Chapter 8 - Carbohydrates

Introduction

Carbohydrates (saccharides) are the most abundant biomolecule. Although chemically simpler \((\text{C H}_2\text{O})_n\) than amino acids and nucleic acids, their derivatives do contain N and S. As recently as the 1960's they were thought to be primarily energy sources and to have structural roles (<1960's), they are now known to have important roles in recognition processes (cell - cell, protein - protein).

Monosaccharides

Monosaccharides, or simple sugars, are polyhydroxy aldehydes (aldose) and ketones (ketoses). Aldoses are shown in Figure 8-1.
Note the presence of 1 chiral carbon for 3-carbon aldoses, 2 for 4-carbon aldoses, or n-2 chiral carbons for n-carbon aldoses. The D-form has the OH on the furthest chiral carbon from the aldehyde group on the right in the Fischer projection, and predominates in nature (whereas L-amino acids predominate). Recall stereochemistry (enantiomers, diastereomers, epimers). You should be able to draw D-glucose, D-galactose, D-fructose (a ketose, see below), D-ribose.

Ketoses (Figure 8-2) with n carbons have n-3 chiral carbons; know D-fructose only. Note that glucose and fructose are structural isomers as compared to glucose and galactose, for example, which are stereoisomers.

![Figure 8-2. The D-ketoses with three to six carbon atoms.](Image)

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cyclic forms: Recall from organic chemistry that alcohols and aldehydes react to form hemiacetals

\[
\text{Alcohol} + \text{Aldehyde} \xrightarrow{W} \text{Hemiacetal}
\]

\[
R-OH + R'-C=O \underset{\text{H}}{\xrightarrow{\text{H}} \underset{\text{R'}}{\text{R'-O-C}}}
\]

and that alcohols and ketones react to form hemiketals:

\[
\text{Alcohol} + \text{Ketone} \xrightarrow{W} \text{Hemiketal}
\]

\[
R-OH + R'-C=O \underset{\text{H}}{\xrightarrow{\text{H}} \underset{\text{R'}}{\text{R'-O-C}}}
\]

Since carbohydrates have the alcohol and carbonyl functionalities in the same molecule, they can react to form intramolecular, or cyclic hemiacetals and cyclic hemiketals (Figure 8-3)
The cyclic forms of carbohydrates are typically represented as Haworth Projections, and are called pyranoses or furanoses based on the parent compounds, pyran and furan.

Conventions: Left in Fisher, up in Haworth, terminal CH$_2$OH group bonded to C5 is up for D isomer. The anomeric carbon is derived from the carbonyl group and has two oxygens bonded to it. I will always draw Haworth structures so that the anomeric carbon, regardless whether is the number 1 carbon or not, will always be the furthest to the right.

Haworth projections do not differentiate between axial vs. equatorial positions, and an alternate projection is the chair conformation (Figure 8-5):

![Figure 8-5: The two chair conformations of β-D-glucopyranose.](https://example.com)

The term conformation refers to shape, whereas configuration refers to different anomers ("-alpha vs. $\beta$-beta).

**Sugar Derivatives**

Some biologically important sugar derivatives which are either oxidized or reduced versions of the originals are shown below:
Another derivative is shown below, D-2-glucosamine, in which the OH at carbon 2 is replaced by an amino group:

N-acetyl glucosamine is another common derivative.
Glucose can react with an alcohol such as methanol to form a glucoside (Figure 8-7). Glucose can be thus linked to other molecules via such a glycosidic linkage:

**Polysaccharides**

**Disaccharides**

polysaccharides, or glycans, are polymers of monosaccharides linked by glycosidic linkages. If the alcohol involved in forming the glycosidic linkage is part of another monosaccharide, such as another glucose, a disaccharide is formed:

Other common disaccharides you should know are lactose, the disaccharide of milk, and sucrose, or common table sugar.
Note that the preferred way to draw sucrose is as shown above, and not as shown in the text on page 215, which breaks a lot of the rules I’ve given you.

Note also that maltose and lactose have the anomeric carbon of one residue (on the left) involved in glycosidic linkage, whereas the other anomeric carbon (on the right) is not involved in a glycosidic linkage; in other words, it is “free.” The hemiacetal forms of the glucose residue (free anomeric carbon) exist in equilibrium with the open chain forms which possess a free carbonyl group. These carbonyl groups can be further oxidized, and maltose and lactose are called reducing sugars because they reduce the oxidizing agent:
The left residue of both maltose and lactose is the non-reducing end, whereas the right residue is the reducing end. There is thus a directionality to these disaccharides and larger oligo- and polysaccharides in that the nonreducing end is on the left, the reducing end on the right (recall for proteins the amino terminus is drawn on the left, the carboxy terminus on the right).

**Polysaccharides (glycans)**

Cellulose, the primary structural component of cell walls, accounts for over half the carbon in the biosphere. It is a linear polymer of up to 15,000 glucose residues in beta (1→4) linkage (Figure 8-9):

Glucose units are rotated 180° with respect to their immediate neighbor, with H-bonds stabilizing the resulting extended conformation.

Each extended chain lines up laterally with others to form sheets, stabilized by H-bonds.

Sheets line up vertically to form an extended, three-dimensional structure stabilized by extensive H-bonding.

In plant cell walls such cellulose fibers are embedded in and cross-linked by a matrix containing other polysaccharides and lignin, a plastic-like phenolic
Chitin, the primary structural component of the exoskeletons of invertebrates, is similar in composition to cellulose, except that N-acetyl glucosamine replaces glucose.

Starch and glycogen, in contrast to cellulose and chitin, are storage polysaccharides. Starch is a mixture of amylose + amylopectin. Amylose is a linear polymer of glucose in alpha (1 - 4) linkage. The result of the alpha linkage is that amylose adopts an irregular aggregating helically coiled conformation (Figure 8-10).
Amylopectin has alpha (1-6) branches every 24 - 30 residues:

![Chemical structure of Amylopectin](image)

**Digestion:**

Saliva contains amylase which randomly hydrolyzes 1 4 linkages

In the small intestine digestion continues via an intestinal amylase to form maltose and maltotriose. Starch fragments containing alpha (1-6) linkages are called dextrins, which are degraded by an alpha-glucosidase and debranching enzyme.

- alpha-glucosidase forms glucose units
- Glycogen = animal starch (branches every 8 - 10 residues)

**Glycosaminoglycans**

These are found in the extracellular spaces of connective tissues such as cartilage, tendon, skin and blood vessel walls. Shown below are the repeating disaccharide units of three glycosaminoglycans.

Hyaluronate is an important component of connective tissue, synovial fluid (lubricates joints), and the vitreous humor of the eye. Hyaluronate has a viscosity dependent on shear. In the absence of shear, it assumes a highly tangled, highly viscous structure, but when sheared the rigid polymers line up, reducing the shear. Hyaluronate solutions are thus excellent biological shock absorbers.
Heparin, in contrast to the other glycosaminoglycans, is found in intracellular granules of the mast cells in arterial walls. Heparin inhibits clotting; thus after injury, release of heparin is thought to prevent runaway clot formation.

Chondroitin-4-sulfate and chondroitin-6-sulfate are found in connective tissue. Supplements of Chondroitin and glucosamine are taken as dietary supplements to foster healthy joints.

**Glycoproteins**

These are proteins with carbohydrate attached via N - or O - linkages.

N-linkage - involves the side chain of Asn residues:
O-linkage - involves the side chain of Ser or Thr residues (Ser shown):

Carbohydrate content ranges from < 1% to > 90%. Glycoproteins include enzymes, transport proteins, receptors, hormones and structural proteins.

Since carbo is attached by enzymes, thus is not under direct genetic control, composition and structure varies (microheterogeneity).

**Proteoglycans**

These are protein/glycosaminoglycan mixes (covalent and noncovalent) that occur in the extracellular matrix (Figure 8-14): A hyaluronic “backbone” has attached to it other glycosaminoglycans, to which are attached up to 100 associated core proteins.
Cartilage consists of a meshwork of collagen fibrils with proteoglycans. Because of the brushlike structure of this structure, and also because of the large number of negatively charged groups, there is a lot of water of hydration associated with it. When the joint is stressed, water is released, but stops after a point due to negative charge repulsion, after which water returns. Since cartilage lacks blood vessels, this aqueous flow nourishes the joint.

**Bacterial Cell Walls**

Bacteria, unlike eukaryotes, have rigid cell walls, in addition to membranes, in order to survive in a hypotonic environment, and to give them shape.

Bacterial cell walls are responsible for virulence, or disease-evoking power. The symptoms of many bacterial diseases can in many cases be elicited by injection of cell walls alone.

Bacteria are classified as gram positive or gram negative according to whether or not they take up the Gram stain (1884, Christian Gram). Gram positive bacteria take up the stain, which penetrates the peptidoglycan cell wall outside the plasma membrane. Gram negative bacteria have a thinner cell wall (3 nm vs 25 nm), but also have a complex outer membrane which cannot be penetrated by the stain.
Gram negative bacteria are also more resistant to antibiotics because it is harder for them to penetrate the outer membrane (Figure 8-15).

Lysozyme (tears) cleaves the glycosidic linkages between carbohydrate residues making up the peptidoglycan of the cell wall.

Penicillin prevents the cross-linking of peptidoglycans by peptides. Its structure resembles a D-amino acid in the cross-link (thus is a “silver bullet”)

**Note:** Almost all secreted and membrane-associated proteins of eukaryotic cells are glycosylated, which are covalently attached to proteins via either N-(Asn) or O-(Ser or Thr) glycosidic linkages

**Oligosaccharides mediate recognition Events**

Because there are OH functional groups at each carbon of glucose, for example, there are \(6 \times 6 = 36\) different ways two glucose molecules can combine, whereas there are only 2 possible ways 2 amino acids can combine. Additionally, polysaccharides can be branched structures. Thus there is the potential for tremendous structural diversity, hence biological information, in carbohydrates.

It is thus not surprising that all cells are coated with carbohydrate in the form of glycoconjugates - carbohydrate linked covalently to proteins or membrane lipids. The carbohydrates form a fuzzy layer up to 1400 angstroms thick in some cells (Figure 8-20)

Additional evidence that cell-surface carbohydrates are involved in recognition events is that lectins frequently appear on cell surfaces. Lectins are
proteins that bind carbohydrates.

Cell-surface carbohydrates are known to be immunochemical markers, such as the ABO blood group antigens. These are the oligosaccharide components of surface glycolipids. A group individuals have A antigens on their cell surfaces and B antibodies; B group individuals have B antigens and A antibodies in their blood; AB individuals have both A and B antigens and no antibodies (thus AB individuals can receive blood from any donor). Type O individuals have no antigens (thus are universal donors) and both A and B antibodies (actually, they possess a “core” oligosaccharide which is non-antigenic).

**Other protein-carbohydrate interactions include:**

N-linked oligosaccharides with mannose-6-phosphate resides tag a protein for processing or degradation by lysosomes.

Removal of sialic acid from circulating glycoproteins results in their selective clearance from the blood.

Normal cells stop growing when they touch each other (contact inhibition). Cancer cells have lost this function, thus form malignant tumors.

Many viruses, bacteria and eukaryotic parasites invade target cells by first binding to cell-surface carbohydrates.

Problems: 1, 6, 8, 9