Lehninger

SIXTH EDITION

Principles of Biochemistry

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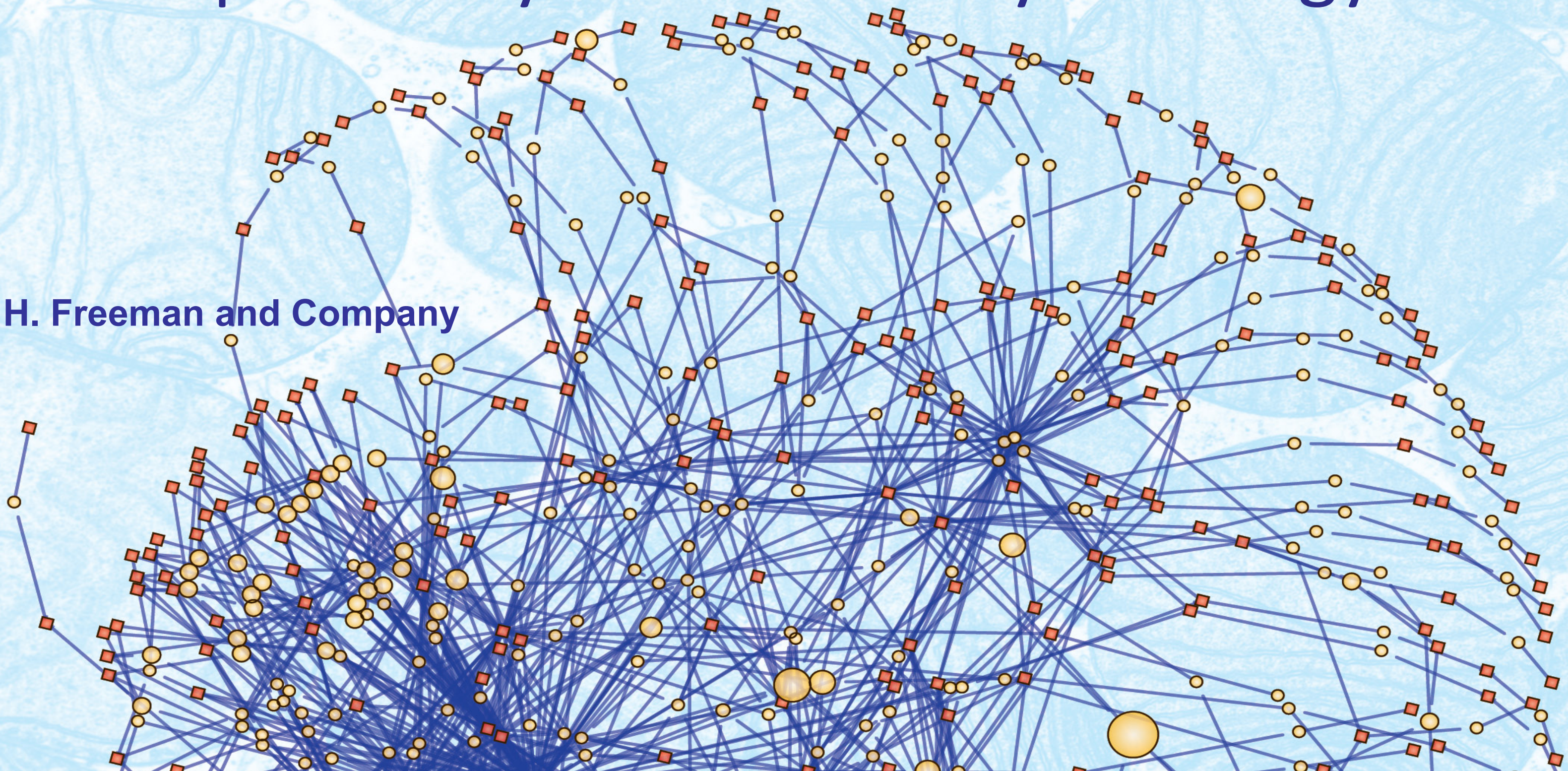
7 | Carbohydrates and Glycobiology



Carbohydrates

- Named so because many have formula $C_n(H_2O)_n$
- Produced from CO_2 and H_2O via photosynthesis in plants
- Range from as small as glyceraldehyde (M_w = 90 g/mol) to as large as amylopectin (M_w = 200,000,000 g/mol)
- Fulfill a variety of functions including:
  - energy source and energy storage
  - structural component of cell walls and exoskeletons
  - informational molecules in cell-cell signaling
- Can be covalently linked with proteins to form glycoproteins and proteoglycans

Carbohydrates

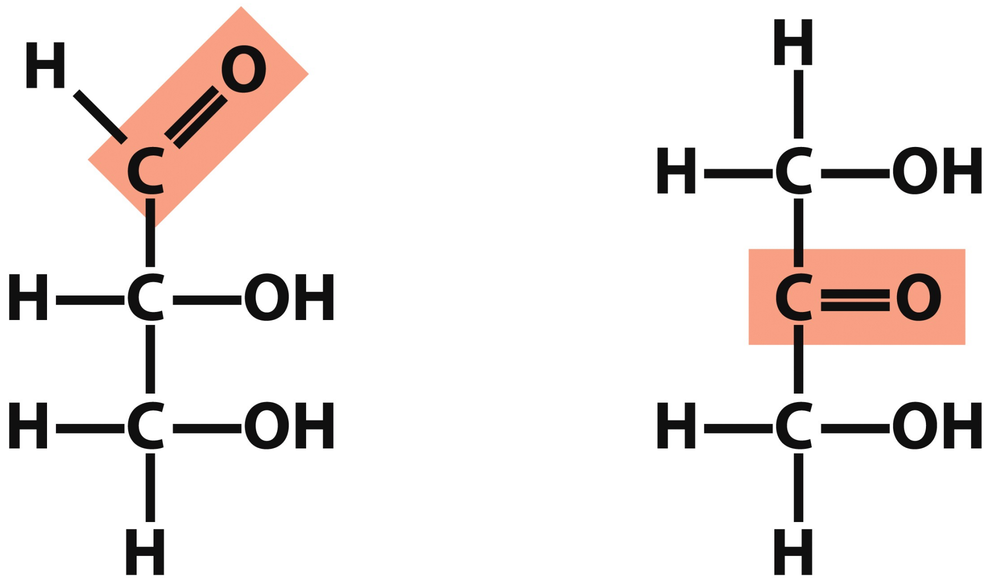
- **Monosaccharides** (simple sugars) – one polyhydroxy aldehyde or ketone unit (glucose)
- **Disaccharides** – two monosaccharide units joined together by a glycosidic linkage (sucrose)
- **Oligosaccharides** – few monosaccharide units joined together (in cells, most oligosaccharides are joined to nonsugar molecule)
- **Polysaccharides** – sugar polymers consisting of >20 monosaccharide units

Monosaccharide Carbon backbone

- 3 C → triose
- 4 C → tetrose
- 5 C → pentose
- 6 C → hexose
- 7 C → heptose

Aldoses and Ketoses

- An aldose contains an aldehyde functional group
- A ketose contains a ketone functional group



Glyceraldehyde, an aldotriose | **Dihydroxyacetone, a ketotriose**

Figure 7-1a
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Stereoisomers

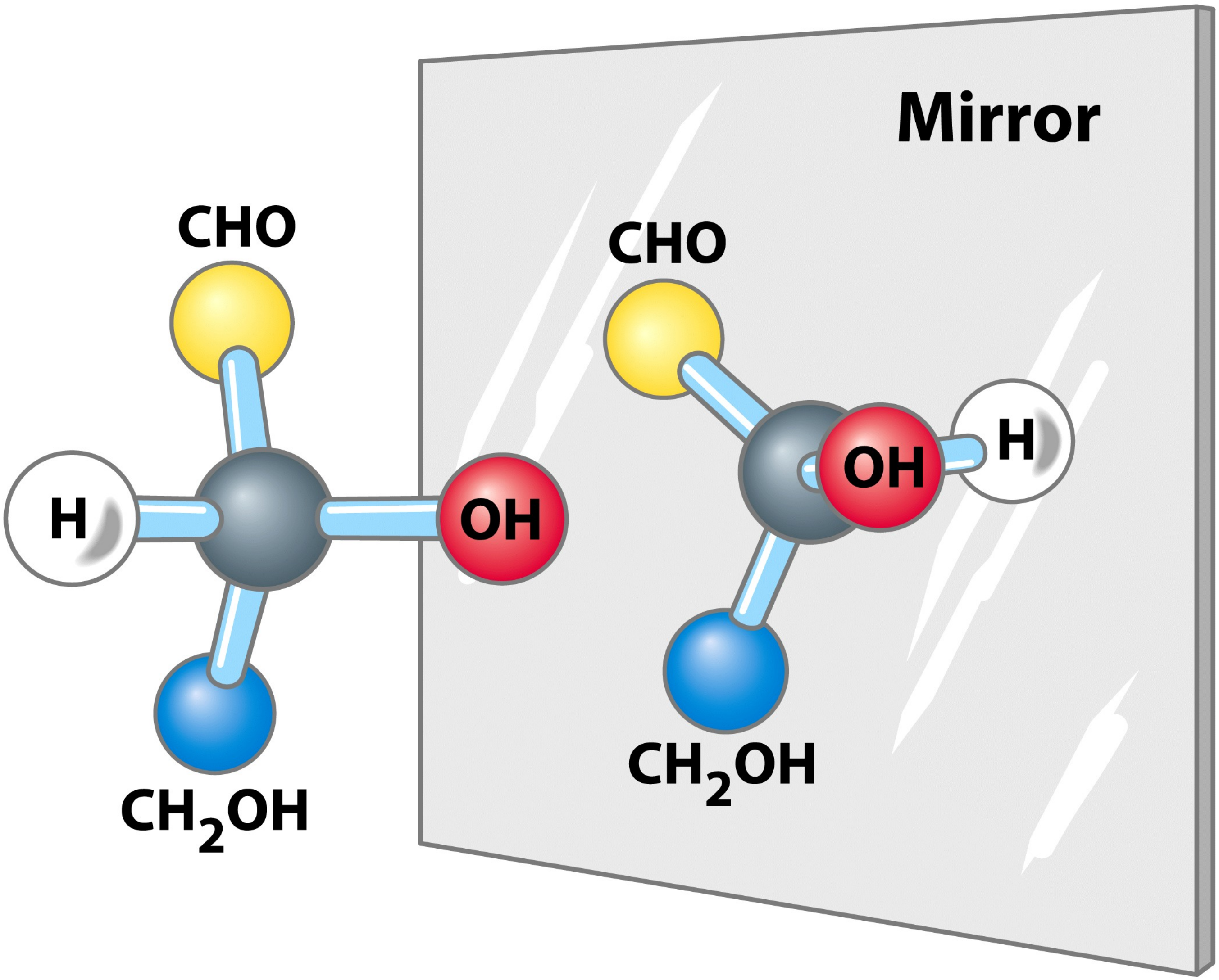
- **All monosaccharides** (except dihydroxyacetone) are chiral compounds, with **at least** one chiral carbon

- A molecule with n chiral centers can have 2^n stereoisomers

- E.g. glyceraldehyde has $2^1 = 2$
  aldohexoses have $2^4 = 16$ stereoisomers

Enantiomers

- **Enantiomers**
  - Stereoisomers that are nonsuperimposable mirror images
- In sugars that contain many chiral centers, only the one that is most distant from the carbonyl carbon is designated as D (right) or L (left)
- D and L isomers of a sugar are enantiomers
  - For example, L and D glucose have the same water solubility
- Most hexoses in living organisms are D stereoisomers
- Some simple sugars occur in the L-form, such as L-arabinose



Ball-and-stick models

Figure 7-2 part 1
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Drawing Monosaccharides

- Chiral compounds can be drawn using **perspective formulas**
- However, chiral carbohydrates are usually represented by **Fischer projections**
- Horizontal bonds are pointing toward you; vertical bonds are projecting away from you

D-Glyceraldehyde L-Glyceraldehyde

Perspective formulas

D-Glyceraldehyde L-Glyceraldehyde

Fischer projection formulas

Diastereomers

- **Diastereomers:** stereoisomers that are not mirror images
- Diastereomers have different physical properties
  - For example, water solubilities of threose and erythrose are different

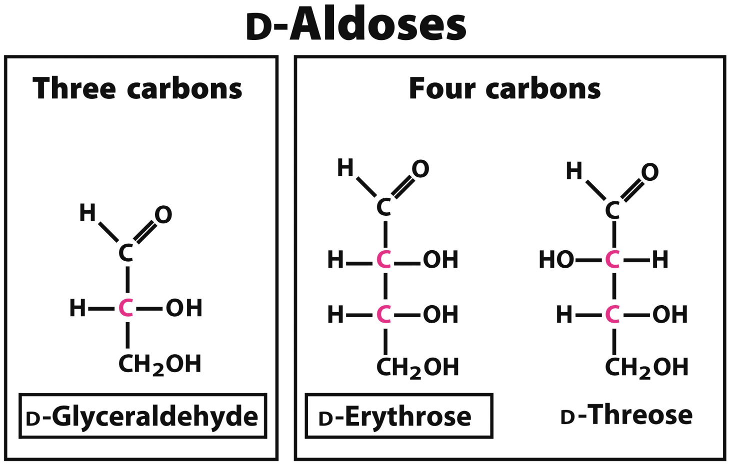

Figure 7-3a part 1
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Epimers

- Epimers are two sugars that differ only in the configuration around one carbon atom

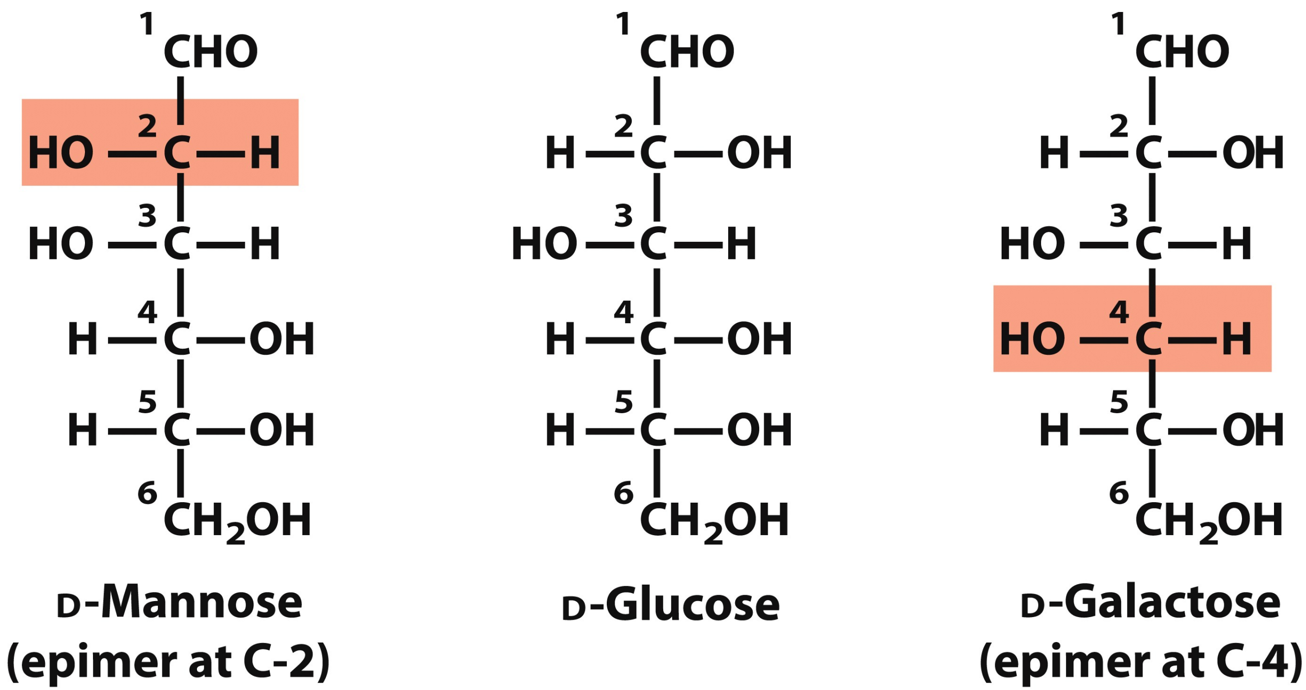

Figure 7-4
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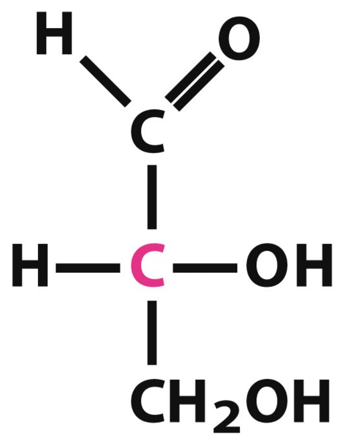
Structures to Know

- Glyceraldehyde & dihydroxyacetone are the standard three-carbon sugars
- Ribose is the standard five-carbon sugar
- Glucose is the standard six-carbon sugar
- Galactose is an epimer of glucose
- Mannose is an epimer of glucose
- Fructose is the ketose form of glucose

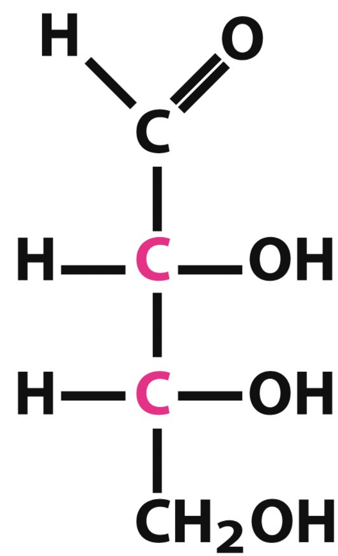
D-Aldoses

Three carbons

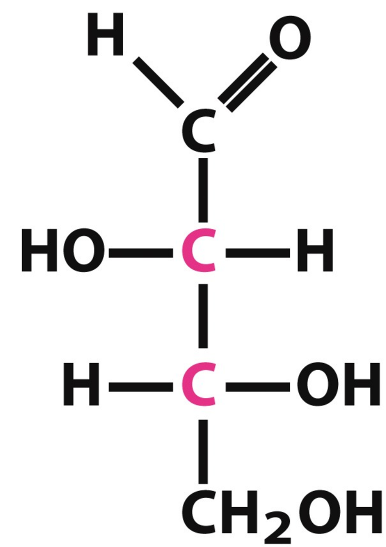


D-Glyceraldehyde

Four carbons



D-Erythrose



D-Threose

Figure 7-3a part 1
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D-Aldoses

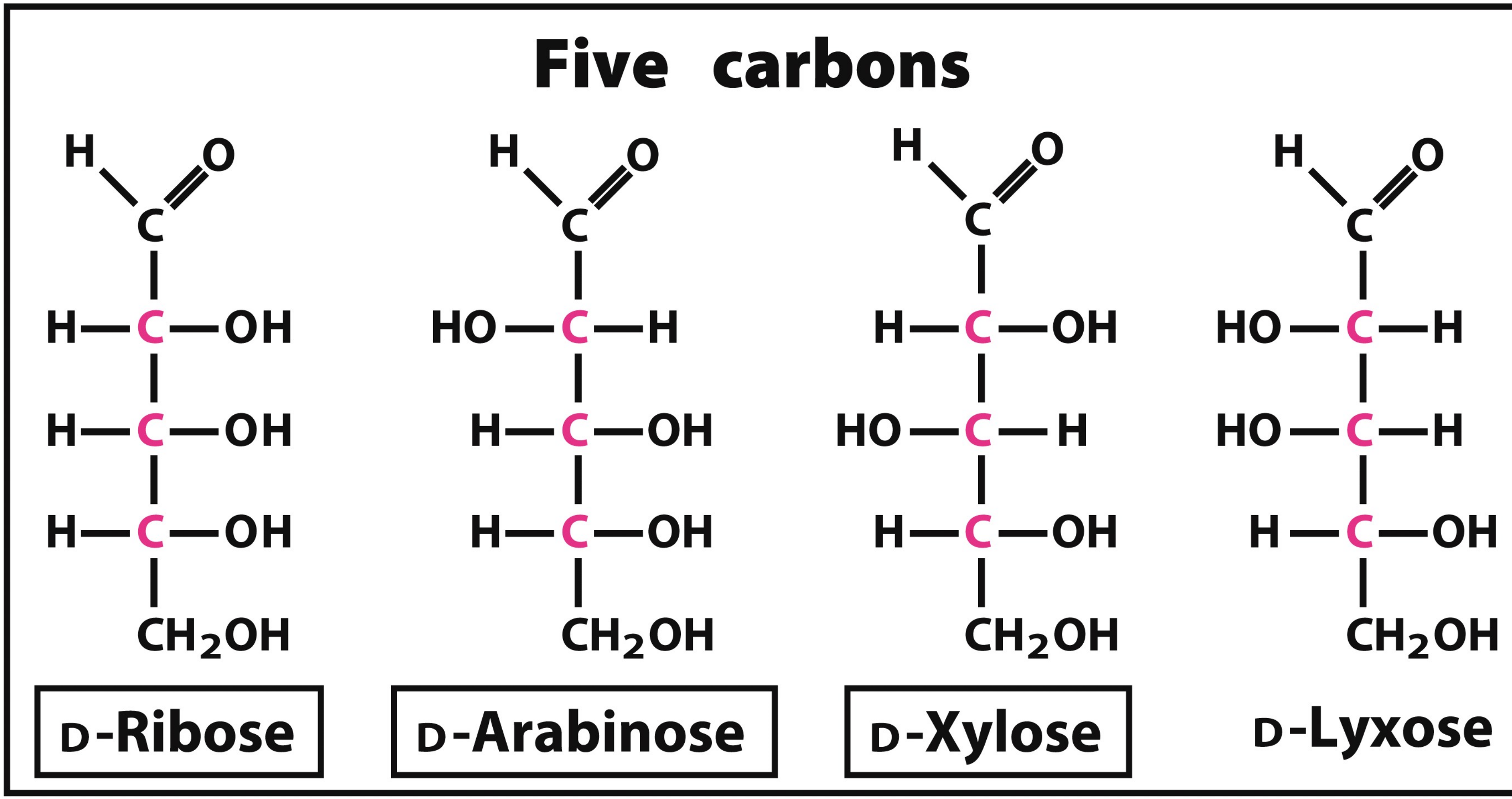

Figure 7-3a part 2
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D-Aldoses

Six carbons

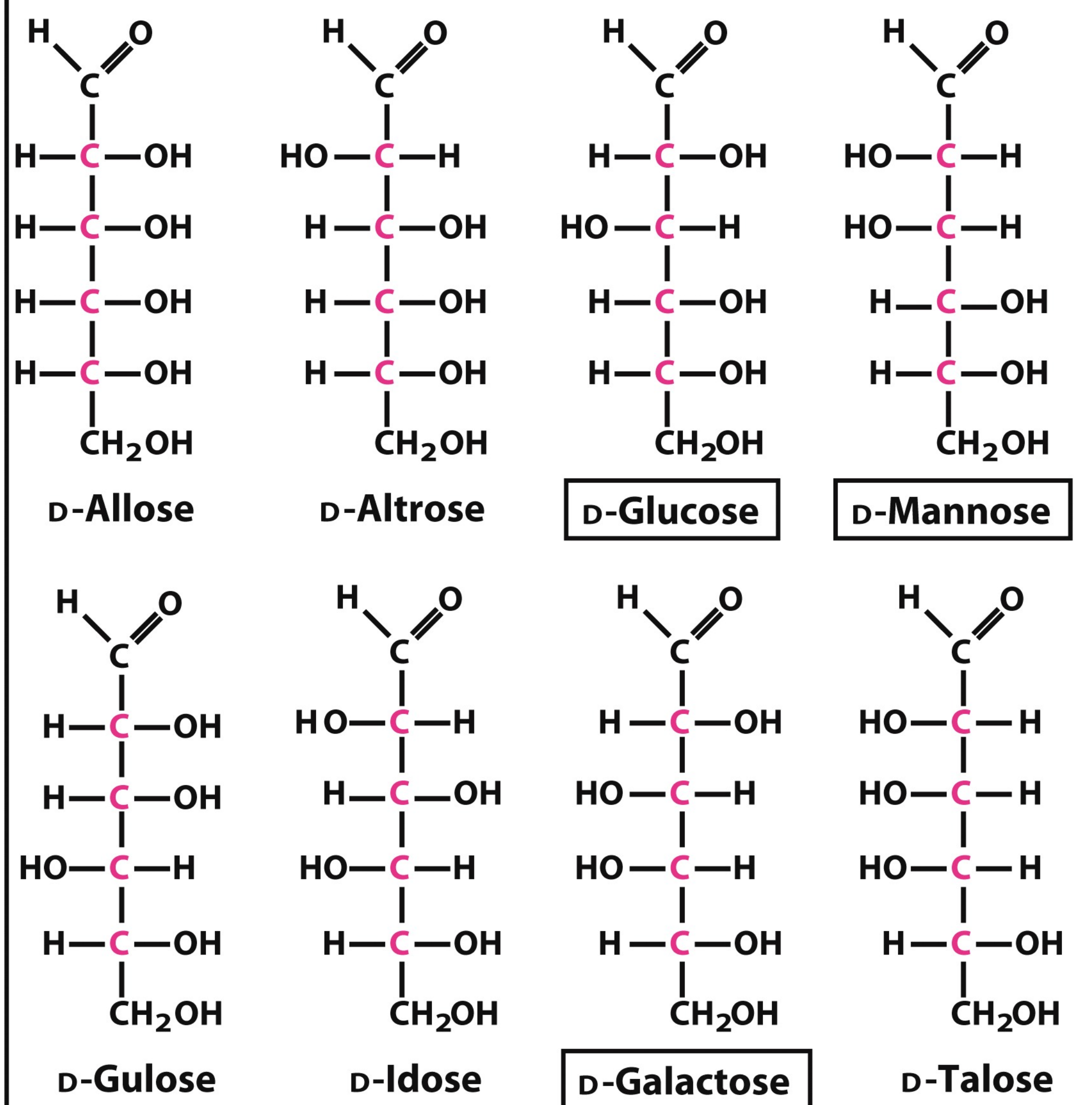

Figure 7-3a part 3

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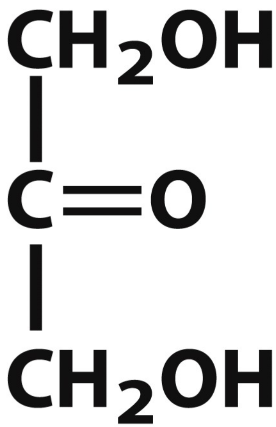
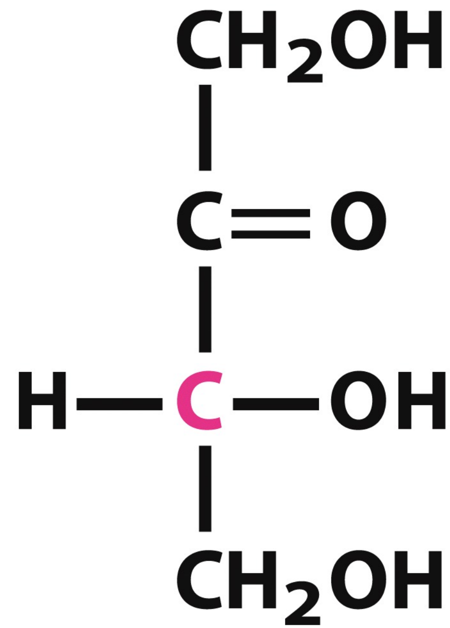
D-Ketoses

Three carbons



Dihydroxyacetone

Four carbons



D-Erythrulose

Figure 7-3b part 1
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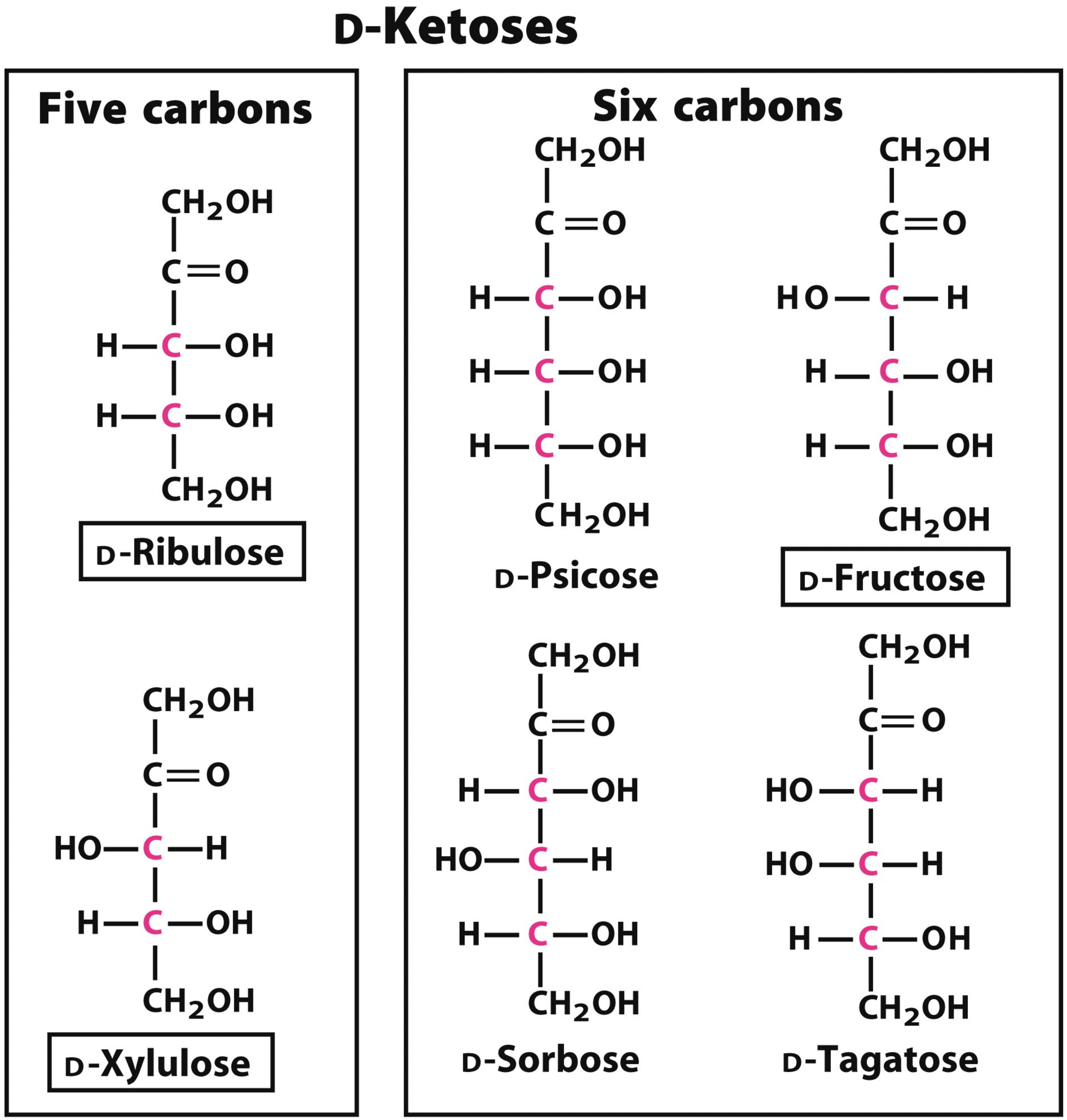

Figure 7-3b part 2
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Common Monosaccharides Have Cyclic Structures

- In solution, monosaccharides with 4 or more carbons form cyclic compounds (ring structures)
- Carbonyl C is attacked by the hydroxyl O forming a covalent bond

Hemiacetals and Hemiketals

- Aldehyde and ketone carbons are electrophilic
- Alcohol oxygen atom is nucleophilic
- When aldehydes are attacked by alcohols, hemiacetals form
- When ketones are attacked by alcohols, hemiketals form

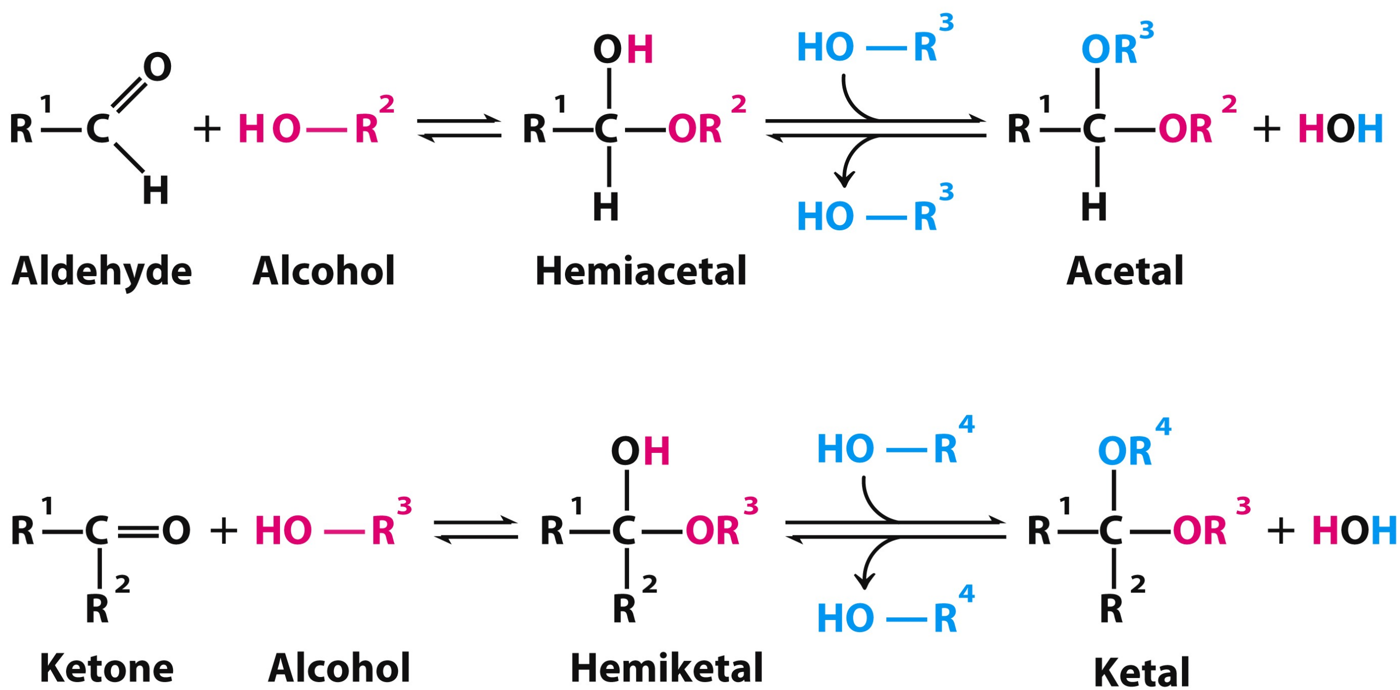

Figure 7-5
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When the second alcohol is part of another sugar molecule, the bond produced is a ***glycosidic bond****.*

Cyclization of Monosaccharides

- Pentoses and hexoses readily undergo intramolecular ring formation
- The former carbonyl carbon becomes a *new chiral center*, called the anomeric carbon
- The former carbonyl oxygen becomes a hydroxyl group; the position of this group determines if the anomer is α or β
- If the *hydroxyl group* is on the *opposite side* (trans) of the ring as the CH_2OH moiety the configuration is α
- In the *hydroxyl group* is on the *same side* (cis) of the ring as the CH_2OH moiety, the configuration is β

Mutarotation – the interconversion of α and β anomers.

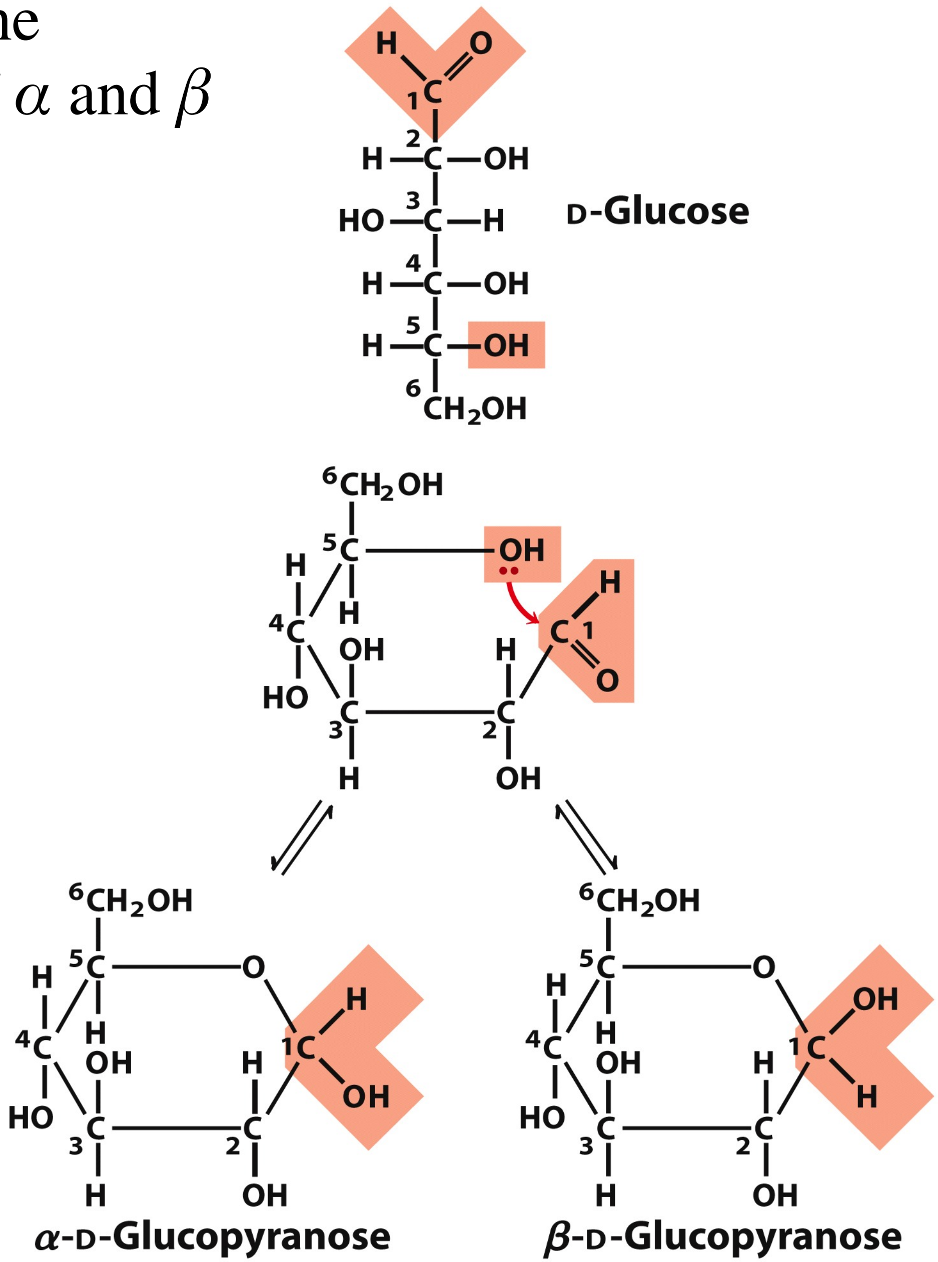

Figure 7-6
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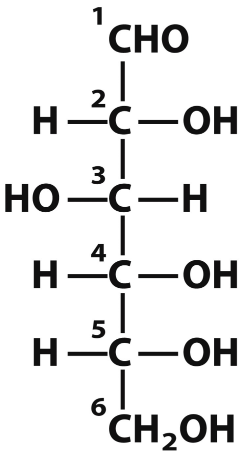
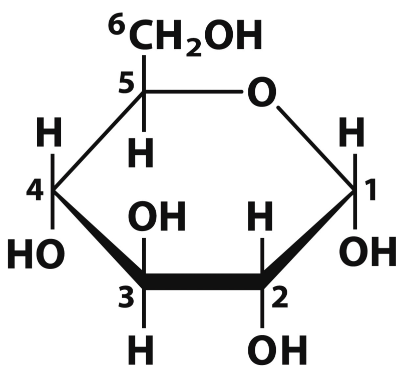
Pyranoses and Furanoses

- Six-membered oxygen-containing rings are called pyranoses
- Five-membered oxygen-containing rings are called furanoses
- The anomeric carbon is usually drawn on the right side
- Cyclic sugar structures are more accurately represented in **Haworth perspective formulas**



D-Glucose
Fischer projection



α-D-Glucopyranose
Haworth perspective

Unnumbered 7 p247
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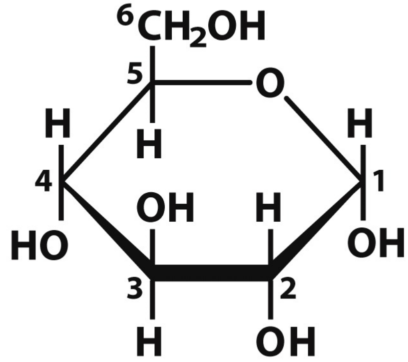
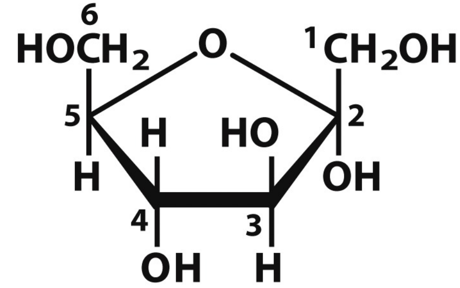
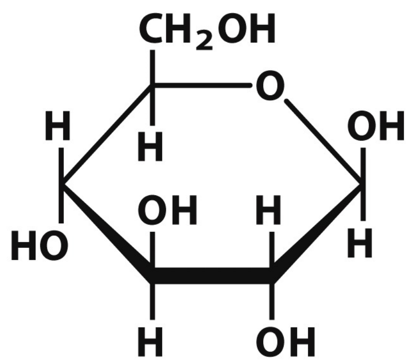


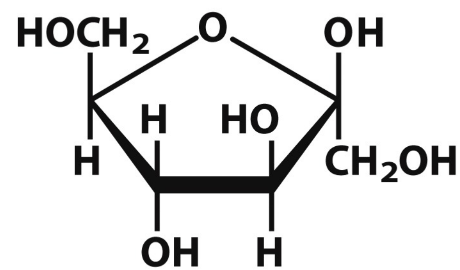
α-D-Glucopyranose



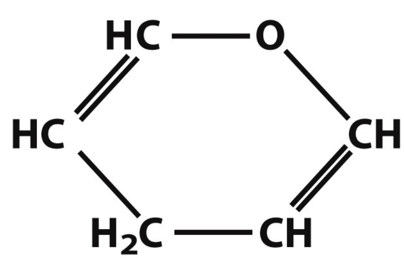
α-D-Fructofuranose



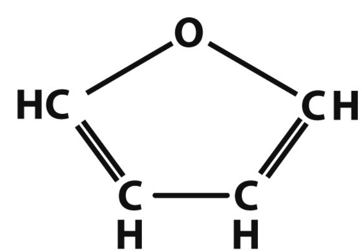
β-D-Glucopyranose



β-D-Fructofuranose



Pyran



Furan

Figure 7-7
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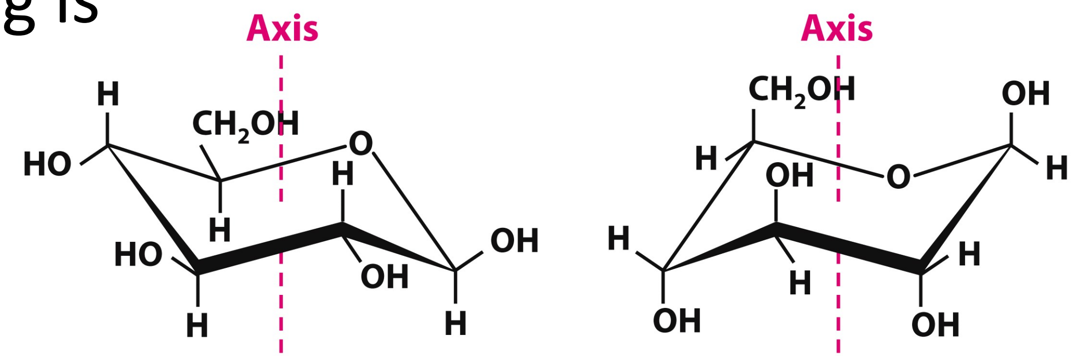
Converting linear to cyclic structures

- For any linear hexose:

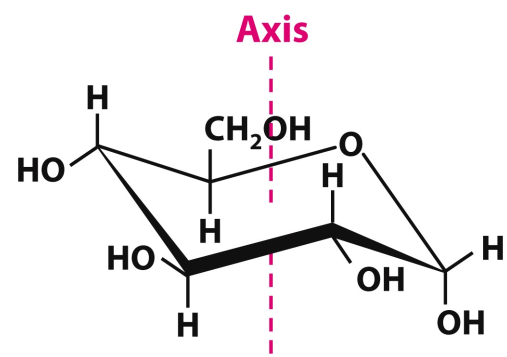
1. Draw 6-membered ring (O at the upper right)
2. Number C's clockwise (start with anomeric)
3. Insert the –OH
   a. if –OH is on the **right**, draw it pointing **down**
   b. if –OH is on the **left**, draw it pointing **up**
4. Insert the terminal $-CH_2OH$
   a. if the sugar is the **D-isomer**, draw it **upwards**
   b. if it is the **L-isomer**, draw it **downwards**
5. Draw the –OH on the anomeric C
   a. if it faces the same side as the $-CH_2OH$, it's β
   b. if it faces the opposite side, it's α

The ring is not planar

- In solution pyranose ring is not planar but it can assume two chair conformations
- Boat conformation is possible but very rare
- The two chair conformations are not readily interconvertible (one conformer is more stable than the other)



Two possible chair forms of β-D-glucopyranose
(a)



α-D-Glucopyranose
(b)

Figure 7-8
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Chain-Ring Equilibrium and Reducing Sugars

- The ring forms exist in equilibrium with the open-chain forms
- Aldehyde can reduce Cu^{2+} to Cu^{+} (Fehling's test)
- Aldehyde can reduce Ag^{+} to Ag^{0} (Tollens' test)
- Allows detection of reducing sugars, such as glucose (by measuring the amount of oxidizing agent reduced by a sugar solution, the sugar concentration can be estimated)

The cuprous ion (Cu^+) produced forms a red cuprous oxide precipitate.

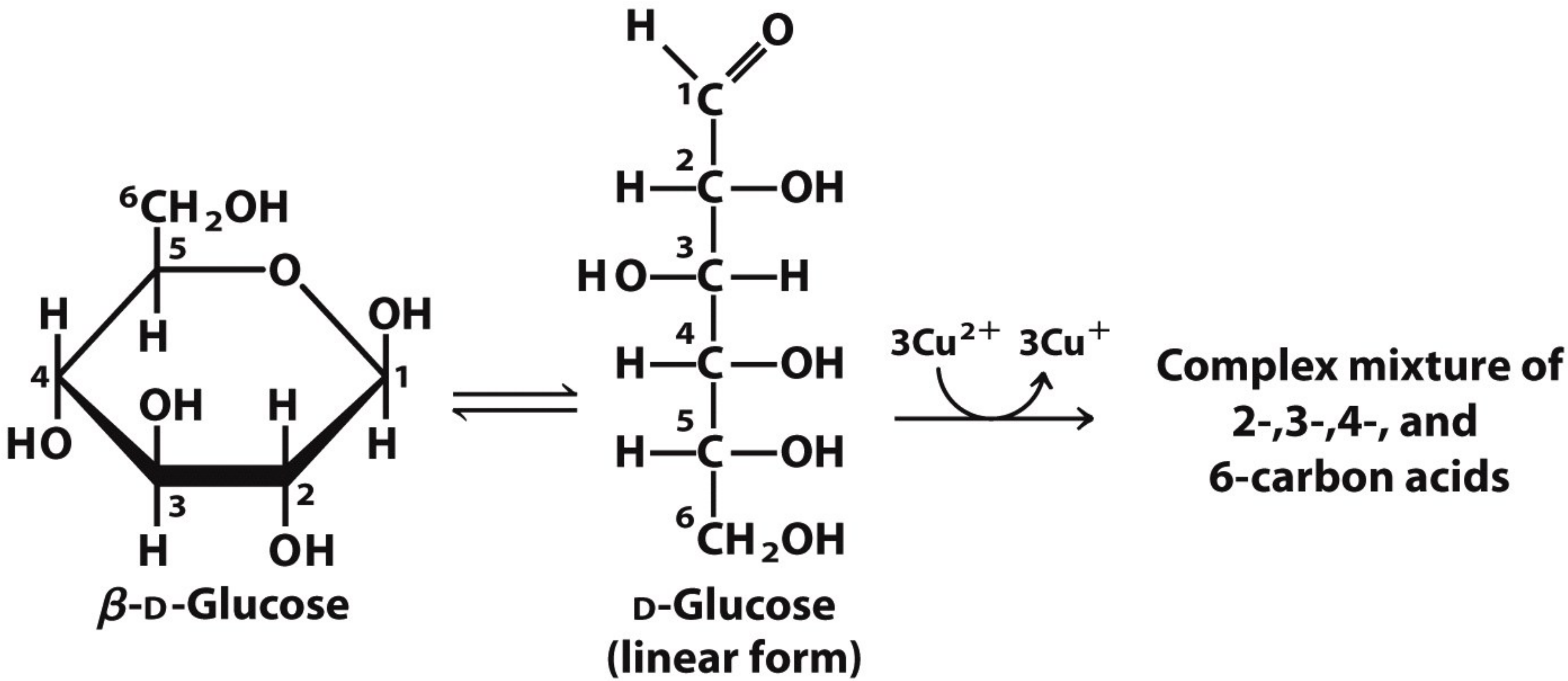

Figure 7-10
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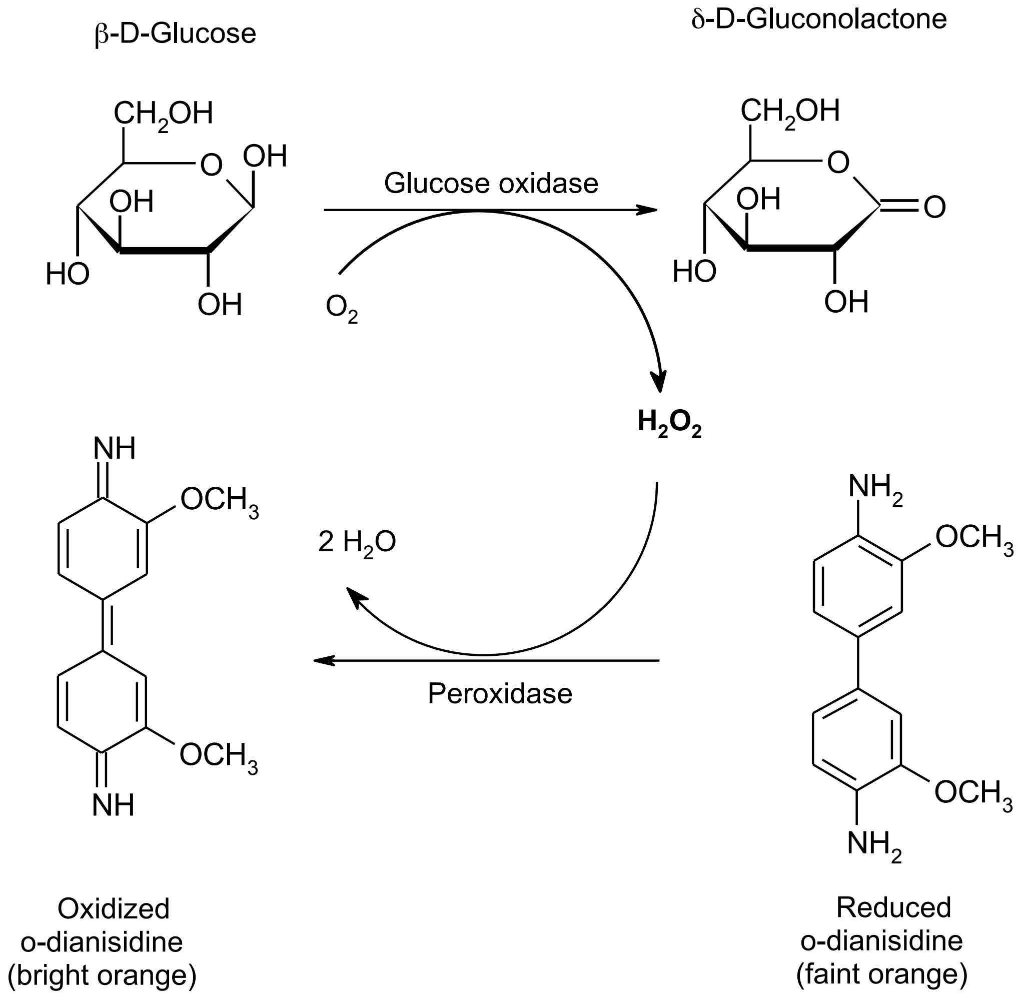
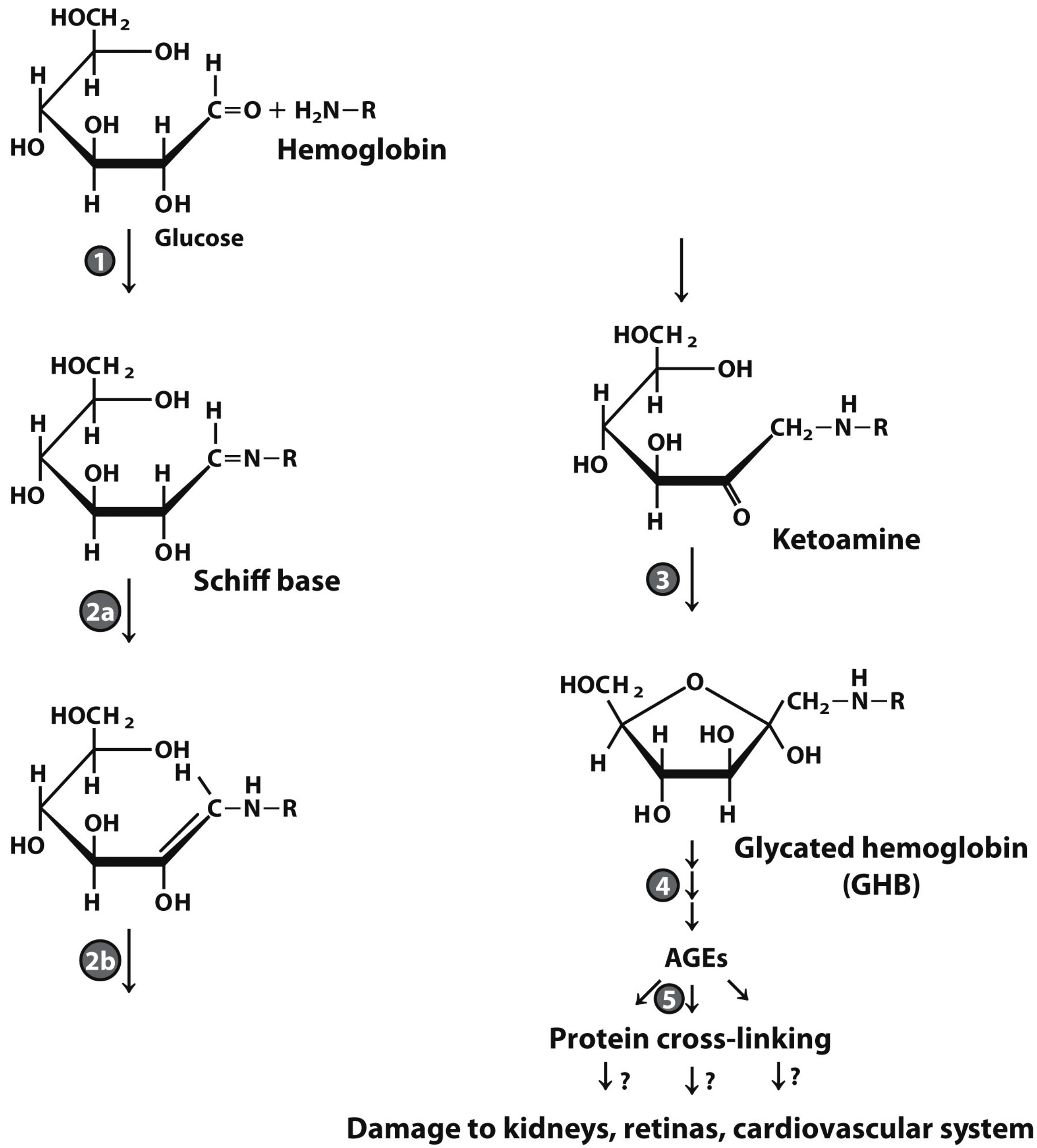
Colorimetric Glucose Analysis



- Nowadays, enzymatic methods are used to quantify reducing sugars such as glucose
  - The enzyme glucose oxidase catalyzes the conversion of glucose to glucono-δ-lactone and hydrogen peroxide
  - Hydrogen peroxide oxidizes organic molecules into highly colored compounds
  - Concentrations of such compounds is measured colorimetrically
- Electrochemical detection is used in portable glucose sensors

Blood glucose measurements in the diagnosis and treatment of diabetes

- Untreated diabetes has several long-term consequences: kidney failure, cardiovascular disease, blindness, impaired wound healing, etc.
- Average $[glc]_{blood}$ over days can be measured because of a nonenzymatic reaction between glc and primary amino groups in Hb
- The amount of glycated Hb (GHB) reflects the average $[glc]_{blood}$ over the circulating lifetime of RBC (~120 days)
- Normal levels ~5% of Hb is GHB
- Diabetic people may have it as high as 13%
- Advanced glycation endproducts (AGEs) contribute to the long term problems associated with diabetes



Box 7-1 figure 1
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Organisms contain many hexose derivatives

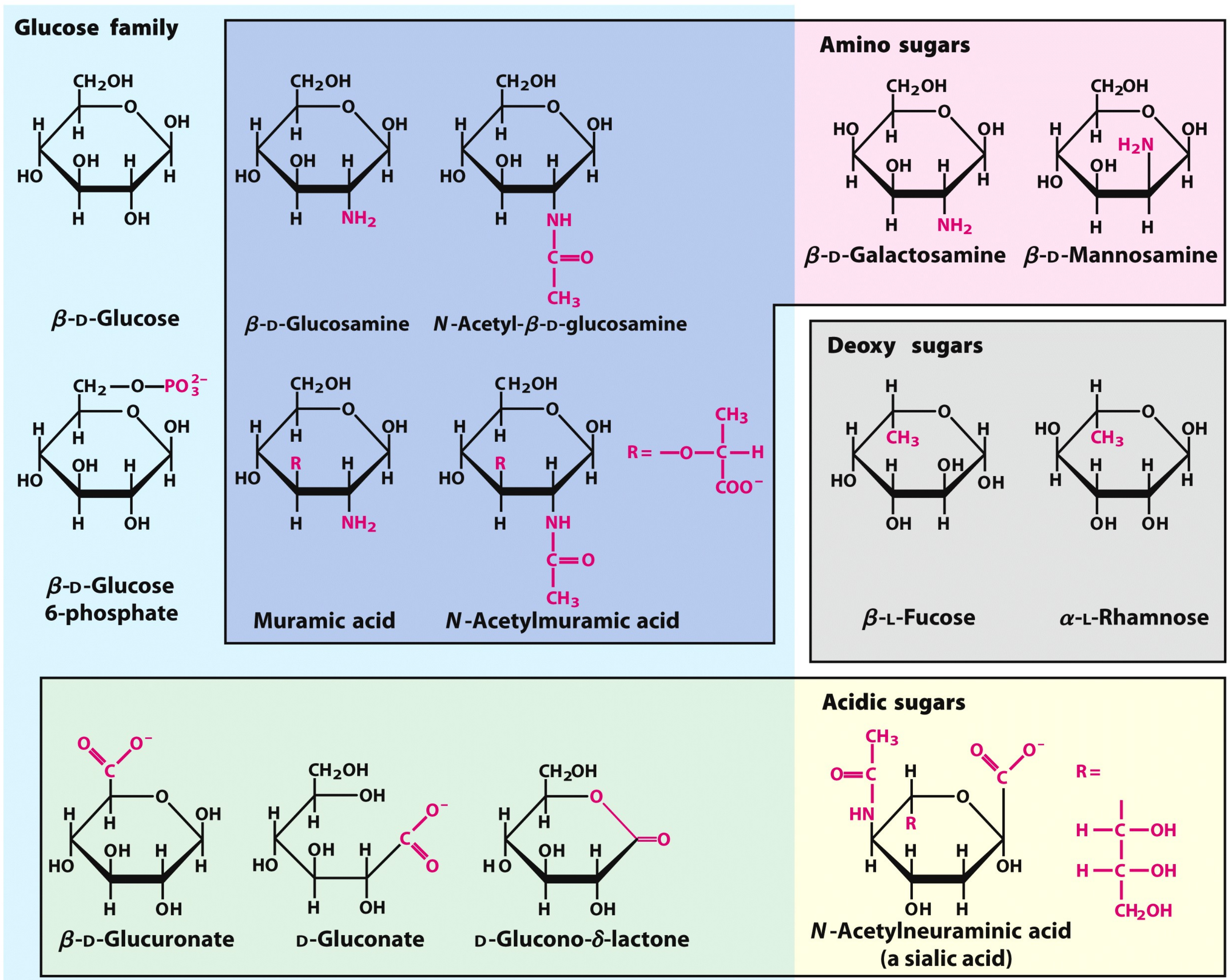

Figure 7-9
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The Glycosidic Bond

- Two sugar molecules can be joined via a glycosidic bond between an anomeric carbon and a hydroxyl carbon
- The resulting compound is a **glycoside**
- The glycosidic bond (an acetal) between monomers is less reactive than the hemiacetal at the second monomer
  - Second monomer, with the hemiacetal, is reducing
  - Anomeric carbon involved in the glycosidic linkage is nonreducing
- The disaccharide formed upon condensation of two glucose molecules via 1 $\rightarrow$ 4 bond is called maltose

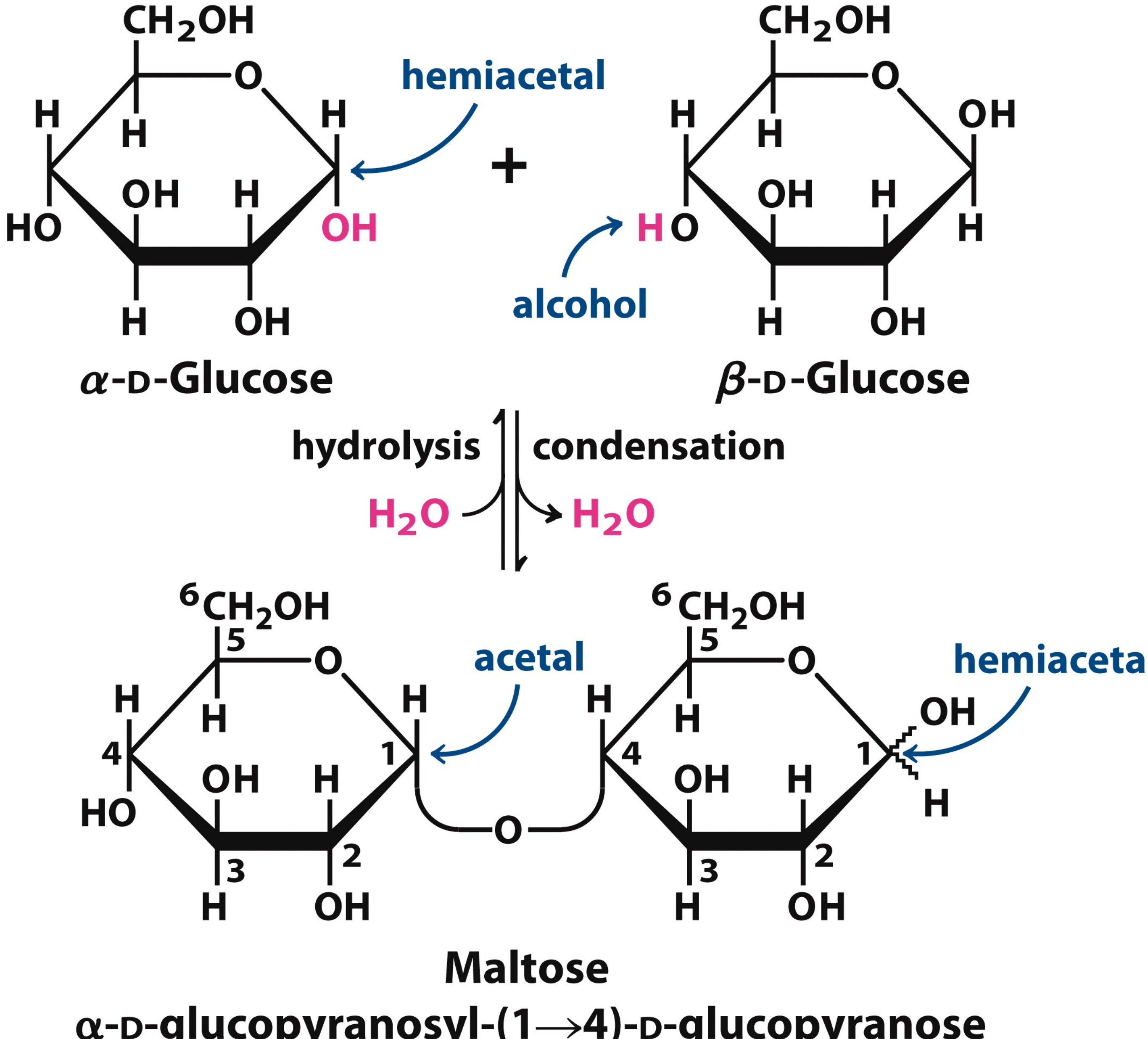

Figure 7-10

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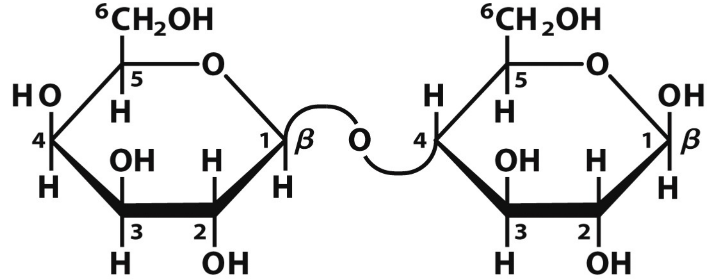
Nonreducing Disaccharides

- Two sugar molecules can be also joined via a glycosidic bond between two anomeric carbons
- The product has two acetal groups and no hemiacetals
- There are no reducing ends, this is a nonreducing sugar
- Trehalose is a constituent of hemolymph of insects
  - Provides protection from drying

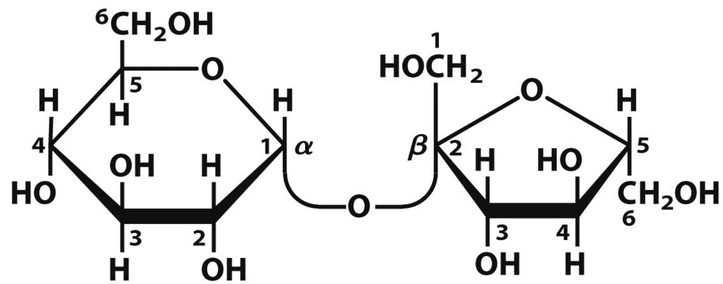
Naming disaccharides

1. Find the nonreducing end
2. Give the configuration (α or β) at the anomeric C joining the first monosaccharide to the other
3. Name the nonreducing residue (use “furano” for 5-membered rings or “pyrano” for 6-membered rings)
4. Add the glycosidic bond in parenthesis (from which C to which C)
5. Name the second residue
6. If there are more residues, repeat step 2

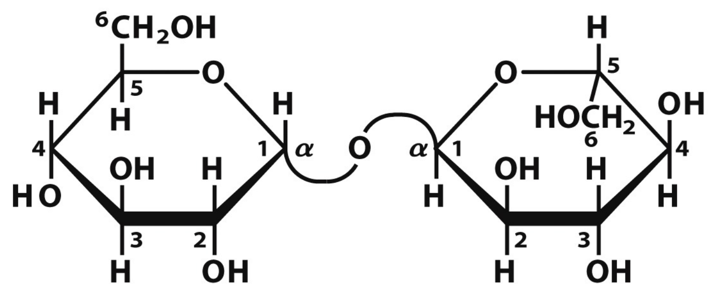
* Abbreviations can be used (Glc, Fru, Gal, Man, GlcN, etc.)



Lactose (β form)
β-D-galactopyranosyl-(1$\rightarrow$4)-β-D-glucopyranose
Gal(β1$\rightarrow$4)Glc



Sucrose
β-D-fructofuranosyl α-D-glucopyranoside
Fru(2$\beta\leftrightarrow\alpha$1)Glc $\equiv$ Glc(α1$\leftrightarrow$2β)Fru



Trehalose
α-D-glucopyranosyl α-D-glucopyranoside
Glc(α1$\leftrightarrow$1α)Glc

Figure 7-11
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Sweet tooth? Anyone?

Box 7-2 figure 1
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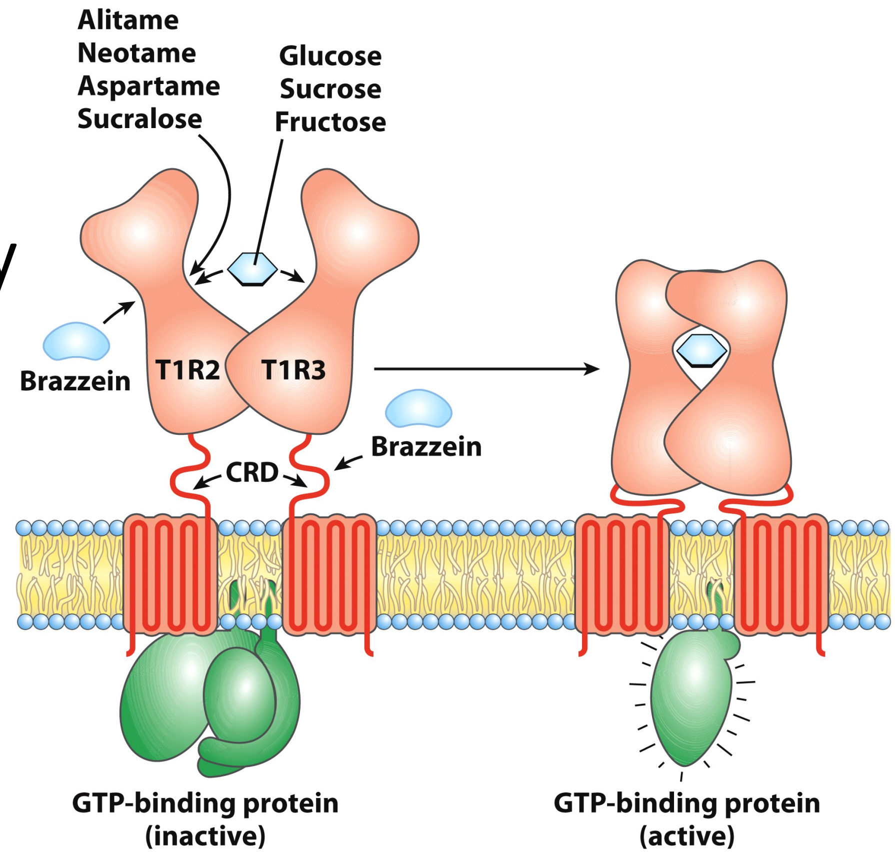
- Most people like sweets
- Sweetness is one of 5 tastes humans can taste
- Due to receptors on gustatory cells on the surface of tongues… T1R2 and T1R3
- Binding of molecules to these receptors, signals are transduced to give the sweet taste



Box 7-2 figure 2
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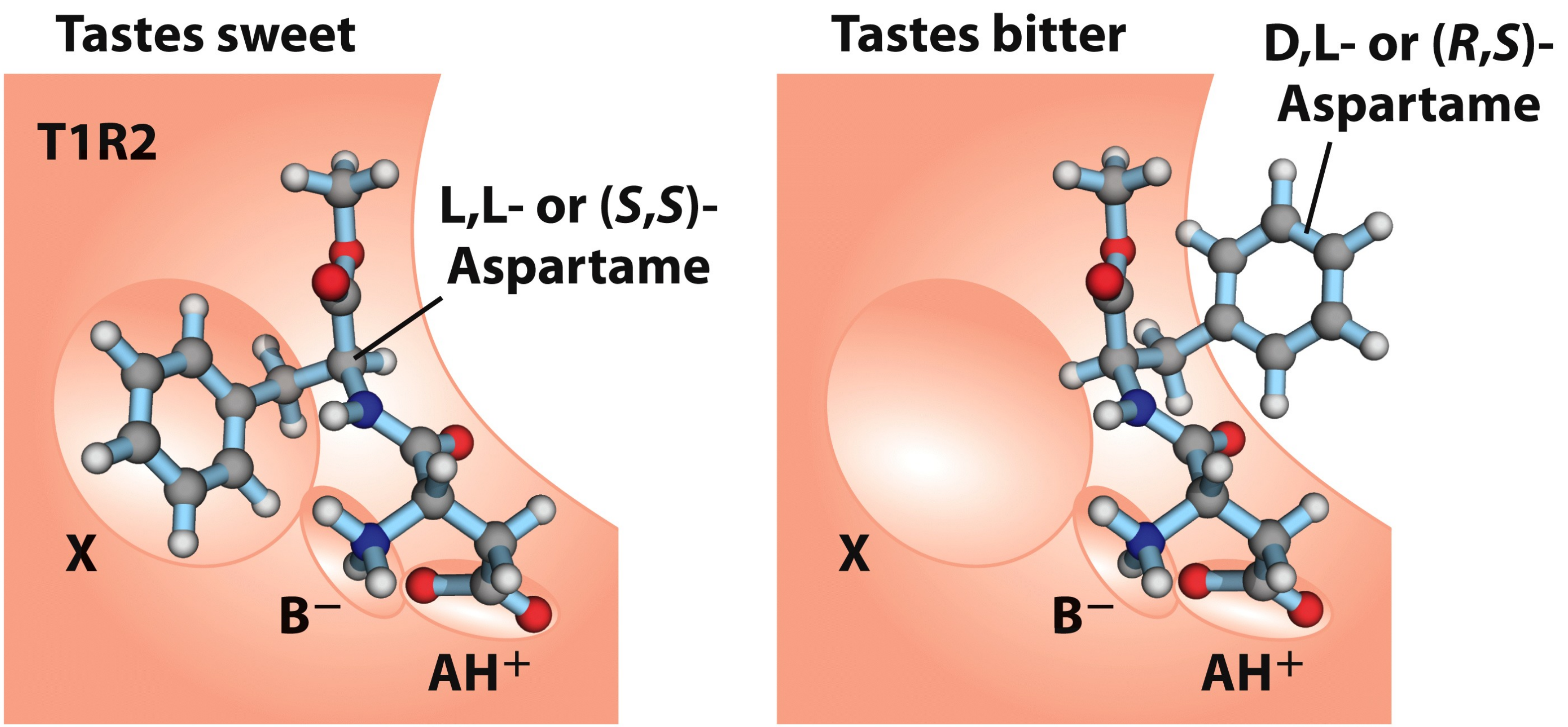
L,L-Aspartame is sweet; D,L-Aspartame is bitter



Box 7-2 figure 3
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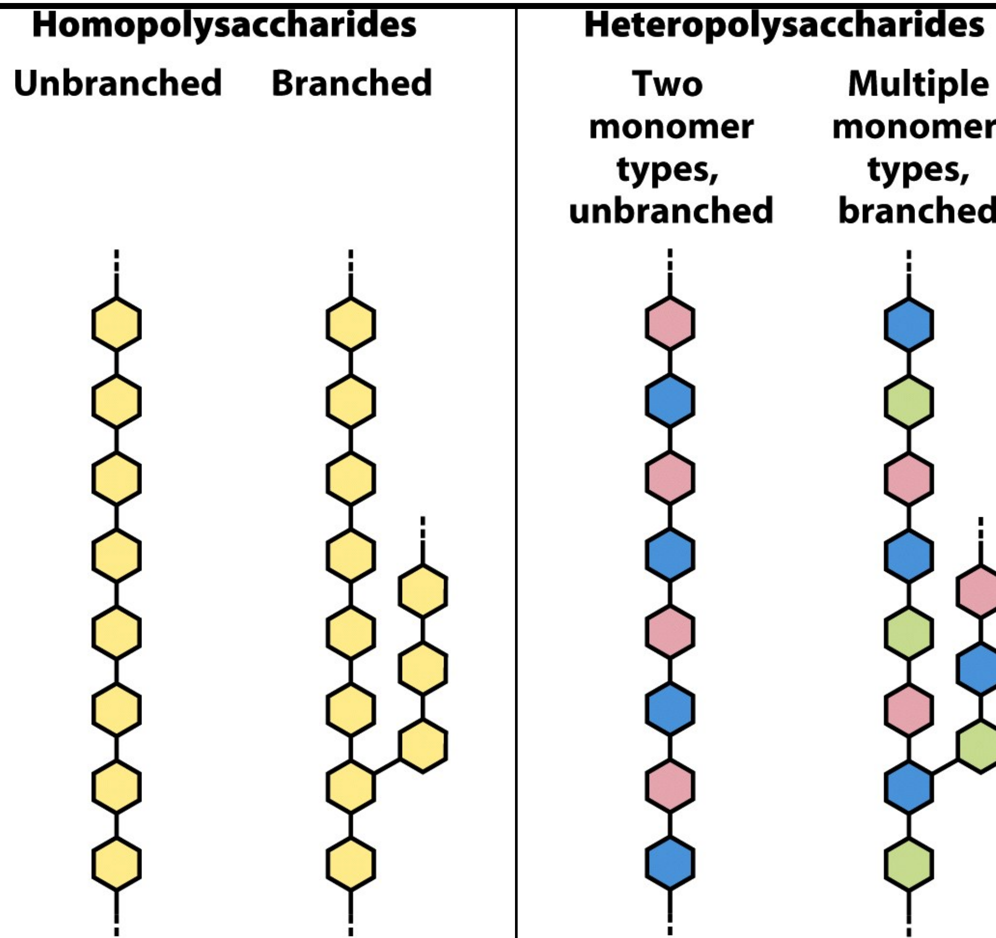
Polysaccharides

- Natural carbohydrates are usually found as polymers
- These polysaccharides can be
  - homopolysaccharides
  - heteropolysaccharides
  - linear
  - branched
- Polysaccharides do not have a defined molecular weight.
  - This is in contrast to proteins because unlike proteins, no template is used to make polysaccharides



Can be: 1) Storage forms of monosaccharides, used for fuel (starch and glycogen) 2) Structural elements in plant cell walls and animal exoskeletons (cellulose and chitin)	Provide extracellular support for organisms of all kingdoms, E.g. 1) Bacterial cell envelope is composed in part of a heteropolysaccharide 2) Extracellular matrix in animal cells

Glycogen

- Glycogen is a branched homopolysaccharide of glucose
  - Glucose monomers form $(\alpha 1 \rightarrow 4)$ linked chains
  - Branch-points with $(\alpha 1 \rightarrow 6)$ linkers every 8–12 residues
  - Molecular weight reaches several millions
  - Functions as the main storage polysaccharide in animals

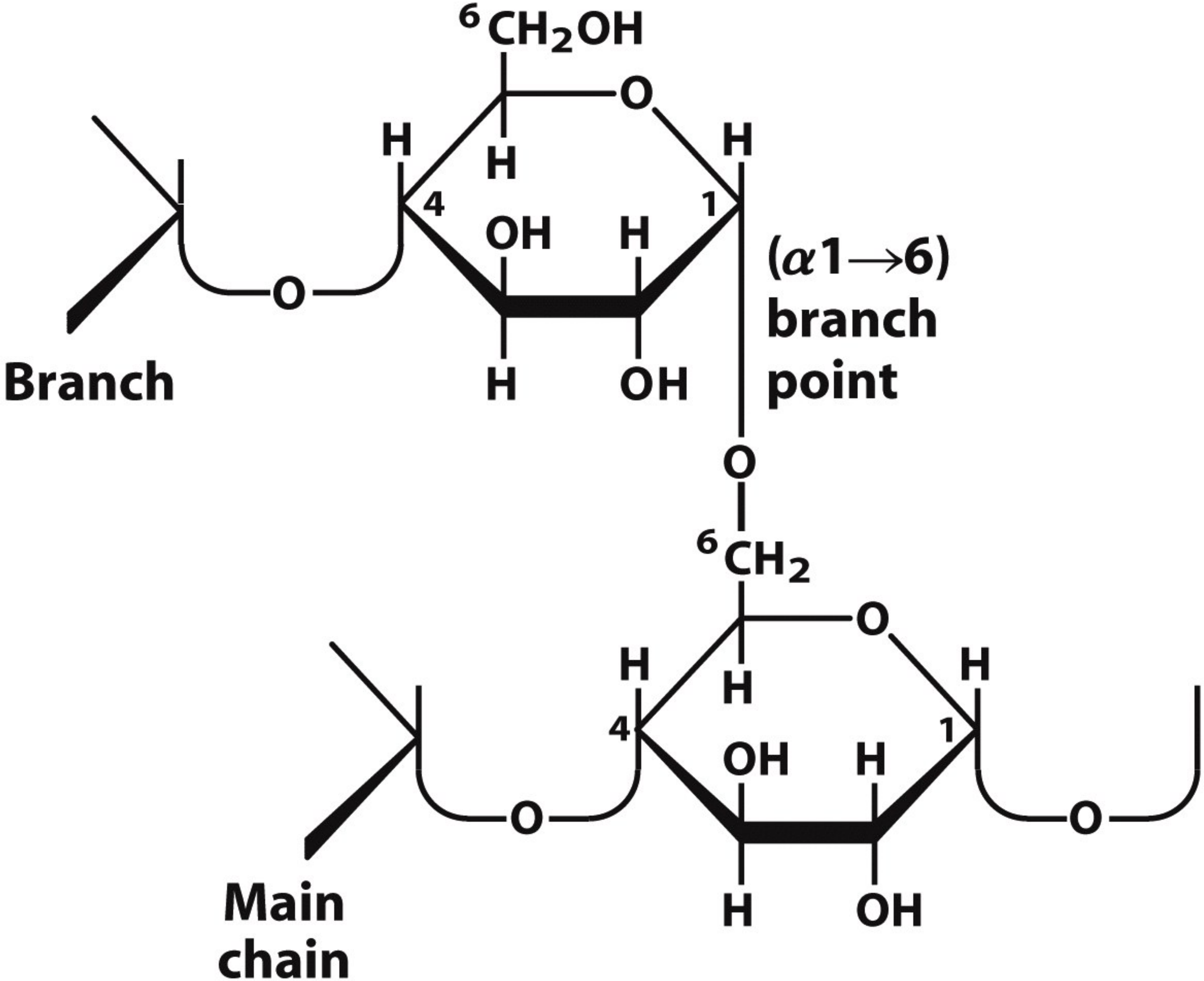


Figure 7-14b
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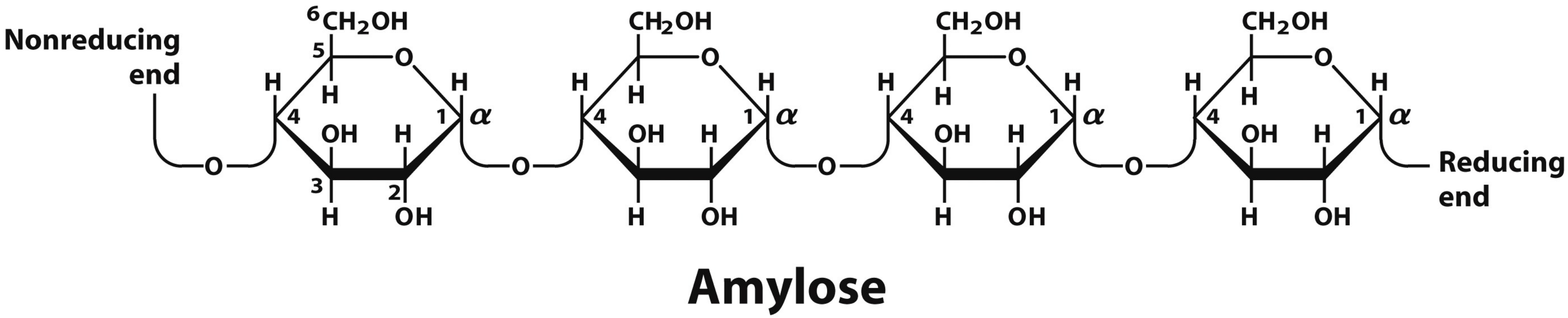
Starch

- Starch is a mixture of two homopolysaccharides of glucose
  - Amylose is an unbranched polymer of ($\alpha 1 \rightarrow 4$) linked residues
  - Amylopectin is branched like glycogen but the branch-points with ($\alpha 1 \rightarrow 6$) linkers occur every 24–30 residues
  - Molecular weight of amylopectin is up to 200 million
- Starch is the main storage polysaccharide in plants

Glycosidic Linkages in Glycogen and Starch



Amylose

Figure 7-13a
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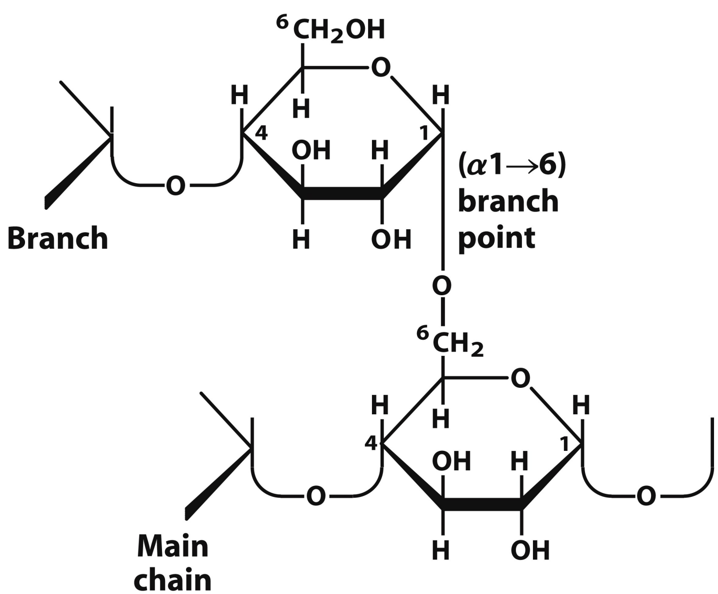

Figure 7-13b
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Mixture of Amylose and Amylopectin in Starch

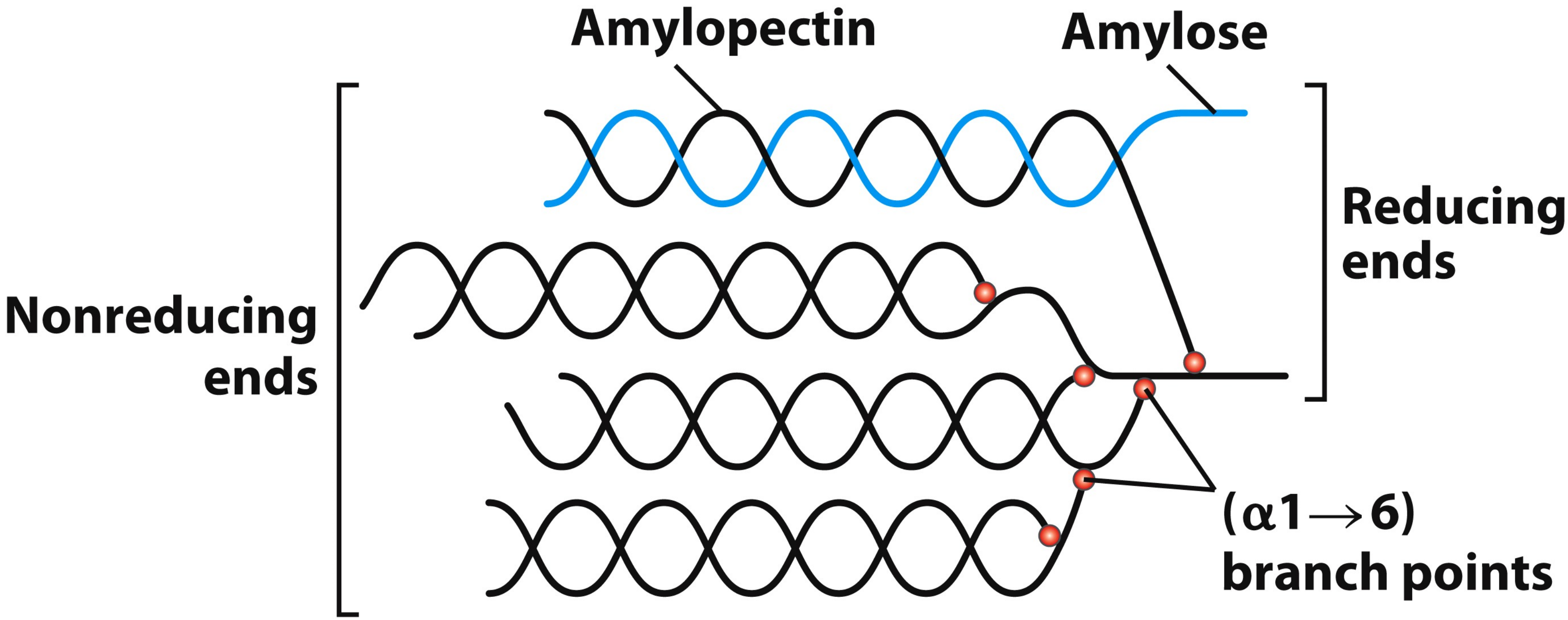

Figure 7-13c
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In starch granules, strands of amylopectin (blue) form double-helical structures with each other or with amylose strands (blue). Glucose residues at the nonreducing ends of the outer branches are removed enzymatically during the mobilization of starch for energy production.

Glycogen has a similar structure but is more highly branched and more compact.

Metabolism of Glycogen and Starch

- Glycogen and starch often form granules in cells
- Granules contain enzymes that synthesize and degrade these polymers
- Glycogen and amylopectin have one reducing end but many nonreducing ends (a polymer with n branches has n + 1 nonreducing ends and only 1 reducing end)
- Enzymatic processing occurs simultaneously in many nonreducing ends

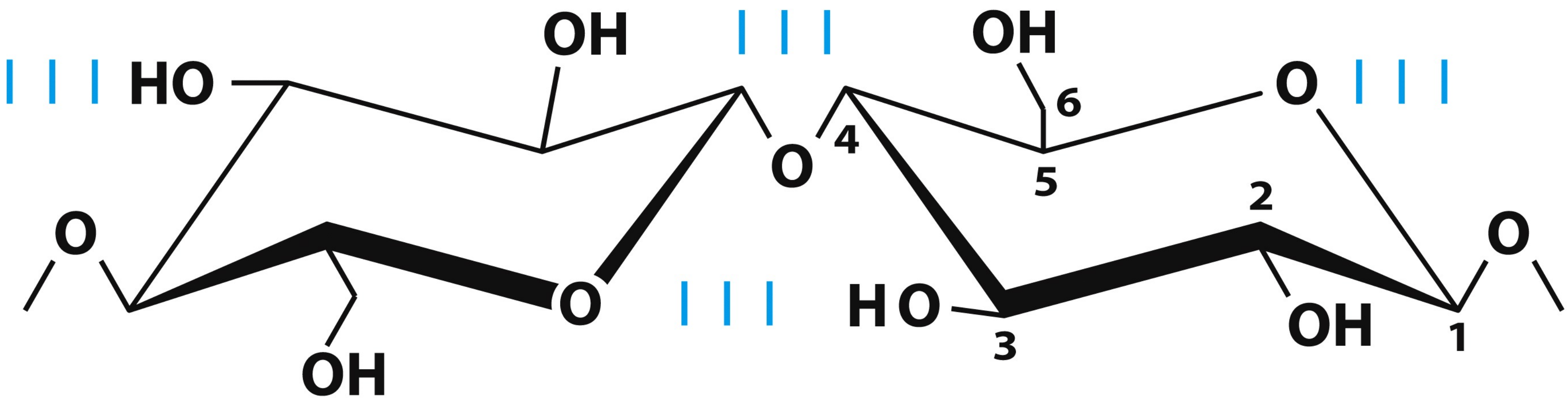
Dextrans

- Bacterial and yeast polysaccharides
- ($\alpha 1 \rightarrow 6$)-linked poly-D-glucose
- All units have ($\alpha 1 \rightarrow 3$) branches
- Some have also ($\alpha 1 \rightarrow 2$) or ($\alpha 1 \rightarrow 4$) branches
- Dental plaque (formed by bacteria on the surface of teeth) is rich in dextrans

Cellulose

- Cellulose is a branched homopolysaccharide of glucose
  - Glucose monomers form $(\beta 1 \rightarrow 4)$ linked chains
  - Hydrogen bonds form between adjacent monomers
  - Additional H-bonds between chains
  - Structure is now tough and water-insoluble
  - Most abundant polysaccharide in nature
  - Cotton is nearly pure fibrous cellulose

Hydrogen Bonding in Cellulose



(β1→4)-linked D-glucose units

Figure 7-14
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Cellulose Metabolism

- The fibrous structure and water-insolubility make cellulose a difficult substrate to act on
- Fungi, bacteria, and protozoa secrete cellulase, which allows them to use wood as source of glucose
- Most animals cannot use cellulose as a fuel source because they lack the enzyme to hydrolyze (β1 $\rightarrow$4) linkages
- Ruminants and termites live symbiotically with microorganisms that produces cellulase
- Cellulases hold promise in the fermentation of biomass into biofuels

Figure 7-16

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Chitin

- Chitin is a linear homopolysaccharide of N-acetylglucosamine
  - N-acetylglucosamine monomers form $(\beta 1 \rightarrow 4)$-linked chains
  - Forms extended fibers that are similar to those of cellulose
  - Hard, insoluble, cannot be digested by vertebrates
  - Structure is tough but flexible, and water-insoluble
  - Found in cell walls in mushrooms, and in exoskeletons of insects, spiders, crabs, and other arthropods
  - 1 billion tons of chitin is produced in the biosphere per year

Chitin

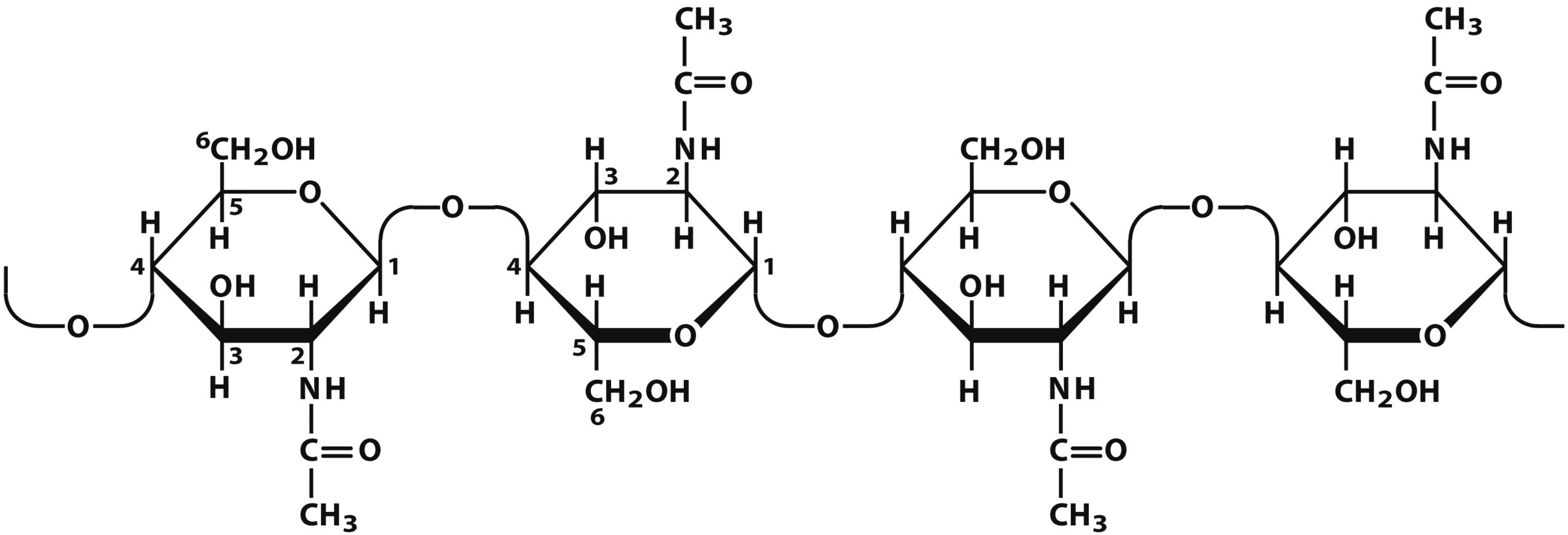


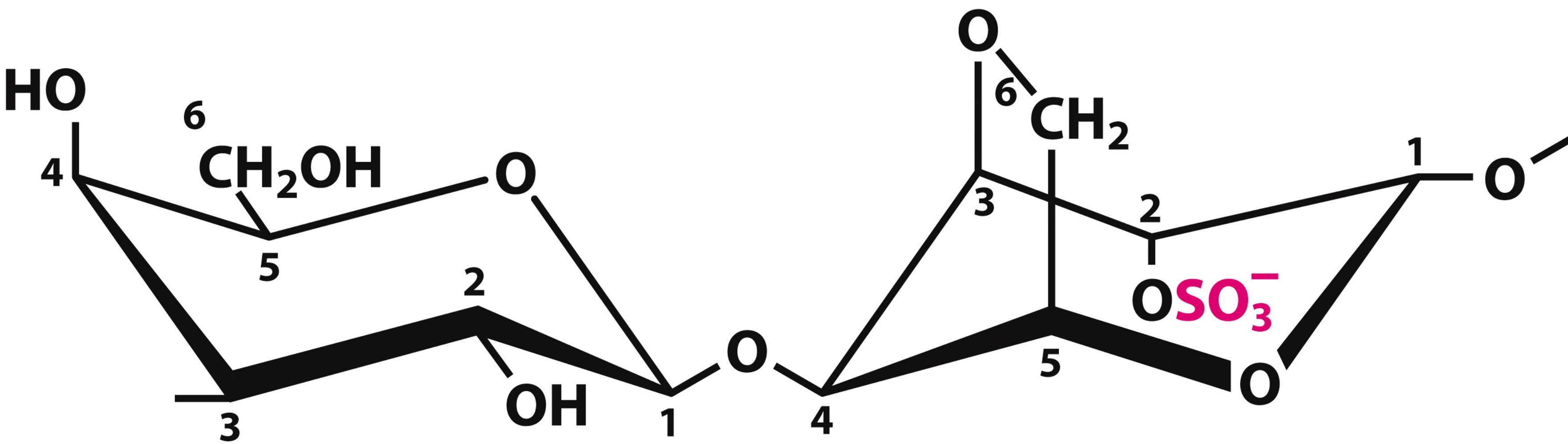
Figure 7-16a
Lehninger Principles of Biochemistry, Sixth Edition

Figure 7-16b
Lehninger Principles of Biochemistry, Sixth Edition

Agar and Agarose

- Agar is a complex mixture of hetereopolysaccharides containing modified galactose units
- Agar serves as a component of cell wall in some seaweeds
- Agarose is one component of agar
- Agar solutions form gels that are commonly used in the laboratory as a surface for growing bacteria
- Agar is also used for capsules in which some drugs and vitamins are packaged
- Agarose solutions form gels that are commonly used in the laboratory for separation DNA by electrophoresis

Agar and Agarose



Agarose

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

Figure 7-21
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Glycosaminoglycans

- Linear polymers of repeating disaccharide units
- One monomer is either
  - N-acetyl-glucosamine or
  - N-acetyl-galactosamine
- Negatively charged
  - Uronic acids (C6 oxidation)
  - Sulfate esters
- Extended hydrated molecule
  - Minimizes charge repulsion
- Forms meshwork with fibrous proteins to form extracellular matrix
  - Connective tissue
  - Lubrication of joints

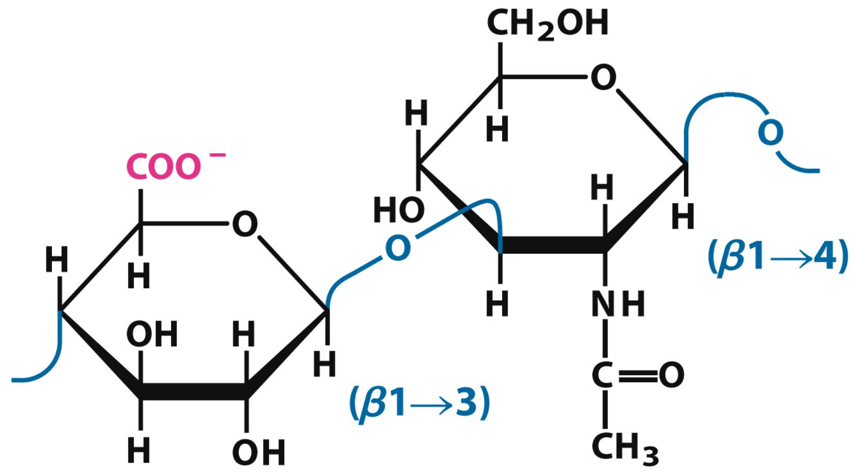
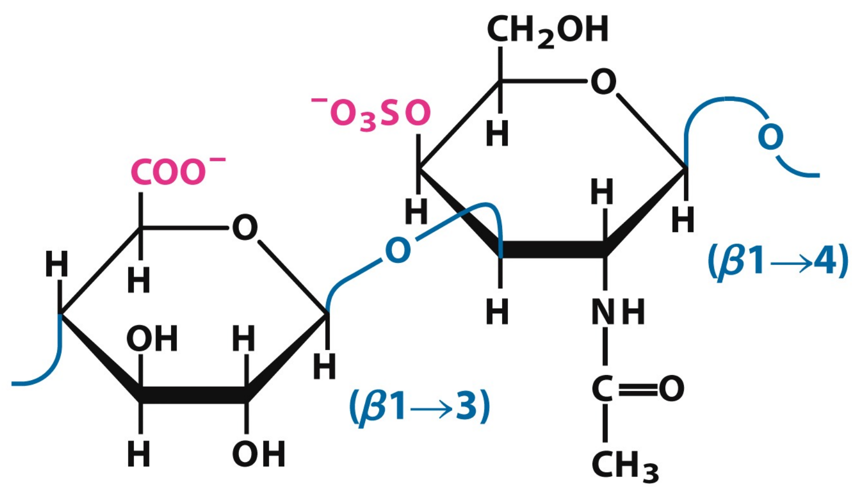
Glycosaminoglycan Number of disaccharides per chain	Repeating disaccharide
Hyaluronate ~50,000	 GlcA GlcNAc
Chondroitin 4-sulfate 20–60	 GlcA GalNAc4S

Figure 7-22 part 1a
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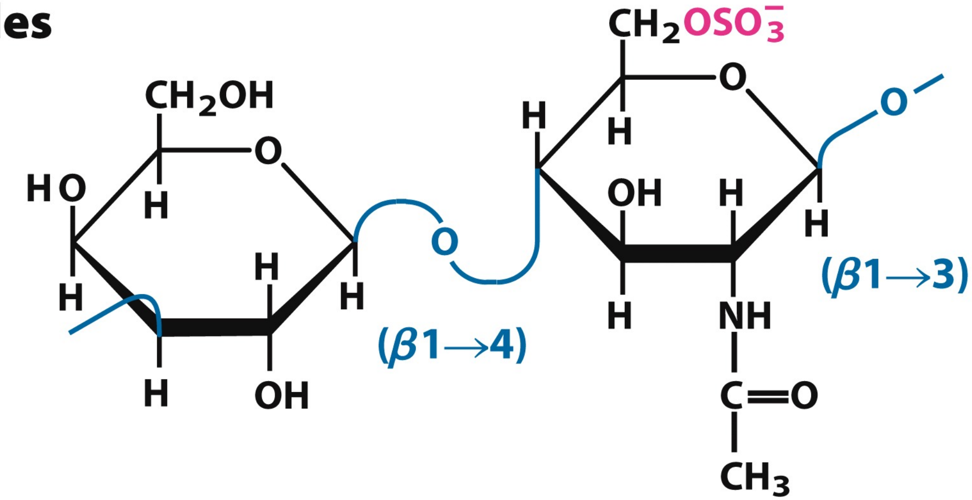
Glycosaminoglycan — **Repeating disaccharide**

Number of disaccharides per chain

Keratan sulfate

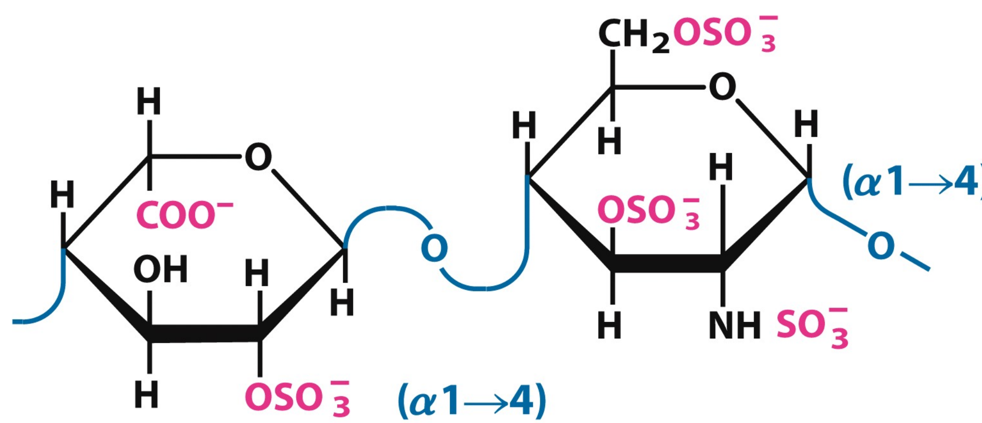
~25



Gal **GlcNAc6S**

Heparin

15–90



IdoA2S **GlcNS3S6S**

Figure 7-22 part 1b

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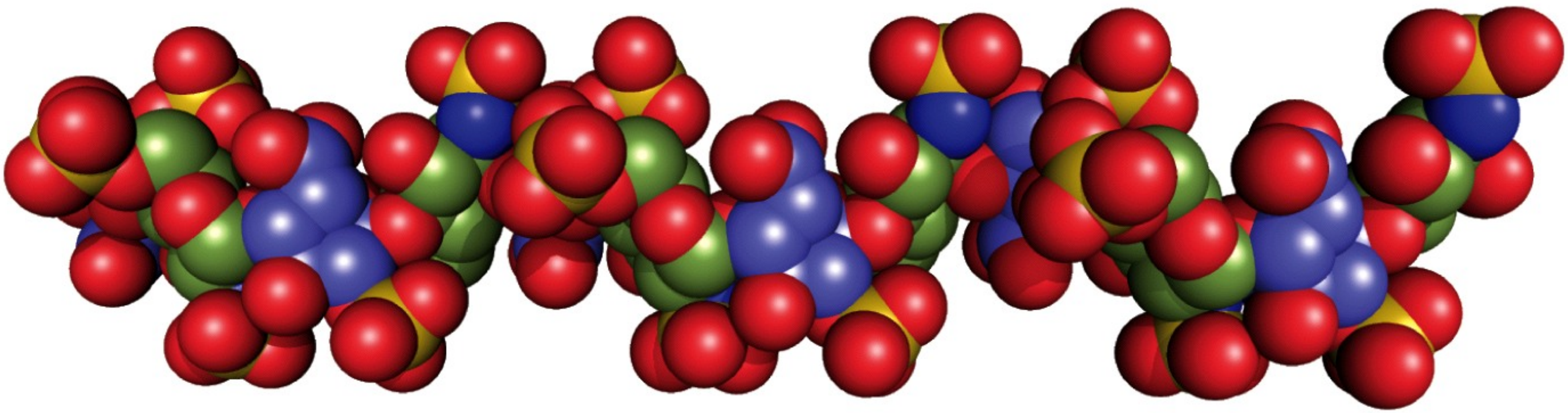
Heparin and Heparan Sulfate

- Heparin is linear polymer, 3–40 kDa
- Heparan sulfate is heparin-like polysaccharide but attached to proteins
- Highest negative charge density biomolecules
- Prevent blood clotting by activating protease inhibitor antithrombin
- Binding to various cells regulates development and formation of blood vessels
- Can also bind to viruses and bacteria and decrease their virulence



Heparin segment

Figure 7-22 part 2
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Glycoconjugates: Glycoprotein

- A protein with small oligosaccharides attached
  - Carbohydrate attached via its anomeric carbon
  - About half of mammalian proteins are glycoproteins
  - Carbohydrates play role in protein-protein recognition
  - Only some bacteria glycosylate few of their proteins
  - Viral proteins heavily glycosylated; helps evade the immune system

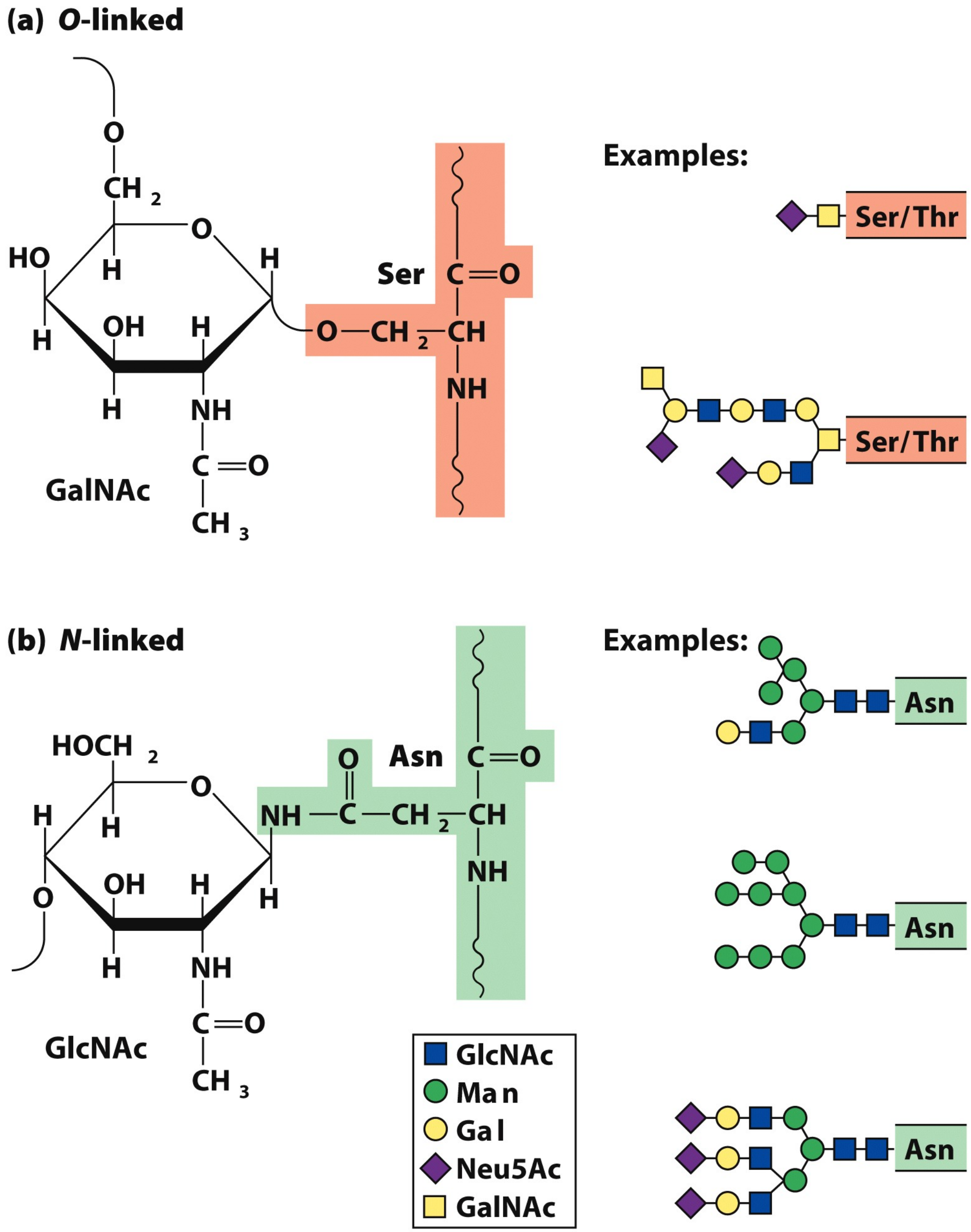

Figure 7-30
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Glycoconjugates: Glycolipids

- A lipid with covalently bound oligosaccharide
  - Parts of plant and animal cell membranes
  - In vertebrates, ganglioside carbohydrate composition determines blood groups
  - In gram-negative bacteria, lipopolysaccharides cover the peptidoglycan layer

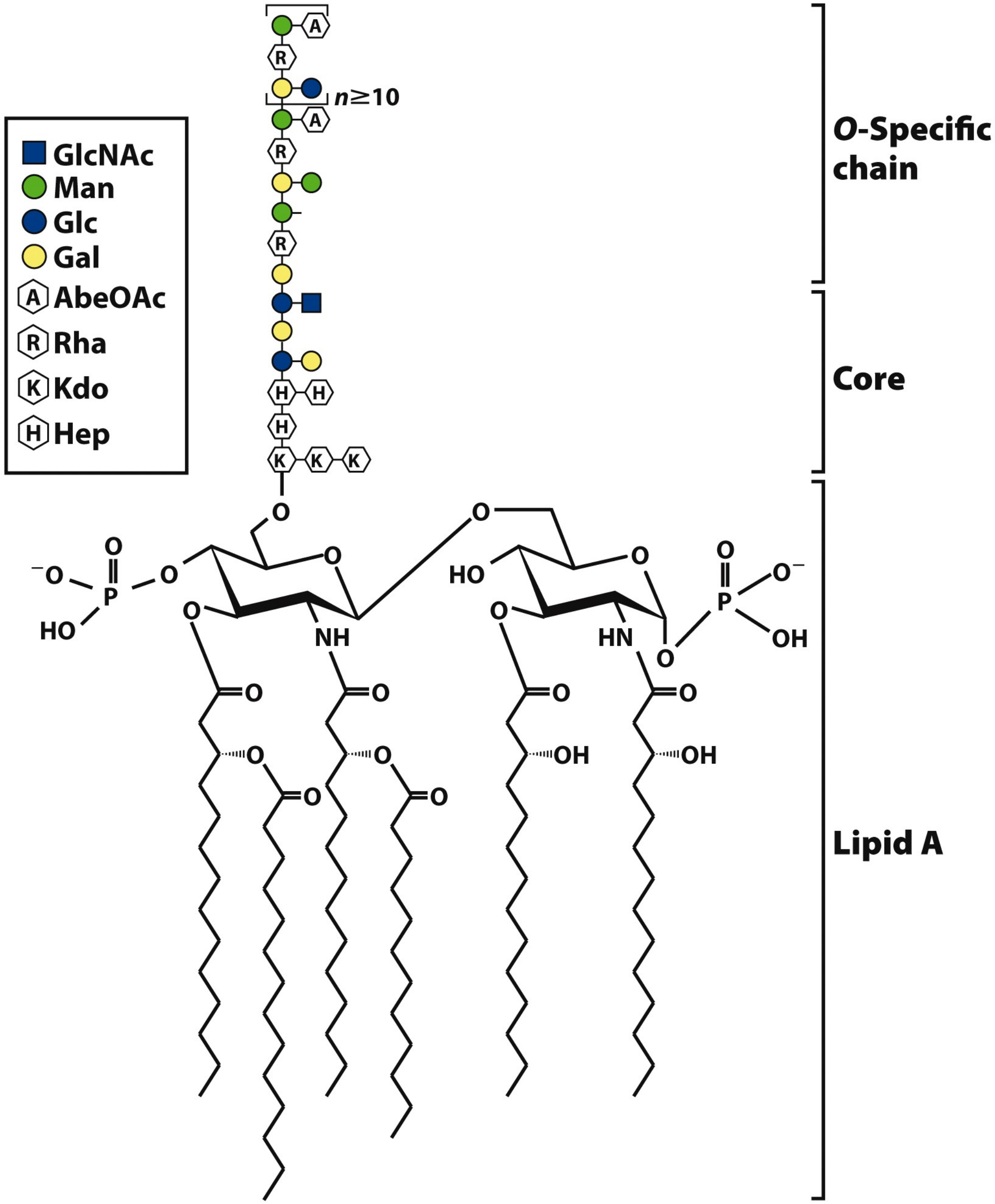

Figure 7-31
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Glycoconjugates: Proteoglycans

- Sulfated glucoseaminoglycans attached to a large rod-shaped protein in cell membrane
  - Syndecans: protein has a single transmembrane domain
  - Glypicans: protein is anchored to a lipid membrane
  - Interact with a variety of receptors from neighboring cells and regulate cell growth

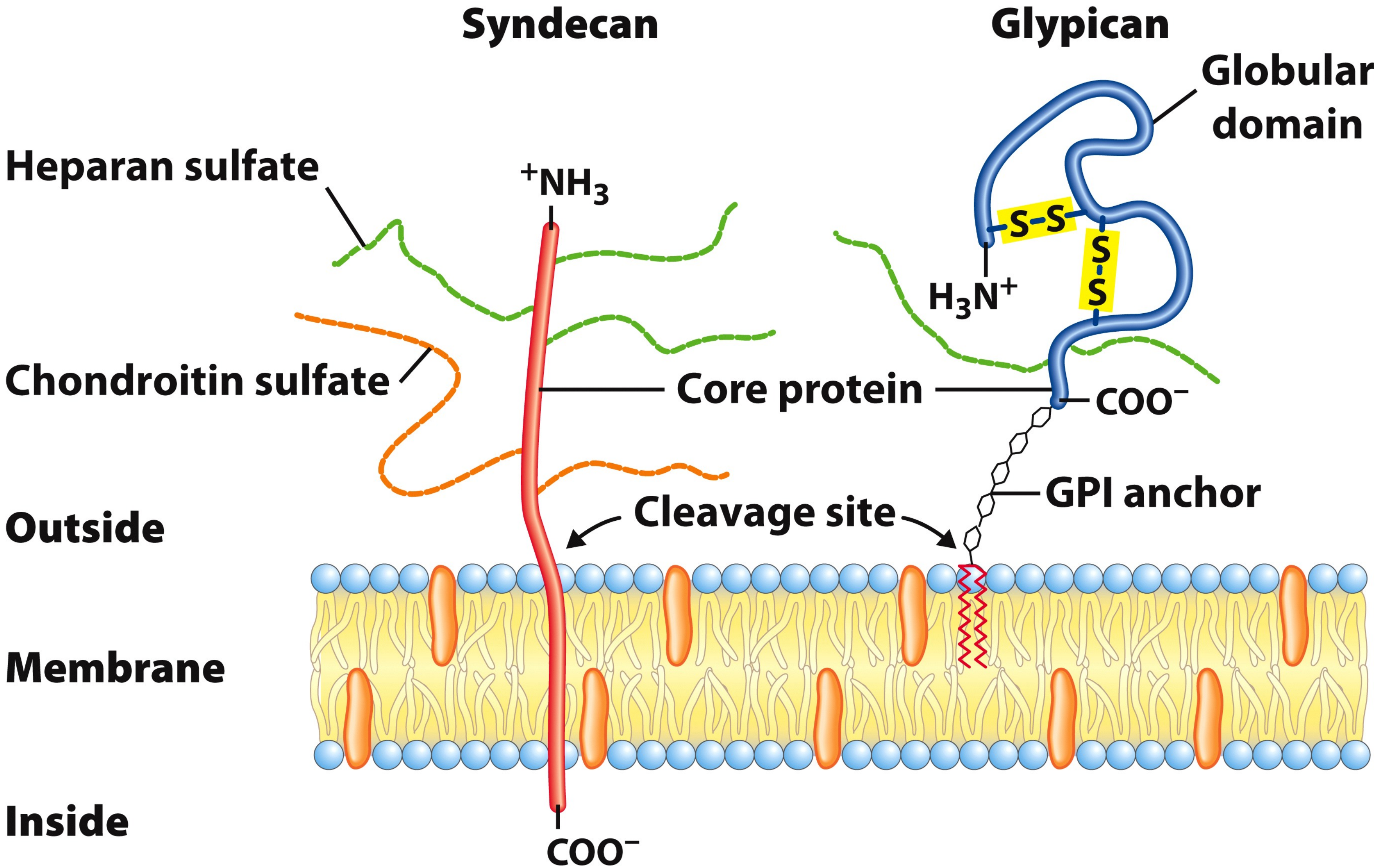

Figure 7-26a

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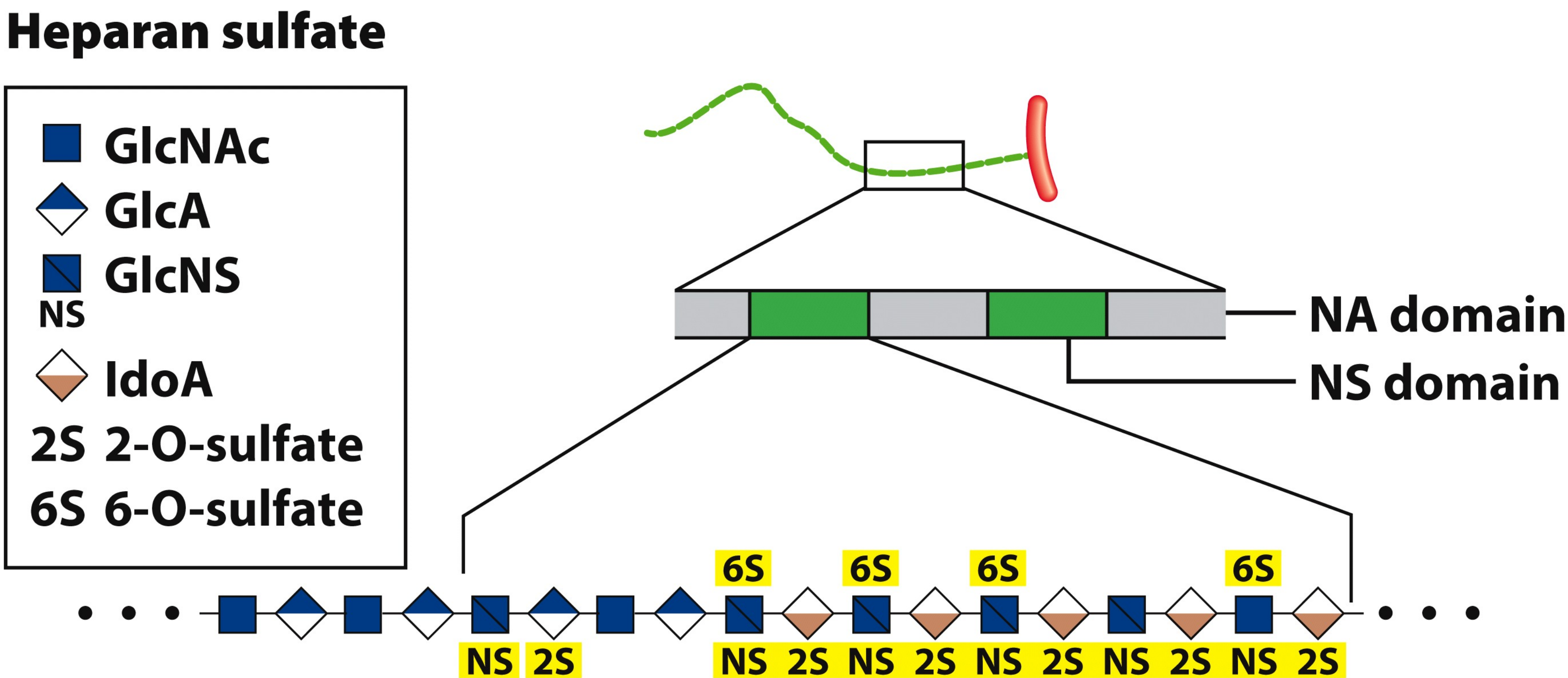

Figure 7-26b
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Proteoglycans

- Different glycosaminoglycans are linked to the core protein
- Linkage from anomeric carbon of xylose to serine hydroxyl
- Our tissues have many different core proteins; aggrecan is the best studied

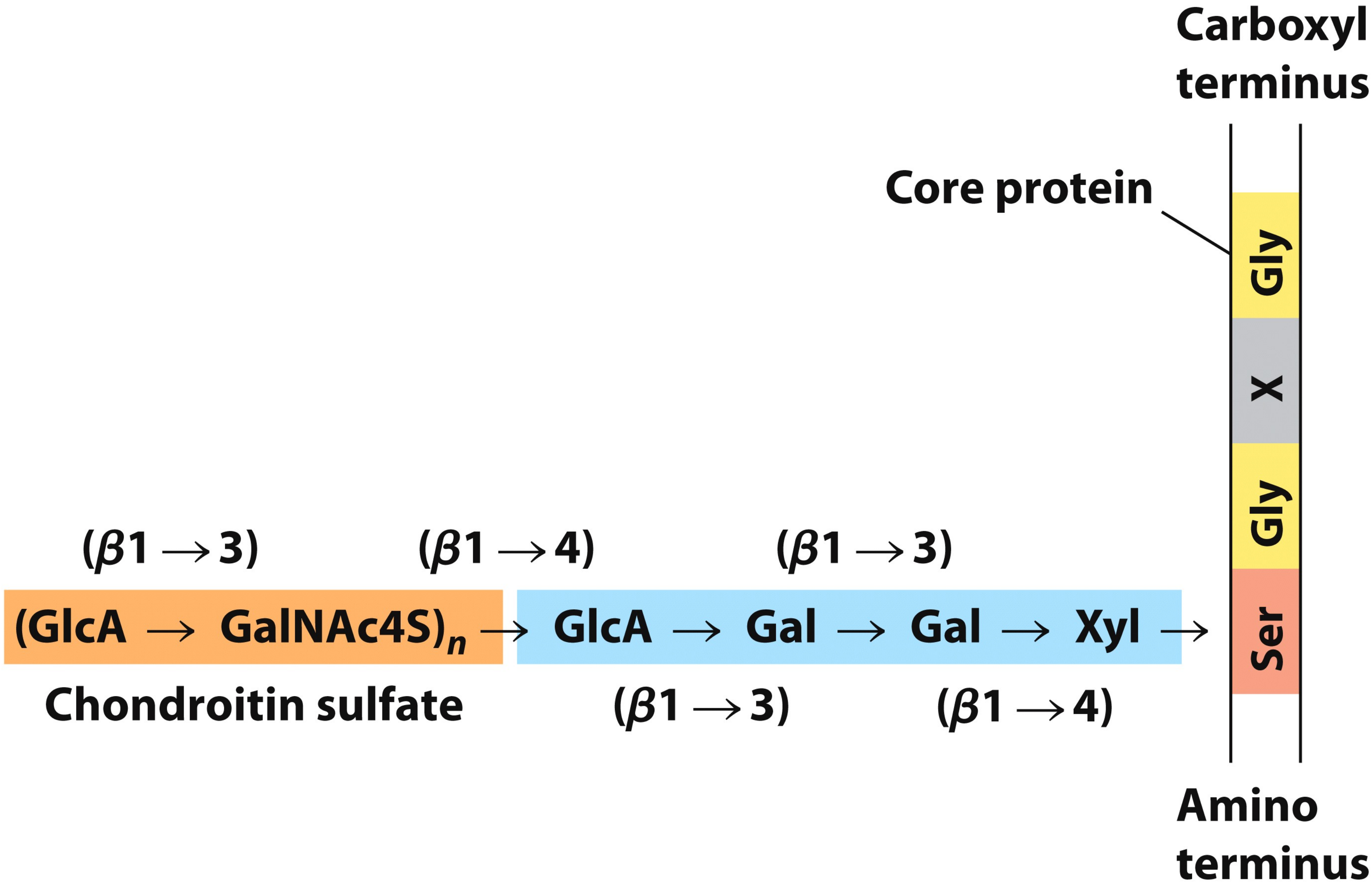

Figure 7-25
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Proteoglycan Aggregates

- Hyaluronan and aggrecan form huge ($M_r > 2 \cdot 10^8$) noncovalent aggregates
- Hold lots of water (1000× its weight); provides lubrication
- Very low friction material
- Covers joint surfaces: articular cartilage
  - Reduced friction
  - Load balancing

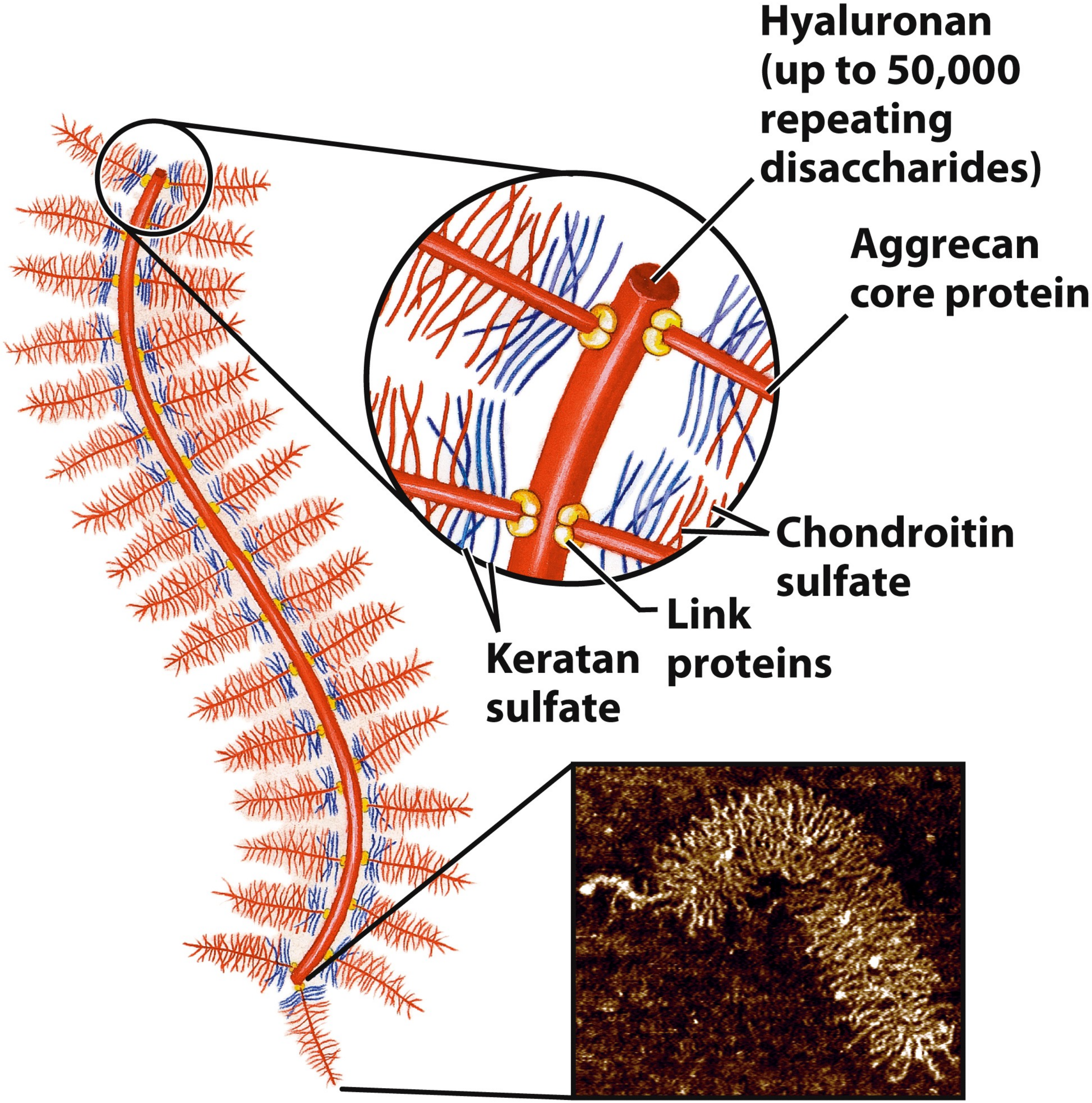

Figure 7-28
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