Part I => CARBS and LIPIDS

§1.2 Monosaccharides
§1.2a Stereochemistry
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Section 1.2a: Stereochemistry
Monosaccharides are carbonyl polyols (or polyhydroxy carbonyls)—they contain a single carbonyl (C=O) group bundled with multiple hydroxyl (OH) moieties—with the general chemical formula (CH$_2$O)$_n$, where n $\geq$ 3

Monosaccharides are classified on the basis of whether the carbonyl group is an aldehyde (aldoses) or a ketone (ketoses)

Aldoses and ketoses are further sub-classified according to the number of C atoms they harbor—e.g., trioses, tetroses, pentoses, hexoses, and so forth

Monosaccharides, or simple sugars, are synthesized from smaller precursors that are ultimately derived from CO$_2$ and H$_2$O by photosynthesis

Monosaccharides display complex stereochemical properties
Monosaccharides are chiral molecules in that they have an asymmetric C atom—i.e., it is attached to four different substituent groups.

Each chiral molecule has a non-superimposable mirror image—the pair of such mirror images are termed “enantiomers.”

Enantiomers are optical isomers—i.e., they rotate the plane of polarized light in opposite directions by equal amounts.

Enantiomers are often designated D and L depending on whether they rotate the plane of polarized light right/dextrorotatory (D) or left/levorotatory (L).

In biochemistry, the so-called Fischer projections are employed to depict the D/L configuration of chiral molecules such as monosaccharides in lieu of the actual rotation of the plane of polarized light.
Polarized Light: Properties

- Light is a form of electromagnetic radiation
- Light is comprised of two electromagnetic wave components that are always in-phase and oscillating perpendicular to each other and to the direction of travel: electric field (E) and magnetic field (B)
- E may oscillate in all directions (non-polarized light)—this includes most sources such as a light bulb or sunlight
- Alternatively, E can be made to oscillate vertically (vertical polarization), horizontally (horizontal polarization), or elliptically (circular polarization)
- It is noteworthy that the polarization of light refers to the direction of oscillation of E (B is always perpendicular to E!)
The direction and angle of rotation of the plane of polarized light can be determined using an instrument called the “polarimeter”.
Stereochemistry: Fischer Projections

Fischer projection is a 2D representation of a 3D molecule.

- In Fischer projection:
  - horizontal lines represent bonds coming out of the page
  - vertical lines represent bonds extending into the page

Monosaccharides are assigned D/L configurations on the basis of the spatial position of the four substituents attached to the asymmetric C atom (harboring four distinct substituents) relative to those of glyceraldehyde:
  - if OH group is to the left → L-isomer
  - if OH group is to the right → D-isomer

L-Glyceraldehyde  D-Glyceraldehyde

Emil Fischer (1852-1919)
Stereochemistry: Enantiomers

- Fischer projections are used to depict the D/L configuration of monosaccharides in lieu of the actual rotation of the plane of polarized light

- Monosaccharides are assigned D/L configurations on the basis of the spatial position of the four substituents attached to the asymmetric C atom (harboring four distinct groups) farthest away from the carbonyl group (e.g., C5 in D-Glucose) relative to those of glyceraldehyde

- L-sugars are simply non-superimposable mirror images of their D counterparts (they are enantiomers)—i.e., they harbor different stereochemical configurations at all chiral centers!

- Because L-sugars are rare in nature, the D- prefix is usually omitted—e.g., glucose implies that it is D-glucose

- Monosaccharides have \(2^n\) stereoisomers, where \(n\) is the number of asymmetric C atoms or chiral centers—e.g., D-glucose is one of \(2^4\) (=16) stereoisomers
Stereochemistry: Enantiomers vs Epimers

- Optical isomers that differ in their configuration at all chiral centers are called enantiomers—hence they are non-superimposable images of each other—all D-sugars and their L-counterparts are enantiomers!

- Optical isomers that differ in their configuration at one or more (but not all) chiral centers are called diastereomers (they are not mirror images)—epimers are a special class of diastereomers!

- Epimers merely differ in the configuration at only one chiral center—eg glucose and galactose differ only in the configuration of OH group @ C4

- Thus, glucose and galactose are epimers—or galactose is an epimer of glucose @ C4 and vice versa

- Like enantiomers, diastereomers and epimers are also optical isomers—a class of stereoisomers that rotate the plane of polarized light due to at least one chiral center!
Aldoses: Aldehyde-Based Monosaccharides

Biologically most common aldoses are boxed!

Configuration around C2 (red) atom distinguishes each pair of epimers

Arrows indicate stereochemical (not biosynthetic) relationships

Aldotrioses

Aldotetraoses

Aldopentoses

Aldohexoses

glucose/mannose are epimers @ C2

glucose/galactose are epimers @ C4
Ketoses: Ketone-Based Monosaccharides

Arrows indicate stereochemical (not biosynthetic) relationships

Configuration around C3 (red) atom distinguishes each pair of epimers

Biologically most common ketoses are boxed!

Ketotriose

Ketotetrose

Ketopentoses

Ketohexoses

fructose/psicose are epimers @ C3
Cyclization: Hemiacetalts and Hemiketals

- Nucleophilic attack of hydroxyl O atom on carbonyl C atom leads to spontaneous production of hemiacetals and hemiketals

- Owing to such nucleophilic reaction (but in an intramolecular manner) between the carbonyl group and one of the hydroxyl moieties, monosaccharides predominantly exist in cyclic forms (comprised of 5- or 6-membered rings) in both liquid and solid state @ thermodynamic equilibrium

- In the cyclic form, the union between the carbonyl and hydroxyl groups creates either an hemiacetal (from aldoses) or hemiketal (from ketoses) group
Owing to nucleophilic reaction between the terminal aldehyde group and the hydroxyl moiety attached to the asymmetric C5 atom farthest from it, the linear form of glucose spontaneously switches to the 6-membered cyclic form termed glucopyranose. Such 6-membered cyclic forms of monosaccharides are called pyranoses in analogy with the heterocyclic pyran ring.
- Owing to nucleophilic reaction between the ketone group and the hydroxyl moiety attached to the asymmetric C5 atom farthest from it, the linear form of fructose spontaneously switches to the 5-membered cyclic form termed fructofuranose.

- Such 5-membered cyclic forms of monosaccharides are called furanoses in analogy with the heterocyclic furan ring.
- The 3D stereochemical configurations of cyclic forms of monosaccharides are usually represented via the so-called Haworth projection.

- In the Haworth projection, the heterocyclic ring lies perpendicular to the plane of the page (with the wedged line denoting atoms coming toward the observer) and the vertical lines indicate atoms above or below the plane of the ring.

- The substituents below the plane of the ring in the Haworth projection are equivalent to those on the right-hand side of Fischer projection—with the position of OH group involved in cyclization replaced with the left-hand side H atom.
Cyclization: Chair conformations

- In the Haworth projection, the heterocyclic ring is non-planar due to tetrahedral (sp$^3$) hybridization of atomic orbitals.

- Since each C atom adopts tetrahedral geometry with respect to its four attached substituents, the heterocyclic ring becomes somewhat “puckered” so as to adopt a “chair conformation” in which steric clashes between attached substituents are minimized.

- In the chair conformation, the bulkiest substituents compete with smaller groups for the less crowded equatorial positions (rather than the more crowded axial positions) resulting in two interconvertible “chairs.”

- The chair conformation in which the bulkiest groups occupy the equatorial positions is thermodynamically the most favorable.
Upon cyclization, the carbonyl C atom (called the anomeric carbon) becomes chiral with two possible stereochemical configurations.

- Such pairs of stereoisomers at the anomeric C atom are referred to as α and β anomers.

- In the α anomer, the anomeric OH group orients below the plane of the ring on the side opposite to the CH₂OH substituent attached to the hydroxyl C atom involved in cyclization.

- In the β anomer, the anomeric OH group orients above the plane of the ring on the same side as the CH₂OH substituent attached to the hydroxyl C atom involved in cyclization.

- α and β anomers freely interconvert at thermodynamic equilibrium—eg glucose is predominantly a mixture of such anomers with negligible contributions from the linear form.
Stereochemistry: Epimers vs Anomers

- Anomers are a special class of epimers in that they are concerned with the stereochemical configuration only at the anomeric C atom (hemiacetal or hemiketal group of cyclic monosaccharides)

- Two anomers of the same linear monosaccharide have distinct physicochemical properties, including their ability to differentially rotate the plane of polarized light

- Since anomers are not mirror images of each other, they are not enantiomers—they are diastereomers and so are epimers!

- $\alpha$-D-glucopyranose and $\alpha$-L-glucopyranose would be enantiomers!
Stereochemistry: Outline

STEREOISOMERS
(spatial configuration of atoms)

OPTICAL ISOMERS
(one or more chiral centers and optical rotation)

CIS-TRANS ISOMERS
(configuration about the double-bond)

DIASTEREOMERS
(different configuration at one or more chiral centers but not all)

ENANTIOMERS
(different configuration at all chiral centers and non-superimposable mirror images)

EPIMERS
(different configuration at only one chiral center)

ANOMERS
(different configuration at the anomeric C atom in cyclic monosaccharides)

What is the difference between chemistry and biology?
The latter is all about stereochemistry!
How does an aldose differ from a ketose?

Draw a Fischer projection of D-glucose. Draw two stereoisomers of this molecule, including one that is an epimer.

Show how aldoses and ketoses can form five- and six-membered rings.

Draw a Haworth projection of D-glucose and identify it as an $\alpha$ or $\beta$ anomer.

Explain why anomers of a monosaccharide can readily interconvert whereas epimers do not.
Section 1.2b: Derivatives
- In addition to serving as fuels to provide living cells with energy, monosaccharides play numerous other regulatory roles central to cellular homeostasis.

- Monosaccharides are the building blocks from which more complex polysaccharides (carbohydrates)—eg starch and glycogen—are synthesized.

- In particular, monosaccharides pull off such remarkable feats by virtue of their ability to exist in the form of numerous derivatives.

- Examples of such derivatives include:
  - alditols
  - aldonic acids
  - alduronic acids
  - deoxy sugars
  - phospho sugars
  - amino sugars
Aldonic Acids: CHO → COOH

Oxidation of the terminal CHO group of an aldose generates the corresponding polyhydroxy carboxylic acid derivative called “aldonic acid”.

- Nomenclature based on simply replacing the suffix –ose in the aldose to –onic in the aldonic acid.

- For example, oxidation of the terminal CHO group of glucose generates gluconic acid—wide occurrence in various fruits.
Alduronic Acids: \( \text{CH}_2\text{OH} \rightarrow \text{COOH} \)

### Oxidation

- **D-Glucose**
  - Oxidation of the terminal \( \text{CH}_2\text{OH} \) group of an aldose generates the corresponding polyhydroxy-carbonyl carboxylic acid called **alduronic acid** (or simply **uronic acid**)

- **D-Glucuronic acid**
  - Nomenclature based on replacing the suffix –ose in the aldose to –uronic in the alduronic acid

- For example, oxidation of the terminal \( \text{CH}_2\text{OH} \) group of **glucose** generates **glucuronic acid** —a component of glycosaminoglycans (see §1.3)
Reduction of the terminal CHO group of an aldose generates the corresponding sugar alcohol (polyol) called alditol.

- Nomenclature based on simply replacing the suffix –ose in the aldose to –itol in the alditol.

- For example, reduction of the terminal CHO group of glucose generates glucitol (more commonly known as sorbitol)—used as a food sweetener.
Deoxy Sugars: OH $\rightarrow$ H

- Reduction (via reductases) of an OH group to H generates the corresponding deoxy sugar

- Nomenclature based on simply prefixing the sugar with n-deoxy-, where n is the position of OH reduced or replaced

- For example, reduction of the OH group @ C2 of ribose generates 2-deoxyribose—a component of DNA (see §4.1)
Phospho Sugars: OH → OPO$_3^{2-}$

- Phosphorylation (via kinases) of an OH group to phosphate moiety generates the corresponding phospho sugar (or sugar phosphate)

- Nomenclature based on simply suffixing the sugar with -n-phosphate, where n is the position of OH phosphorylated

- For example, phosphorylation of the OH group @ C6 of glucose generates glucose-6-phosphate—a key intermediate involved in the oxidation of glucose (from food) via glycolysis to produce energy (see §3.2)
Amino Sugars: \( \text{OH} \rightarrow \text{NH}_2 \)

- Replacement (or amination) of an OH group with \( \text{NH}_2 \) moiety generates the corresponding amino sugar

- Nomenclature based on simply prefixing the sugar with \( n\)-amino-\( n\)-deoxy-, where \( n \) is the position of OH replaced

- For example, amination of the OH group @ C2 of glucose generates 2-amino-2-deoxy-\( \alpha \)-D-glucopyranose (\( \alpha \)-D-glucosamine)—a component of glycosaminoglycans (see §1.3)
Acetyl Sugars: OH → NH₂ → HNCOCH₃

- Amino sugars are frequently subject to further modifications such as acetylation at the NH₂ moiety so as to generate the corresponding acetyl sugar.

- Nomenclature based on simply prefixing the sugar with n-acetylamino-n-deoxy-, where n is the position of OH replaced.

- For example, acetylation of the NH₂ group @ C2 of glucose generates 2-acetylamino-2-deoxy-α-D-glucopyranose (N-acetyl-α-D-glucosamine)—a component of glycosaminoglycans (see §1.3).
O-Glycosides: OH → OR

- Anomeric C atom—or hemi(acetal)ketal group—of sugars can undergo condensation with OH group from another alcohol (e.g., ROH), which may or may not be another sugar.

- Such condensation results in the formation of an “O-glycosidic” bond between anomeric C atom and alcohol O atom—the product is called “O-glycoside.”

- O-glycosides are extremely common in nature—e.g., they serve as the building blocks of disaccharides and more complex polysaccharides (see §1.3).
N-Glycosides: OH → N(H)R

- Anomeric C atom of sugars can also undergo condensation with an –NH or -NH2 group from an amine (eg R-NH₂)

- Such condensation results in the formation of an “N-glycosidic” bond between anomeric C atom and amine N atom—the product is called “N-glycoside”

- N-glycosides are also common in nature—eg they serve as the building blocks of RNA and DNA in the form of (deoxy)ribonucleotides (see §4.1)
Exercise 1.2b

- Write down reaction schemes that generate aldonic acids, uronic acids, alditols, deoxy sugars, and amino sugars

- Explain why a sugar can form at least two different glycosides
DIET COKE EXPOSED—an Alternative Fact Rather Than Alternative Soda!

- Due to its calorie-free nature, diet coke (0 cal/can) is often perceived to be a better substitute for the regular calorie-rich coke (140 cal/can)

- However, diet coke typically contains aspartame as an artificial sweetener

- Not only aspartame is linked to serious health risks ranging from diabetes and heart disease to cancer and neurological disorders but it is also believed to enhance your natural cravings for sugary foods resulting in unnecessary weight gain—ditto for most other artificial sweeteners such as splenda

- If you must sip it, the regular coke is by far the better of the two evils!