Structures of Monosaccharides

Hemiacetals

• Although, the open chain structures of monosaccharides are consistent with the chemistry of carbohydrates, in reality they are oversimplifications of the true structure of carbohydrates.

• It is common knowledge that aldehydes react with alcohols to form hemiacetals. In cases where a molecule is a hydroxyaldehyde such as 4-hydroxybutanal or 5-hydroxypentanal, cyclic hemiacetals result.
Structures of Monosaccharides
Hemiacetals

• Aldoses often contain an aldehyde group and several hydroxyl groups as part of the same molecule; they have a greater tendency of forming cyclic hemiacetals. In fact, in aqueous solution carbohydrates exist almost exclusively in the ring-closed form. At equilibrium, the linear aldehyde or ketone structure represents less than 1% of the sugar present.
• Five and six-membered rings are thermodynamically more stable than their corresponding four and seven membered rings, since they are less strained.
• Five- (furanoses) and six-membered cyclic hemiacetals (pyranoses) are often more stable than their open-chain forms. In particular the six-membered rings which can adopt a chair conformation are essentially free from all types of strains.
Structures of Monosaccharides
Evidence for Existence of Monosaccharides as Hemiacetals

What physical, chemical and spectroscopic evidence support the existence of monosaccharide sugars as cyclic hemi-acetals.

(a) Two anomers of glucose capable of existing independently with different physical (melting points and specific optical rotation) and chemical properties can be obtained by recrystallization.

(b) the $^1$H-NMR and IR-spectra of solutions of pure sugars show the presence of mixtures (anomeric hemiacetals) and absence of an aldehydic peak is a sufficient indicator that the sugars exist in some other form other than the open-chain form.
Structures of Monosaccharides
Evidence for Existence of Monosacharides as Hemiacetals

What physical, chemical and spectroscopic evidence support the existence of monosaccharide sugars as cyclic hemi-acetals.

(c) That the various anomers are interconvertible through mutarotation in solution is further evidence that sugars exist in more than one form. Mutarotation of sugars was the earliest evidence of the existence of sugars as hemiacetals.

(d) Under certain conditions the two anomers react at different rates, but under closely regulated conditions can provide the same product. Since the two anomers are diastereomeric, they react at different rates with chiral reagents such as enzymes.
Structures of Monosaccharides
Hemiacetals of Monosaccharides

• Five-membered cyclic hemiacetals of carbohydrates are called furanoses, in conformity with their parent five-membered oxygen heterocycle (cyclic ether) furan or its unfunctionalized analogue, tetrahydrofuran.

\[ \text{Furan} \quad \text{Tetrahydrofuran} \]

• Six-membered ring hemiacetals of carbohydrates are called pyranoses after the six-membered oxygen heterocycle pyran or its saturated analogue tetrahydropyran.

\[ \text{Pyran} \quad \text{Tetrahydropyran} \]
Structures of Monosaccharides

Haworth Projections

• The Haworth projection is named after the British carbohydrate chemist and also the 1937 Nobel Prize laureate Walter Haworth, who introduced this way of representing cyclic forms of sugars.

• In a Haworth projection, the ring is represented as if it were planar and viewed edge on, with the oxygen at the upper right. The carbons are arranged clockwise numerically, with C-1 at the right.

• The Haworth projection and the chair conformation should always be drawn with the oxygen at the back, right-hand corner, with C-1 at the far right. C-1 is easily identified, because it is the hemiacetal carbon—the only carbon bonded to two oxygen atoms. Substituents attached to the ring lie above or below the plane.
Structures of Monosaccharides
Haworth Projections of Hemiacetals of Monosaccharides

To draw a Haworth projection of a monosaccharide sugar:

(i) Draw either a 5 or 6-membered ring including oxygen as one of the atoms. The oxygen should be at the top right corner.

- Aldotetroses, aldopentoses, ketohexoses have a tendency to form 5-membered ring hemiacetals (furanoses).
- Most aldohexoses exist as six-membered ring hemiacetals (pyranoses).
Structures of Monosaccharides
Drawing Haworth Projections of Furanoses of D-Erythrose

To draw a Haworth projection of a monosaccharide sugar from its Fischer projection:

(i) Turn the Fischer projection to place the carbonyl on the right hand side.

(ii) Identify the OH group required to make the ring size required and turn it to bring it on the plane.

Fischer projection of D-Erythrose

Reoriented eclipsed conformation of D-Erythrose

D-Erythrose

D-Erythrofuranose
Structures of Monosaccharides
Anomers of Furanoses of D-Erythrose

• Notice that the formation of the cyclic, hemiacetal introduces a new chiral centre on C-1, the anomeric centre.

• The **anomeric centre** is the **hemiacetal carbon** of the cyclic form of a monosaccharide.

• Note that the anomeric carbon is the carbon in the ring that is attached to **two oxygens**.

• At the anomeric carbon, the hydroxyl group on C-1 can either be up or down thus for every monosaccharide sugar, two anomers are possible.
The strict definition of α and β is whether the C-1 substituent is formally cis (α), or trans (β) to the oxygen atom at the highest numbered chiral centre, when the sugar is drawn in the Haworth projection.

However this precise definition is rather cumbersome, and for almost all purposes the simple rule of thumb that α is axial (down in D-sugars) and β is equatorial (up in D-sugars) can be applied.
Structures of Monosaccharides
Drawing Haworth Projections of Pyranoses

Harworth projections of pyranoses of cyclic hemiacetals can easily be drawn starting with its Fischer projection through the following process:

(i) Turn the Fischer projection 90° clockwise to lie horizontally on its right side. In this form, the groups that are on the right in the Fischer projection face downwards and the left face upwards.

(ii) Curl C-5 and C-6 to the back away from you in such a way that brings the OH group on C-5 within bonding distance of the carbonyl group.

(iii) Rotate the C(4)-C(5) bond so that the C-5 hydroxyl group can form a part of the ring. For a sugar of the D-series, this rotation puts the terminal CH$_2$OH (C-6 in glucose) upward.

(iv) Close the ring and draw the result.
Structures of Monosaccharides
Drawing Haworth Projections of Pyranoses of D-Glucose

Glucose exists almost entirely in the pyranose form, and only extremely small amounts are either in the furanose or open chain forms.

D-Glucose
HOCH₂
CHO
OH
OH
OH
OH
CHO
OHH
HHO
OHH
OHH
CH₂OH
CHO
OH
H
H
OH
OH
H
OH
H
HOCH₂
Zigzag representation

Fischer projection

90° Clockwise Rotation

Haworth projection

Sitting on right side

C-6 rotated up

H⁺
Structures of Monosaccharides
Are Haworth Projections Realistic Representations of Furanoses?

• The furanoses approximate the conformations of oxacyclopentanes in which the lowest energy conformation is the envelope conformation.

• Since the Haworth projections approximates the envelope conformation, Haworth projections are therefore not overly unrealistic as representations of the furanoses.
Structures of Monosaccharides
Are Haworth Projections Realistic Representations of Pyranoses?

- The conformation of pyranoses approximates the lowest energy chair conformation of oxacyclohexane systems.
- Haworth projections of pyranoses have bonds that are eclipsed and hence of higher energy, while the chair conformation has bonds that are staggered and hence stable conformation.
- The most realistic representation of the pyranoses is as the chair representation.

![Oxacyclohexane](image)

Eclipsed conformation  
High energy representation

Staggered conformation  
Low energy representation
Chair conformations of monosaccharides can easily be derived from their respective Haworth projections through the following protocol:

(i) Start by identifying C-1 (hemiacetal carbon) and C-4 on the Haworth projection.

(ii) Push the hemiacetal carbon (C-1) downwards from the top to provide a footrest for the chair and push C-4 upwards from the bottom to provide a backrest for the chair conformation.

(iii) Note that at each push the bonds at the affected carbons reorient to maintain a tetrahedral arrangement at each carbon. The result is a puckered arrangement of bonds around an oxacyclohexane template with groups in staggered conformations around the ring.
Start by identifying C-1 and C-4 on the Haworth projection of D-Glucose.

- In the chair conformation, the ring substituents are drawn as either equatorial (almost coplanar with the ring) or axial (parallel to a central axis running perpendicular to the plane of the ring).
• It is probably not by accident that glucose is the most abundant natural monosaccharide because in one of the conformations of D-glucopyranose, the larger substituent at each carbon is equatorial.
• The only exception occurs at the anomeric carbon (C-1), where the hydroxyl group may be axial (in the α anomer) or equatorial (in the β anomer). This difference provides one reason why the β anomer is preferred at equilibrium.
Uniqueness of the Chair Conformations of D-Glucose

• With the observation that glucose has its substituents on alternating sides of the ring, it would be the easiest, among the hexopyranoses to remember and to draw. Consequently, in drawing the chair conformation of D-glucose, just put all the ring substituents in equatorial position.

• Other aldohexoses behave similarly in adopting chair conformations that permit the CH₂OH substituent to occupy an equatorial orientation. Normally the CH₂OH group is the bulkiest substituent in the pyranose form of a hexose.

• This observation can be readily exploited in drawing the chair conformations of the other monosaccharides of the D-series in that by identifying how they differ from glucose, one can make the appropriate changes starting from a D-glucose template.
Chair Conformations of Sugars related to D-Glucose

- The most notable monosacharides related to D-glucose are D-mannose, which is epimeric to D-glucose at C-2 and D-galactose, which is epimeric at C-4.
- These can be readily derived from chair conformation of β-D-glucopyranose.