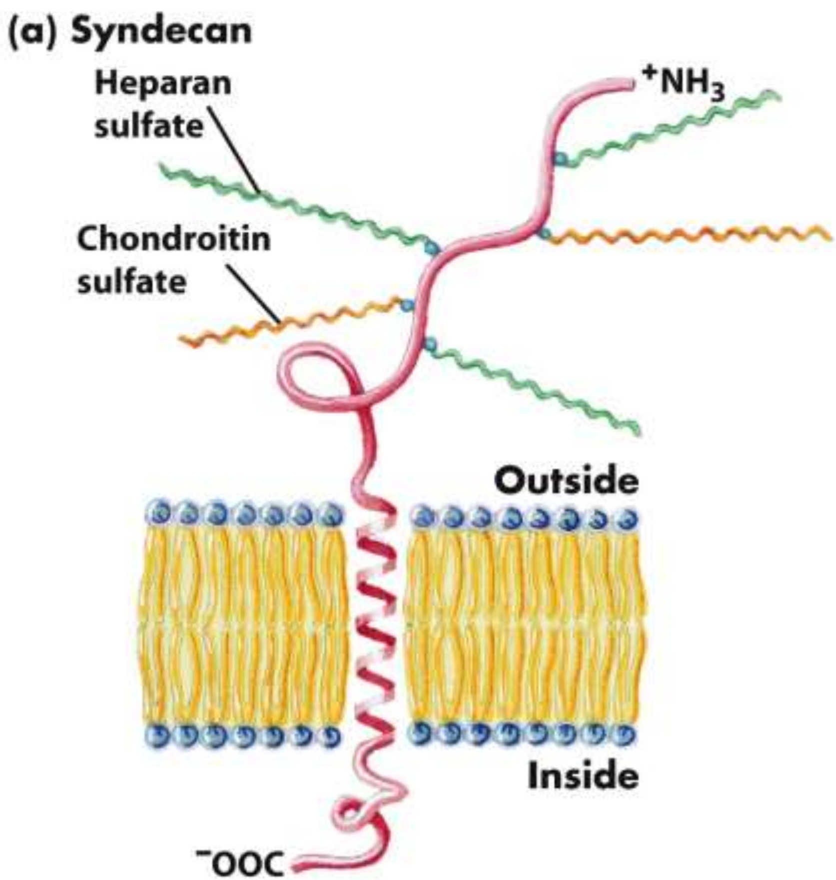
In all these cases, the carbohydrate parts serve as the information carrier by providing **specific, high affinity recognition sites.**

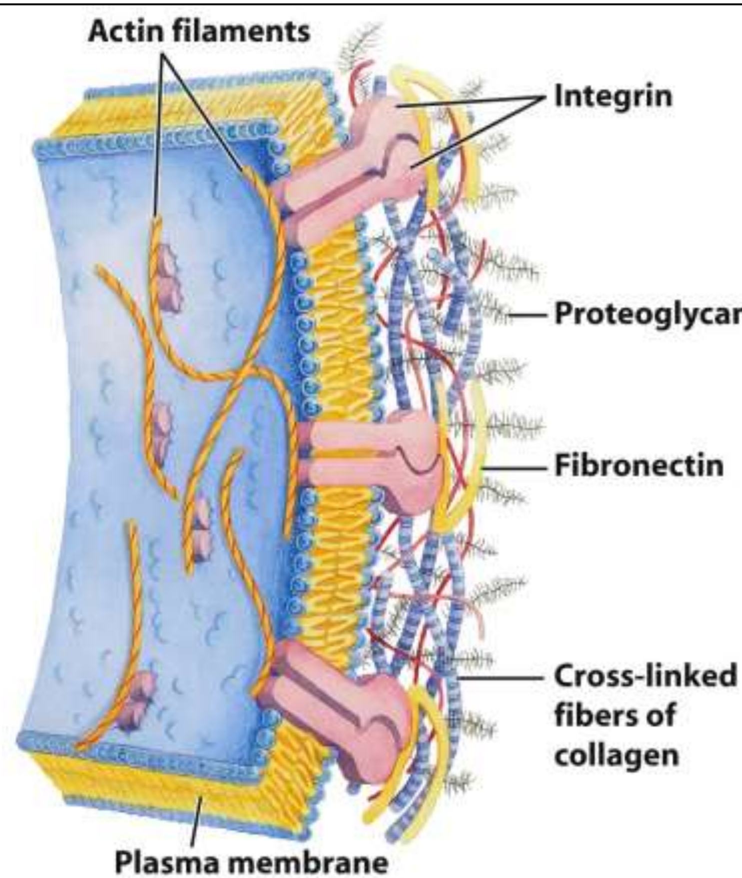
(1) Proteoglycans

- At the cell surface and extracellular matrix.
- “Core protein” w/ covalently attached glycoaminoglycan(s) *via* a trisaccharide bridge.
- Major components of connective tissue, providing strength and resilience.
- The glycoaminoglycan parts (the S domain of heparin sulfate) bind specifically to extracellular proteins and signaling molecules to alter their activities.



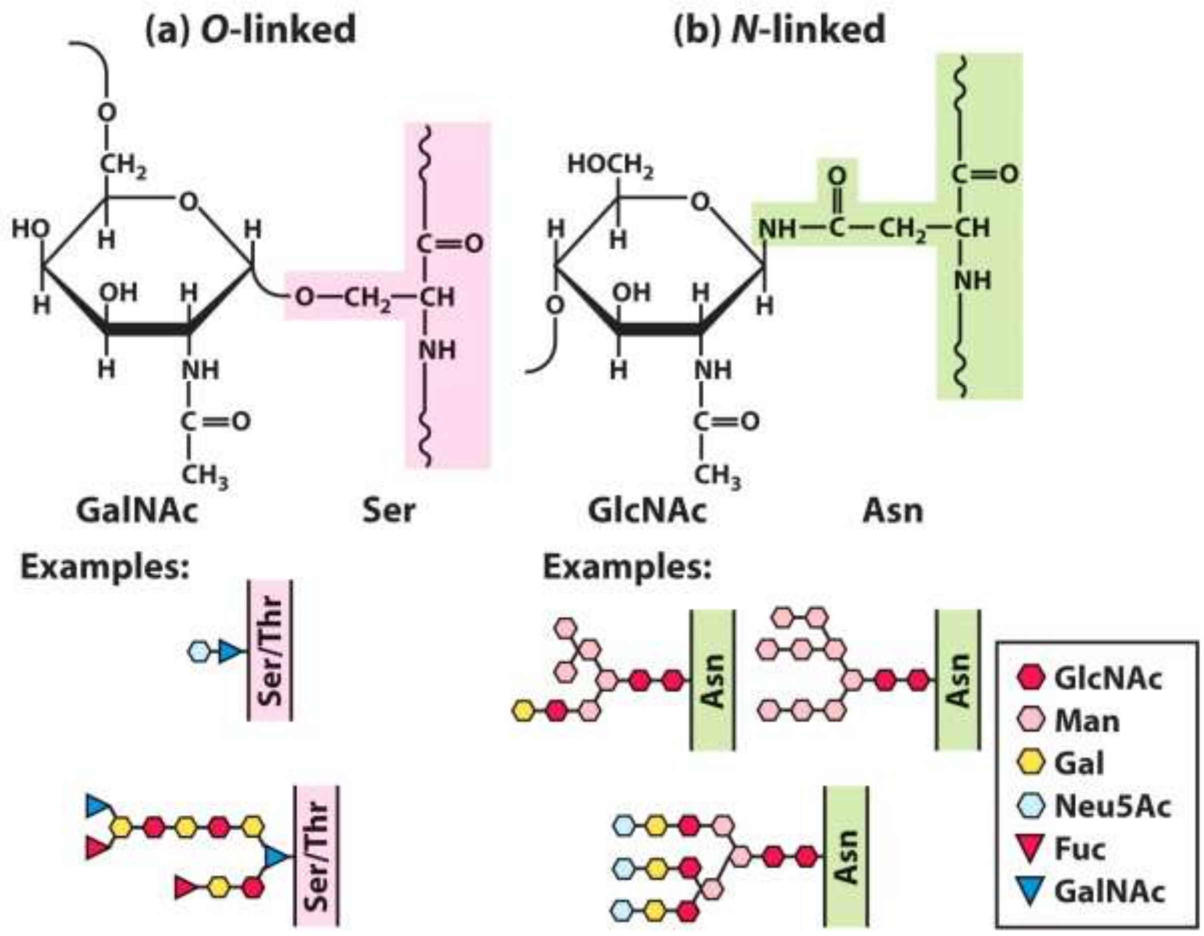
Interaction between cells and the extracellular matrix is mediated by a membrane protein (integrin) and by an extracellular protein (fibronectin). Proteoglycan interacts with collagen, forming a meshwork to give the whole matrix strength. These multi-pronged interactions also guide cell migration in development (and during cancer metastasis).





(2) Glycoproteins

- (Smaller and diverse) carbohydrate (1~70% by mass)-protein conjugates.
- Carbohydrate forms a glycosidic linkage with the – OH of Ser or Thr through its anomeric end (*O*-linked), or an *N*-glycosyl link through the amide of Asn (*N*-linked).



- Glycoproteins are found on the outer surface of plasma membrane, in the extracellular matrix, in the blood, and in specific organelles, Golgi complexes, lysosomes, and secretory granules.

• When are proteins glycosylated? - Following translation in the lumen of the ER – further processing in the Golgi.
• The sugar label can be used to direct proteins to different cell areas (i.e. cell membrane)

• Why glycoproteins? – The biological advantages of adding oligosaccharides to proteins:
  - Increase polarity and solubility of the proteins.
  - May influence the folding process.
  - Protect from proteolytic enzymes.
  - Responsible for specific biological activities:
    Intracellular targeting of proteins
    Cell-cell interactions, Tissue development
    Extracellular signaling

(3) Carbohydrates as Informational Molecules (the Sugar Code).

Two different hexoses can combine in many different ways!
What a vast number of different structures for recognition purposes.

$> 10^{15}$ hexa-oligosaccharides with 20 different monosaccharide.
$> 10^{7}$ ($= 20^{6}$) hexapeptides with 20 amino acids.
~4000 ($= 4^{6}$) hexanucleotides with 4 nucleotide subunits.

The sugar part of glycoconjugates presents a unique code readable by the interacting proteins.

(4) Metabolism

Polysaccharides are broken down to simple sugars
(i.e. glucose in the case of the storage molecule glycogen)
in the intestine or individual cells …

Glucose $\rightarrow$ CO_2 + H_2O yields 36 ATP!!!

ATP is an energy storage molecule found in all cells.
Sugars are the most easily mobilized storage unit as a result of the way they are packaged.

(5) Glycolipids and Blood Group

- Blood group antigens are immunochemical markers made of glycolipids on the surface of red blood cells.
- Those with type A cells have type A antigens on their cell surfaces, B have B antigens, AB have both, O carry the O antigen

- The only difference appears at the terminal sugar
- Blood group O is considered the universal donor.
– this is why!

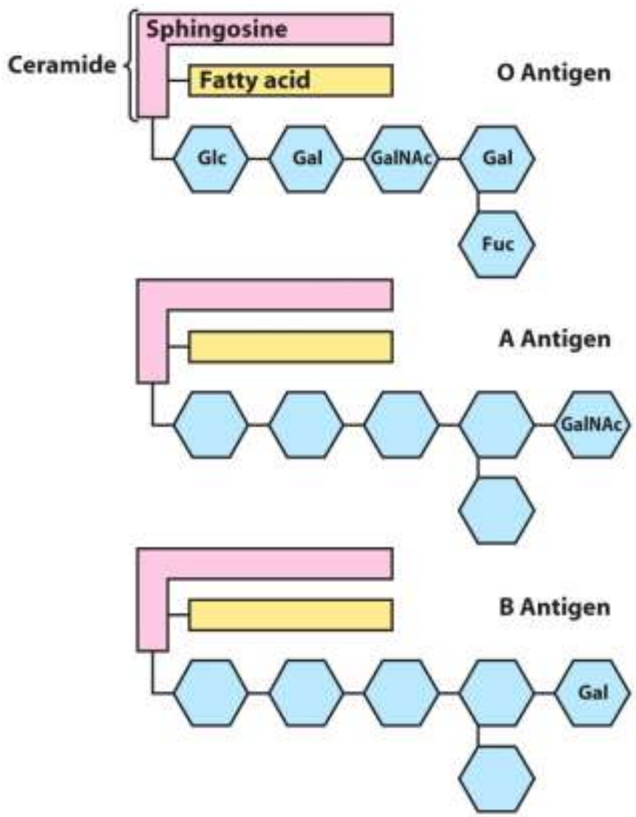


Fig 10-14