Aldotetrasoses

Be sure you have chosen position next to #1 (aldehyde)

This also works for non OH (Use regular rules)

D-(-)-Erythrose  \[\text{zig-zag} \]

erythro  same side (syn)

Fischer  opposite sides (anti)

threo  opposite sides (anti)

same side (syn)
Erythro and Threo

- Terms used for diastereomers with two adjacent chiral carbons, without symmetric ends.
- For symmetric molecules, use meso or $d,l$.

2,3-dibromopentane

Meso tartaric acid
Epimers

Sugars that differ only in their stereochemistry at a single carbon.

- D-mannose
- D-glucose
- D-galactose
Cyclic Structure for Glucose

Glucose cyclic hemiacetal formed by reaction of -CHO with -OH on C5.

Fischer projection on right side

C6 rotated up

Haworth projection

Chair conformation (all substituents equatorial)

Chair conformation (OH on C1 axial)

\( \text{D-gluco} \)pyranose
Anomers

α-d-glucopyranose

open-chain form

β-d-glucopyranose

α-d-fructofuranose

β-d-fructofuranose
Reactions of monosaccharides

• Normal chemical reactions related to the presence of
  – C=O in aldehyde and ketone groups
  – OH groups

• Special reactions due to the large number of very closely spaced functional groups in the molecule
Reactions of carbohydrates

Epimerization
Enediol Rearrangement
Hemiacetal Formation
Reduction
Oxidation
Osazone Formation
Chain Shortening
Chain Lengthening
Epimerization

In base, H on C2 may be removed to form enolate ion. Reprotonation may change the stereochemistry of C2.
Enediol Rearrangement

In base, the position of the C=O can shift. Chemists use acidic or neutral solutions of sugars to preserve their identity.

Step 1: Remove the $\alpha$ proton
Step 2: Reprotonate on O
Step 3: Deprotonate the O on C2
Step 4: Reprotonate on C1

$d$-glucose \[\rightarrow\] enolate \[\leftrightarrow\] enediol \[\rightarrow\] enolate \[\leftrightarrow\] $d$-fructose
Formation of Glycosides

- React the sugar with alcohol in acid.
- Since the open chain sugar is in equilibrium with its $\alpha$- and $\beta$-hemiacetal, both anomers of the acetal are formed.
- Aglycone is the term used for the group bonded to the anomeric carbon.
Ether Formation
Conversion of all -OH groups to -OR,

- Modified Williamson synthesis
- After converting sugar to acetal, stable in base.
- Helps to purify by recrystallization from water.

Example

\[
\text{α-D-glucopyranose} \rightarrow \text{methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside}
\]
Ester Formation

Acetic anhydride with pyridine catalyst converts all the free oxygens to acetate esters.

Example

\[
\begin{align*}
\text{HOCH}_2 & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{HO} & \quad \text{OH} \\
\text{CH}_2\text{OH} & \quad \text{OH} \\
\beta-\text{d-fructofuranose} & \quad \text{pyridine}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{CH}_3
\end{align*}
\]

penta-\text{O-acetyl-\beta-d-fructofuranoside}
Reduction to Alditols

The carbonyl group of a monosaccharide can be reduced to a hydroxyl group by a variety of reducing agents, including NaBH₄ and H₂/M

![Chemical structures]

D-Glucose

D-Glucitol
(D-Sorbitol)
Reduction of Simple Sugars

• C=O of aldoses or ketoses can be reduced to C-OH by NaBH$_4$ or H$_2$/Ni.

• Name the sugar alcohol by adding -itol to the root name of the sugar.

• Reduction of D-glucose produces D-glucitol, commonly called D-sorbitol.

• Reduction of D-fructose produces a mixture of D-glucitol and D-mannitol.
Sorbitol

• About 60% as sweet as sucrose

• Sugar substitute for diabetics

• Used in manufactured of sweets
  – ‘Sugar-free’ really means ‘sucrose-free’

• Moisturing creams (‘Sorbolene’)
Nonreducing Sugars

• Glycosides are acetals, stable in base, so they do not react with Tollens reagent.
• Disaccharides and polysaccharides are also acetals, nonreducing sugars.

Examples of nonreducing sugars

- methyl β-D-glucopyranoside (or methyl β-D-glucoside)
- ethyl α-D-fructofuranoside (or ethyl α-D-fructoside)
Oxidation by Tollens Reagent

Tollens reagent reacts with aldehyde, but the base promotes enediol rearrangements, ketoses react too.

 Sugars that give a silver mirror with Tollens are called reducing sugars.
Oxidation by Bromine

Bromine water oxidizes aldehyde, but not ketone or alcohol; forms aldonic acid.

Example

[Diagram showing the oxidation of aldehyde to aldonic acid (glyconic acid) and the oxidation of glucose to gluconic acid]
Oxidation to Aldonic Acids

- Oxidation of the -CHO group of an aldose to a -CO₂H group can be carried out using Tollens’, Benedict’s, or Fehling’s solutions.

\[
\text{RCH} + \text{Ag}\left(\text{NH}_3\right)_{2}^{+} + \text{NH}_3, \text{H}_2\text{O} \rightarrow \text{RCO}^- \text{NH}_4^+ + \text{Ag} \quad \text{Tollens’ solution}
\]

Precipitates as a silver mirror

\[
\text{RCH} + \text{Cu}^{2+} \rightarrow \text{RCO}^- + \text{Cu}_2\text{O} \quad \text{Precipitates as a red solid}
\]

- Tollens’ solution: \(\text{NH}_3, \text{H}_2\text{O} + \) citrate or tartrate buffer
- Benedict’s solution: \(\text{NH}_3, \text{H}_2\text{O} + \) citrate or tartrate buffer
- Fehling’s solution: \(\text{NH}_3, \text{H}_2\text{O} + \) citrate or tartrate buffer
Oxidation to Aldonic Acids

- 2-Ketoses are also oxidized by these reagents because, under the conditions of the oxidation, 2-ketoses equilibrate with isomeric aldoses.

\[
\begin{align*}
\text{A 2-ketose} & \quad \leftrightarrow \quad \text{An enediol} \\
\text{An aldose} & \quad \leftrightarrow \quad \text{An aldose}
\end{align*}
\]
Oxidation by Nitric Acid

Nitric acid oxidizes the aldehyde and the terminal alcohol; forms aldaric acid.

Example

\[
\text{aldehyde} \quad \text{(CHOH)}_n \xrightarrow{\text{HNO}_3} \quad \text{acid} \quad \text{COOH} \\
\text{alcohol} \quad \text{CH}_2\text{OH} \quad \text{aldaric acid (glycaric acid)} \\
\text{glucose} \quad \text{CH}_2\text{OH} \quad \text{glucaric acid}
\]
Oxidation to Aldaric Acids

D-(-)-ribose → ribaric acid (achiral)

D-(-)-arabinose → D-arabinaric acid \equiv D-lyxaric acid → D-(-)-lyxose

This aldaric acid is achiral and is optically inactive.
Question #1
Which of the following aldaric acids are optically active?

C and D
Question #2

Draw a hexose that would give the same aldonic acid product as D-Glucose

D·(+)- glucose

Same product
Question #3
There are four D-aldopentoses. Draw Fischer projections of each of them. Then draw Fischer projections of the aldaric acids they would yield. Which of those aldaric acids would be optically active?

D-Ribose  D-Arabinose  D-Xylose  D-Lyxose
(2R, 3R, 4R)  (2S, 3R, 4R)  (2R, 3S, 4R)  (2S, 3S, 4R)
Osazone Formation

Both C1 and C2 react with phenylhydrazine.
Osazone

Sugars differ in configuration only at the $\alpha$-carbon.
Question #4

Select the compounds that would produce the same osazone.
Aldoses versus Ketoses

Reductions provide the same alcohol products.

Ketoses are not easily oxidized by Tollens' reagent but slowly react via enol.

Tollen's is not useful for distinguishing aldoses from ketoses

Oxidation by HOBr reacts only with aldehydes to form aldonic acids.

Oxidation with HNO\textsubscript{3} gives the same aldaric acids.

Both form the same phenylhydrozones.
Ruff Degradation

Aldose chain is shortened by oxidizing the aldehyde to -COOH, then decarboxylation.
Question #5

Aldohexose 2 would yield the same aldopentose as.
Aldohexose 3 would yield the same aldopentose as.
Aldohexose 4 would yield the same aldopentose as.
Question #6

Draw a Fischer projection of L-mannose, then select the aldose that is formed by Ruff degradation of L-mannose.
Kilian-Fischer Synthesis

- This process lengthens the aldose chain.
- A mixture of C2 epimers is formed.
Chain Lengthening

$C_n$ aldose \[\xrightarrow{HCN, H_3O^+} \xrightarrow{1\text{ lactonization}} \xrightarrow{2\text{ reduction}} \text{ mixture of } C_{n+1}\text{ aldonic acid} + C_{n+1}\text{ aldonic acid} \]

Kiliiani-Fischer synthesis
Question #7

Select the aldoses that would be formed by a Kiliani-Fischer synthesis in which D-threose was the starting material:
Determination of Ring Size

• Haworth determined the pyranose structure of glucose in 1926.

• The anomeric carbon can be found by methylation of the -OH’s, then hydrolysis.
Periodic Acid Cleavage

- Periodic acid cleaves vicinal diols to give two carbonyl compounds.
- Separation and identification of the products determine the size of the ring.
Fischer’s Proof

• Emil Fischer determined the configuration around each chiral carbon in \( \text{D}-\text{glucose} \) in 1891, using Ruff degradation and oxidation reactions.
• He assumed that the \(-\text{OH}\) is on the right in the Fischer projection for \( \text{D}-\text{glyceraldehyde} \).
• This guess turned out to be correct.
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(HI):</td>
<td></td>
</tr>
<tr>
<td>Cyanohydrin formation (HCN)</td>
<td></td>
</tr>
<tr>
<td>Reduction (Ni / H₂)</td>
<td></td>
</tr>
<tr>
<td>Mild oxidation (Br₂ / H₂O):</td>
<td></td>
</tr>
<tr>
<td>Strong oxidation (dil.HNO₃)</td>
<td></td>
</tr>
<tr>
<td>React with Acetate</td>
<td></td>
</tr>
<tr>
<td>Reduce then react with Acetate:</td>
<td></td>
</tr>
</tbody>
</table>
The four chiral centers in glucose tells us there are sixteen \( 2^4 \) stereoisomers.

There are eight diastereomeric pairs of enantiomers.
Aldohexoses

Each of these aldohexoses is a diastereomer of each of the others. Each is a D-aldohexose (the OH on the bottom chiral carbon is to the right). Each has a mirror image which is its enantiomer and is an L-aldohexose. (The mirror images have the OH on the bottom chiral carbon to the left -- draw them and see.)
Question #8
Which of the following aldohexoses would produce optically active aldaric acids?
Question #9
Which of the three structures below would yield an optically active aldaric acid?
Pentanepentols

Four Stereoisomeric $\text{C}_5\text{H}_{12}\text{O}_5$ Pentanepentols

Enantiomers

2-(S), 4-(S)

2-(R), 4-(R)

meso-Compounds

2-(S), 4-(R)

2-(S), 4-(R)
Stereochemistry

2,3-dihydroxybutanedioic acid \textit{meso} achiral diastereomer, (optically inactive overall)

(+)-tartaric acid: \([\alpha]_D = +12^\circ\) m.p. 170 °C

(-)-tartaric acid: \([\alpha]_D = -12^\circ\) m.p. 170 °C

\textit{meso}-tartaric acid: \([\alpha]_D = 0^\circ\) m.p. 140 °C
C2 Epimers

\[
\begin{align*}
\text{glucose} & : \text{CHO} & \text{mannose} & : \text{CHO} \\
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} & \\
\text{HO} & & \text{HO} & \\
\text{H} & & \text{H} & \\
\text{H} & & \text{H} & \\
\text{OH} & & \text{OH} & \\
\text{H} & & \text{OH} & \\
\text{H} & & \text{OH} & \\
\end{align*}
\]

Core of alcohols - mild oxidation or strong oxidation

\[
\begin{align*}
\text{glucose} & \quad \text{mannose} \\
\text{X} & & \text{X} & \\
\text{HO} & & \text{HO} & \\
\text{H} & & \text{H} & \\
\text{H} & & \text{H} & \\
\text{HO} & & \text{HO} & \\
\text{H} & & \text{HO} & \\
\text{H} & & \text{OH} & \\
\end{align*}
\]

No Symmetry

\[
\begin{align*}
\text{mannose} & \quad \text{C}_2\text{- symmetry} \\
\text{X} & & \text{X} & \\
\text{HO} & & \text{HO} & \\
\text{H} & & \text{H} & \\
\text{H} & & \text{H} & \\
\text{HO} & & \text{HO} & \\
\text{H} & & \text{OH} & \\
\text{H} & & \text{OH} & \\
\end{align*}
\]
Conclusions

D-(+)-glyceraldehyde

D-(-)-erythrose

D-(-)-threose

D-(-)-ribose

D-(-)-arabinose

D-(+)-xylose

D-(-)-lyxose

D-(+)-allose D-(+)-altrose D-(+)-glucose D-(+)-mannose D-(-)-gulose D-(-)-idose D-(+)-galactose D-(+)-talose
Fischer's Reasons

1. Osazone formation with glucose and mannose →

2. a) Ruff shortening: glucose →
   b) Kiliani-Fischer synthesis on arabinose →

3. a) Ruff degradation: Ribose and arabinose →
   b) Kiliani-Fischer synthesis on erythrose →

4. Oxidation of erythrose →

5. Oxidation of ribose →

6. Identify:
Question #10

Draw Fischer projections of the aldaric acids that would be formed from aldohexoses 2 and 6 and 4 and 8. Select the compounds that would yield optically active aldaric acids.

D-glucose and D-mannose must be
Question #11
Which of these two would provide a new sugar when the ends were interchanged.