Carbohydrates

For B.SC. Botany 3rd

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Carbohydrates

Carbohydrates are the most abundant organic compounds in the plant world. They act as storehouses of chemical energy (glucose, starch, glycogen); are components of supportive structures in plants (cellulose), crustacean shells (chitin), and connective tissues in animals (acidic polysaccharides); and are essential components of nucleic acids (D-ribose and 2-deoxy-D-ribose). Carbohydrates make up about three fourths of the dry weight of plants. Animals (including humans) get their carbohydrates by eating plants, but they do not store much of what they consume. Less than 1% of the body weight of animals is made up of carbohydrates. Carbohydrates are the most abundant class of organic compounds found in living organisms. They originate as products of photosynthesis, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll.

$$nCO_2 + nH_2O + \text{energy} \xrightarrow[\text{chlorophyll}]{\text{sunlight}} C_nH_{2n}O_n + nO_2$$

The name carbohydrate means hydrate of carbon and derives from the formula $C_n\ (H_2O)_m$. Following are two examples of carbohydrates with molecular formulas that can be written alternatively as hydrates of carbon.

Glucose (blood sugar): $C_6H_{12}O_6$, or alternatively $C_6\ (H_2O)_6$

Sucrose (table sugar): $C_{12}H_{22}O_{11}$, or alternatively $C_{12}\ (H_2O)_{11}$

Not all carbohydrates, however, have this general formula. Some contain too few oxygen atoms to fit this formula, and some others contain too many oxygens. Some also contain nitrogen. The term carbohydrate has become so firmly rooted in chemical nomenclature that, although not completely accurate, it persists as the name for this class of compounds.

At the molecular level, most carbohydrates are polyhydroxyaldehydes, polyhydroxyketones, or compounds that yield either of these after hydrolysis. Therefore, the chemistry of carbohydrates is essentially the chemistry of hydroxyl groups and carbonyl groups, and of the acetal bonds formed between these two functional groups.

The fact that carbohydrates have only two types of functional groups, however, belies the complexity of their chemistry. All but the simplest carbohydrates contain multiple chiral centers. For example, glucose, the most abundant carbohydrate in the biological world, contains one aldehyde group, one primary and four secondary hydroxyl groups, such as four chiral centers. Working with molecules of this complexity presents enormous challenges to organic chemists and biochemists alike. The carbohydrates are a major source of metabolic energy, both for plants and for animals that depend on plants for food. Carbohydrates are called saccharides or if they are relatively small, sugars. Several classifications of carbohydrates have proven useful and are outlined in the following table 1.

Table 1:

Complexity	**Simple Carbohydrates** Monosaccharides			**Complex Carbohydrates** Disaccharides, oligosaccharides & polysaccharides		
Size	Triose $C_3H_6O_3$	**Tetrose** $C_4H_8O_4$	**Pentose** $C_5H_{10}O_5$	**Hexose** $C_6H_{12}O_6$	**Heptose** $C_7H_{14}O_7$	**Octose** $C_8H_{16}O_8$
C=O Function	**Aldose** Sugars having an aldehyde function or an acetal equivalent. **Ketose** Sugars having a ketone function or an acetal equivalent.					
Reactivity	**Reducing** Sugars oxidized by Tollen's reagent (or Benedict's or Fehling's reagents)**.** **Non-reducing** Sugars not oxidized by Tollen's or other reagents.					

Monosaccharides

A. Structure and Nomenclature

Monosaccharides have the general formula $C_nH_{2n}O_n$ with one of the carbons being the carbonyl group of either an aldehyde or a ketone. The most common monosaccharides have three to eight carbon atoms. The suffix-**ose** indicates that a molecule is a carbohydrate, and the prefixes *tri-*, *tetr-*, *pent-*, and so forth indicate the number of carbon atoms in the chain. Monosaccharides containing an aldehyde group

are classified as **aldoses**; those containing a ketone group are classified as **ketoses**. A ketose can also be indicated with the suffix **ulose**; thus, a five- carbon ketose is also termed a **Pentulose**.

Another type of classification scheme is based on the hydrolysis of certain carbohydrates to simpler carbohydrates i.e. classifications based on number of sugar units in total chain.

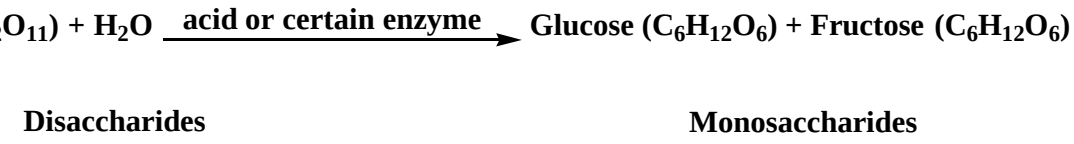
Monosaccharides: single sugar unit

Disaccharides: two sugar units

Oligosaccharides: 3 to 10 sugar units

Polysaccharides: more than 10 units

Monosaccharides cannot be converted into simpler carbohydrates by hydrolysis. Glucose and fructose are examples of monosacchides. Sucrose, however, is a disaccharide-a compound that can be converted by hydrolysis into two monosaccharides.



Disaccharides **Monosaccharides**

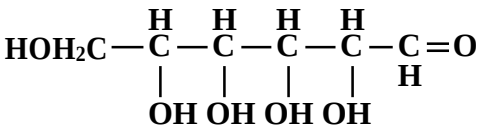
There are only two trioses: the aldotriose glyceraldehyde and the ketotriose dihydroxyacetone.

Glyceraldehyde (an aldotriose) **Didroxyacetone (a ketotriose)**

B. Stereochemistry and Configuration:

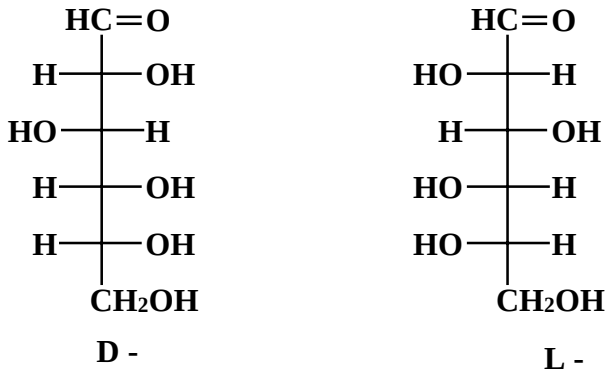
We'll consider the stereochemistry of carbohydrates by focusing largely on the aldoses with six or fewer carbons. The aldohexoses have four asymmetric carbons

and therefore exist as 2^4 orsixteen possible stereoisomers. These can be divided into two enantiomeric sets of eight diastereomers.



Aldohexoses
four asymmetric carbons
2^4 = 16 stereoisomers

Similarly, there are two enantiomeric sets of four diastereomers (eight stereoisomers total) in the aldopentose series. Each diastereomer is *a different carbohydrate with different properties, known by a different name. The aldoses with six or fewer carbons are given as Fischer projections. Be sure you understand how to draw and interpret Fischer projections, as they are widely used in carbohydrate chemistry. Each of the monosaccharides has an enantiomer. For example, the two enantiomers of glucose have the following structures:*



Enantiomers of glucose

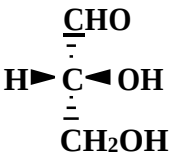
It is important to specify the enantiomers of carbohydrates in a simple way. Suppose you had a model of one of these glucose enantiomers in your hand. You could, of course, use the *R,S* system to describe the configuration of one or more of the asymmetric carbon atoms. A different system, however, was in use long before the *R,S* system was established. The D,L system, which came from proposals made in 1906 by M. A. Rosanoff, is used for this purpose.

Often the designations *aldo*- and *keto*- are omitted, and these molecules are referred to simply as trioses, tetroses, and the like.

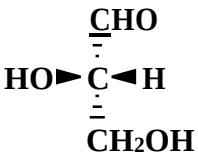
C. Fischer Projection Formulas:

Glyceraldehydes contains a chiral center and therefore exists as a pair of enantiomers.

Glyceraldehyde is a common name; the IUPAC name for this monosaccharide is 2,3-dihydroxypropanal. Similarly, dihydroxyacetone is a common name; its IUPAC name is 1,3-dihydroxypropanone. The common names for these and other monosaccharides, however, are so firmly rooted in the literature of organic chemistry and biochemistry that they are used almost exclusively to refer to these compounds. Therefore, throughout our discussions of the chemistry and biochemistry of carbohydrates, we use the names most common in the literature of chemistry and biochemistry.



(*R*)-Glyceraldehyde

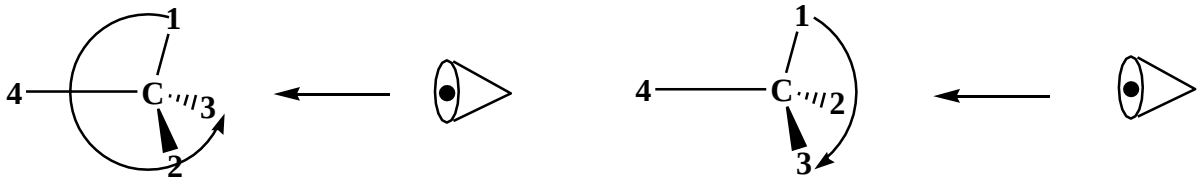


(*S*)-Glyceraldehyde

Chemists commonly use two-dimensional representations called **Fischer projections** to show the configuration of carbohydrates. Following is an illustration of how a three-dimensional representation is converted to a Fischer projection.

(*R*)-Glyceraldehyde (three-dimensional representation)

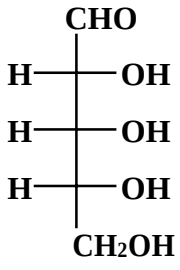
(*R*)-Glyceraldehyde (Fischer projection)



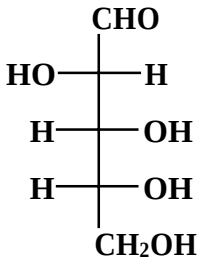
(S) *(R)*

The horizontal segments of a Fischer projection represent bonds directed toward you and the vertical segments represent bonds directed away from you. The only atom in the plane of the paper is the chiral center.

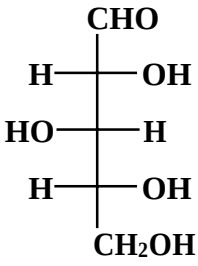
Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



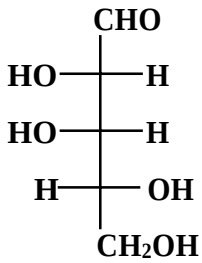
D-(-)-ribose
(2R,3R,4R)



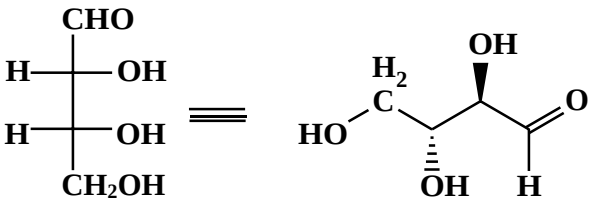
D-(-)-arabinose
(2S,3R,4R)



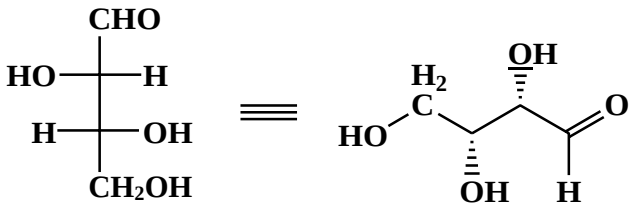
D-(+)-xylose
(2R,3S,4R)



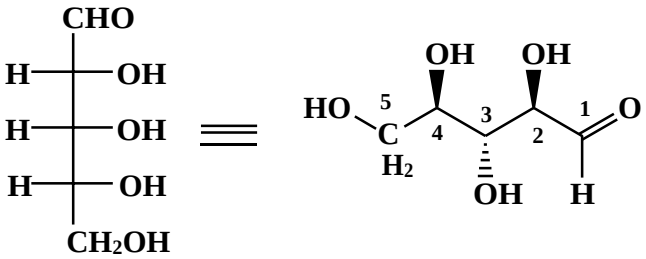
D-(-)-lyxose
(2S,3S,4R)



D-(-)-Erythrose



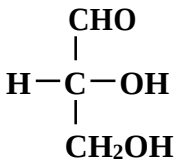
D-(-)-Threose



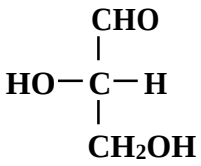
D-(-)-Ribose
2(R),3(R),4(R),5-tetrahydroxypentanal

D. D-and L-Monosaccharides:

Even though the *R,S* system is widely accepted today as a standard for designating configuration, the configuration of carbohydrates as well as those of amino acids and many other compounds in biochemistry is commonly designated by the *D,L* system proposed by Emil Fischer in 1891. At that time, it was known that one enantiomer of glyceraldehyde has a specific rotation of + 13.5; the other has a specific rotation of -13.5. Fischer proposed that these enantiomers be designated *D* and *L* (for dextro and levorotatory) but he had no experimental way to determine which enantiomer has which specific rotation. Fischer, therefore, did the only possible thing-he made an arbitrary assignment. He assigned the dextrorotatory enantiomer an arbitrary configuration and named it *D*-glyceraldehyde. He named its enantiomer *L*-glyceraldehyde.



D-Glyceraldehyde
$[\alpha]_D^{25}$ = +13.5



L-Glyceraldehyde
$[\alpha]_D^{25}$ = -13.5

Fischer could have been wrong, but by a stroke of good fortune he was correct, as proven in 1952 by a special application of X-ray crystallography.

D- and L-glyceraldehyde serve as reference points for the assignment of relative configuration to all other aldoses and ketoses. The reference point is the chiral center farthest from the carbonyl group. Because this chiral center is always the next to the last carbon on the chain, it is called the penultimate carbon. A D-monosaccharide has the same configuration at its penultimate carbon as D-glyceraldehyde (its-OH is on the right when written as a Fischer projection); an L-monosaccharide has the same configuration at its penultimate carbon as L-glyceraldehyde (its-OH is on the left).

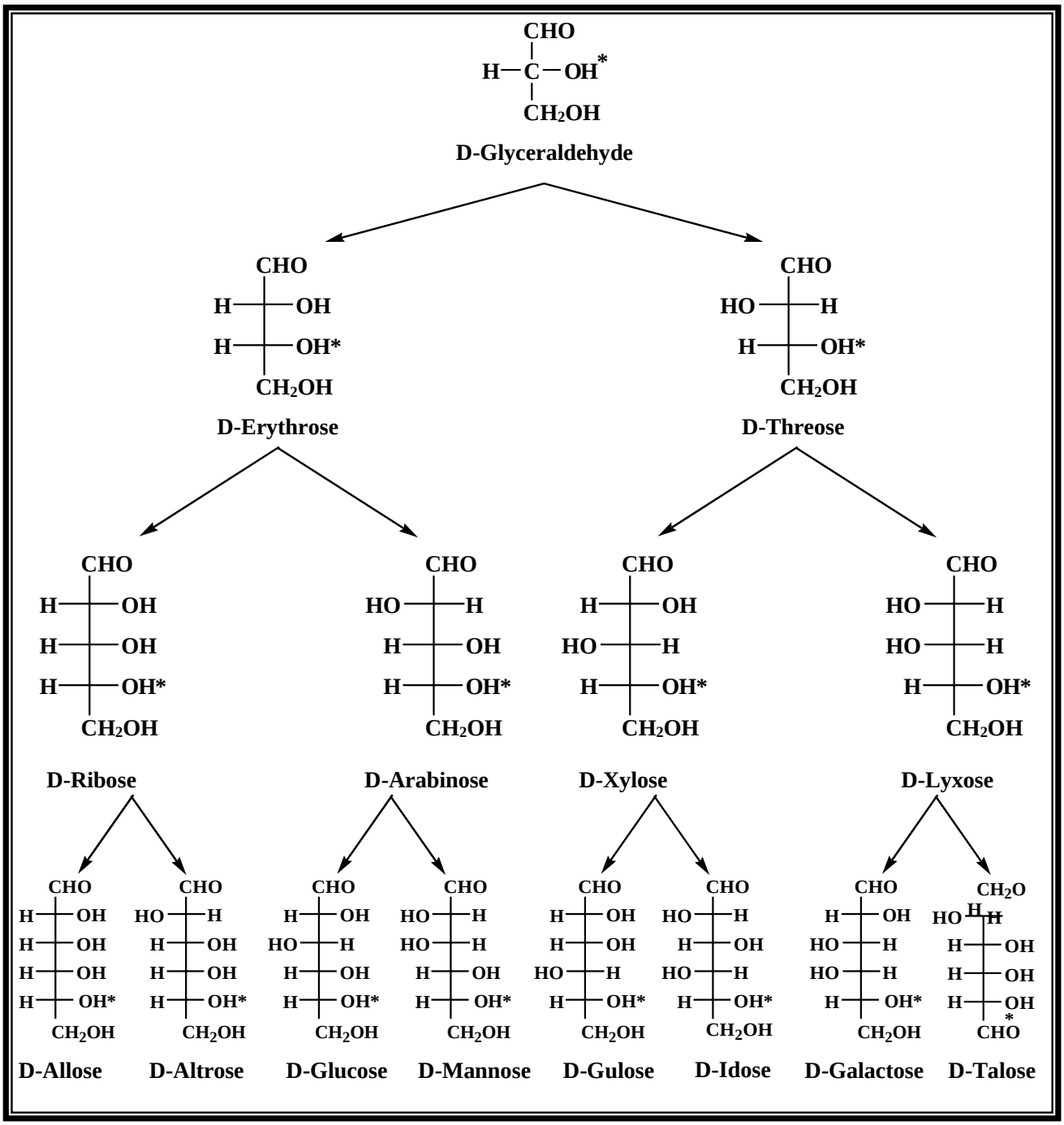
Table.2 shows names and Fischer projections for all D-aldotetroses, pentoses, and hexoses. Each name consists of three parts. The letter D specifies the configuration of the penultimate carbon. Prefixes such as *rib*-, *arabin*-, and *gluc*- specify the configuration of all other chiral centers in the monosaccharide. The suffix -*ose* shows that the compound is a carbohydrate.

The three most abundant hexoses in the biological world are D-glucose, D-galactose, and D-fructose. The first two are D-aldohexoses; the third is a D-2-ketohexose. Glucose, by far the most common hexose, is also known as dextrose because it is dextrorotatory. Other names for this monosaccharide are grape sugar and blood sugar. Human blood normally contains 65-110 mg of glucose/100 mL of blood. Glucose is synthesized by chlorophyll-containing plants using sunlight as a source of energy. In the process called photosynthesis, plants convert carbon dioxide from the air and water from the soil to glucose and oxygen.

D-Fructose is found combined with glucose in the disaccharide sucrose (table sugar). D-Galactose is obtained with glucose in the disaccharide lactose (milk sugar).

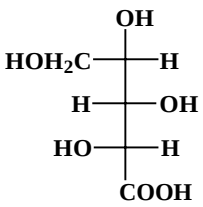
D-Ribose and 2-deoxy-D-ribose, the most abundant pentoses in the biological world, are essential building blocks of nucleic acids; D-ribose in ribonucleic acids (RNA) and 2-deoxy-Dribose in deoxyribonucleic acids (DNA).

Table 2: Configarational Relationships Among the Isomeric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses



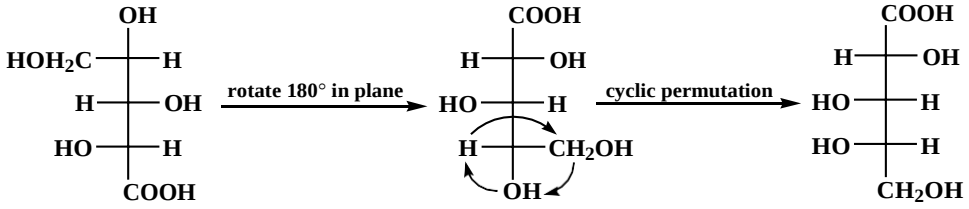
Study Proplem:

Determine whether the following carbohydrate derivative, shown in Fischer projection, has the 0 or L configuration.

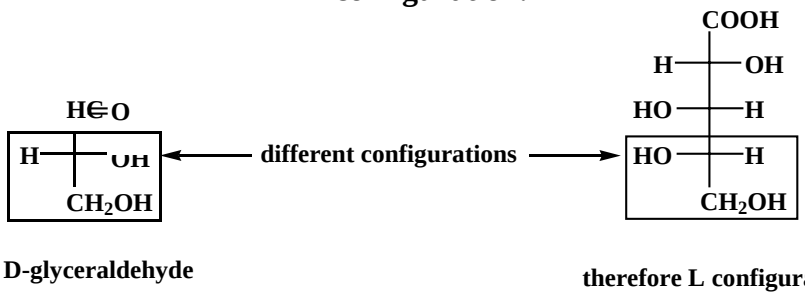


Solution:

First redraw the structure so that the carbon with the lowest number in substitutive nomenclature the carboxylic acid group is at the top. This can be done by rotating the structure 1800° in the plane of the page. Then carry out a cyclic permutation of the three groups at the bottom so that all carbons lie in a vertical line. Fischer projections.

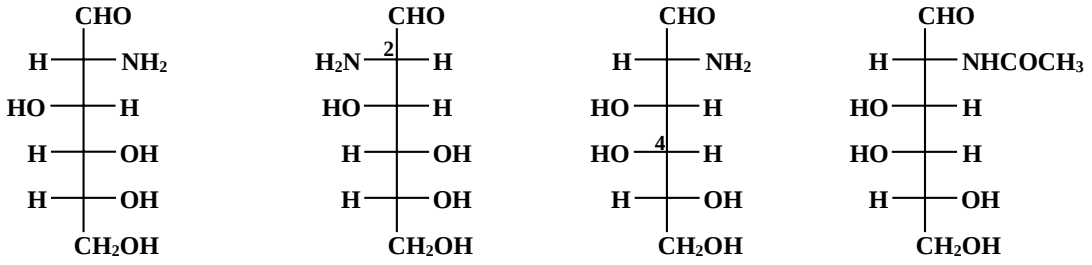


Finally, compare the configuration of the highest-numbered asymmetric carbon with that of D-glyceraldehyde. Because the configuration is different, the molecule has the L configuration.



E. Amino Sugars:

Amino sugars contain an -NH_2 group in place of an -OH group. Only three amino sugars are common in nature: D-glucosamine, D-mannosamine, and D-galactosamine.



D-Glucosamine

D-Mannosamine (C-2 stereoisomer of D-Glucosamine)

D-Galactosamine (C-4 stereoisomer of D-Glucosamine)

***N*-Acetyl-D-Glucosamine**

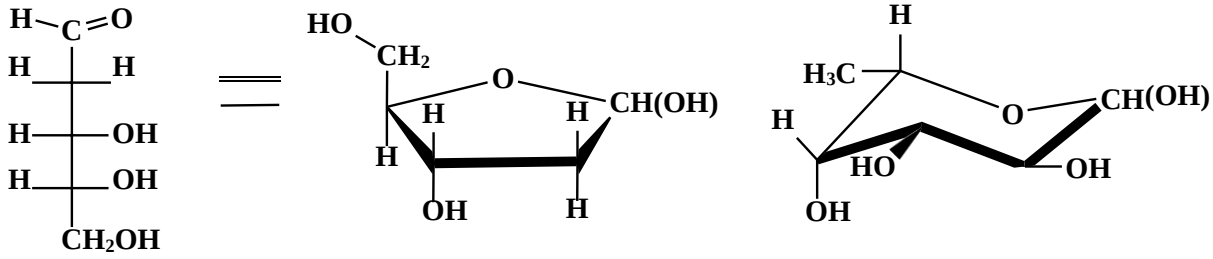
N-Acetyl-D-glucosamine, a derivative of D-glucosamine, is a component of many polysaccharides, including chitin, the hard shell-like exoskeleton of lobsters, crabs, shrimp, and other shellfish. Many other amino sugars are components of naturally occurring antibiotics.

F. Physical Properties:

Monosaccharides are colorless, crystalline solids, sweet to the taste, although they often crystallize with difficulty. Because hydrogen bonding is possible between their polar OH groups and water, all monosaccharides are very soluble in water. They are only slightly soluble in ethanol and are insoluble in nonpolar solvents such as diethyl ether, chloroform, and benzene.

G. Modified Monosaccharides:

Many modified monosaccharides are deoxy-derivatives. In other words, one or more of the hydroxyl groups present in a normal sygar are missing. Examples of two such deoxy-sugars are given in the following diagram.

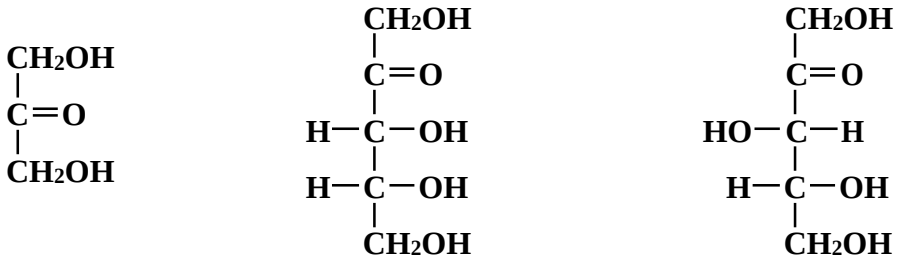


2-deoxy-D-ribose
(an important component of DNA)

L-Fucose
6-deoxy-L-galactose
(found in seaweed)

3. Ketoses

If a monosaccharide has a carbonyl function on one of the inner atoms of the carbon chain it is classified as a ketose. Dihydroxyacetone may not be a sugar, but it is included as the ketose analog of glyceraldehyde. The carbonyl group is commonly found at C-2.

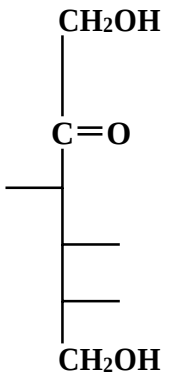


Dihydroxyacetone **D-(-)-Ribulose** **D-(-)-Xylulose**

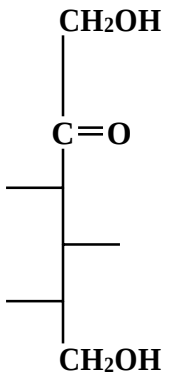
As expected, the carbonyl function of a ketose may be reduced by sodium borohydride, usually to a mixture of epimeric products. D-Fructose, the sweetest of the common natural sugars, is for example reduced to a mixture of D-glucitol

(sorbitol) and D-mannitol, named after the aldohexoses from which they may also be obtained by analogous reduction. Mannitol is itself a common natural carbohydrate. Although the ketoses are distinct isomers of the aldose monosaccharides, the chemistry of both classes is linked due to their facile interconversion in the presence of acid or base catalysts. This interconversion, and the corresponding epimerization at sites alpha to the carbonyl functions, occurs by way of an enediol tautomeric intermediate.

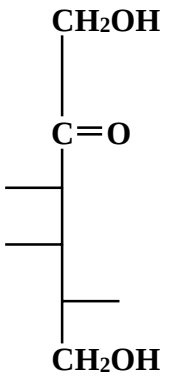
Since ketohexoses contains three dissimilar carbon atoms, there are eight optically active forms (four pairs of enantiomorphe) possible theoretically of only six are known. Only D(-) fructose, L (-) sorbose and D (+) tagatose occur naturally.



D(-)-Fructose



L(-)-Sorbose



D(+)-Tagatose

Structure and stereochemistry of glucose:

A- Structure of glucose:

The structure of glucose is based on the following experimental facts:

Experimental facts:

1- Combustion analysis and molecular weight determination give the molecular formula $C_6H_{12}O_6$

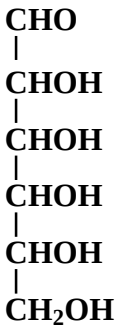
2- Reduction with hydroiodic acid and red phosphorus yielded several products among them hexaiodo-n-hexane and n-hexane itself, denoting that in glucose the carbon atoms are linked in an open chain, as zigzag stracture.

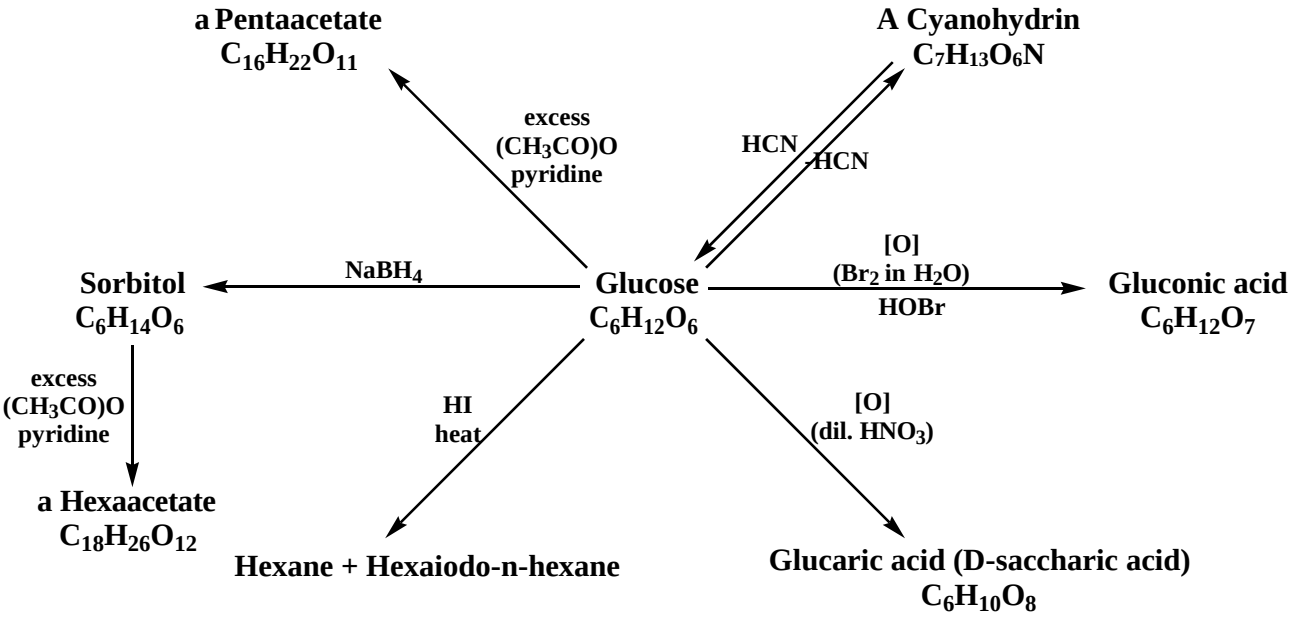
3- Glucose gives the characteristic reactions of carbonyl compounds, e.g. it gives an oxime, semicarbazone, and phenylhydrazone etc……

4- On oxidation it gives gluconic acid which possess the same number of carbon atoms, we then can concludes that the carbonyl group is aldehydic.

5- On acetylation it gives a pentaecetate denoting that it contains 5 hydroxyl groups.

6- The 6 remaining hydrogen atoms are then added to complete the valency of carbone atoms. It is clear that such a molecule have 4-asymmetric carbon atoms.





B- Proof of Glucose Stereochemistry:

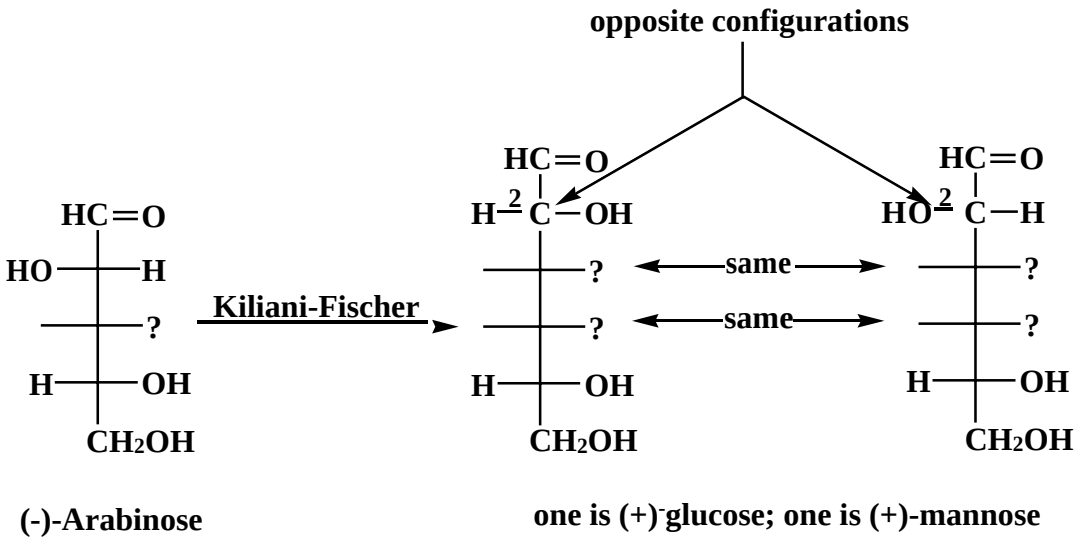
The aldohexose structure of (+)-glucose (that is, the structure without any stereochemical details) was established around 1870. The van't Hoff-LeBel theory of the tetrahedral carbon atom, published in 1874, suggested the possibility that glucose and the other aldohexoses could be stereoisomers. The problem to be solved, then,

was: Which one of the 2^4 possible stereoisomers is glucose? This problem was solved in two stages.

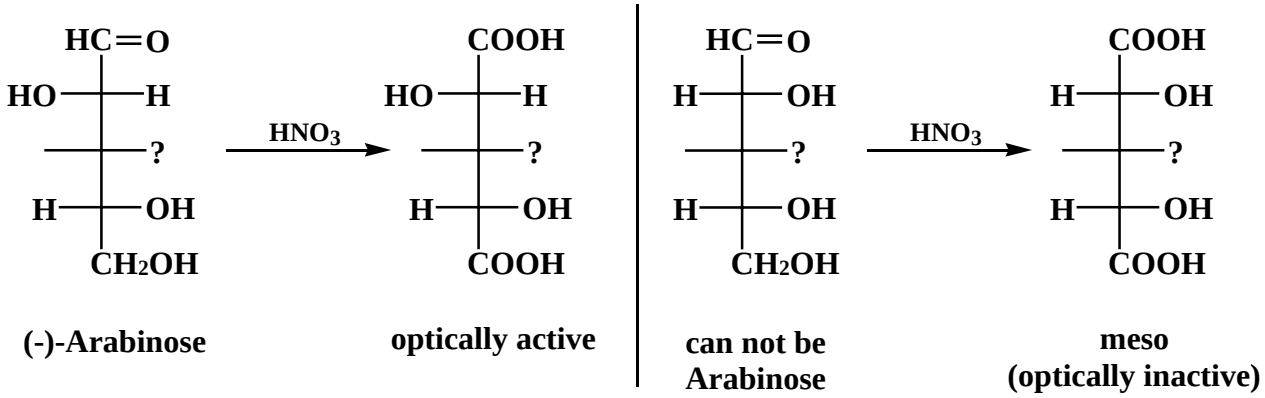
1- Which Diastereomer? The Fischer Proof:

The first (and major) part of the solution to the problem of glucose stereochemistry was published in 1891 by Emil Fischer. It would be reason enough to study Fischer's proof as one of the most brilliant pieces of reasoning in the history of chemistry. However, it also will serve to sharpen your understanding of stereo-chemical relationships. It is important to understand that in Fischer's day there was no way to determine the absolute stereochemical configuration of any chemical compound. Consequently, Fischer arbitrarily assumed that carbon-5 (the configurational carbon in the D,L system) of (+)-glucose has the OH on the right in the standard Fischer projection; that is, Fischer assumed that (+)-glucose has what we now call the D-configuration. No one knew whether this assumption was correct; the solution to this problem had to await the development of special physical methods some sixty years after Fischer's work. If Fischer's guess had been wrong, then it would have been necessary to reverse all of his stereochemical assignments. Fischer, then, proved the stereochemistry of (+)-glucose relative to an assumed configuration at carbon-5. The remarkable thing about his proof is that it allowed him to assign relative configurations in space using only chemical reactions and optical activity. The logic involved is direct, simple, and elegant, and it can be summarized in four steps:

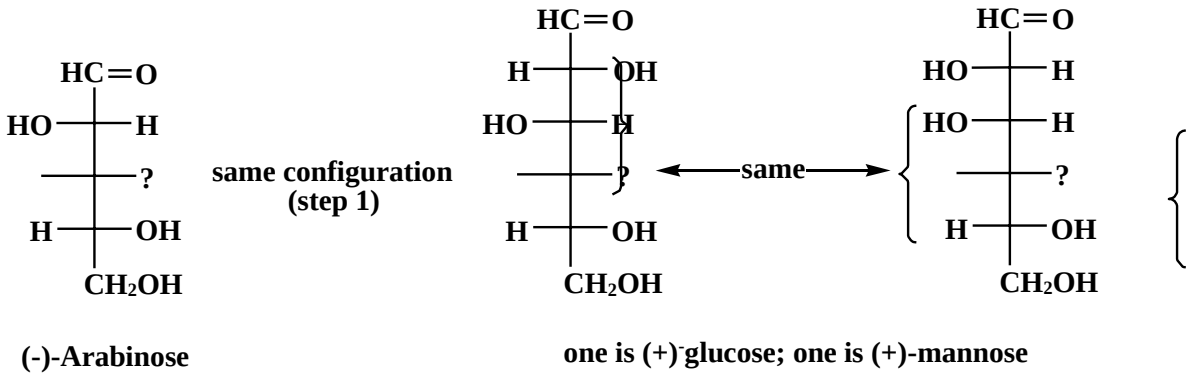
Step 1 (-)-Arabinose, an aldopentose, is converted into both (+)-glucose and (+)-mannose by a Kiliani-Fischer synthesis. From this fact, Fischer deduced that (+)-glucose and (+)-mannose are epimeric at carbon-2, and that the configuration of (-)-arabinose at carbons-2,-3, and -4 is the same as that of (+)-glucose and (+)-mannose at carbons-3, -4, and -5, respectively.



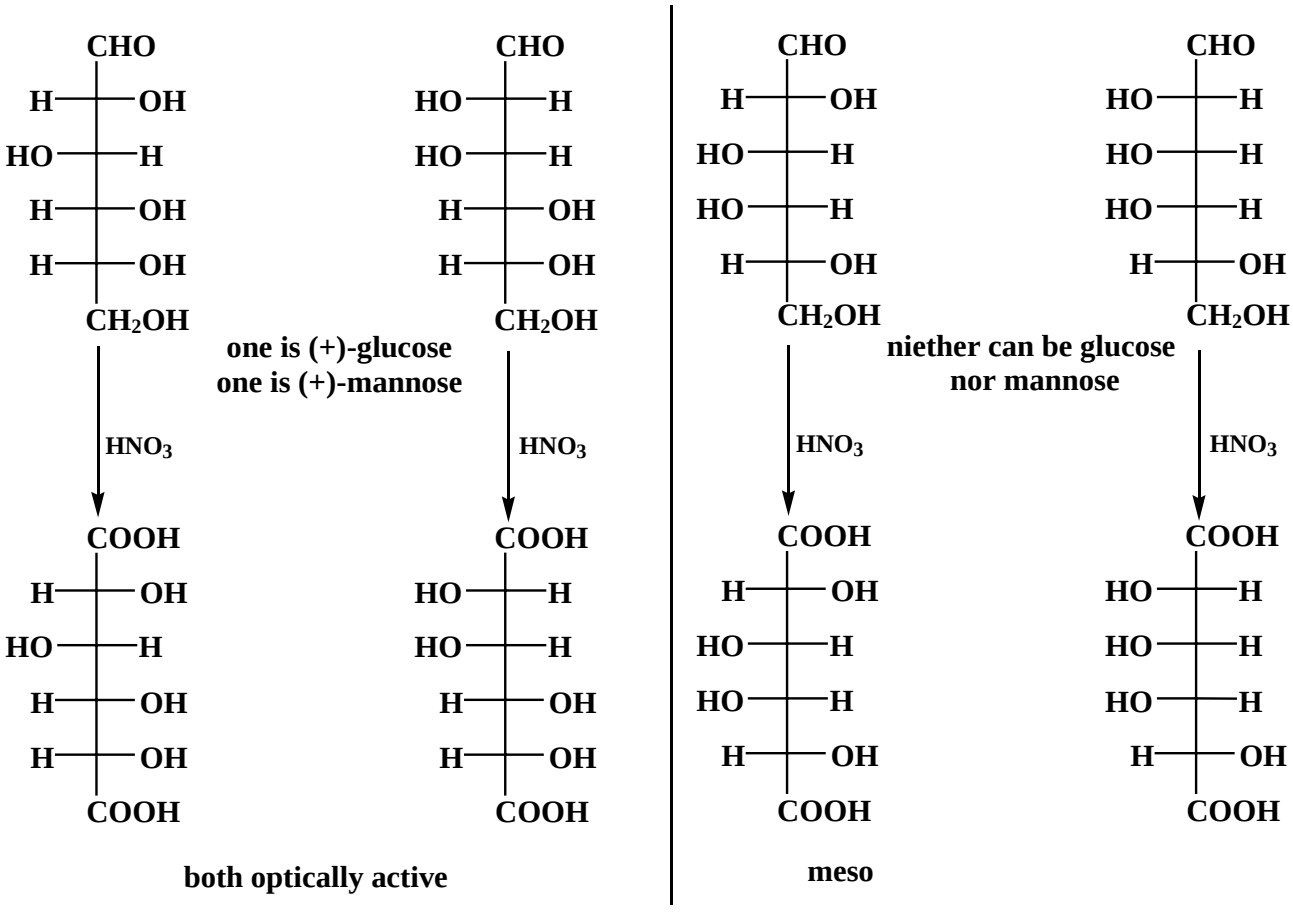
Step 2 (-)-Arabinose can be oxidized by dilute HNO_3 to an optically active aldaric acid. From this, Fischer concluded that the OH group at carbon-2 of arabinose must be on the left. If this OH group were on the right, then the aldaric acid of arabinose would have to be meso, and thus optically inactive, regardless of the configuration of the OH group at carbon-3. (Be sure you see why this is so; if necessary, draw both possible structures for (-)-arabinose to verify this deduction.)



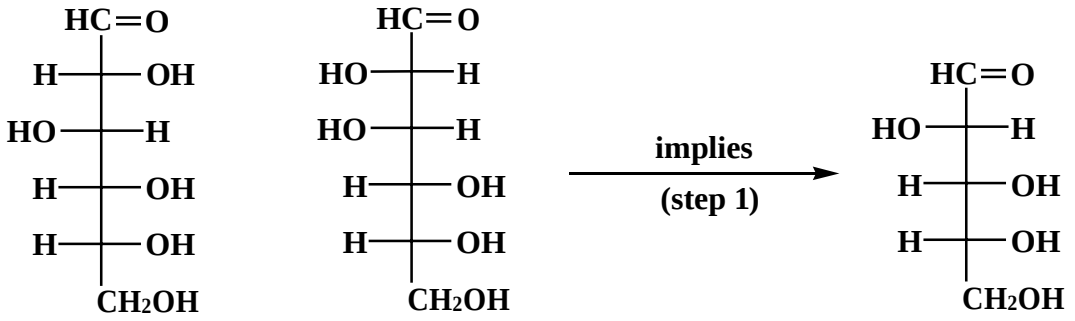
The relationships among arabinose, glucose, and mannose established in steps 1 and 2 require the following partial structures for (+)-glucose and (+)-mannose.



Step 3 Oxidations of both (+)-glucose and (+)-mannose with HNO_3 give optically active aldaric acids. From this, Fischer deduced that the -OH group at carbon-4 is on the right in both (+)-glucose and (+)-mannose. Recall that whatever the configuration at carbon-4 in these two aldohexoses, it must be the same in both. Only if the -OH is on the right will *both* structures yield, on oxidation, optically active aldaric acids. If the -OH were on the left, one of the two aldohexoses would have given a meso, and hence, optically inactive, aldaric acid.

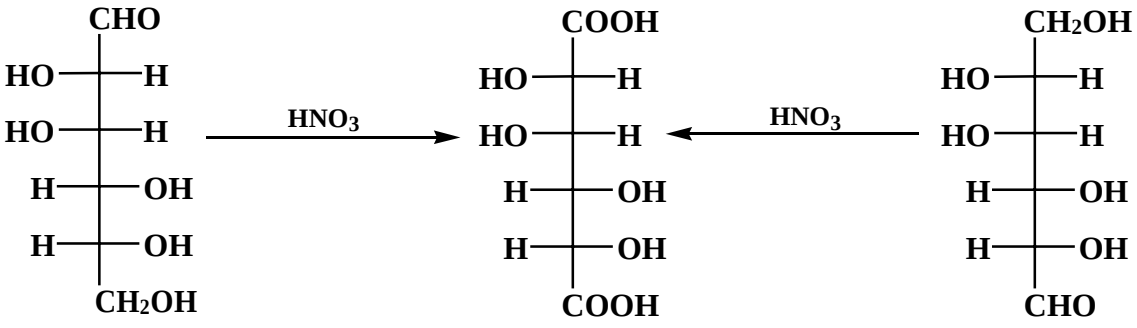


Because the configuration at carbon-4 of (+)-glucose and (+)-mannose is the same as that at carbon-3 of (-)-arabinose *(step 1)*, at this point Fischer could deduce the complete structure of (-)-arabinose.



one is (+)-glucose; one is (+)-mannose **(-)-Arabinose**

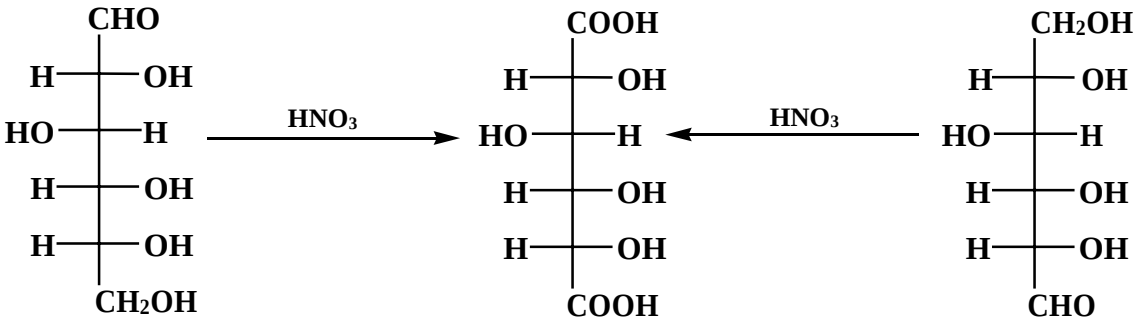
Step 4 The previous steps had established that (+)-glucose had one of the two structures and (+)-mannose had the other, but Fischer did not yet know which structure goes with which sugar. This point is confusing to some students. Fischer knew the structures associated with both (+)-glucose and (+)-mannose, he did not yet know how to correlate each aldose with each structure. This problem was solved when Fischer found that another aldose, (+)-gulose, can be oxidized with HNO_3 to the same aldaric acid as (+)-glucose. (Fischer had synthesized (+)-gulose in the course of his research.) How does this fact differentiate between (+)-glucose and (+)-mannose? Two different aldoses can give the same aldaric acid only if their CH=O and CH_2OH groups are at opposite ends of an otherwise identical molecule. Interchange of the CH_2OH and CH=O groups in one of the aldohexose structures in gives the same aldohexose. (You should verify that these two structures are identical by rotating either one 180° in the plane of the page and comparing it with the other.)



same aldohexose: (+)-mannose

Because only one aldohexose can be oxidized to this aldaric acid, that aldohexose cannot be (+)-glucose; therefore it must be (+)-mannose. Interchanging the end groups of the.

Other aldohexose structure in gives a different aldose:



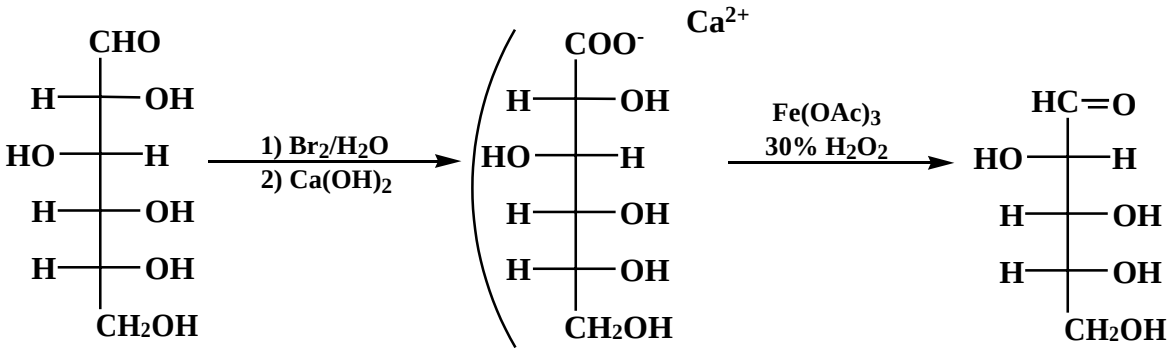
D-(+)-Glucose **L-(+)-Gulose**

different aldohexoses

Consequently, one of these two structures must be that of (+)-glucose. Only the structure on the left is one of the possibilities listed consequently, this is the structure of (+)-glucose. The structure on the right then, is that of (+)-gulose. (Note that (+)-gulose has the L configuration; that is, the OH group at carbon-5 in the standard Fischer projection is on the left. Rotate the (+)-gulose structure 180° in the plane of the page to see this.)

2- Which Enantiomer? The Absolute Configuration of D-(+)-Glucose:

Fischer never learned whether his arbitrary assignment of the absolute configuration of (+)-glucose was correct, that is, whether the OH at carbon-5 of (+)-glucose was really on the right in its Fischer projection (as assumed) or on the left. The groundwork for solving this problem was laid when the configuration of (+)-glucose was correlated to that of (-)-tartaric acid. This was done in the following way. (+)-Glucose was converted into (-)-arabinose by a reaction called the Ruff degradation. In this reaction sequence, an aldose is oxidized to its aldonic acid, and the calcium salt of the aldonic acid is treated with ferric ion and hydrogen peroxide. This treatment decarboxylates the calcium salt and simultaneously oxidizes carbon-2 to an aldehyde.

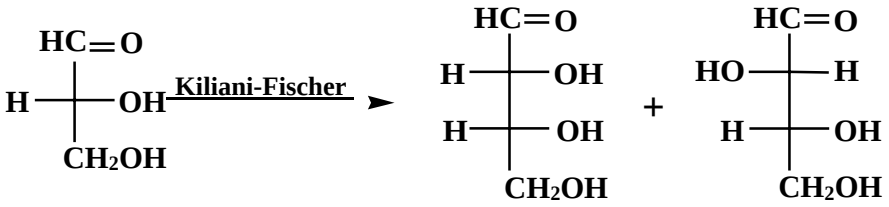


D-(+)-Glucose **Calcium gluconate** **D-Arabinose (41% yield)**

In other words, an aldose is degraded to another aldose with one fewer carbon atom, its stereochemistry otherwise remaining the same. Because the relationship between (+)-glucose and (-)-arabinose was already known from the Kiliani-Fischer synthesis, this reaction served to establish the course of the Ruff degradation. Next, (-)-arabinose was converted into (-)-erythrose by another cycle of the Ruff degradation.

(-)-arabinose $\xrightarrow{\text{Ruff degradation}}$ **(-)-erythrose**

D-Glyceraldehyde, in turn, was related to (-)-erythrose by a Kiliani-Fischer synthesis:

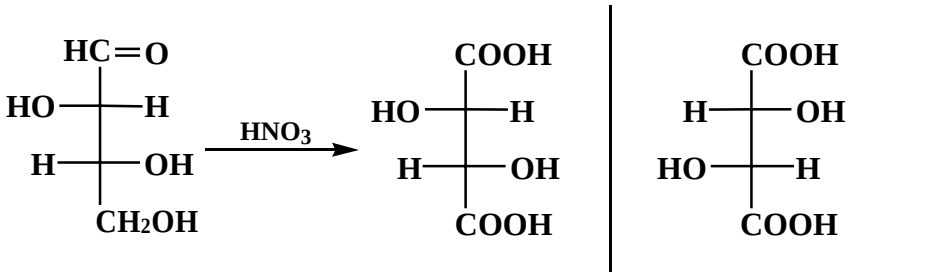


D-(+)-Glyceraldehyde (absolute configuration assumed by convention) **D-(-)-Erythrose (configuration at carbon-3 assumed by convention)** **D-(-)-Threose**

This sequence of reactions showed that (+)-glucose, (-)-erythrose, (-)-threose, and (+)-glyceraldehydes were all of the same stereochemical series: the D series. Oxidation of D-(-)-threose with dilute HNO_3 gave D-(-)-tartaric acid.

In 1950 the absolute configuration of naturally occurring (+)-tartaric acid (as its potassium rubidium double salt) was determined by a special technique of X-ray crystallography called anomalous dispersion. This determination was made by J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel. If Fischer had made the right

choice for the D-configuration, the assumed structure for D-(-)-tartaric acid and the experimentally determined structure of (+)-tartaric acid determined by the Dutch crystallographers would be enantiomers. If Fischer had guessed incorrectly, the assumed structure for (-)-tartaric acid would be the same as the experimentally determined structure of (+)-tartaric acid, and would have to be reversed. To quote Bijvoet and his colleagues: The result is that Emil Fischer's convention (for the D configuration) appears to answer to reality.

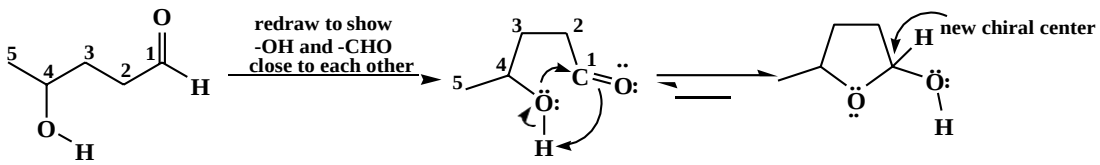


D-(-)Threose **D-(-)-Tartaric acid** **L-(+)-Tartaric acid**
(by X-ray crystallography)

Enantiomers

The Cyclic Structure of Monosaccharides:

We saw that aldehydes and ketones react with alcohols to form hemiacetals. We also saw that cyclic hemiacetals form very readily when hydroxyl and carbonyl groups are part of the same molecule and their interaction can form a five- or six-membered ring, For example, 4-hydroxypentanal forms a five-membcred cyclic hemiacetai.



A Cyclic hemiacetal

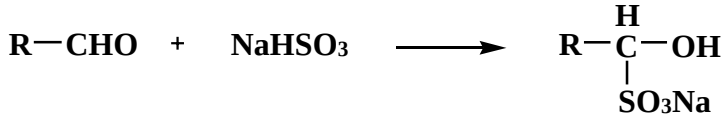
Note that 4-hydroxentanal contains one chiral center and that a second chiral center is generated at carbon 1 as a result of hemiacetal formation.

Monosaccharides have hydroxyl and carbonyl groups in the same molecule. As a resuLt, they too exist almost exclusively as five- and six-memhered cyclic hemiacecals.

The cyclic structure of Glucose:

Soon after the formulation of glucose it is apparent that the open chain structure proposed by E. Fischer dose not account for all the reactions of glucose thus:

1- Glucose dose not give the characteristic reagent of aldehydes such as the colour with Schiff's reagent and the formation of stable addition product with sodium bisulphit.

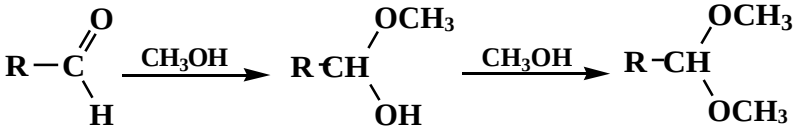


2- On acetylation glucose yields 2 different pentacetates (designated α and β).

3- Glucose forms crystalline products when refluxed with methanolic hydrogen chloride: methyl α and methyl β-D-glucosides, two stereoisomers with: α-isomer $(\alpha)_D$ + 158°, m.p. 166° and β-isomer $(\alpha)_D$ - 34°, m.p. 108°

These glucosides have no reducing properties. In the D-series the sugar isomer with the most positive rotation is the α-isomer, the isomer with the lower rotation being called β-isomer.

In case of a normal aldehyde a hemi-acetal then an acetal are formed with methanolic hydrogen chloride.



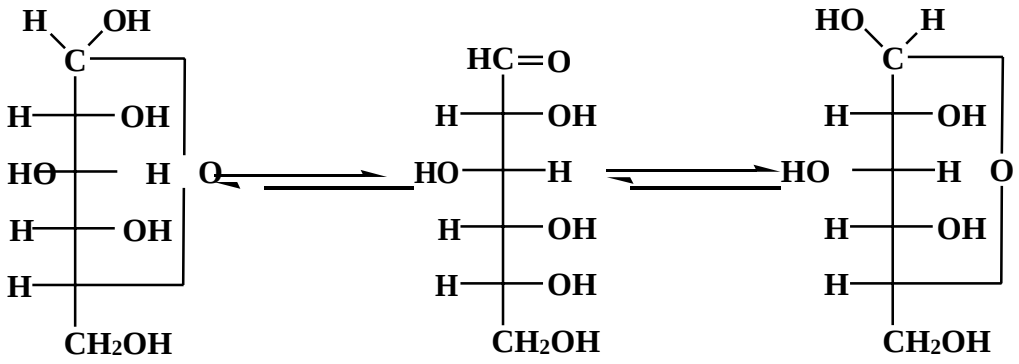
hemi-acetal **acetal**

Whereas only one (OCH_3) group is introduced into glucose to form the glucoside (hemi-acetal).

4- Corresponding with the glucosides two α- and β-modifications of D-glucose itself were isolated: α-$(\alpha)_D$ + 112°, m.p. 146° and β-$(\alpha)_D$ + 18.7°, m.p. 156°

α-D-glucose crystallizes from water below 35° or from cold ethanol. β-D-glucose crystallizes from water above 98° or from hot pyridine or hot acetic acid, or may be prepared by heating α-D-glucose at 105° for some time.

The two forms are interconvertible in solution when either form is dissolved in water the rotation gradually changes (mutarotation) until an equilibrium value (+52.7°) is reached. Mutarotation occurs throught the aldehyde form as intermediates this form being present normally to the extent of less than 1%. The low concentration of the aldehyde form dose not favours reaction with Schiff's reagent.



α-D-Glucopyranose **D-Glucose** **β-D-Glucopyranose**

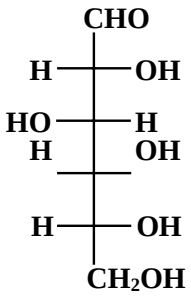
The α- and β-forms which differ in configuration at C_1 only are known as anomers (ano, upper). That the hydroxyl group on C_1 is cis to the hydroxyl on C_2 in the α-form and trans in the β-form was deduced by Boeseken who found that the α-form of D-glucose increaseases conductivity of boric acid solution of boric acid considerably and the increase is greate for the cis-than the trans-arrangement of hydroxyl group.

The ring structure of glucose (1,5) is a six-membered ring and is described as a pyranose ring by similarity to pyran while the five-membered ring is described as a furanose ring.

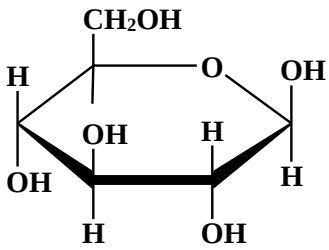
pyran **furan**

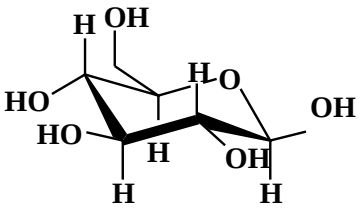
The glycosides of the pyranose sugars are described as pyranosides and those of the furanose sugars as furanosides.

A monosaccharide existing as a five-membered ring is a furanose; one existing as a six-membered ring is a pyranose. A pyranose is most commonly drawn as either a Haworth projection or a chair conformation.



D-Glucose

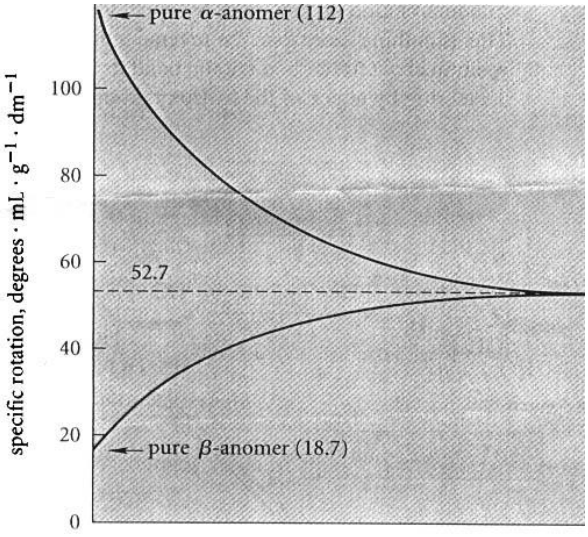




β-D-Glucopyranose
(β-D-Glucose)

C. Mutarotation:

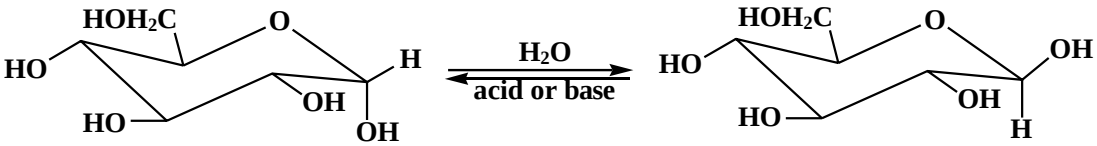
Mutarotation is the change in specific rotation that accompanies the interconversion of α and β-anomers in aqueous solution. As an example, a solution prepared by dissolving crystalline α-D-glucopyranose in water shows an initial rotation of + 112, which gradually decreases to an equilibrium value of + 52.7 as α-D-glucopyraiose reaches an equilibrium with β-D-glucopyranose. A solution of β-D-glucopyranose also undergoes mutarotation, during which the specific rotation changes from an initial value of + 18.7 to the same equilibrium va1ue of + 52.7. The equilibrium mixture consists of 64% β-D-glucopyranose and 36% α-D-glucopyranose. It contains only traces (0.003%) of the open-chain form. Mutarotation is common to all carbohydrates that exist in hemiacetal forms.



Mutarotation of D-glucose. Equimolar aqueous solutions of pure α-or β-glucopyranose gradually change their specific optical rotations to the same final value that is characteristic of the equilibrium mixture.

When pure β-D-glucopyranose is dissolved in water, it has a specific rotation of + 18.7 degrees mL g^{-1} – dm^{-1}. The specific rotation of this solution increases with time, also to + 52.7 degrees. mL g^{-1} dm^{-1}. This change of optical rotation with time is called mutarotation (muta, meaning change). Mutarotation also occurs when pure anomers of other carbohydrates are dissolved in aqueous solution.

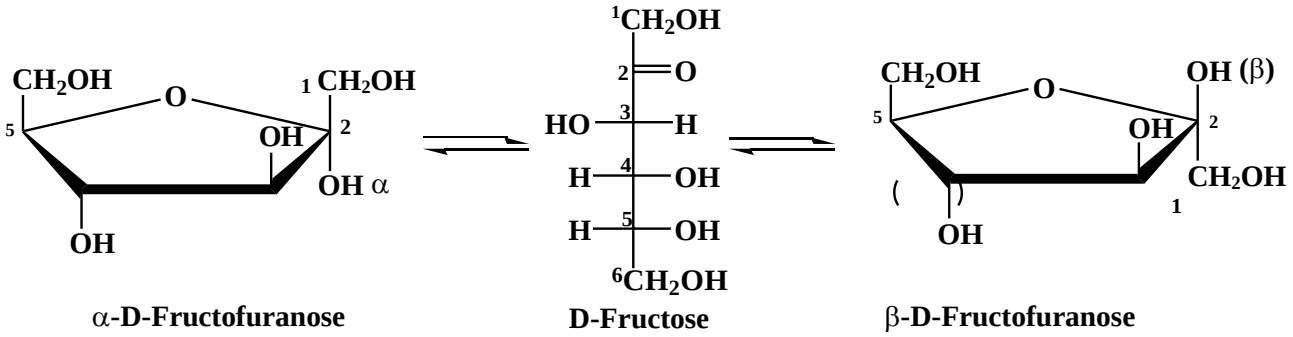
The mutarotation of glucose is caused by the conversion of the α- and β-glucopyranose anomers into an equilibrium mixture of both. The same equilibrium mixture is formed, as it must be, from either pure α-D-glucopyranose or β-D-glueopyranose. Mutarotation is catalyzed by both acid and base, but also occurs even in pure water.



α-anomer (36%)
$[\alpha]_D$ = + 112 degrees.mL.g^{-1}.dm^{-1}

β-anomer (36%)
$[\alpha]_D$ = + 18.7 degrees.mL.g^{-1}.dm^{-1}

Notice that mutarotation is characteristic of the cyclic hemiaceral forms of glucose; an aldehyde cannot undergo mutarotation. Mutarotation was one of the phenomena that suggested to early carbohydrate chemists that aldoses might exist as cyclic hemiacetals.



α-**D-Fructofuranose** **D-Fructose** β-**D-Fructofuranose**

The β-D-fructofuranose form is found in the disaccharide sucrose.

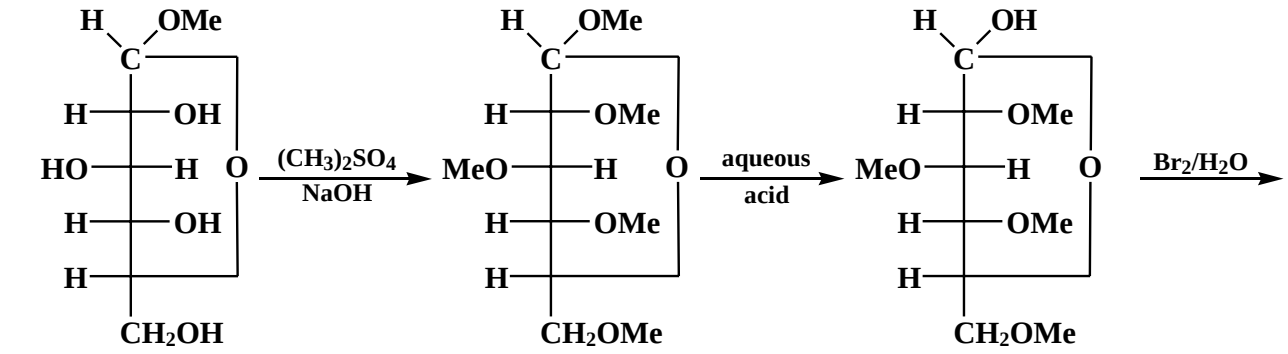
.

Size of the ring:

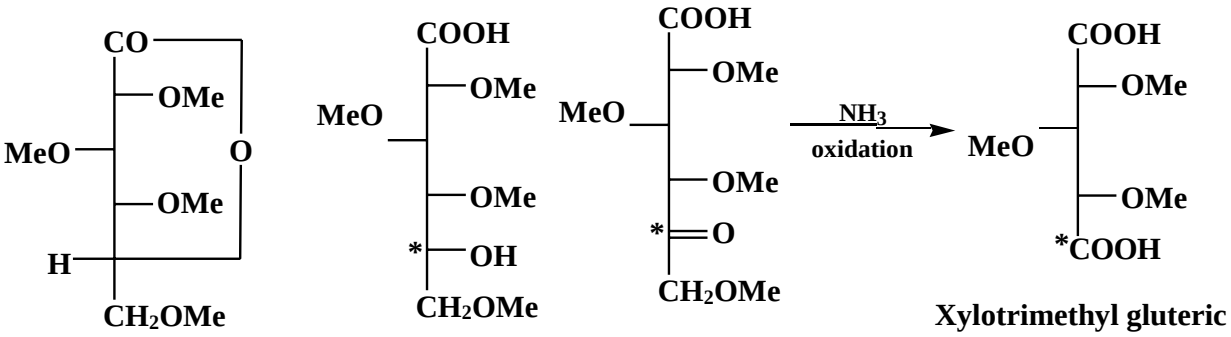
In order to determine the size of the ring structure we must therefore study compounds which cannot be converted to the open chain structure e.g. glucosides, and the structure of methyl glucoside was demonstrated by:

1- Haworth method: methylation experiment:

Methyl glucoside was completely methyulated to methyl tetra-O-methyl glucoside which, on acidification and oxidation with nitric acid, gives xylotrimethoxy glutaric acid:



Methyl glucoside | **Methyl tetra-O-methyl glucoside** | **Tetra-O-methyl glucoside**



Lactone | **Xylotrimethyl gluteric acid**

A 1,4-ring would give dimethoxysuccinic acid, but 1,5-ring gives rylotrimethoxyglutaric acid (the groups which engage the ring are converted to carboxylic group on oxidation.

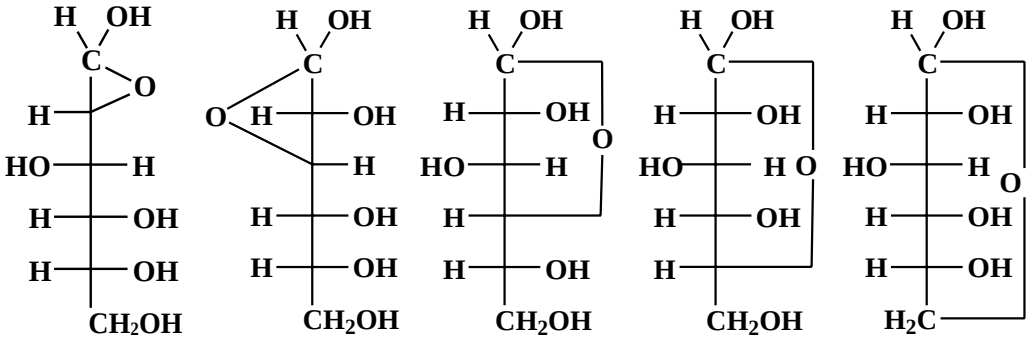
2- Jackson and Hudson: Periodic acid oxidation

An elengant and more direct method of establishing the size of the involves the oxidation of the glucosides by periodic acid. The reagent cleaves the linkage between adjacent hydroxyl-bearing carbon atoms. A primary alcohol (-CH_2OH) yields formaldehyde, a secondary alcohol (-CHOH) gives an aldehyde group or, if flanked by two secondary alcohol groups, splits out formic acid.

The reaction with periodic acid is quantitative and the consumption of periodic acid or periodate gives a measure of the number of adjacent hydroxyl groups in a compound. The yield of formic acid and formaldehyde is also quantitative and can be estimated after the reaction.

Let us now consider the result of a periodic acid oxidation of the 5 possible ring structures of methyl glucoside.

We find that each structure will give different reaction products. When the reaction is carried out experimentally we obtain the following results: 2 moles of periodic acid are consumed, no formaldehyde, one mole of formic acid. These resilts are in agreement with what we expect with 1,5-ring.



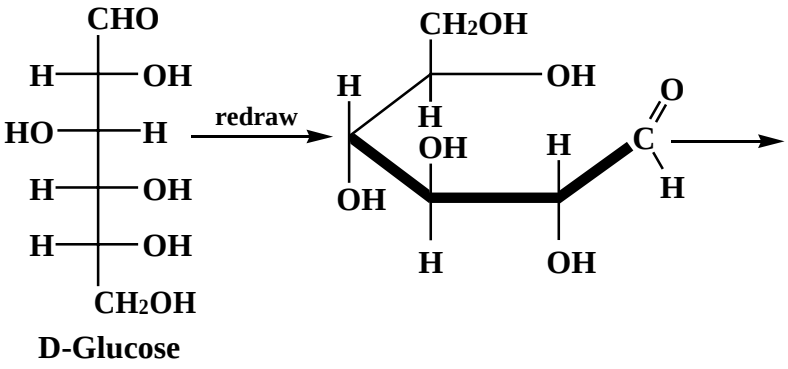
No. of moles of periodic acid	3	2	2	2	3
No. of moles of formaldehyde	1	1	1	0	0
No. of moles of formic acid	2	1	0	1	2

Haworth Projections:

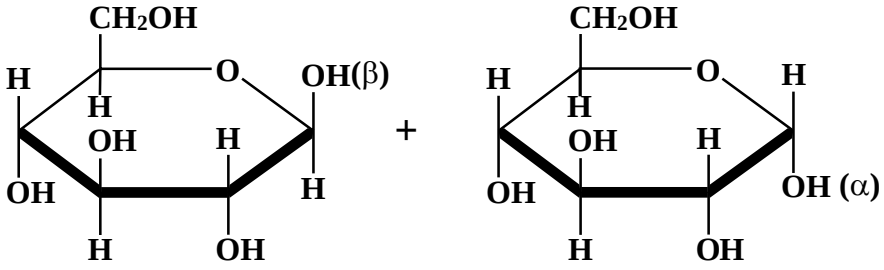
A common way of representing the cyclic structure of monosaccharides is the Haworth projection, named after the English chemist Sir Walter N. Haworth (1937 Nobel Prize for chemistry). In a Haworth projection, a five-or six-membered cyclic hemiacetal is represented as a planar pentagon or hexagon, as the case may be, lying perpendicular to the plane of the paper. Groups bonded to the carbons of the ring then lie either above or below the plane of the ring. The new chiral center created in forming the cyclic structures called an anomeric carbon. Stercoisomers that differ in configuration only at the anomeric carbon are called anomers. The anomeric carbon of an aldose is carbon 1; that of the most common ketoses is carbon 2.

Haworth projections are most commonly written with the anomeric carbon to the right and the hemiacetal oxygen to the back. In the terminology of carbohydrate chemistry, the designation β means that the OH on the anomeric carbon of the cyclic

hemiacetal is on the same side of the ring as the terminal CH_2OH. Conversely, the designation α means that the OH on the anomeric carbon of the cyclic hemiactal is on the opposite side of the ring as the terminal CH_2OH.



D-Glucose

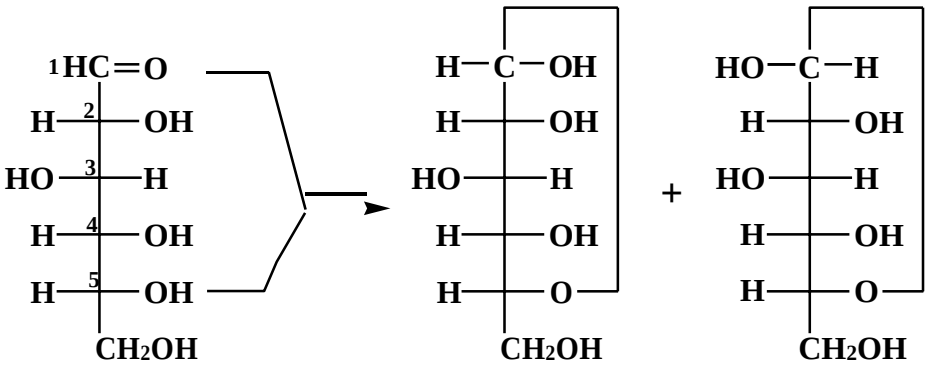


β-D-Glucopyranose
(β-D-Glucose)

α-D-Glucopyranose
(α-D-Glucose)

Haworth projection for α-D-glucopyranose and β-D-glucopyranose

Anomers it is important to notice that the furanose or pyranose of a carbohydrate has one more asymmetric carbon than the open chain form carbon-1 in the case of the aldoses. Thus there are two possible diastereomers of D-glucopyranose.

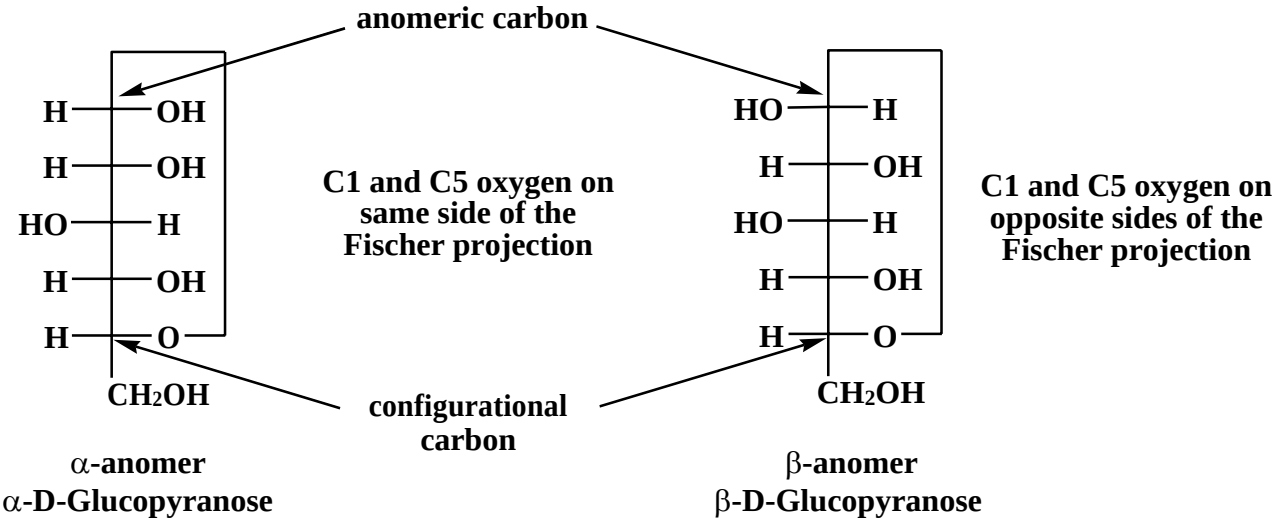


α-anomer β-anomer

anomers of D-Glucopyranose

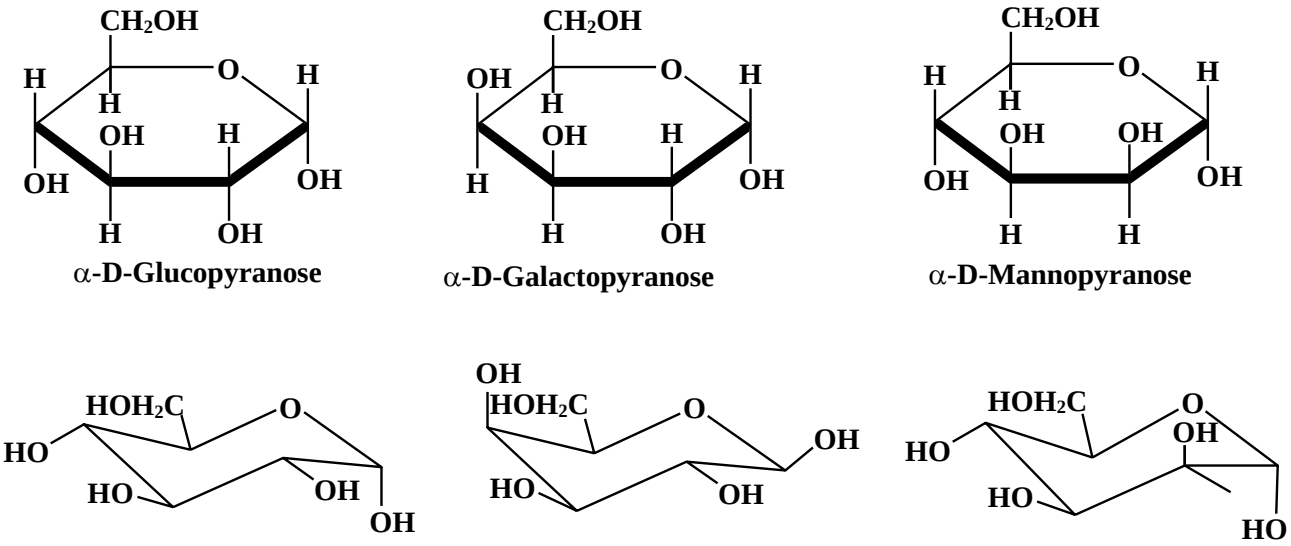
Both of these compounds are forms of D-glucopyranose, and in fact, glucose in solution exists as a mixture of both. They are diastereomers and are therefore separable compounds with different properties. When two cyclic forms of a carbohydrate differ in configuration only at their hemiacetal carbons, they are said to be anomers. In other words, anomers are cyclic forms of carbohydrates that are epimeric at the hemiacetal carbon. Thus, the two forms of D-glucopyranose are anomers of glucose. The hemiacetal carbon (carbon-1 of an aldose) is sometimes referred to as the anomerie carbon.

As the preceding structures illustrate, anomers arc named with the Greek letters α and β. This nomenclature refers to the Fischer projection of the cyclic form of a carbohydrate, written with all carbon atoms in a straight vertical line. In the α-anomer the hemiacetal OH group is on the same side of the Fischer projection as the oxygen at the configurational carbon. (The configurational carbon is the one used for specifying the D,L designation; that is, carbon-5 for the aldohexoses.) Conversely, in the β-anomer the hemiacetal OH group is on the side of the Fischer projection opposite the oxygen at the configurational carbon. The application of these definitions to the nomenclature of the D-glucopyranose anomers is as follows:



Conformational Representations of Pyranoses:

Fischer projections of carbohydrates are convenient for specifying their *configurations* at each asymmetric carbon, but Fischer projections contain no information about the *conformations* of carbohydrates. It is important to relate Fischer projections to conformational representations of the carbohydrates. The following study problem shows how to establish this relationship in a systematic manner for the pyranoses,



Examples of Some Pyranose forms of Hexoses

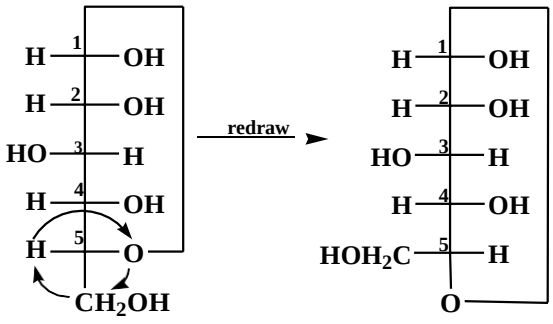
The following study problem shows how to establish this relationship in a systematic manner for the pyranoses,

Study problem:

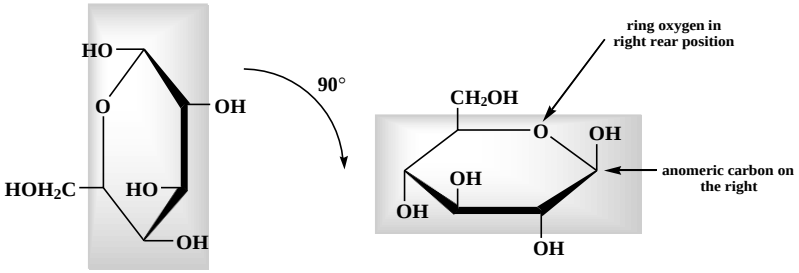
Convert the Fischer projection of β-D-glucopyranose into chair conformation.

Solution.

First redraw the Fischer projection for β-D-glucopyranose in an equivalent Fischer projection in which the ring oxygen is in a down position. This is done by using a cyclic permutation of the groups on carbon-5, an allowed manipulation of Fischer projections

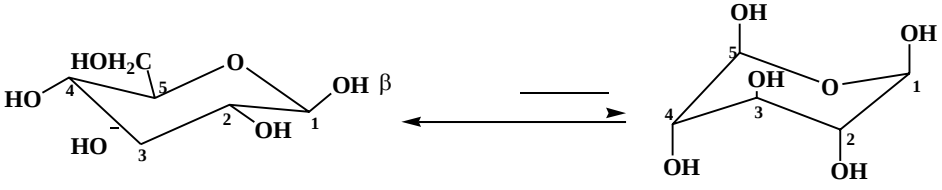


Such an interpretation of the Fischer projection of β-D-glucopyranose yields the following structure, in which the ring lies in a plane perpendicular to the page. (The ring hydrogens are not shown.)



When the plane of the ring is turned 90° so that *the anomeric carbon is on the ring, and the ring oxygen is in the rear*; the groups in *up* positions are those that are on the *left* in the Fischer projection; the groups in *down* positions are those that are on the *right* in the Fischer projection. A planar structure of this son is called a *Haworth projection*. In a Haworth projection, the ring is drawn in a plane at right angles to the page and the positions of the substituents are indicated with up or down bonds. The shaded bonds are in front of the page, and the others are in back.

A Haworth projection does not indicate the conformation of the ring. Six-membered carbohydrate rings resemble substituted cyclohexanes, and, like substituted cyclohexanes, exist in chair conformations. Thus, to complete the conformational representation of β-D-glucopyranose, draw either one of the two chair conformations in which the anomeric carbon and the ring oxygen are in the same relative positions as they are in the preceding Haworth projection. Then place *up* and *down* groups in *axial* or *equatorial* positions, as appropriate.

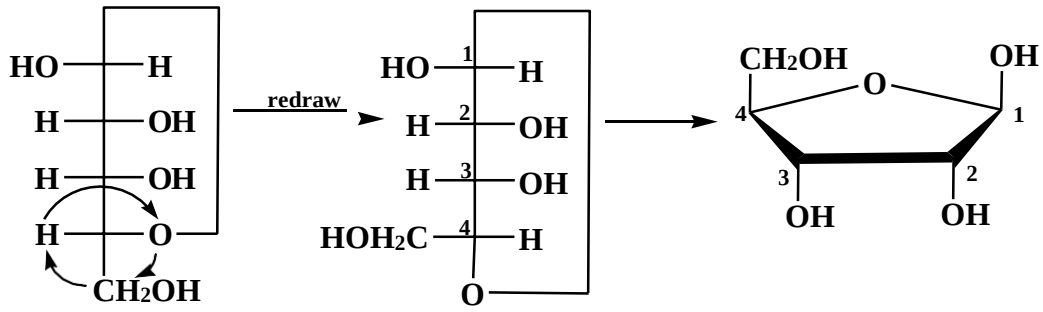


( )

Remember: Although the chair flip changes equatorial groups to axial, and vice versa, it does not change whether a group is up or down, Consequently, it doesn't matter which of the two possible chair conformations you draw first.

To summarize the conclusions of the previous study Problem. When a carbohydrate ring is drawn with the anomeric carbon on the right and the ring oxygen in the rear, substituents that are on the left in the Fischer projection are up in either the Haworth projection or the chair structures; groups that are on the right in the Fischer projection are down in either the Haworth projection or the chair structures.

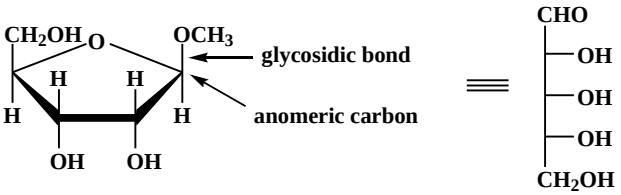
Although the five-membered rings of furanoses are nonplanar, they are close enough to planarity that Haworth formulas are good approximations to their actual structures. Haworth projections are frequently used for furanoses for this reason. Thus, a Haworth projection of β-D-ribofuranose is derived as follows:



Example:

Draw a structural formula for methyl β-D-ribofturanoside (methyl β-D-riboside). Label the anomeric carbon and the glycosidic bond.

Solution:



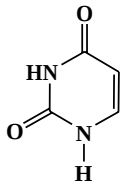
Problem:

Draw a Haworth projection and a chair conformation for methyl α-D-mannopyranoside (methyl α-D-mannoside). Label the anomeric carbon and the glycosidic bond.

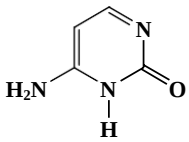
Just as the anomeric carbon of a cyclic hemiacetal undergoes reaction with the -OH group of an alcohol to form a glycoside, it also undergoes reaction with the

N-H group of an amine to form an *N*-glycoside. Especially important in the biological world are the *N*-glycosides formed between D-ribose and 2-deoxy-D-ribosc, each as a furanose, and the heterocycflc aromatic amines (uracil, cytosne, thyrnine, adenine, and guanine). *N*-Glycosides of these pyrimidinc and purine bases are structural units of nucleic acids.

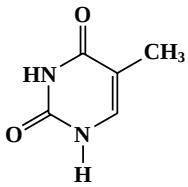
Example:



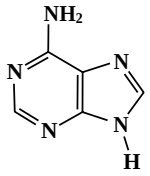
Uracil



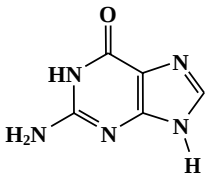
Cytosine



Thymine



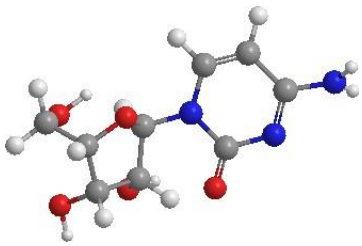
Adenine

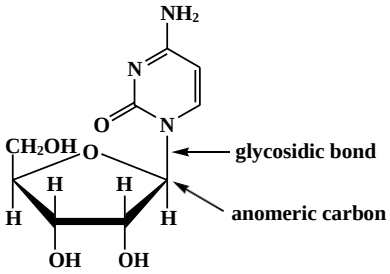


Guanine

Draw a structural formula for cytidine, the β-*N*-glycosidc formed between D-ribofuranose and cytosine.

Solution:





Problem:

Draw a structural formula for the β-*N*-glycoside formed between 2.deoxy-D-nose and adenine.

aqueous solution.

At this point, you should compare the relative orientations of groups **Ascorbic Acid**

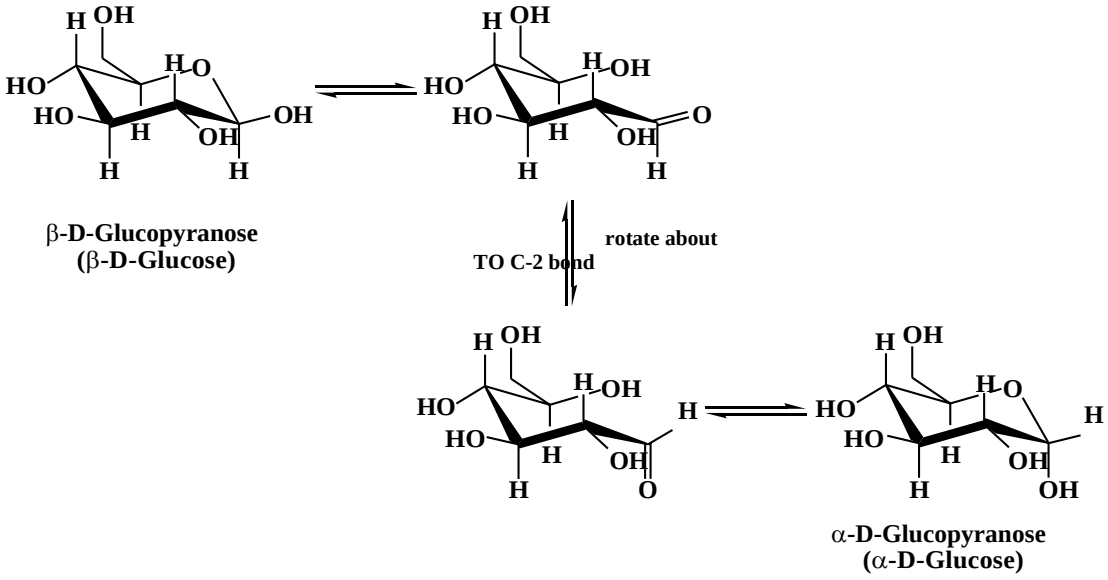
Ascorbic acid is one of the, most important antioxidants (the H in the enolic OH is weakly bonded and easily abstracted by radicals). One of the most important roles it plays may be to replenish the lipid-soluble plement. Approximately 66 million kilograms of vitamin C are synthesized every year in the United States.

L-Ascirbic acid is very easily oxidized to L-dehydroascorbic acid, a diketone. Both L-ascorbic acid and L-dehydroascorbic acid are physiokogically active and are found together in most body fluids.

antioxidant α-tocopherol by transferring a hydrogen atom to the tocopherol radical, formed by reaction with radicals in the autoxidation process.

B. Conformation Representations:

A five-membered ring is so close to being planar that Haworth projections are adequate representations of furanoses. For pyranoses, however, the six-membered ring is more accurately represented as a chair conformation. Following are structural formulas for α-D-glucopyranose and β-D-glucopyranose drawn as chair conformations. Also shown is the open chain or free aldehyde form with which the cyclic hemiacetal forms are in equilibrium in aqueous solution.



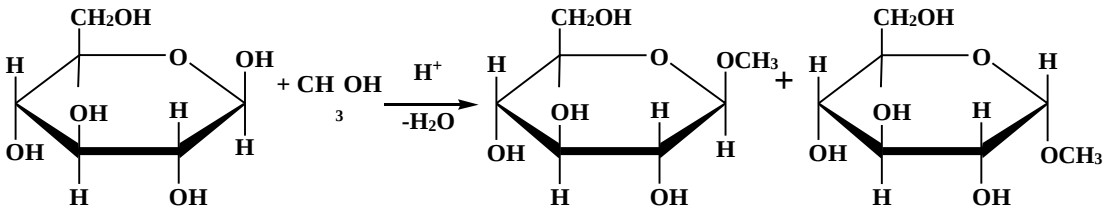
Notice that each group, including the anomeric OH, on the chair conformation of β-D-glucopyranosc is equatorial. Notice also that the OH group on the anomeric carbon is axial in α-D-glucopyranose. Because of the equatorial orientation of the OH on its anomeric carbon, β-D-glucopyranose is more stable and predominates in on the D-glucopyranose ring in the Haworth projection and the chair conformation. The orientations of groups on carbons through 5 of β-S-glucopyranose, for example, are up, down, up, down, and up in both representations.

25.3 Reactions of Monosaccharides:

A. Formation of Glycosides (Acetals):

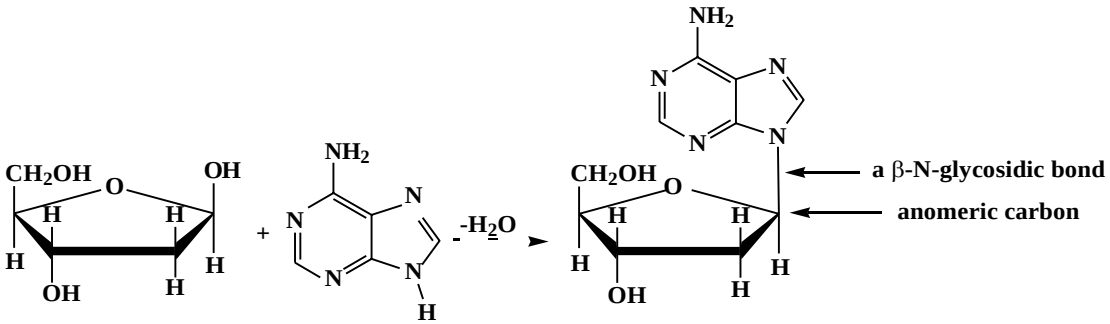
i-Formation ofC-Glycosides:

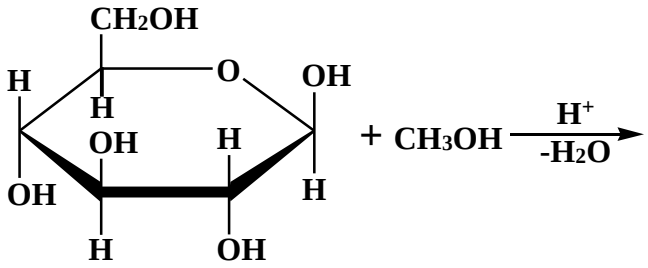
We saw that treatment of an aldehyde or ketone with one molecule of alcohol gives a hemiacetal, and that treatment of the hemiacetal with a molecule of alcohol gives an acetal. Treatment of monosaccharides, all of which exist almost exclusively in a cyclic he, naceta1 form, also gives acetals, as illustrated by the reaction of β-D-glucopyranose with methanol.



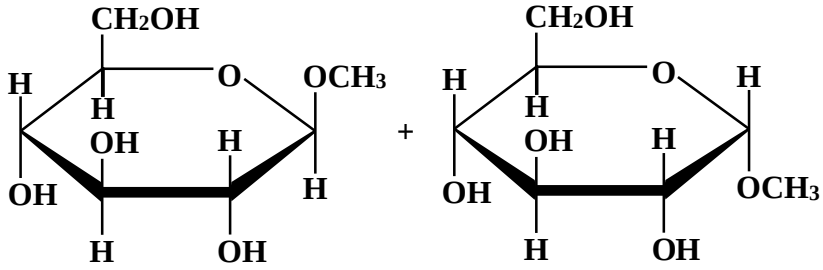
ii. Formation of N-Glycosides:

N-Glycosides formed between a monosaccharide and a heterocyclic aromatic amine are especially important in the biological world.





β-**D-Glucopyranose**
(β-**D-Glucose)**



Methyl β**-D-Glucopyranose**
(**Methyl** β**-D-Glucoside)**

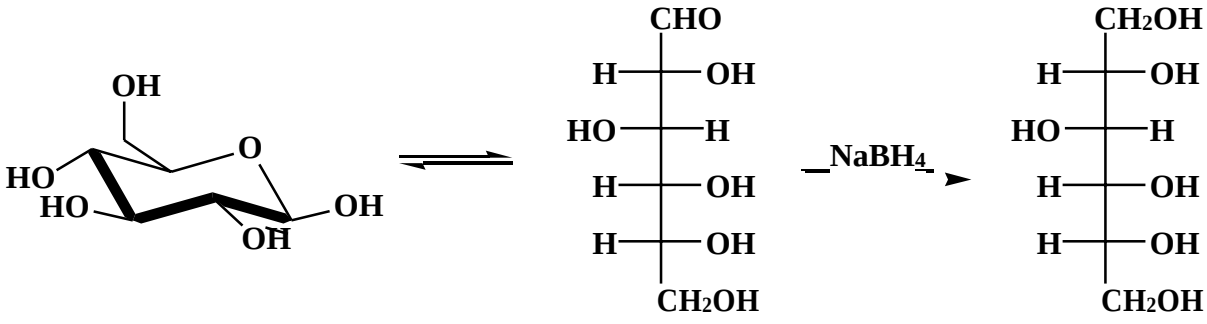
Methyl α**-D-Glucopyranose**
(**Methyl** α**-D-Glucoside)**

A cyclic acelal derived from a monosaccharide is called a glycoside, and the bond from the anomeric carbon to the OR group is called a glycosidic bond. MutatotaLion is not possible in a glycoside because an acelal is no longer in equilibrium with the open-chain carbonyl-containing compound. Glycosides are stable in water and aqueous base, but like other acetals (Section 16.7), they are hydrolyzed in aqueous acid to an alcohol and a monosaccharide.

Glycosides are named by listing the alkyl or aryl group bonded to oxygen followed by the name of the carbohydrate in which the ending *-e* is replaced by *-ide*. For example, the glycosides derived from β-D-glucopyranose are named β-D-glucopyranosides; those derived from β-D-ribofuranose are named β-D-ribofuranosides.

B. Reduction to Alditols

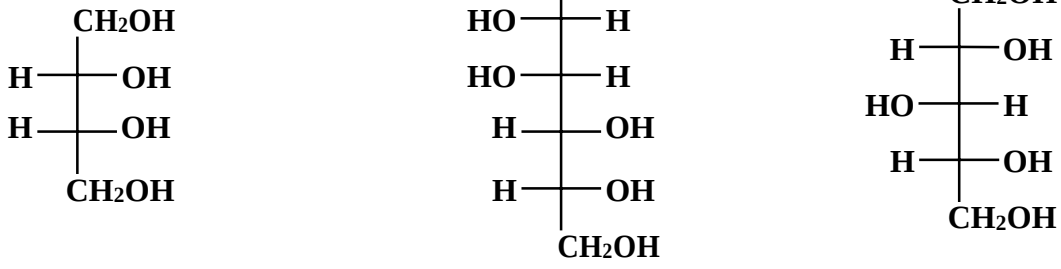
The carbonyl group of a monosaccharide can be reduced to a hydroxyi group by a variety of reducing agents, including sodium borohydride and hydrogen in the presence of a transition metal catalyst. The reduction products are known as alditols. Reduction of D-glucose gives D-glucitol, more commonly known as D-sorbitol. Note that D-glucose is shown here in the open-chain form. Only a small amount of this form is present in solution, but, as it is reduced, the equilibrium between cyclic hemiacetal forms and the open-chain form shifts to replace it.



β-**D-Glucopyranose** **D-Glucose** **D-Glucitol (D-Sorbitol)**

Sorbitol is found in the plant world in many berries and in cherries, plums, pears, apples, seaweed, and algae. It is about 60% as sweet as sucrose (table sugar) and is used in the manufacture of candies and as a sugar substitute for diabetics. D-Sorbitol is an important food additive, usually added to prevent dehydration of foods and other materials on exposure to air because it binds water strongly.

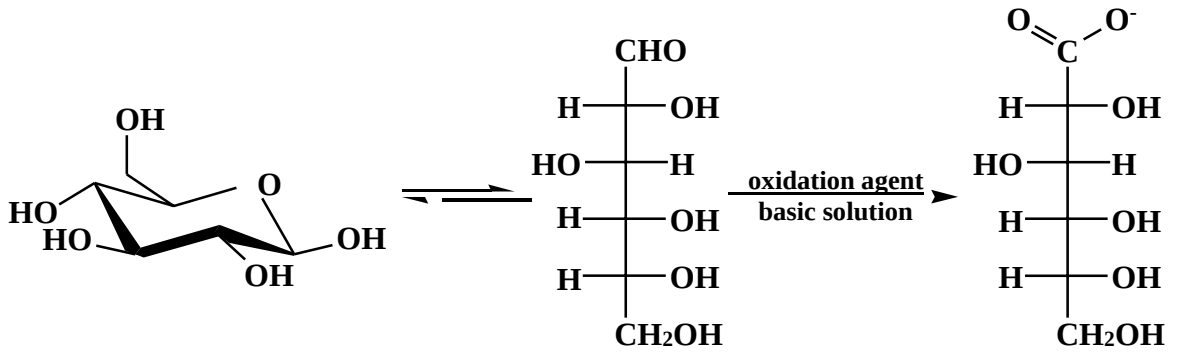
Other alditols common in the biological world are erythritol, D-mannitol, and xylitol. Xylitol is used as a sweetening agent in “sugarless” gum, candy, and sweet cereals.



Erythritol **D-Mannitol** **Xylitol**

C. Oxidation to Aldonic Acids: Reducing Sugars:

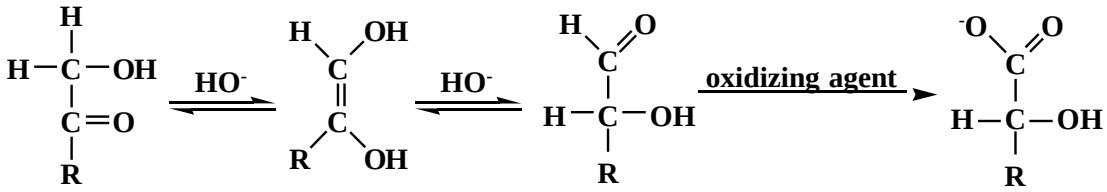
As we saw in Section, aldehydes (RCHO) are oxidized to carboxylic acids (RCOOH) by several oxidizing agents, including oxygen, O_2. Similarly, the aldehyde group of an aldose can be oxidized, under basic conditions, to a carboxylate group. Oxidizing agents for this purpose include bromine in aqueous calcium carbonate (Br_2, $CaCO_3$, H_2O) and Tollen's solution [$Ag(NH_3)_2^+$]. Under these conditions, the cyclic form of an aldose is in equilibrium with the open-chain form, which is then, oxidized by the mild oxidizing agent. D-Glucose, for example, is oxidized to D-gluconate (the anion of D-gluconic acid).



β-**D-Glucopyranose** (β-**D-Glucose)** **D-Glucose** **D-Gluconate**

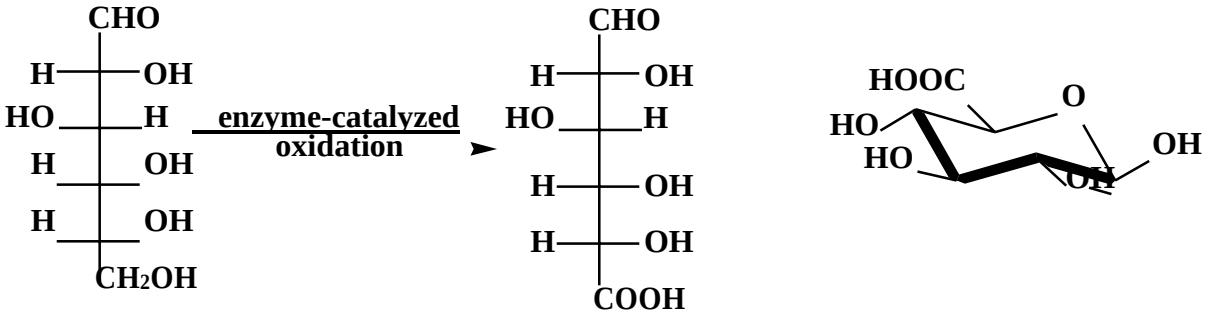
Any carbohydrate that reacts with an oxidizing agent to form an aldonic acid is classified as a reducing sugar (it reduces the oxidizing agent).

Surprisingly, 2-ketoses are also reducing sugars. Carbon 1(a CH_2OH group) of a 2-ketose is not oxidized directly. Rather, under the basic conditions of this oxidation a 2-ketose is in equilibrium with an aldose by way of an enediol intermediate. The aldose is then oxidized by the mild oxidizing agent.



D. Oxidation to Uronic Acids:

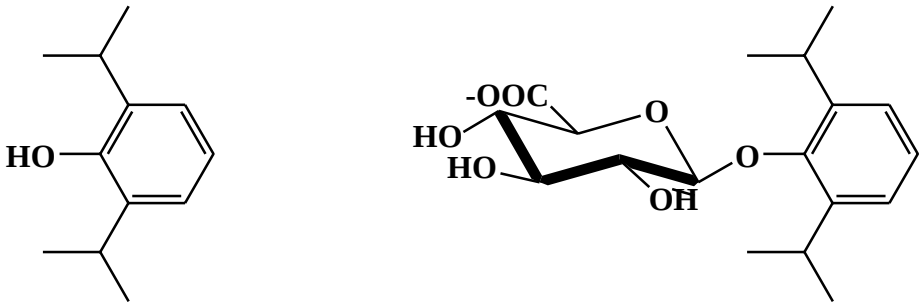
Enzyme-catalyzed oxidation of the primary hydroxyl group at carbon 6 of a hexose yields a uronic acid. Enzyme-catalyzed oxidation of D-glucose, for example, yields D-glucuronic acid, shown here in both its open-chain and cyclic hemiacetal forms.



D-Glucose **Fischer projection** **Chair conformation**

D-Glucuronic acid
(a uronic acid)

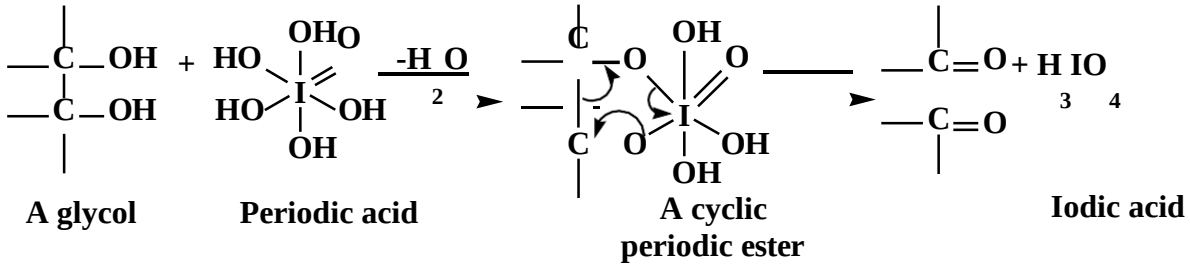
D-Glucuronic acid is widely distributed in both the plant and animal world. In humans, it is an important component of the acidic polysaccharides of connective tissues. It is also used by the body to detoxify foreign hydroxyl-containing compounds, such as phenols and alcohols. In the liver, these compounds are converted to glycosides of glucuronic acid (glucuronides) and excreted in the urine. The intravenous anesthetic propofol, for example, is converted to the following glucuronide and excreted in the urine.



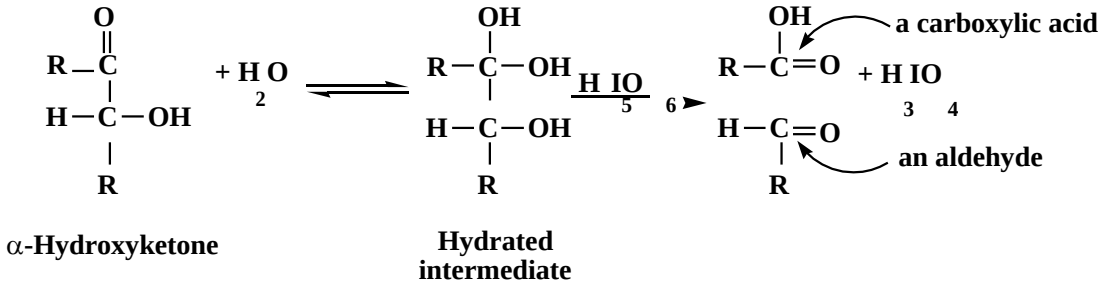
Propofol **A urine-soluble glucuronide**

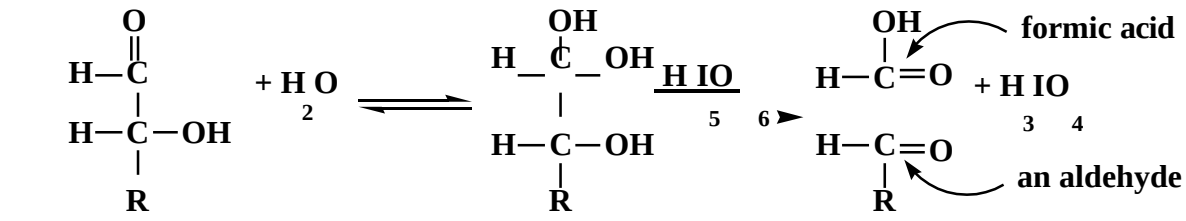
E. Oxidation by Periodic Acid:

Oxidation by periodic acid has proven useful in structure determinations of carbohydrates, particularly in determining the size of glycoside rings. Periodic acid cleaves the carbon-carbon bond of a glycol in a reaction that proceeds through a cyclic periodic ester. In this reaction, iodine (VII) of periodic acid is reduced to iodine (V) of iodic acid.



Periodic acid also cleaves carbon-carbon bonds of a-hydroxyketones and α-hydroxyaldehydes by a similar mechanism. Following are abbreviated structural formulas for these functional groups and the products of their oxidative cleavage by periodic acid. As a way to help you understand how each set of products is formed, each carbonyl in a starting material is shown as a hydrated intermediate that is then oxidized. In this way, each oxidation can be viewed as analogous to oxidation of a glycol.

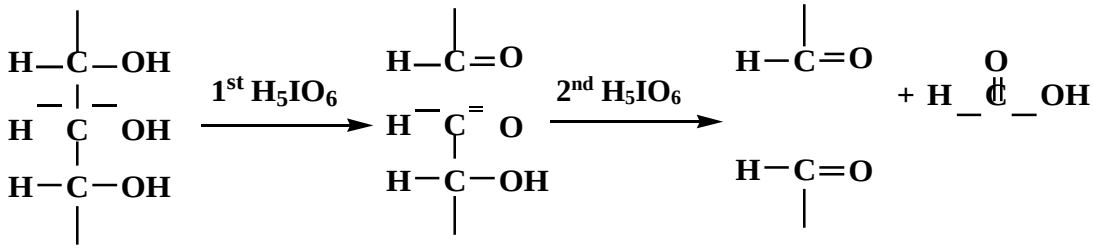




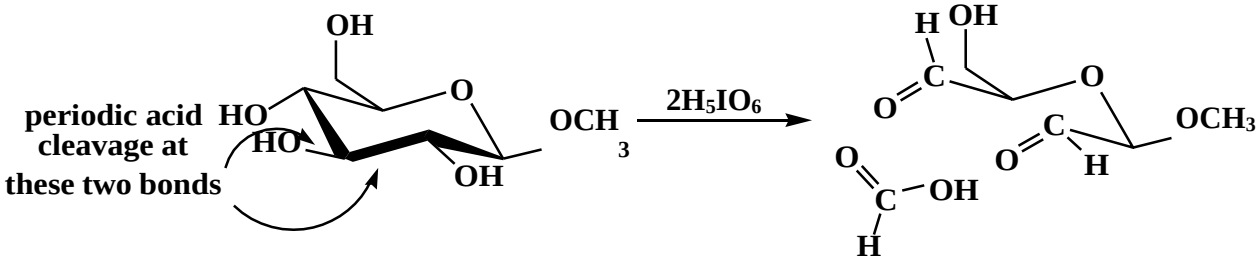
α-Hydroxyaldehyde

Hydrated intermediate

As an example of the usefulness of this reaction in carbohydrate chemistry, oxidation of methyl β-D-glucoside consumes two moles of periodic acid and produces one mole of formic acid. This stoichiometry and the formation of formic acid are possible only if OH groups are on three adjacent carbon atoms.

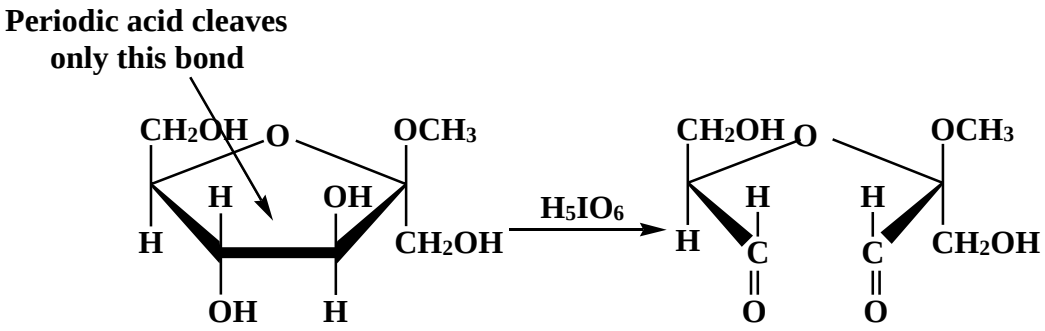


This is evidence that methyl β-D-glucoside is indeed a pyranoside.



Methyl β-D-Glucopyranoside

Only at one site in the molecule. The fructoside, therefore, must be a five-membered ring (a fructofuranoside).



Methyl β-D-Fructofuranoside

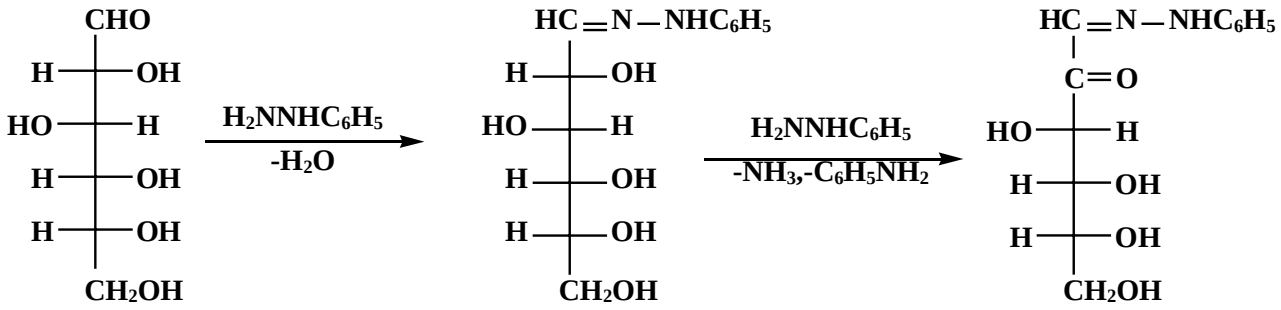
Methyl β-D-fructoside consumes only one mole of periodic acid and produces neither formaldehyde nor formic acid. Thus, oxidizable groups exist on adjacent carbons.

F- Action of pheny1 hydrazine:

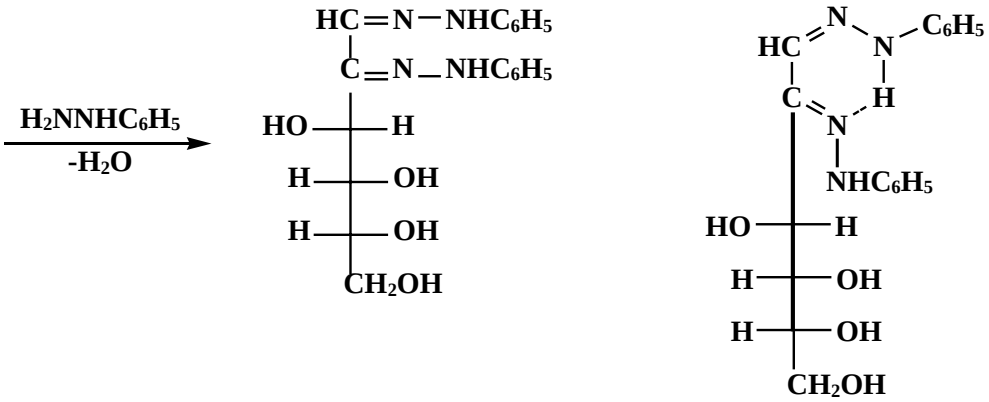
In the cold pheny1 hydrazine and other substituted hydrazine react with sugar to from hydrazones (osazones). Some of with are of values for the identification purposes, also they are valuable for the preparation of many sugar derivatives

Formation of Osazones:

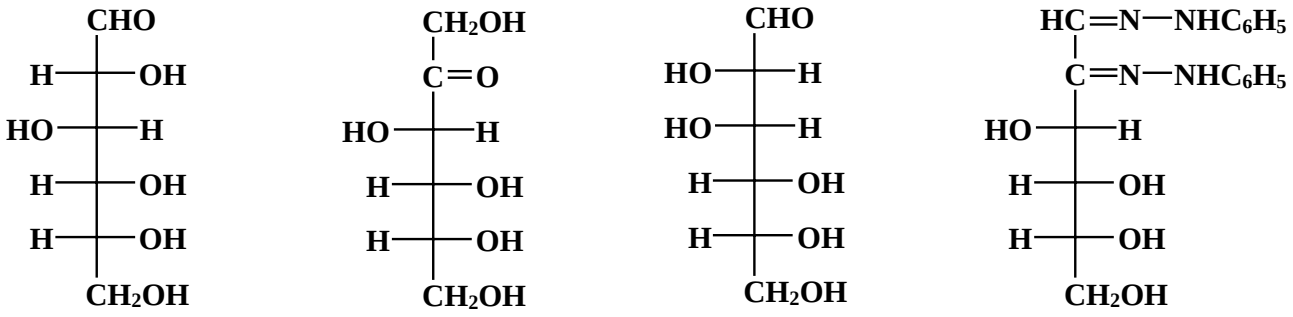
During osazone formation the hydroxyl group adjacent to the carbony1 group is oxidized to keto group which is then attacked by phenyl hydrazine to from osazone. During this oxidation the hydrazine is reduced to aniline and ammonia.



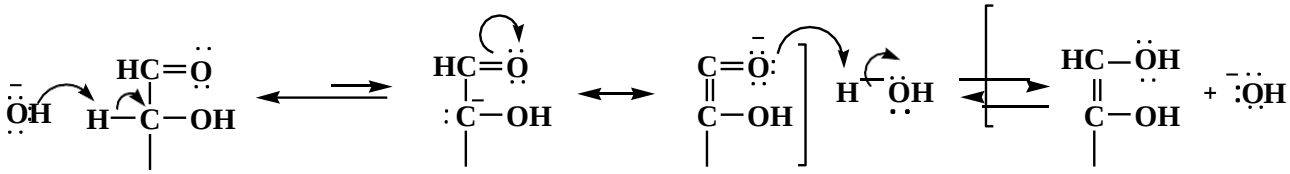
Glucose **Glucose phenylhydrazone** **Phenylhydrazone of glucosone**

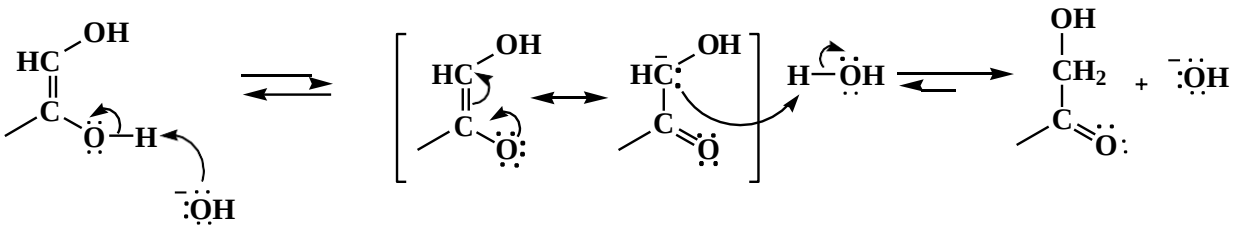


There are 2 aldoses and one ketose which yield the same osazone. Thus glucose, mannose and fructose give the same osazone. This is because osazone formation involves the reaction with C_1 and C_2 and the asymmetry in both carbon atoms is destroyed. Sugars which give the same osazone are known as Epimers "aldoses which differ in the configuration of C_2"



Glucose **Fructose** **Mannose** **phenylosazone**

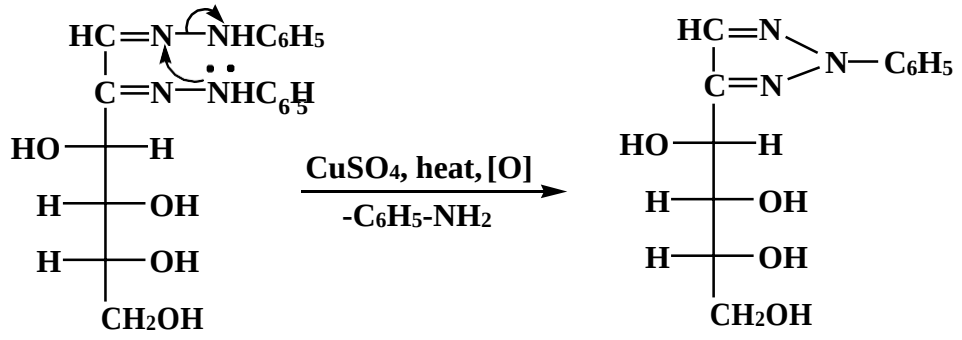




Reactions of osazones:

a) Conversion into the corresponding osatriazoles:

Hudson found that when osazones are refluxed with aqueous copper sulphate, they are converted into the osatriazoles.

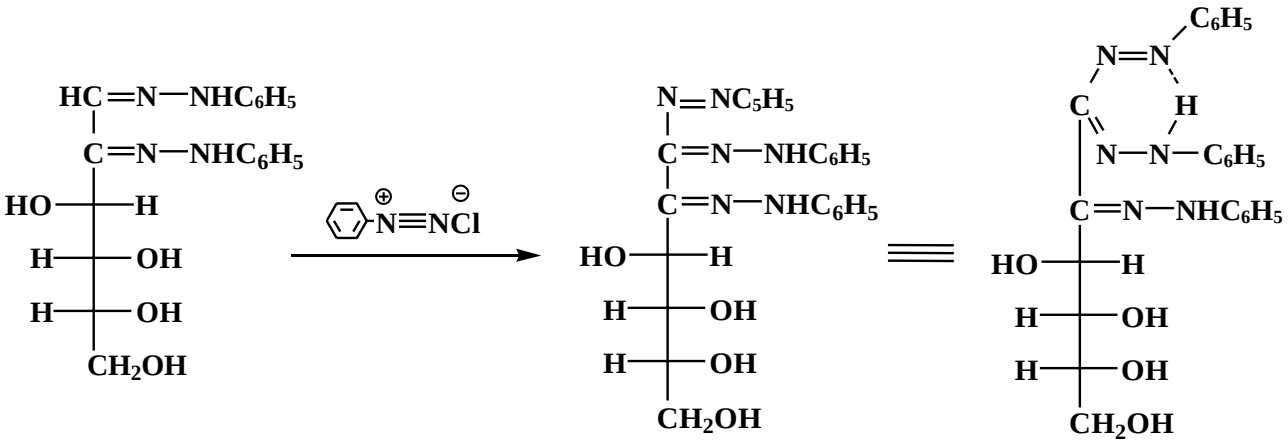


Glucose phenylosazone **Glucose phenylosatriazole**

In this reaction it has been shown that other oxidizing agents such as ferric salts and bromine water also can be used for glucose phenyl osatriazole formation. The osazone first being oxidized to unstable intermediate which is then converted into the osatriazoles.

b) Foramazan:

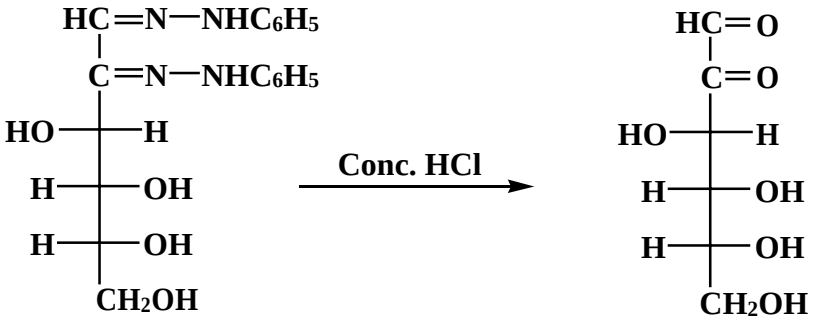
The reaction of carbohydrate phenylosazone with aryldiazonium compound yield formazan.



Glucose phenylosazone **Formazone**

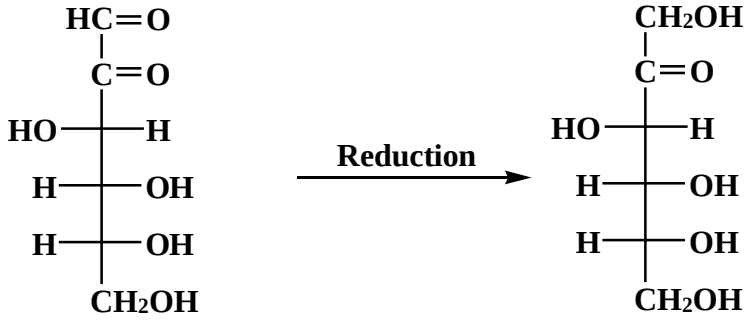
c) Conversion of osazones into osones:

This reaction is the first carried out by E. Fischer using conc. Hydrochloric acid, but it is now performed with aromatic aldehydes. e.g. benzaldehyde because benzald. phenylhydrazone is precipitated leaving the ozone in solution. Osones react with phenylhydrazine in cold to form osazones.

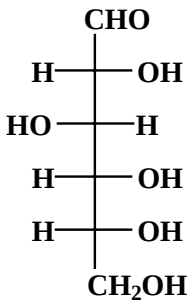


Glucose phenylosazone **Glucosone**

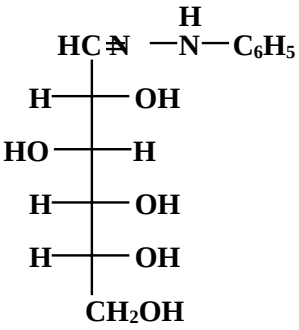
The osones are available starting materials for the synthesis of ascorbic acid, its homologous. They can also be reduced to give the corresponding ketoses. So we can convert the aldoses to ketoses through the reduction of osones.



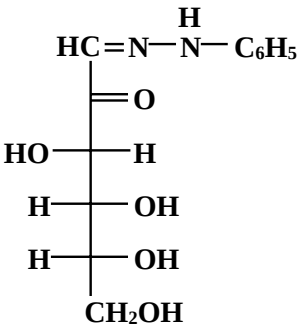
1- Conversion of glucose to fructose:



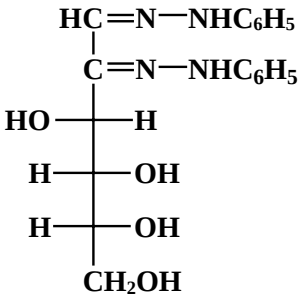
Glucose



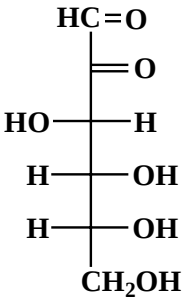
Glucose phenylhydrazone



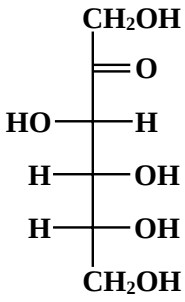
Phenylhydrazone of glucosone



Glucose phenylosazone



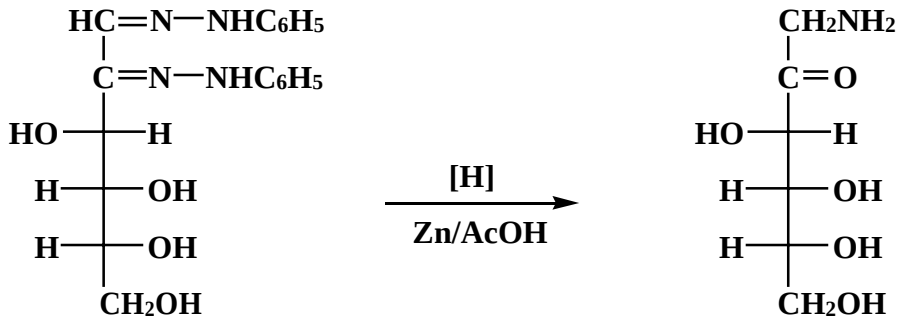
Glucosone



Fructose

d) Reduction of Osazones:

When osazones are reduced with nacent hydrogen or better catalically they give iso-glucosamine.

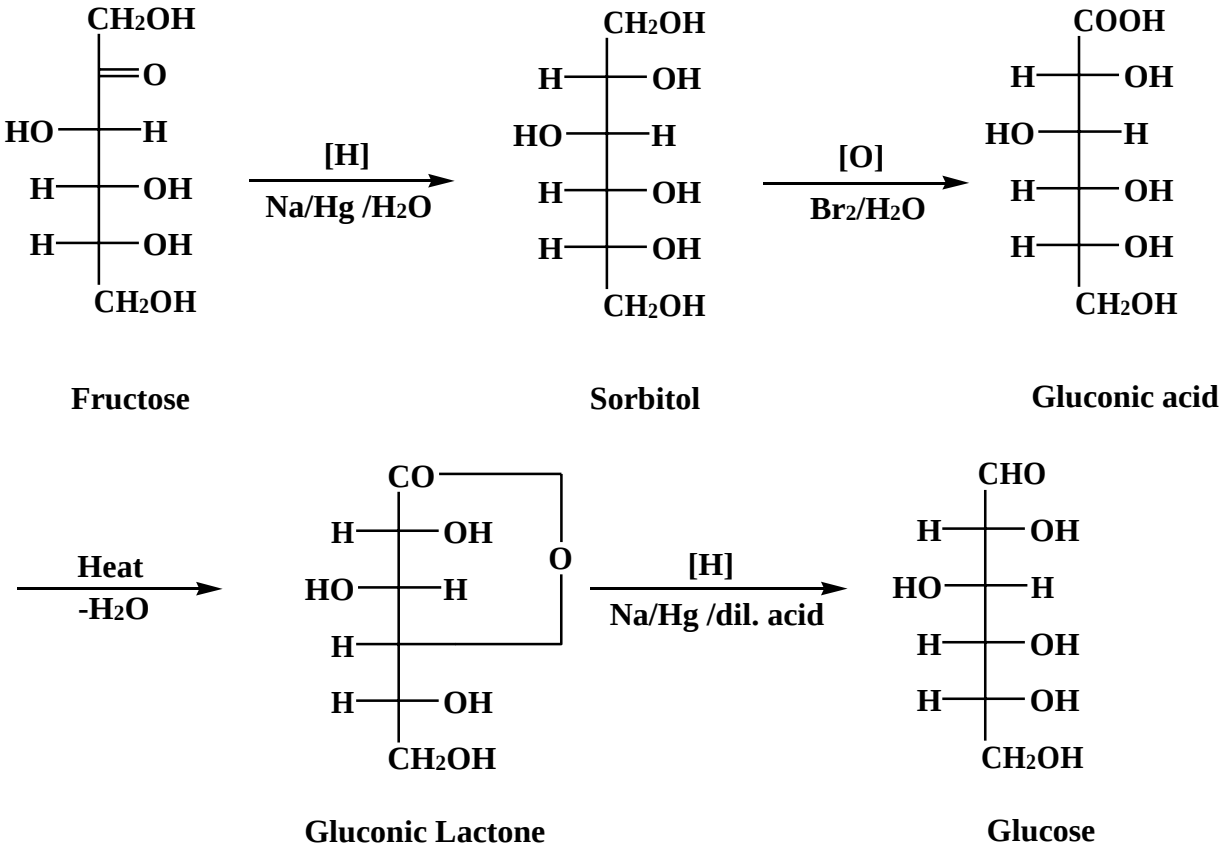


Isoglucosamine

Isoglucosamine can be converted into fructose by nitrous acid, affording another way for converting aldoses into ketoses.

2- Conversion of Ketoses to Aldoses:

The ketose is first reduced to hexahydro alcohol using Na/Hg and water, then the alcohol is oxidized to the corresponding aldonic acid which is then lactonised and reduced. The carboxylic group cannot be reduced directly, but firstly it might be converted into lactone.

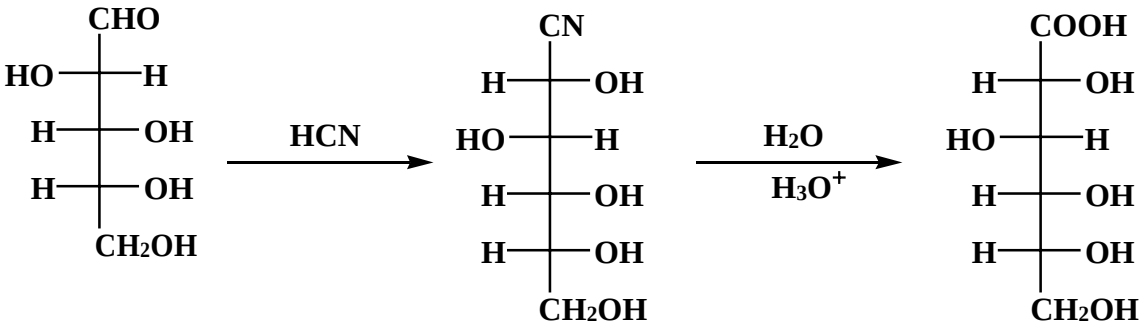


3- Ascent of the Sugur Series:

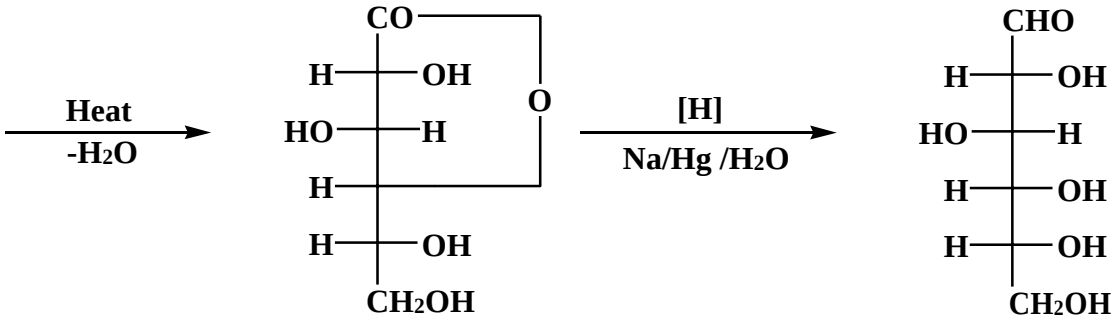
Conversion of pentoses into Hexoses:

a) Kiliani Cyanohydrin Synthesis:

This reaction is used for ascending the series. The sugur is treated with HCN to give the cyanohydrin which is then hydrolysed to give the acid then lactonised and reduced.

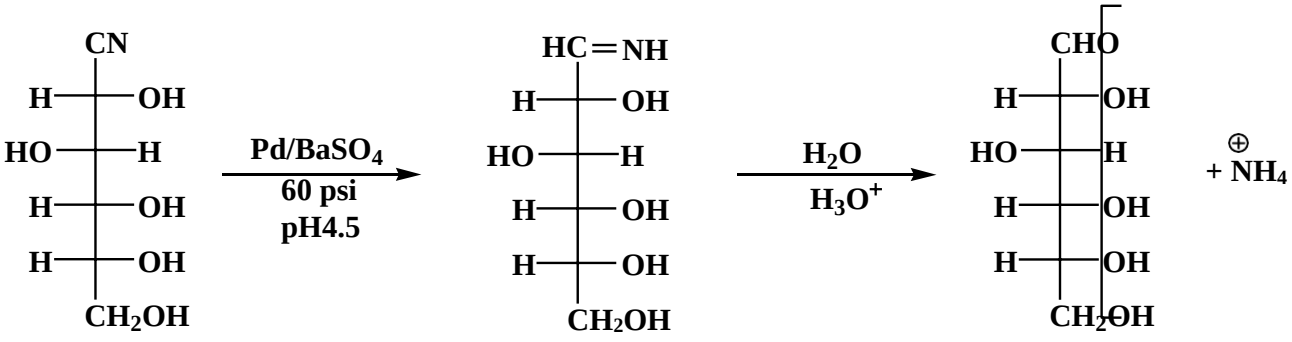


Arabinose **Cyanohydrin**



Gluconic Lactone **Glucose**

The mixture of cyanohydrins can be converted into a mixture of aldoses by catalytic hydrogenation, and these aldoses can be separated.



imine intermediate

In the previous reaction a new asymmetric carbon atom is formed and one would expect equal quantaties of the epimers would be formed, but this is not the case, one of the two isomers predominates usually, this is because the starting material is optically active and the reaction is therefore an asymmetric synthesis.

The Kiliani reaction has been used to prepare sugars having 10 carbon atoms.

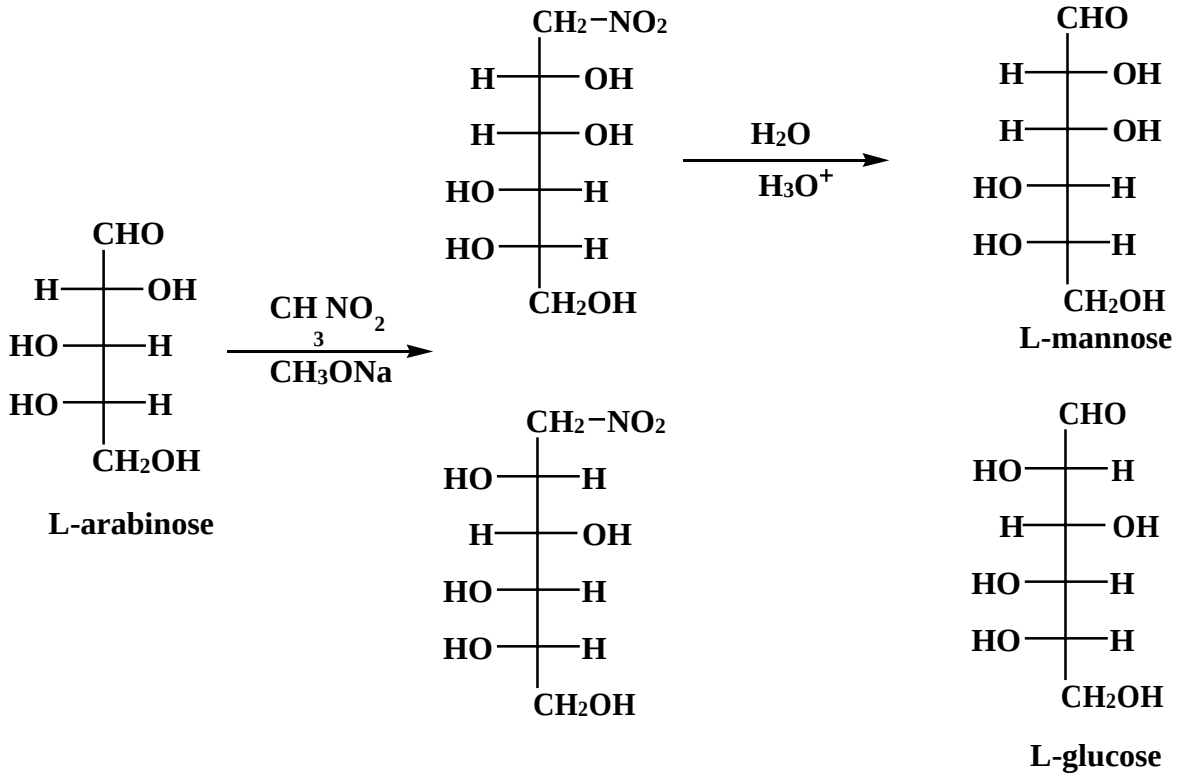
b) The Nitromethane Synthesis (Sowden-fischer):

Another method of extending the length of the carbon chain involves the base-catalysed condensation of nitromethane with an aldehyde to produce a C-nitroalcohol and decomposition of the sodium salt of the latter with cold mineral acid to give an aldehyde containing one more carbon atom than the original aldehyde.

$$R\text{-}CHO + CH_3NO_2 \xrightarrow{NaOH} R\text{-}CHOH\text{-}CH{=}NO_2.Na + H_2O$$

$$R\text{-}CHOH\text{-}CH{=}NO_2.Na + 2H_2SO_4 \rightarrow 2R\text{-}CHOH\text{-}CHO + 2\ NaHSO_4 + N_2O + H_2O$$

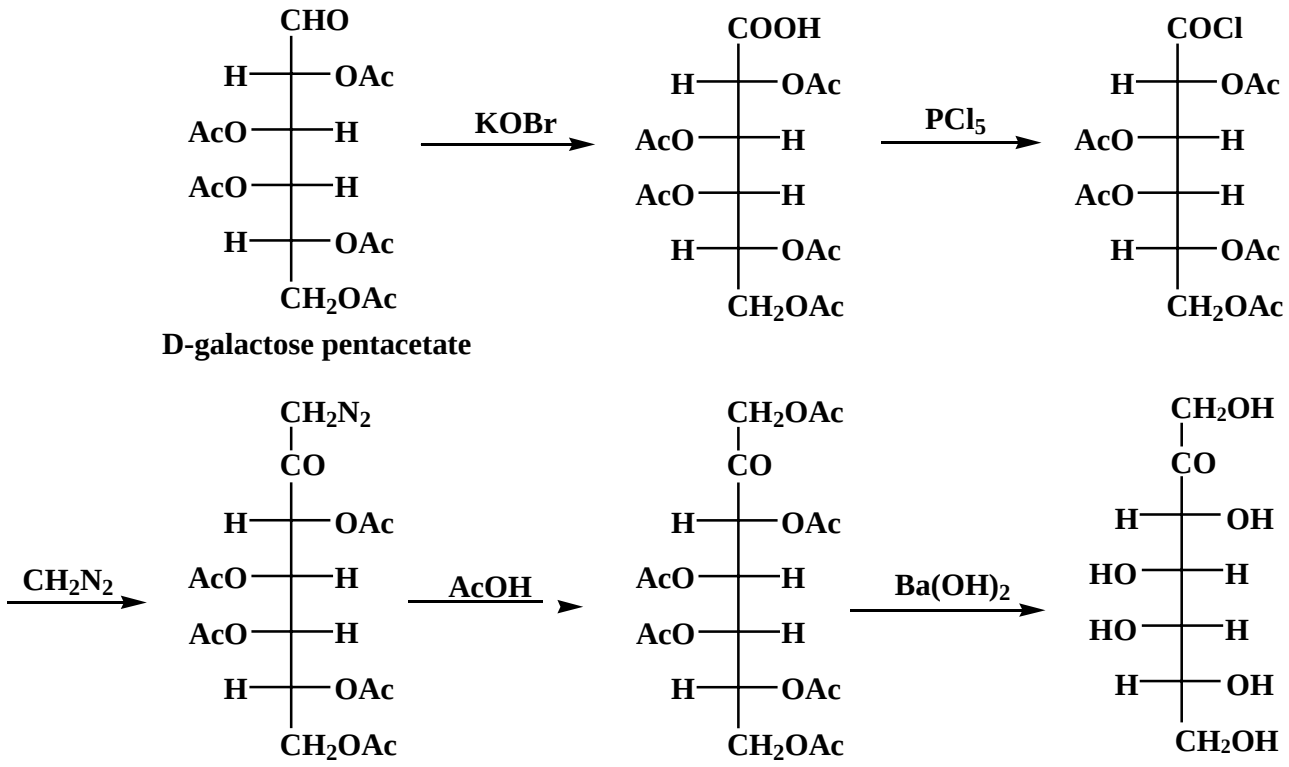
The reaction is usually carried out in methanol with sodium as basic catalyst. As in the cyanohydrin synthesis two epimeric products are formed. The mixed epimeric C-nitroalcohols are readily separated by fractional crystallization, and decomposition of the sodium C-nitroalcohols gives the higher sugars in good yield.



Sowden, by the above method, but using 2-nitro-ethanol instead of nitromethane, converted an aldose into a ketose containing two additional carbon atoms.

c) Diazomethane Synthesis:

The action of diazomethane on an acid chloride to give a diazomethylketone has been employed in ascent of the sugar series, the sequence of reactions being as follows:

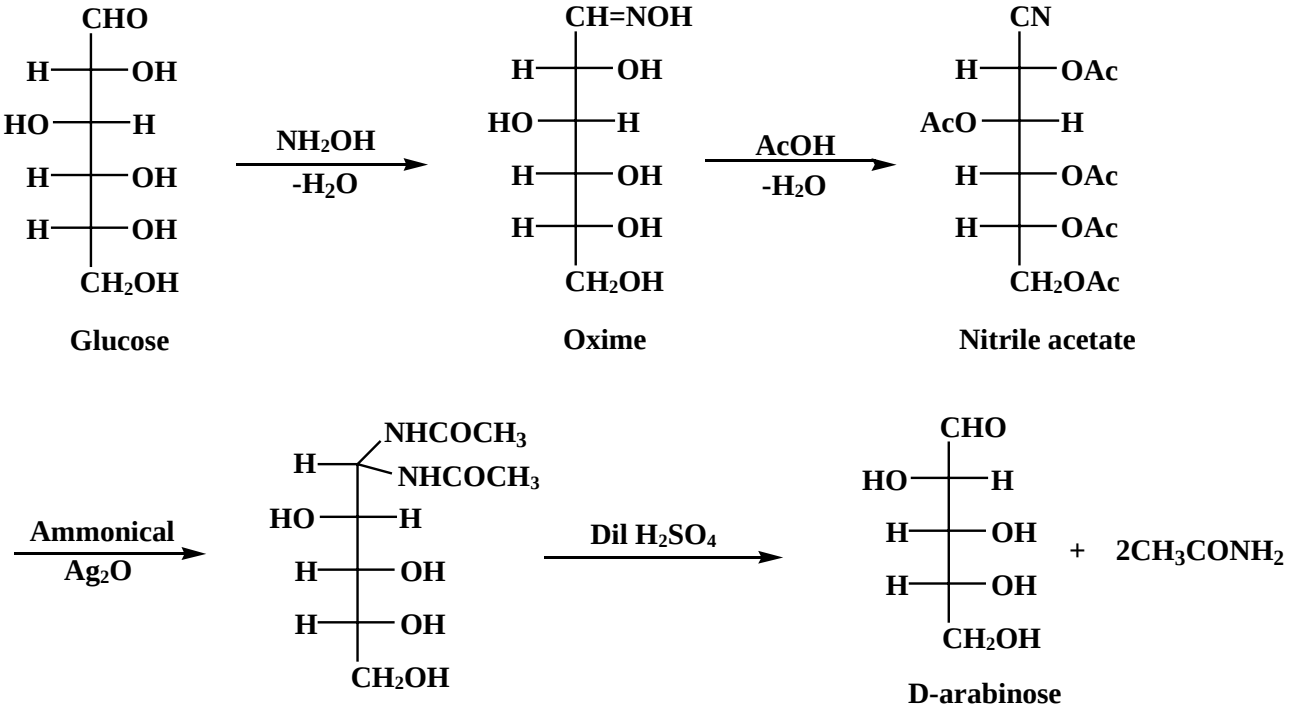


D-galactose pentacetate

4- Desent of the sugar series conversion of hexoses t pentose.

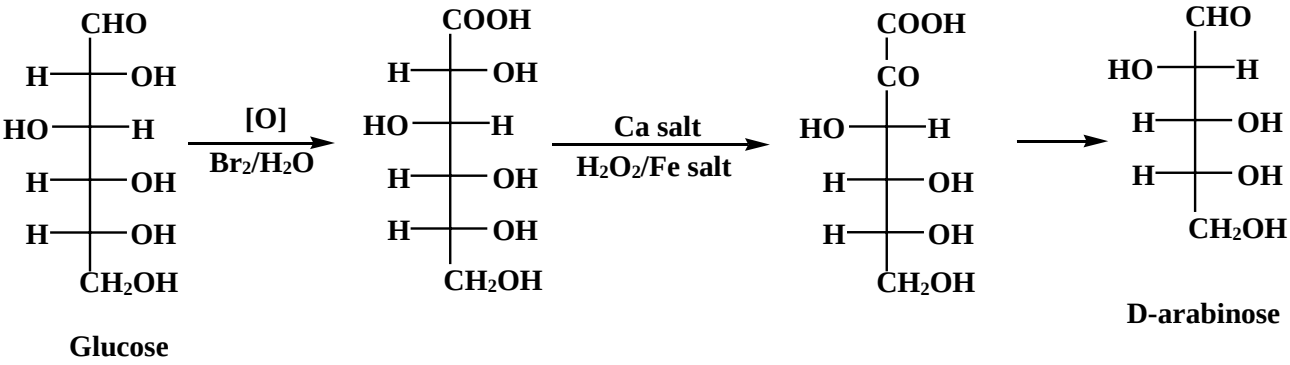
a) Method of whol:

This method consists in converting the aldose into oxime which on treatment with acetic anhydride is converted into the nitrole and acetylated. On treatment this nitrile acetate with ammoniacal silver oxide a splitting of HCN takes place together with the hydrolysis of the acetate groups resulting in the lower aldosugar. An intermediate of the last reaction usually obtained which is an addition product of acetamide and the sugar, this is readily hydrolysied with acid.



b) Method of Ruff:

This method consists in oxidizing the aldose to aldonic acid and reacting its calcium salt with hydrogen peroxide in the presence of ferric salt to give first an intermediate α-keto acid immediately decomposes giving carbon dioxide and lower sugar.



5) Action of Alkalies:

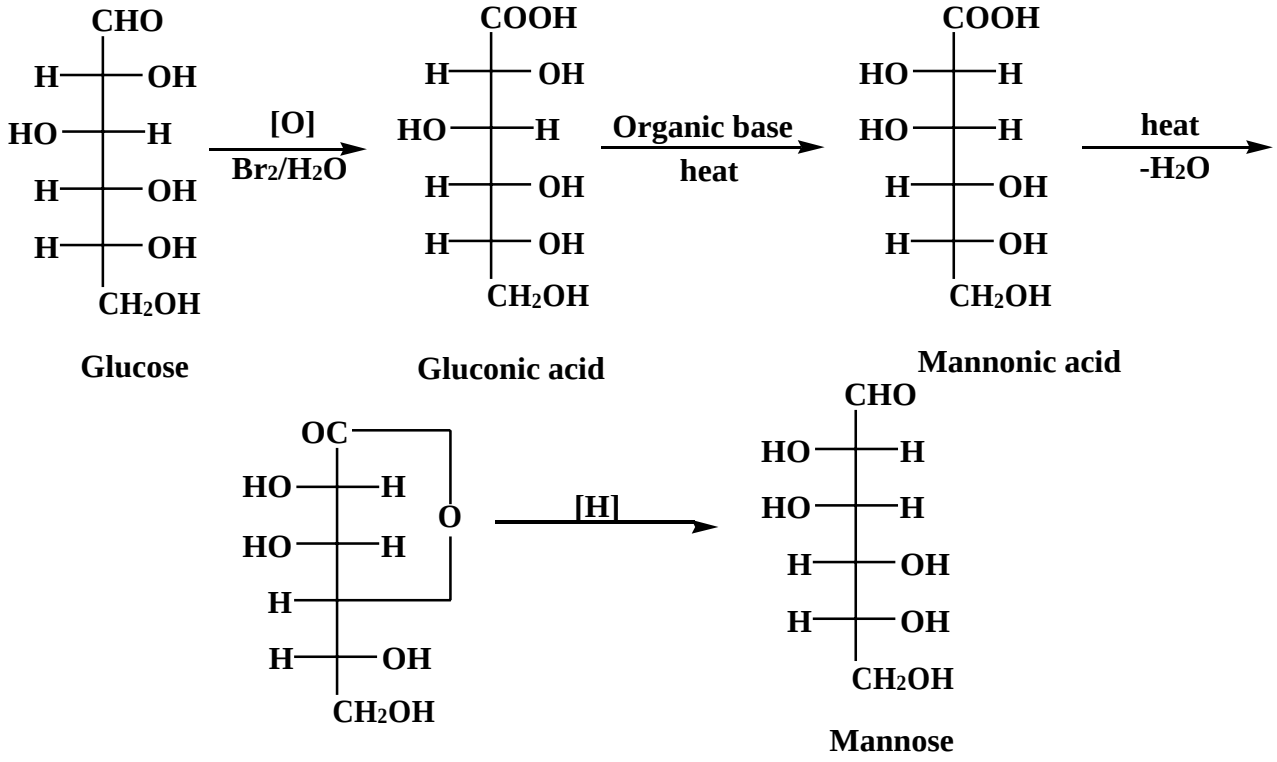
The sugar molecule is unstable toward alkalies. It undergoes a series of isomerisation and degradation leading to a number of compounds. Thus more than 100 different compounds have been isolated from the reaction product of glucose and sodium hydroxide.

6) Epimerisation:

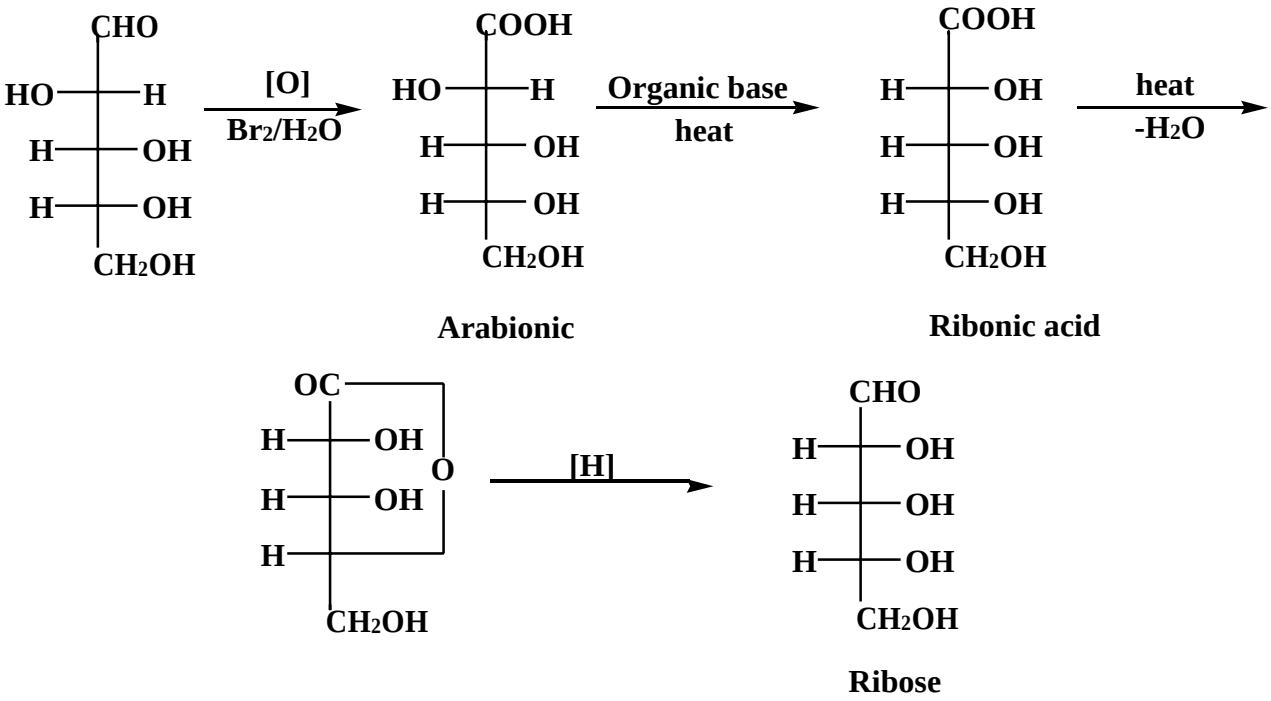
When glucose is treated with very dilute alkalies or better when treated with organic bases such as pyridine or quincline, epimerization is said to take place, that is sugar epimers are obtained. Thus glucose yields a mixture of mannose, fructose and unreacted glucose. This reaction is useful in the preparation of rare sugars from their epimers. The mechanism of this reaction was suggested by Lobrg de Druyn and Van Ekenstein involving the formation of an intermediate enediol.

The hydrogen atom attached to the carbon to the carbonyl (C_2 in glucose) enolysis to form an enediol, thus destroying the asymmetry of C_2. On ketonisation the 2 epimeric aldoses are formed. If the second hydrogen on C_2 migrates to C_1 a ketose is formed (fructose). Thus we can convert glucose into mannose and fructose. This process however is usually accompanied by a considerable decomposition and it is now no more used for laboratory purposes.

The reaction is best carried out by the epimerization of aldonic acids which are more stable towards alkaline medium. Thus the aldose is first oxidized to the aldonic acid say gluconic acid, which is then heated with an organic base like pyridine or quinoline and thus it converted to mannonic acid which is then lactonised and reduced to give mannose.



Conversion of arabinose to ribose:



7) Action of acids:

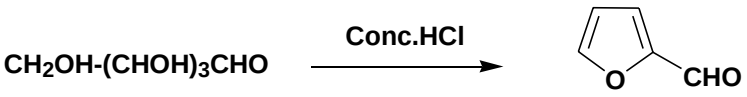
The sugar molecule is very stable towards dilute acids, but with concentrated acids it is distorted:

a- *Conc. Sulphuric acid* removes the elements of water and converts the sugar into carbon.

b- *Conc. Nitric acid* oxidizes the aldose into dicarboxylic acid.

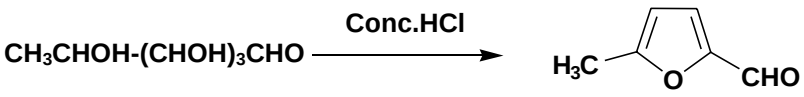
c- *Conc. Hydrochloric acid* reacts with aldoses giving different products:

i) With pentoses it yields furfural which is steam volatile and can therefore be used for the estimation of pentoses (this reaction is used in wood analysis).



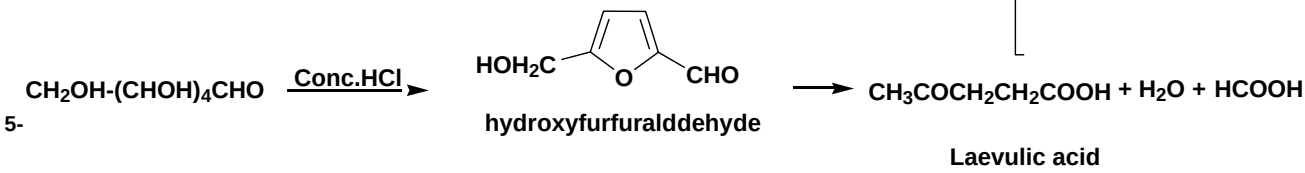
furfuraldehyde

ii) With methyl pentoses we obtain methyl furfural which is steam volatile.



Methylfurfuraldehyde

iii) With hexoses the reaction proceeds in 2 steps first hydroxymethyl-furfuraldehyde is obtained but this rapidly decomposes giving levolinic acid which is not steam volatile, this affords a means for the estimation of pentoses in the presence of hexoses.

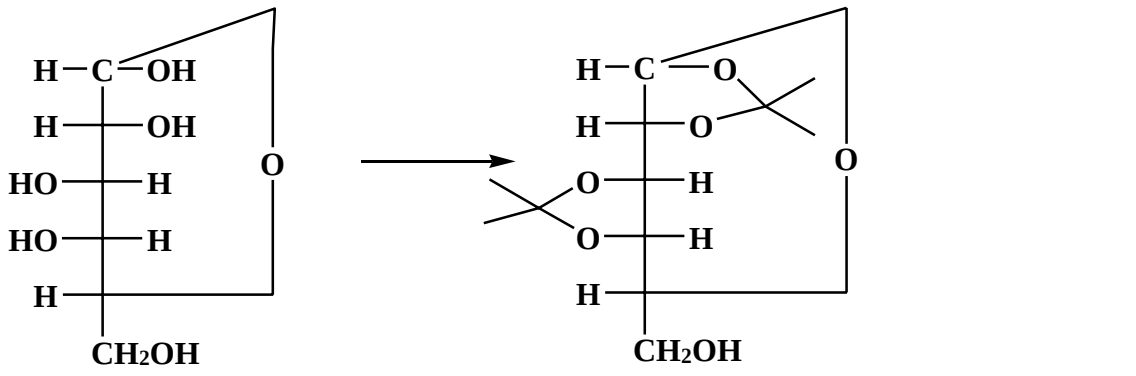


5-

Condensation Products of monosaccharides:

a- Isopropylidine derivatives:

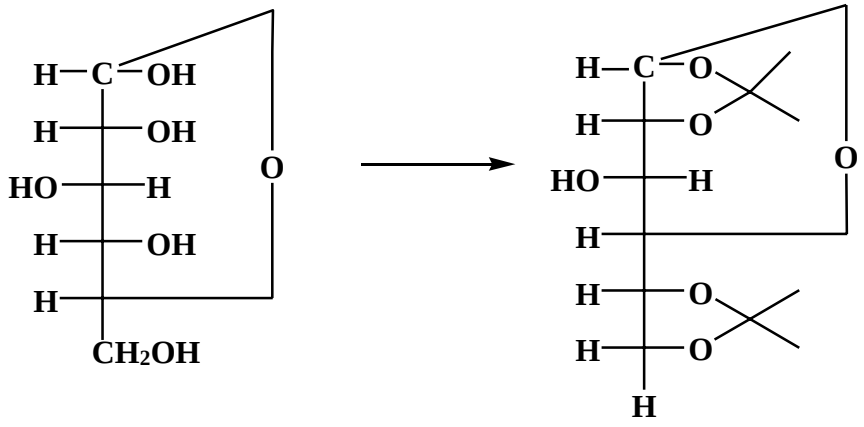
Sugars condense with anhydrous- acetone in the presence of HCL, H_2SO_4, …etc at room temperature to from mono- and di-isopropylidene derivative. These are stahle towards alkalies, but are hydrolysed by acids and always one is hydrolysed more rapidly than the other. Acetone usually condenses with cis-vicinal-OH groups on adjacent carbon atoms and the condensation occurs in such a way as to favour the formation of the di-isopropylidene derivative even if this necessitates the changes in the size of the ring. In α-D- galactopyranose the –OH groups on C_1 and C_2 are cis and also those on C_3 and C_4. Thus galactose forms the 1:2-3:4-di-o-isopropylidene D-galactofuranose (i.e.; no change in the size of the ring).



α–D-galactopyrano -

1:2-3:4-di-O-isopropylidine-D-galctopyranose

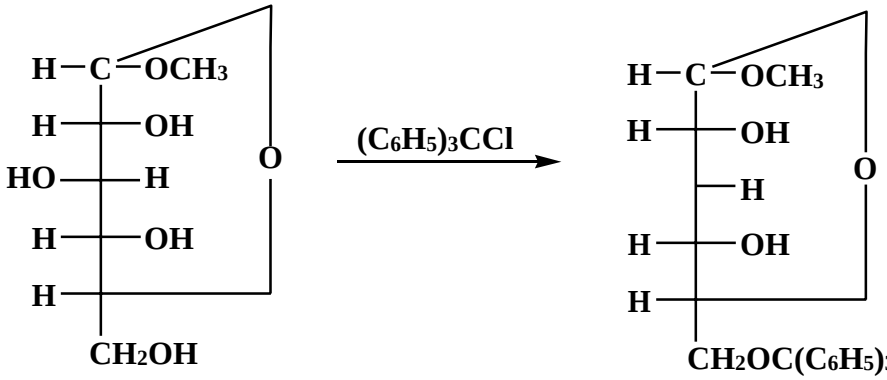
On the other hand in α-D-glucopyrannose, only the two hydroxyl groups on C_1 and C_2 are in the cis position and thus in order to form the di-isopropylidene derivative the ring changes from pyranose to give furanose to give finally 1:2-5:6-di-O-iospropylidene-D-glucopyranose.



α–**D-glucopyranose**

b- Trityl derivatives:

Triphenyl methyl chloride reacts with sugars to form triphenylmethyl derivatives commonly known as trityl derivatives. Trityl ethers are formed much faster with primary alcoholic group than with secondary ones.

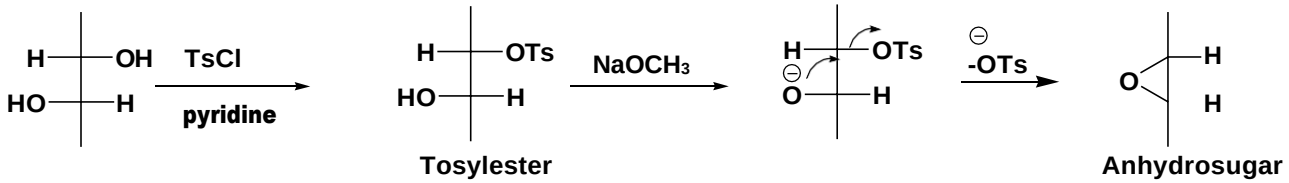


α– **Methyl-D-glucopyranoside**

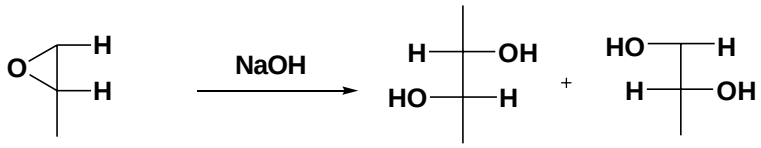
α–M**ethyl**–6–**trityl-D-glucopyranoside**

c- <u>Tosyl derivatives and formation of anhydrosugars:</u>

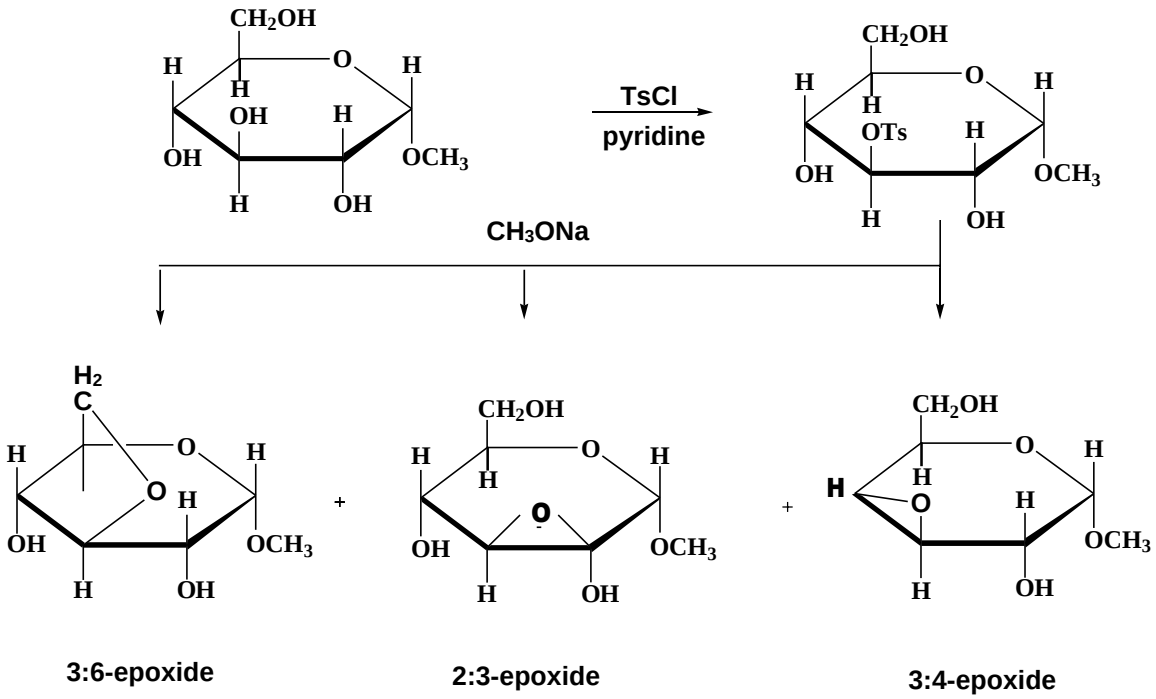
Sugars react with p- toluenesulphonyl chloride in the presence of pyridine to form tosyl ester, these ester usually produce epoxy-sugars known as anhydro sugars when treated with ethoxide on the cold if there is a free –OH on an adjacent carbon atom and that this hydroxyl group and the tosyl group are trans to each other.



Anhydrosugars on hydrolysis with alkali will form two different sugars.



Sometimes there is more than one possibility for the formation of the anhydrosugar and in this case a mixture of the different anhydrosugars is formed. The possibility of formation of an oxide ring larger than the 1:2- one results in additional anhydro sugars are seen from the following example:



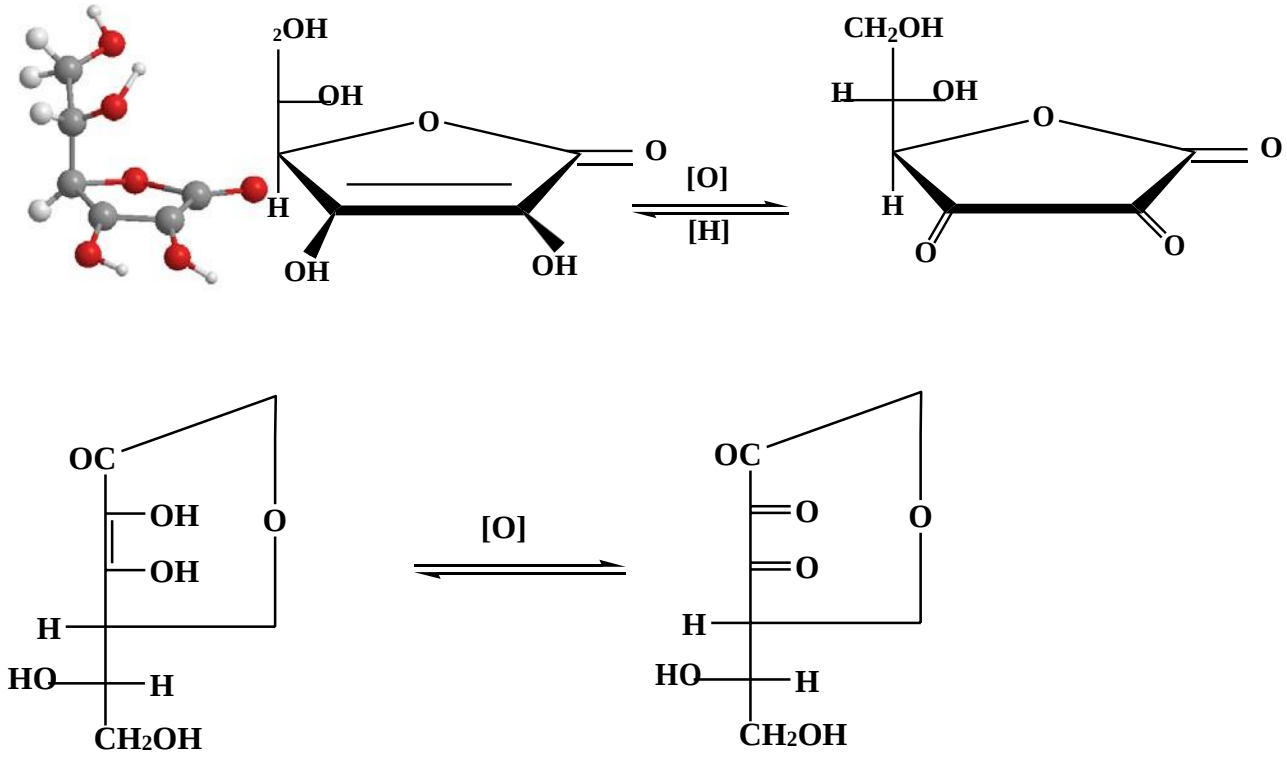
It is noticed that when the tosyl group is trans to two hydroxyl groups on adjacent carbon atoms, two anhydro sugars are formed. At the same time, however larger epoxide rings may be produced without inversion.

L-Aααascorbic acid (Vitamin C)

The structure of L-ascorbic acid (vitamin C) resembles that of a monosaccharide. In fact, this vitamin is synthesized both biochemically by plants and some animals and commercially from D-glucose. Humans do not have the enzymes required for this synthesis and, therefore, we must obtain it in the food we eat or as a vitamin supplement. It is an important water soluble biological reducing agent that complements lipid soluble antioxidants such as vitamine E.

It function in the living tissues as a hydrogen carrier.

L-Ascorbic acid is very easily oxidized to L-dehydroascorbic acid, a diketone. Both L-ascorbic acid and L-dehydroascorbic acid are physiologically active arid are found together in most body fluids.

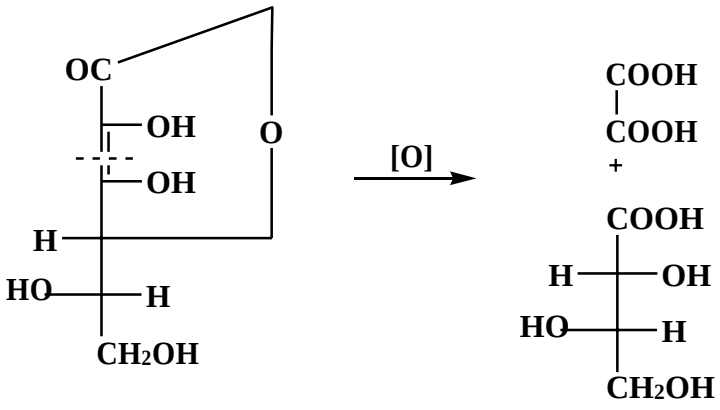


Structure of L- ascorbic acid:

1- On very mild oxidation such as passing air in an aqueous solution of ascorbic acid dehydroascorbic acid was obtained which readily forms an osazone, and since L-ascorbic acid does not form hydrazone.

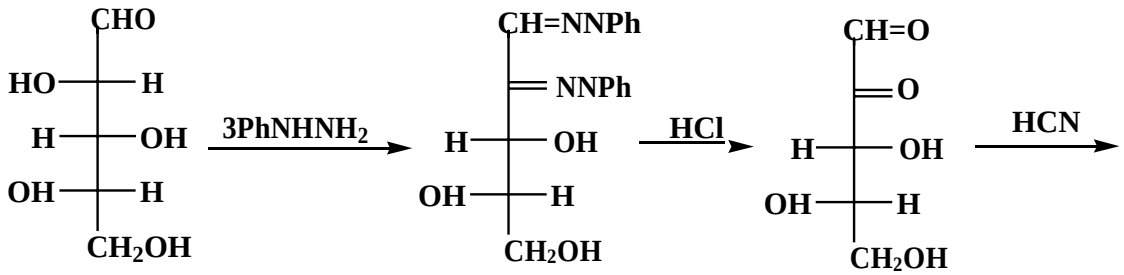
2- Ascorbic acid gives characteristic enolic reaction such as colour with $FeCl_3$ suggesting the prescence of enols which are probably oxidized to form the diketones-dehydroascorbic acid.

3- In stronger oxidation ascorbic acid is broken up at the postion of the double bond in the enediol.

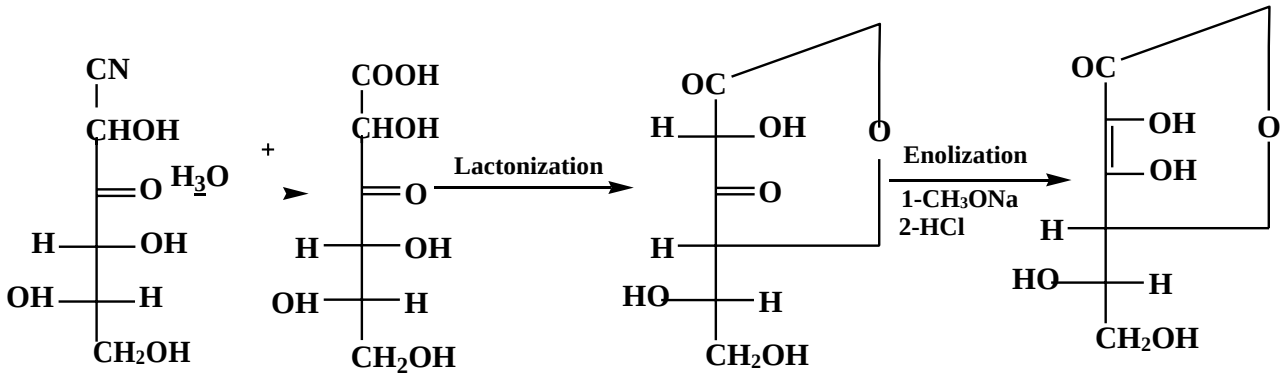


L-Threonic acid

4- Synthesis of ascorbic acid was carried out simaltinously by Reichstein &Haworth(1934). The starting material was L-xylose which was converted into the osazone, then treated with HCl to give ozone then react with HCN to give the cyanohydrin which was lactonised to give ascorbic acid by enolization.



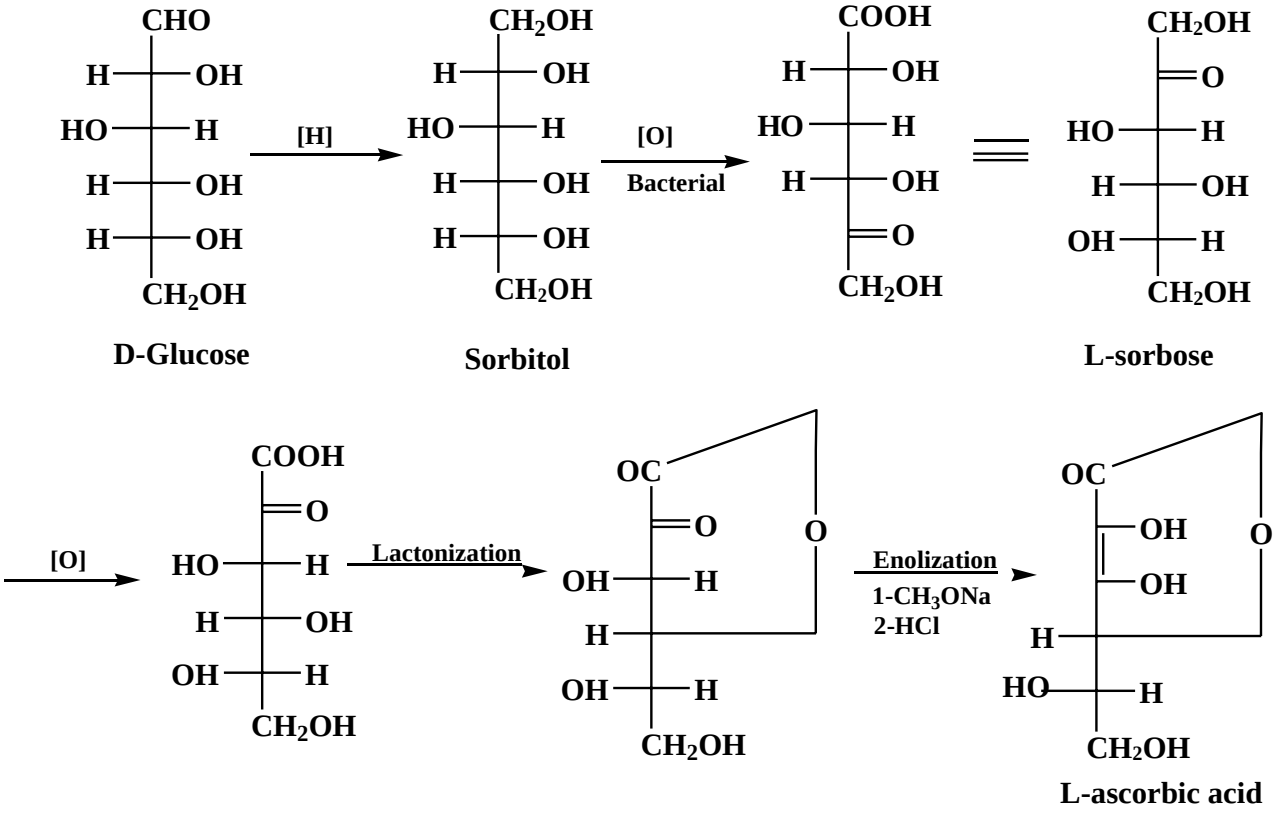
L-xylose **L-xylosone**



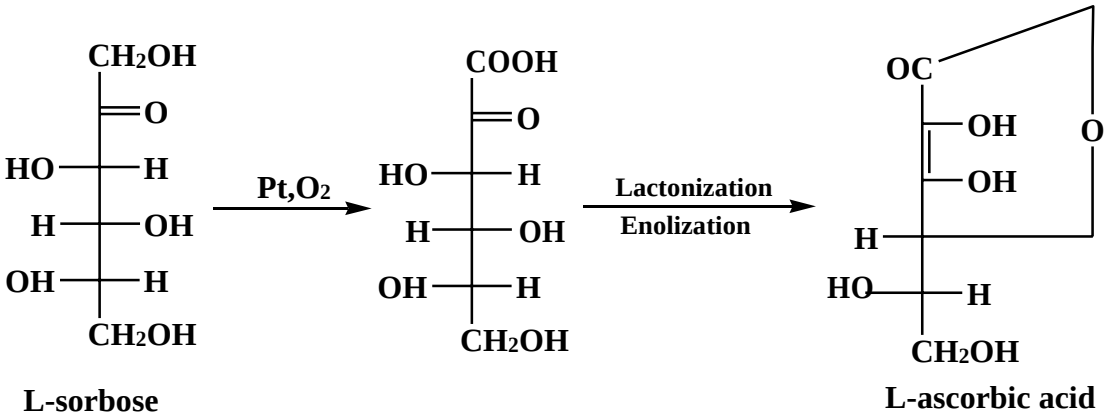
L-ascorbic acid

5- The above synthesis although proving the structure of ascorbic acid is not used in industry for the preparation of the acid. Commercially the starting material is D-glucose which is then oxidized to L-sorbose.Two alternative ways can be followed:

a- Either careful oxidation into 2-keto-L-gluconic acid with on lactonization and enolization gives L-ascorbic acid.



b-Scince the oxidation of L-sorbose results in considerable decomposition.



Disaccharides and Oligosaccharides:

Most carbohydrates in nature contain more than one monosaccharide unit. Those that contain two units are called disaccharides, those that contain three units are called trisaceharides, and so forth. The general term oligosaechariде is often used for carbohydrates that contain from four to ten monosaccharide units. Carbohydrates containing larger numbers of monosaccharide units are called polysaccharides.

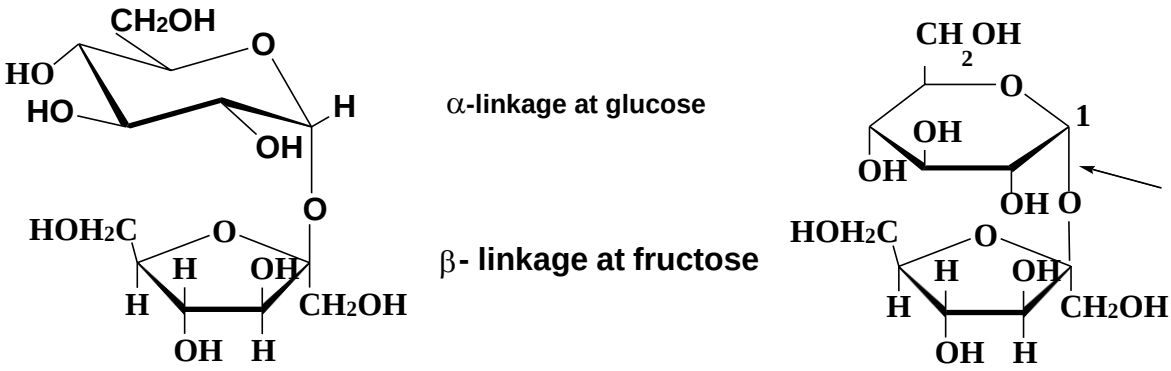
In a disaccharide, two monosaccharide units are joined together by a glycosidic bond between the anomeric carbon of one unit and an OH of the other. Three important disaccharides are sucrose, lactose, and maltose.On hydrolysis, disaccharides yield two molecules of monosaccharide.

$$C_{12}H_{22}O_{11}+H_2O \xrightarrow[\text{Enzyme}]{\text{Acid or}} C_{12}H_{12}O_{12}$$

Many disaccharides are known. Disaccharides may differ in the constituent of monosaccahrides they yield on hydrolysis. For example, sucrose yields D-glucose and D-fructose on hydrolysis; lactose yields D-glucose and D-galactose; and maltose yields two molecules of D- glucose. Two disaccaharides may yield the same mono-saccharides on hydrolysis. In these cases the difference between the two disaccharides may lie in the nature of glycosidic linkage or in the point of attachement of the glycosidic linkage on the second molecule.

Maltose, cellobiose and Gentiobiose yield only D- glucose on hydrolysis. In maltose glucose moieties are joined by an α-glucoside linkage, in cellobiose and gentiobiose they are joined by a B-glucoside linkage between C_1 to C_4 and finally C_1 to C_6 as a B-glycoside. ***A. Sucrose:***

Sucrose (table sugar) is the most abundant disaccharide in the biological world. It is obtained principally from the juice of sugar cane and sugar beets. In sucrose, carbon 1 of α-D-glucopyranose is joined to carbon 2 of β-D-fructofuranose by an α-1,2-glycosidic bond.

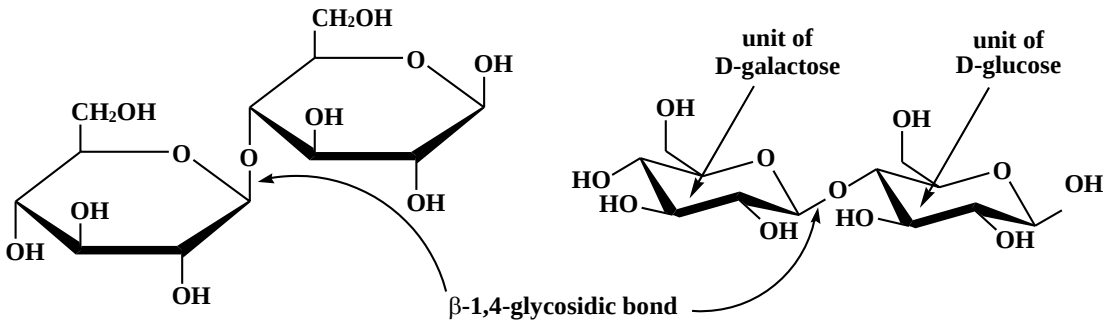


(+)-sucrose or α -D- glucopyranosyl-β -D-fructofuranoside

Note that glucose is a six-membered (pyranose) ring, whereas fructose is a five-membered (furanose) ring. Because the anomeric carbons of both the glucopyranose and fructofuranose units are involved in formation of the glycosidic bond, sucrose is a nonreducing sugar.

B. Lactose:

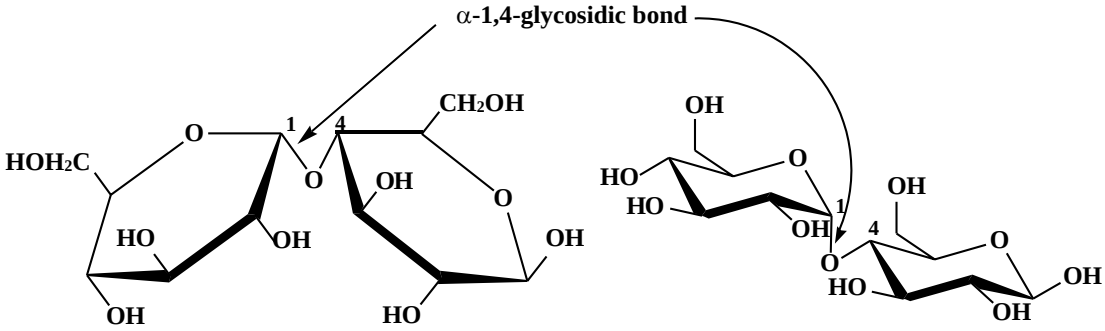
Lactose is the principal sugar present in milk. It makes up about 5-8% of human milk and 4-6% of cow's milk. It consists of D-galactopyranose bonded by a β-1-4-glycosidic bond to carbon 4 of D-glucopyranose. Lactose is a reducing sugar.



C. Maltose:

Maltose derives its name from its presence in malt, the juice from sprouted barley and other cereal grains (from which beer is brewed). Maltose consists of two molecules of D-glucopyranose joined by an α-1,4-glycosidic bond between carbon 1 (the anomeric carbon) of one unit and carbon 4 of the other unit. Following are

representations for fl-maltose, so named because the OH on the anomeric carbon of the glucose unit on the right is beta.

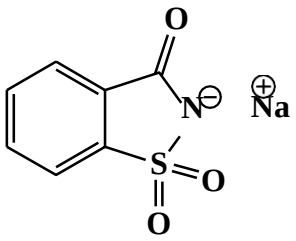


Maltose is a reducing sugar because the hemiacetal group on the right unit of D-glucopyranose is in equilibrium with the free aldehyde and can be oxidized to a carboxylic acid.

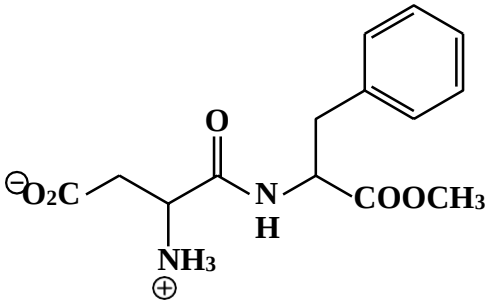
D. Relative Sweetness of Some Carbohydrate and Artificial Sweeteners:

Although all monosaccharides are sweet to the taste, some are sweeter than others (Table 4). D-Fructose tastes the sweetest, even sweeter than sucrose. The sweet taste of honey is attributable largely to D-fructose and D-glucose. Lactose has almost no sweetness. It occurs in many milk products and is sometimes added to foods as a filler. Some people lack an enzyme that allows them to tolerate lactose well; they should avoid these foods.

The sweetening power of sugars is undoubtedly their most important characteristic, insofar as the public is concerned. If the sweetness of sucrose is taken as a standard, then other sweet tasting compounds may be ranked accordingly, as shown here. Saccharin and aspartame are synthetic sweeteners, their structures are shown on the right. The other compounds are natural sugars.



Sacchrin



Aspartame

Table 4: Relative Sweetness of Some Carbohydrates and Arificial Sweetening Agents:

Carbohydrate	Sweetness Relative to Sucrose	Artificial Sweetener	Sweetness Relative to Sucrose
Fructose	1.74	Saccharin	450
Invert sugar	1.25	Aspartame	160
Sucrose (table sugar)	1.00		
Honey	0.97		
Glucose	0.74		
Maltose	0.33		
Galactose	0.32		
Lactose (milk sugra)	0.16		

Determination of the structure of disaccharides:

(1) On acid hydrolysis the disaccharide, yields either one type of monosaccharide or 2 types, e.g. maltose and cellobiose give on hydrolysis glucose, where as lactose yield glucose and galactose, sucrose give on hydrolysis glucose and fructose. If the disaccharide give only one type of mono-saccharide on hydrolysis, its identification (of mono-) offer no difficulty, but when 2 types of monosaccharides are obtained their identification is more difficult.

The separation and identification of sugar mixtures is best accomplished by paper chromatography using a miscible solvent such as butanol-water, phenol-water, etc… and developing the color of the sugar spots with say Ammonial silver nitrate.

$$R_f \text{ value} = \frac{\text{distance travelled by spot}}{\text{distance travelled by solvent}}$$

$$= a/b$$

Another method in the separation of sugar mixtures is the use of paper electrophoresis the spot of the sugar mixture is put in a sheet of filter paper previously soaked in a buffer such as sodium borate and an electric current pase through the sheet. The sugar form complexes withboric acid which will move at different rates in the electric field. The sheet is then dried and sprayed with a reagent to reveal the sugar spots.

(2) The next step is to determine the <u>reducing power of the disaccharide</u>. F the disaccharide is non reducing then the linkage is either

2 aldoses linked 1:1

1 ketoses and aldose linked 2:1

2 ketoses linked 2:2

And the position of the linakge is at once known.

If on the other the disaccharide is reducing then the position of linkage will be 1: x for aldoses or 2: x for ketoses, i.e. the linkage in between the reducing group of one and the othe except the reducing one e.g.

<u>Non reducing</u>

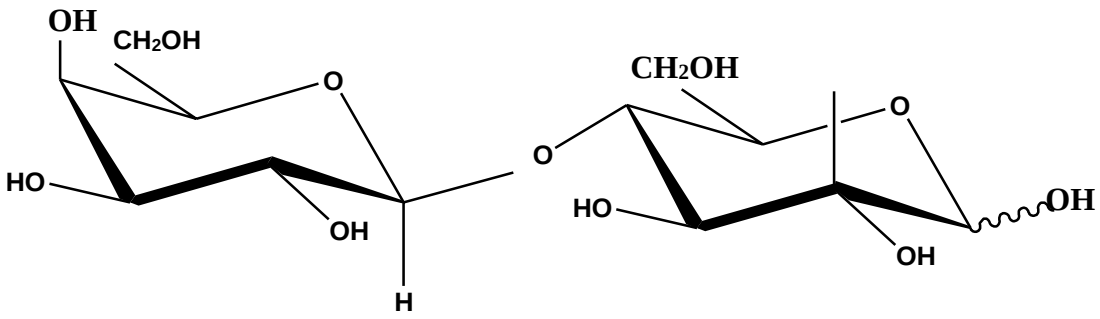
Sucrose : fructose + glucose 2:1

<u>Reducing</u>

Maltose : glucose + glucose α - 1:4

Cellobiose: glucose + glucose β- 1:4

Lactose: galactose + glucose β- 1:4

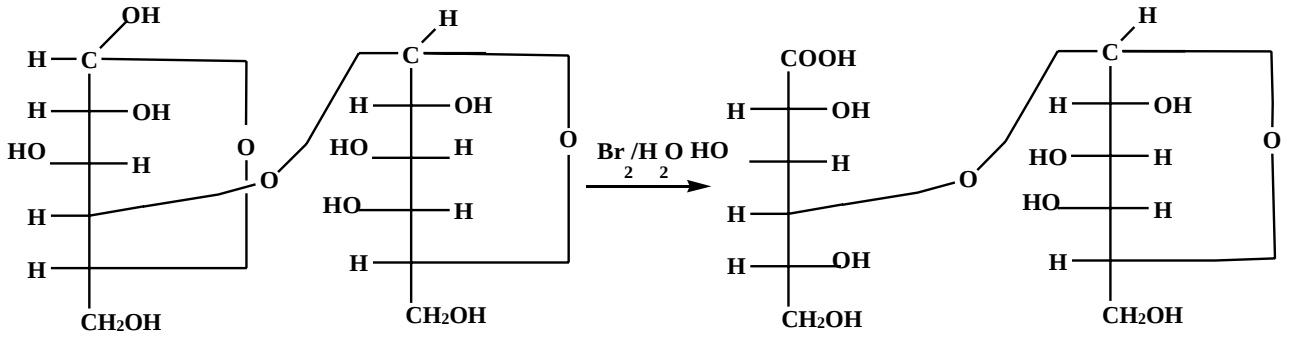


galactose residue **glucose residue**

(+)- lactose or 4-O-(β - D-galactopyranosyl)-D-glucopyranose

(3) In the case of reducing disaccharide containing 2 different monosaccharide we must determine which of these monosaccharides is linked in position 1, i.e. non reducing.

This is carried out by oxidizing the disaccharide into aldobionic acid, which is then hydrolysided to give an aldonic acid from the reducing sugar and a free sugar from the non reducing component, e.g. lactose yields galactose and gluconic acid denoting that galactose in the non reducing component (linked in position 1) and glucose is the reducing one (linked in position x =4).



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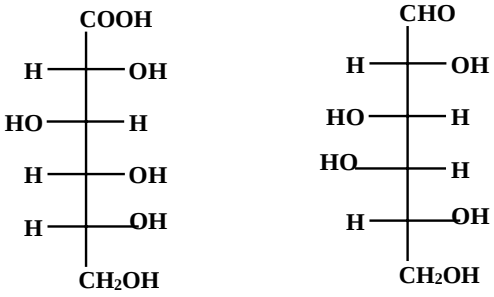


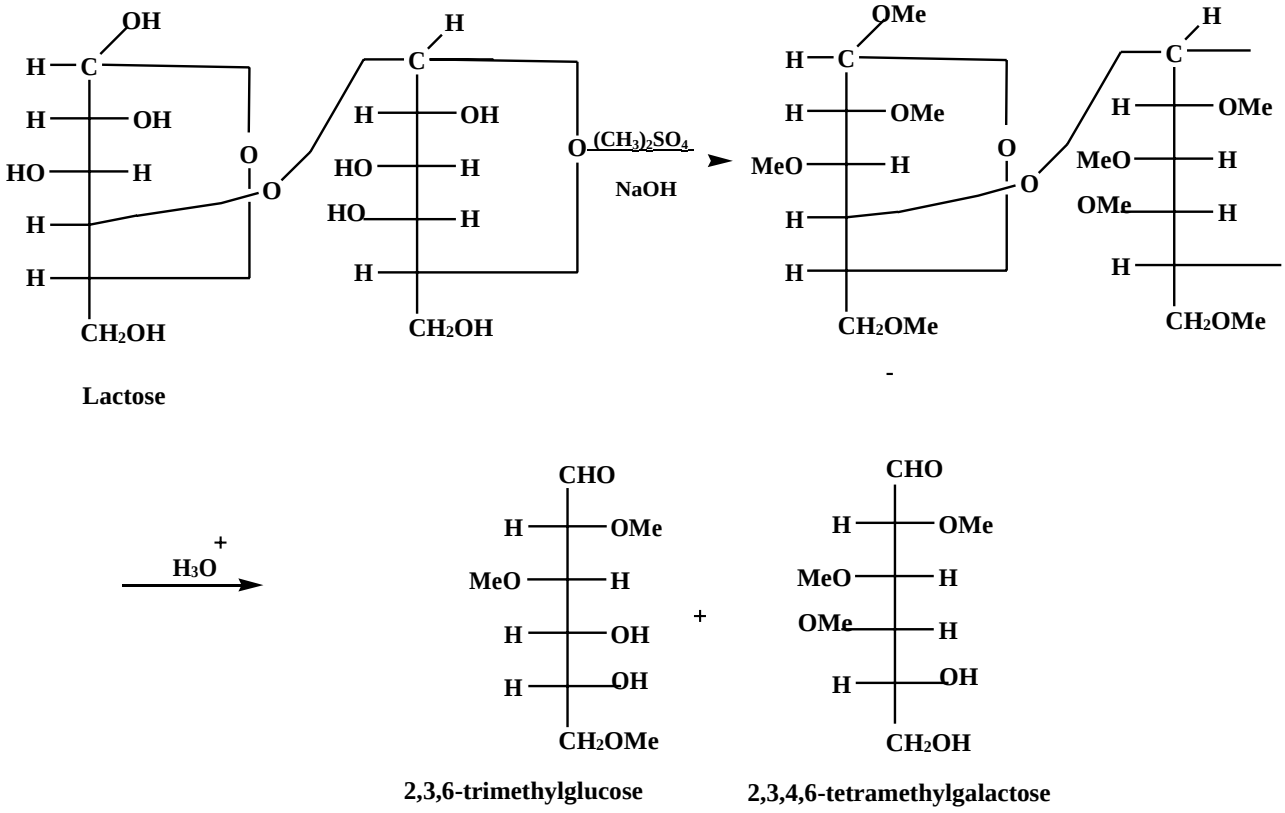
Gluconic acid

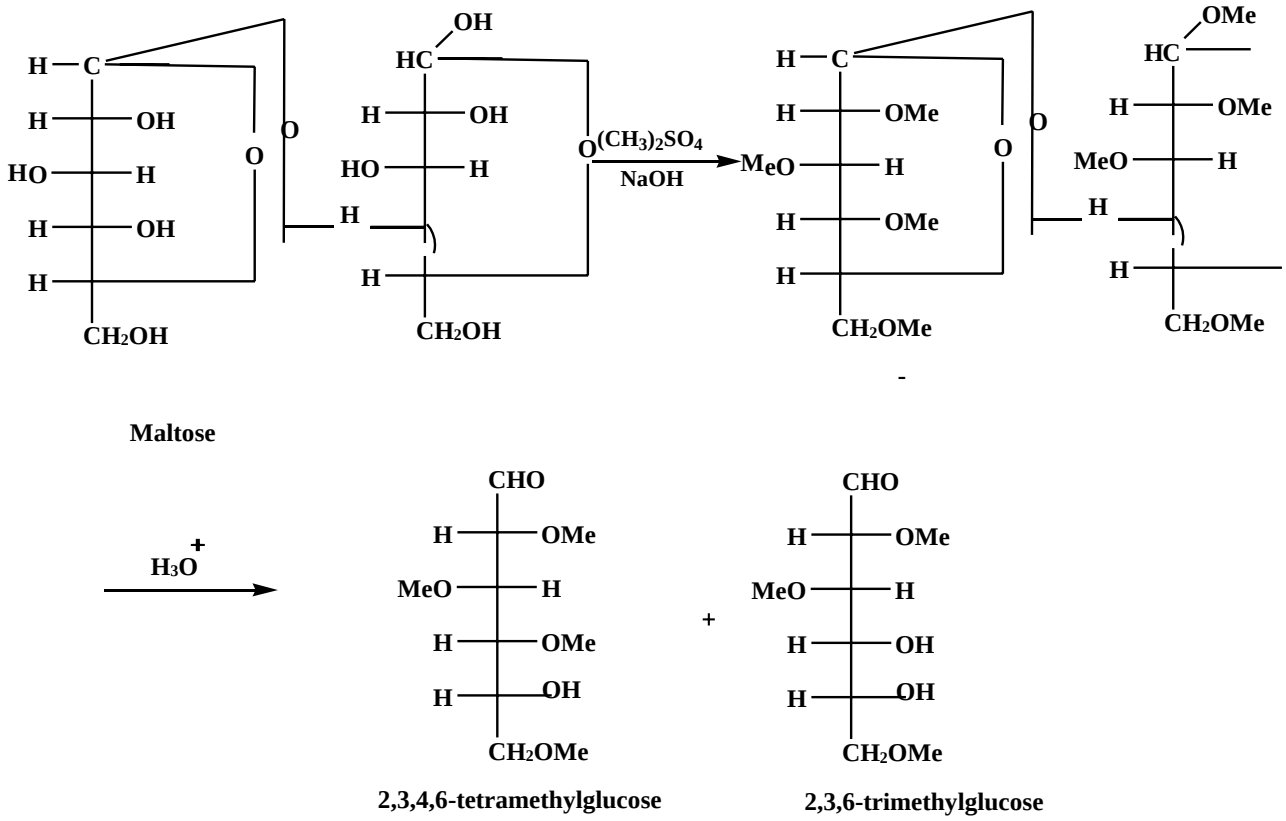
Galactose

(4) Methylation experiment can then give an idea about the position of linkage and the ring size of the disaccharide. Methylation is best carried out with dimethyl sulphate and dilute alkali or methyl iodide and silver hydroxide. The completely methylated disaccharide is then hydrolysed and from the study of the components (methyalted monosaccharides) we can conclude where the position of glycosidic linkage and hemiacetol linkage are. In case of lactose if the octamethylated lactose is hydrolysied it give 2, 3, 4, 6- tetramethylated galactose (from the non reducing half of the olecule) which has only position 5 free, hence, it is pyranose; and 2, 3, 6- trimethyl glucose (from the reducing part of the molecule which denotes that it can be furanose linked at position 5, or pyranose linked at position 4.

Thus in the case of maltose the hydrolysis of the octamethyl derivative yield 2, 3, 4, 6- tetramethyl glucose (from the non reducing half of the molecule) which has only positions 5 free, hence it is pyranose; and 2, 3, 6- trimethyl glucose (from the reducing half of the molecule) which denotes that it can either be pyranose linked at

position 4 or furanose linked at position 5 (on hydolysis, only the acetal methoxy group is removed, since acetale hyrolyse more readily then do ethers).



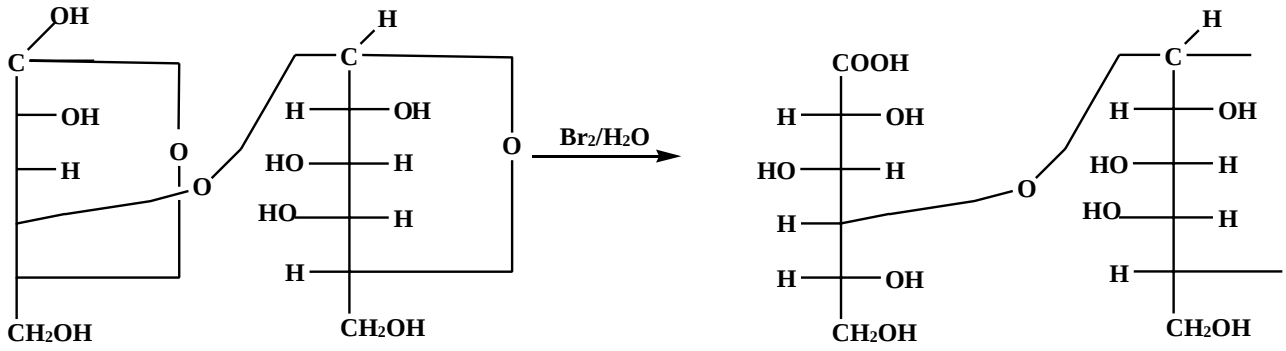


(5) To determine accurately the position of linkage and the ring size in the reducing half of the molecule we oxidize the disaccharide into the aldobionic acid, where the reducing half will be oxidized and will not exist in the ring form, then the free position in the methylated aldonic acid will be the position of linkage.

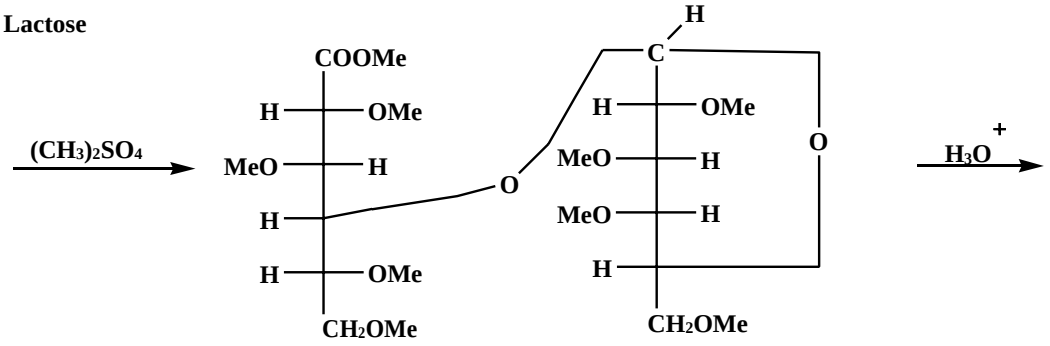
In the case of lactose we obtain:

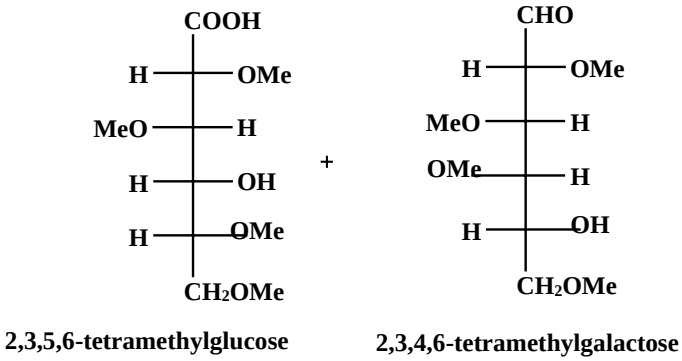
a- A reducing methylated sugar 2, 3, 4, 6- tetramethyl galactose (from the non-reducing half) which has position 5 non- methylated indicating that the ring is pyranose and,

b- A methylated aldonic acid 2, 3, 5, 6- tetramethyl glucose denoting that the linkage in lactose was in position 4.



Lactose





2,3,5,6-tetramethylglucose

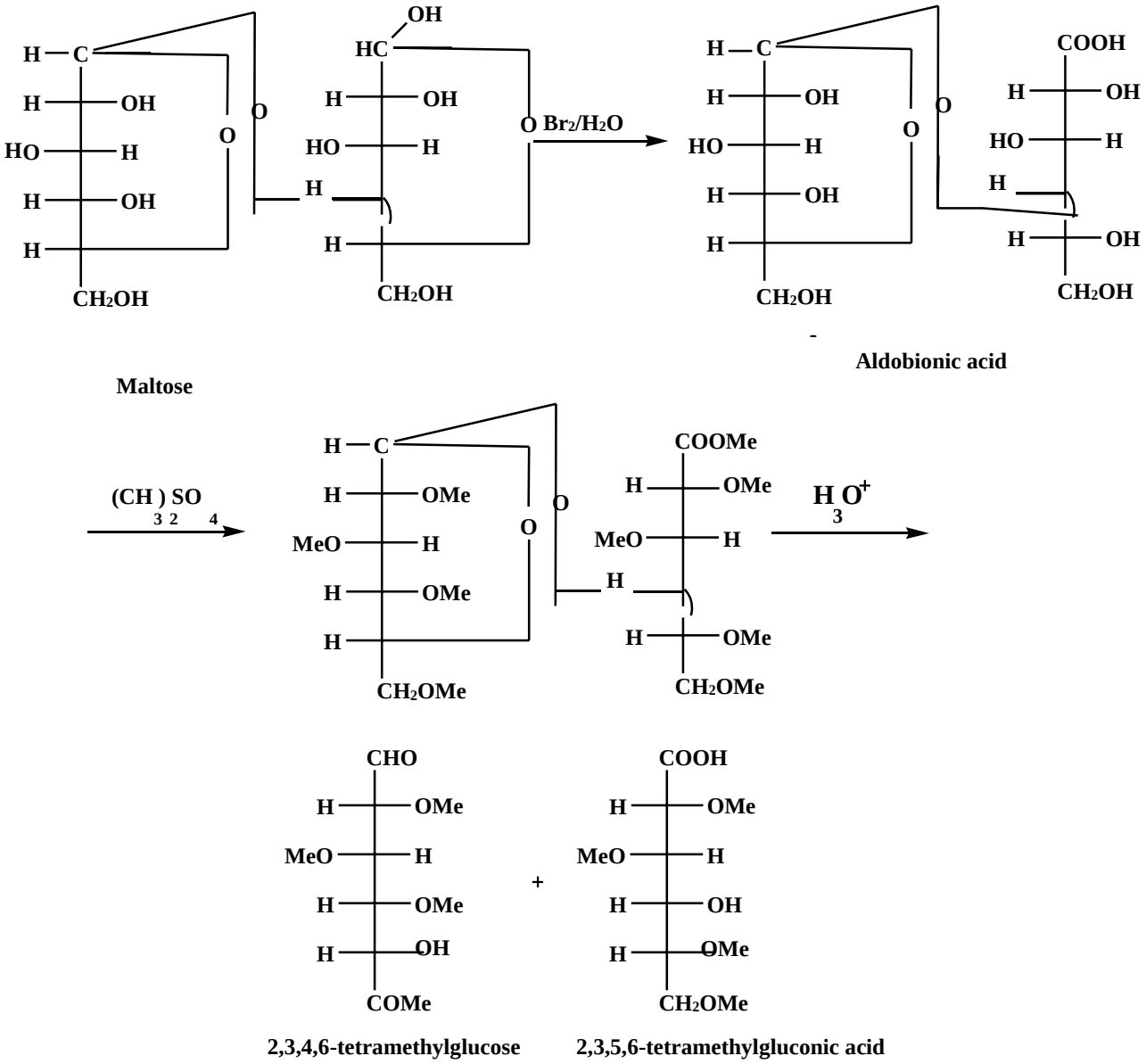
2,3,4,6-tetramethylgalactose

In the case of maltose:

If we carry out this operation with maltose we obtain from the hydrolysis of the methylated aldobinic acid;

a- A reducing methylated sugar (from the non reducing half of the molecule) 2, 3, 5, 6- tetramethyl glucose, which has position 5 non methylated denoting that the ring is pyranose and,

b- A methylated aldonic acid 2, 3, 5, 6- tetramethyl gluconic acid, which has position 4 non-methylated indicating that the linkage in maltose was in position 4, and since in the previous experiments position 4 and 5 were free, then the ring must have been in position 5 i.e. pyranose.



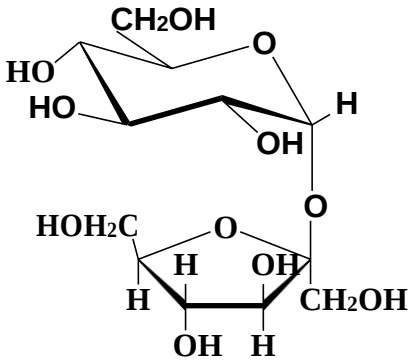
(6) We are now left with the problem of determining the type of the glycosidic linkage (α- or β-). This is a more difficult problem; it can however be setteled by enzymatic hydrolysis. Certain enzymes (for instance emulsion from bitter almonds) are known to hydroyse one type of glycosidic linkage and not the other, thus emulsion for exampleis known to hydrolyse β isomer but not the α- isomer, this enzyme is classed as β-glucosidase. It will therefore hydrolyze cellobiose and not maltose.

Structure of sucrose:

(1) On acid hydrolysis of sucrose it yields 2 types of monosaccharides. By using paper chromatography and paper electrophresis it was found that this disaccharide consists of a D-fructose molecule linked to a D-glucose molecule.

(2) On determining the reducing power of sucrose we found that it is non reducing, indicating that the linkage between fructose and glucose is 2:1.

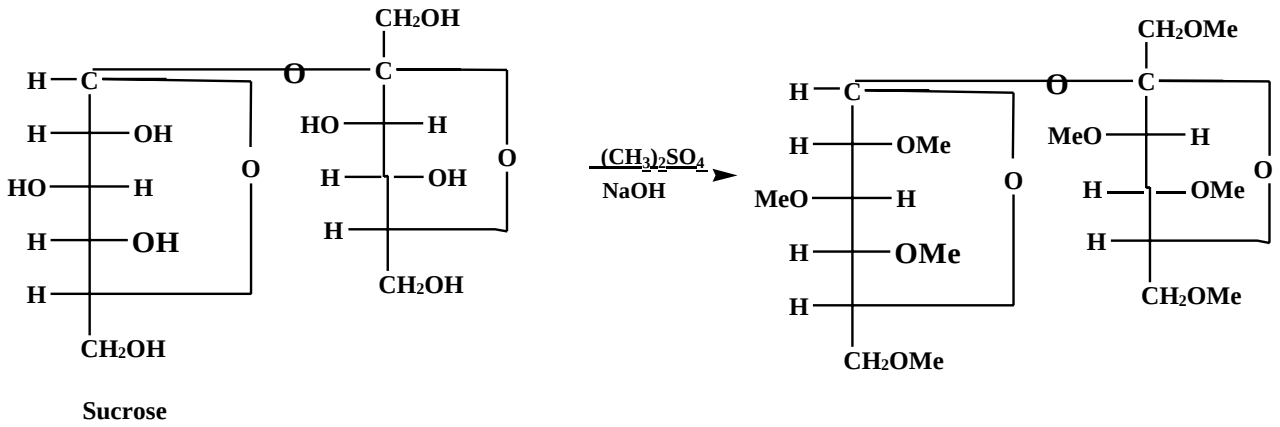
(3) By carrying methylation with dimethyl sulphate and dilute alkali than hydrolyzing the completely methylated sugar we obtain the following components:



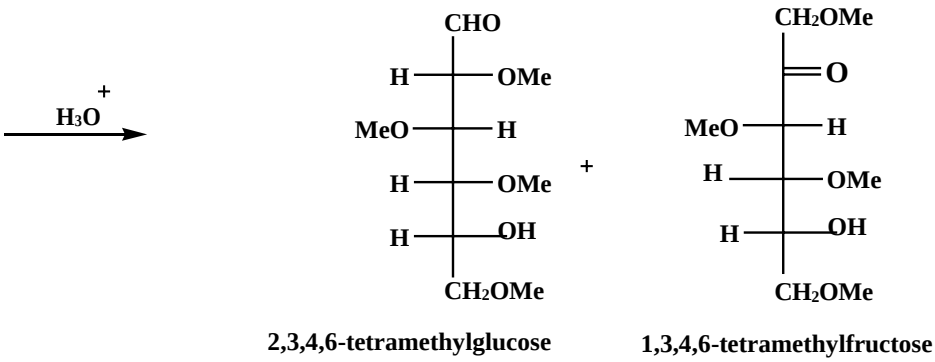
α-linkage at glucose

β - linkage at fructose

(+)-sucrose or α -D- glucopyranosyl-β -D-fructofuranoside



Sucrose



2,3,4,6-tetramethylglucose

1,3,4,6-tetramethylfructose

(a) 2, 3, 4, 6- tetramethylglucose which is reducing and have only position 5 non methylated denoting that it is a pyranose ring.

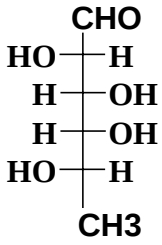
(b) 1, 3, 4, 6- tetramethyl fructose which have position 5 non methylated denoting that fructose molecule is furanose.

(4) From enzymatic hydrolysis studies it has been concluded that the linkage between the two moieties is an –glucoside linkage and a β-fructoside linkage.

A,B,AB and O Blood Group substances:

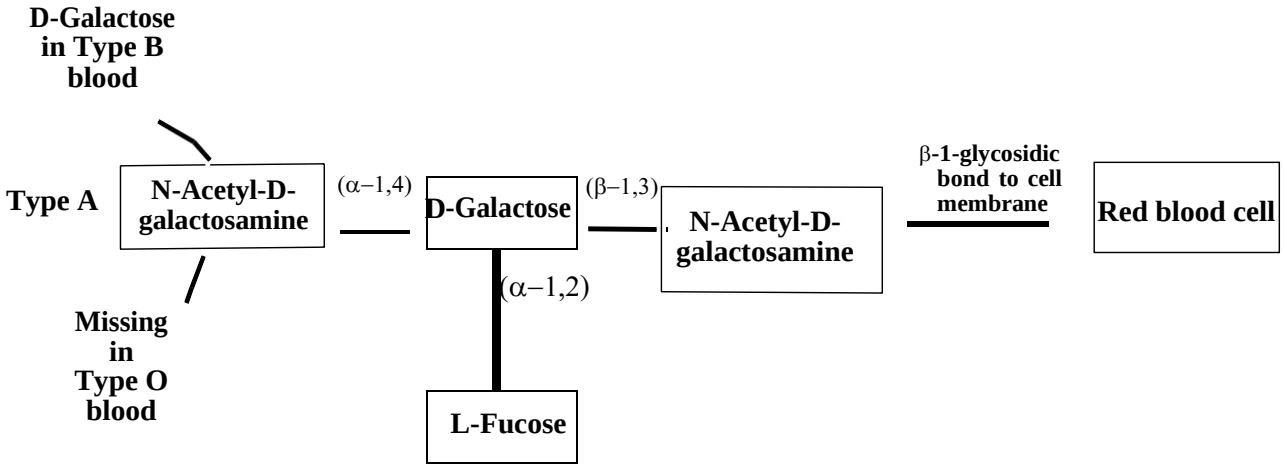
Membranes of animal plasma tells have large numbers of relatively small carbohydrates bound to them. In fact, the outsides of most plasma cell membranes are literally "sugar-coated." These membrane-bound carbohydrates are part of the mechanism by which cell types recognize each other and, in effect, act as biochemical markers.

Typically, these membrane-bound carbohydrates contain from 4 to 17 monosaccharide units consisting primarily of relatively few monosaccharides, including D-galactose, D-mannose, L-fucose, *N*-acetyl-D-glucosamine, and *N*-acety-D-galactosamine. L-Fucose is a 6-deoxyaldohexose.



L-Fucose (6-deoxy-L-galactose)

Among the first discovered and best understood of these membrane-hound carbohydrates are those of the A130 blood group system, discovered in 1900 by Karl Landsteiner (1868-1943). Whether an individual has type A, B, AB, or O blood is genetically determined and depends on the type of trisaccharide, or tetrasaccharide bound to the surface of the persons red blood cells. The monosaccharides of each blood group and the type of glycosidic bond joining them are shown in the figure. The configurations of the glycosidic bonds are shown in parentheses.

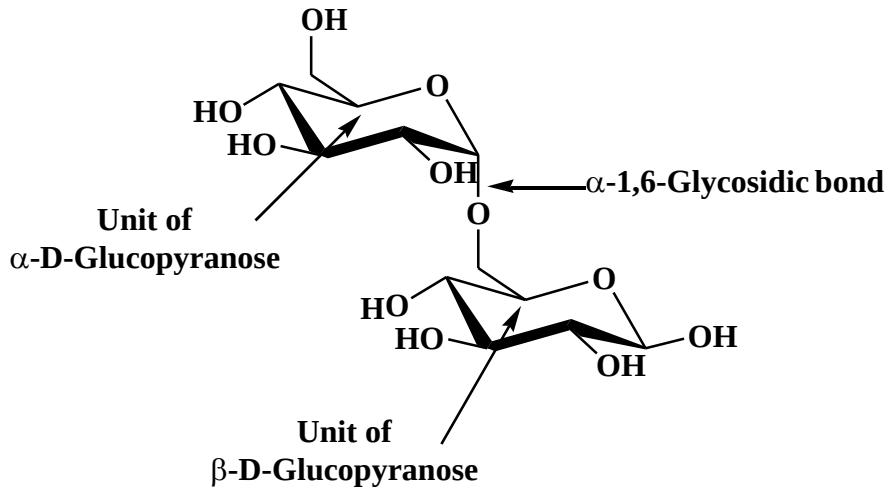


Example

Draw a chair conformation for the β anomer of a disaccharide in which two units of D-glucopyranose are joined by an α-1,6-glycosidic bond.

Solution:

First draw a chair conformation of α-D-g1ucopyranose. Then connect the anomeric carbon of this monosaccharide to carbon 6 of a second D-glucopyranose unit by an α-glycosidic bond. The resulting molecule is either α or β depending on the orientation of the OH group on the reducing end of the disaccharide. The disaccharide shown here is β.



Problem

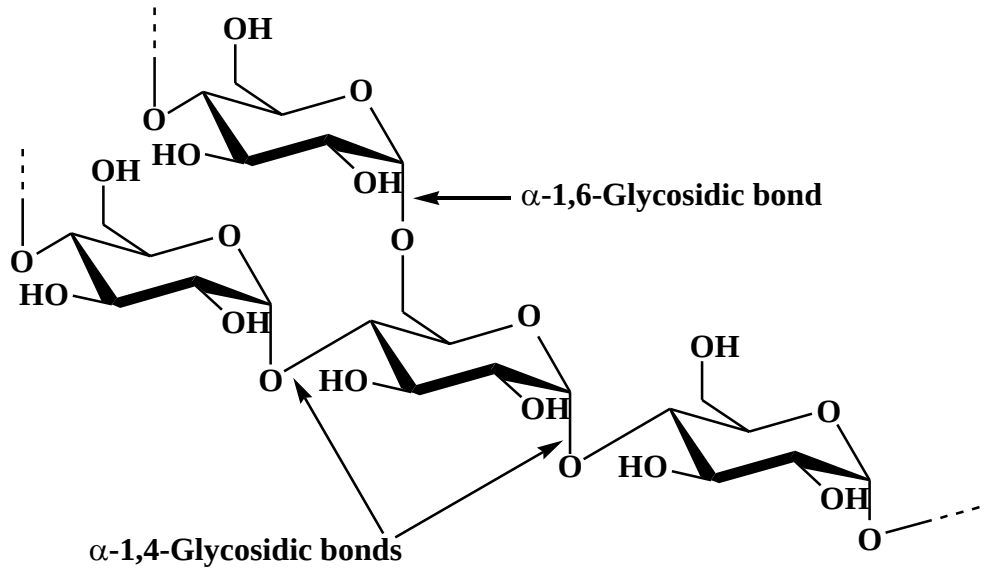
Draw a chair conformation for the a form of a disaccharide in which two units of D-glucopyranose are joined by a β-1,3-glycosidic bond.

Polysaccharides;

Polysaccharides consist of large numbers of monosaccharide units bonded together by glycosidic bonds. Four important polysaccharides, all made up of glucose units, are starch, glycogen, cellulose and chitin.

A. Starch: Amylose and Amylopectin:

Starch is used for energy storage in plants. It is found in all pant seeds and tubers and is the form in which glucose is stored for later use. Starch can be separated into two principal polysaccharides: amylose and amylopectin. Although the starch from each plant is unique, most starches contain 20-25% amylose and 75-80% amylopectin.



Complete hydrolysis of both amylose and amylopectin yields only D-glucose. Amy-lose is composed of unbranched chains of up to 4000 D-glucose units joined by

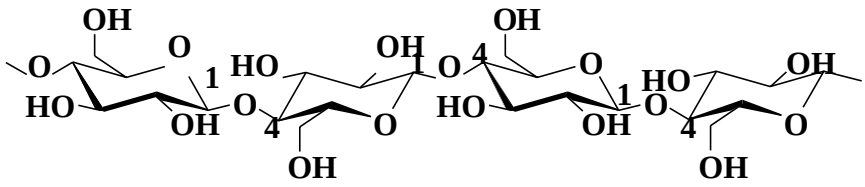
α-1,4-glycosidic bonds. Amylopectin contains chains up to 10,000 D-glucose units also joined by α-1,4-glycosidic bonds. In addition, there is considerable branching form this linear network. At branch points, new chains of 24 to 30 units are started by 1,6-glycosidic bonds.

B. Glycogen:

Glycogen is the energy-reserve carbohydrate for animals. Like amylopectin, glycogen is a branched polysaccharide of approximately 10° glucose units joined by α-1,4- and β-1,6-gycosidic bonds. The total amount of glycogen in the body of a well-nourished adult human is about 350 g, divided almost equally between liver and muscle.

C. Cellulose:

Cellulose, the most widely distributed plant skeletal polysaccharide, constitutes almost half of the cell waft material of wood. Cotton is almost pure cellulose, Celluiose is a linear polysaccharide of u-glucose units joined by β-1, 4-glycosidic bonds. It has an average molecular weight of 400,000 g/mol, corresponding

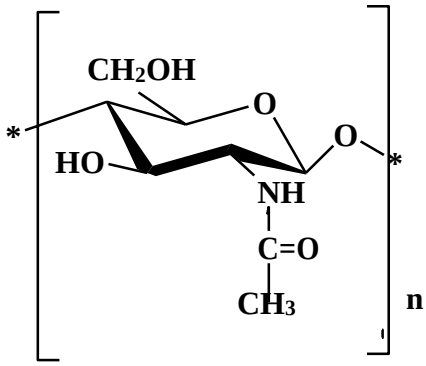


To approximately 2200 glucose units per molecule. Cellulose molecules act very much like stiff rods, a feature that enables them to align themselves side by side into well- organized water-insoluble fibers in which the OH groups form numerous intermolecular hydrogen bonds. This arrangement of parallel chains in bundles gives cellulose fibers their high mechanical strength. It is also the reason cellulose is insoluble in water. When a piece of cellulose-containing material is placed in water, there are not enough water molecules on the surface of the fiber to pull individual cellulose molecules away from the strongly hydrogen-bonded fiber.

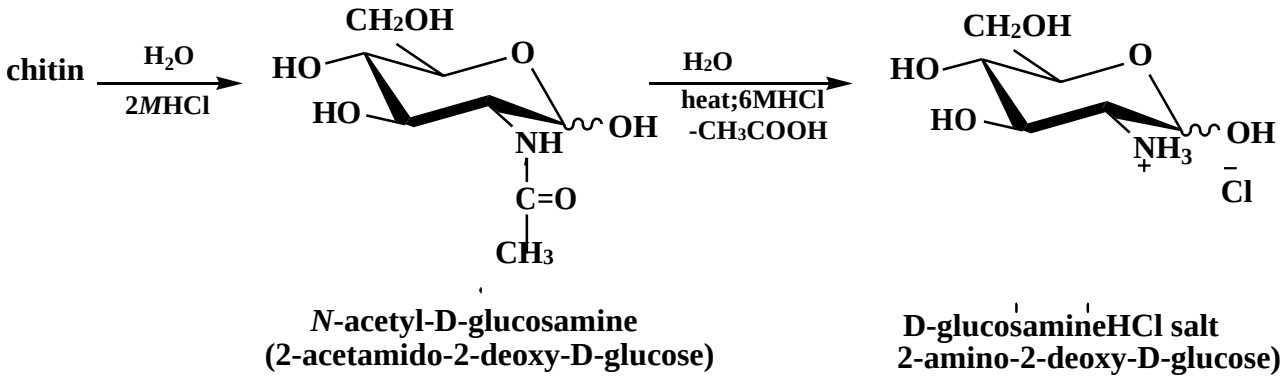
Humans and other animals cannot use cellulose as food because our digestive systems do not contain β-glucosidases, enzymes that catalyze hydrolysis of β-glucosidic bonds. Instead, we have only α-glucosidases; hence, the polysaccharides we use as sources of glucose are starch and glycogen. On the other hand, many bacteria and microorganisms do contain β-glucosidases and so can digest cellulose. Termites are fortunate (much to our regret) to have such bacteria in their gum and can use wood as their principal food. Ruminants (cud-chewing animals) and horses can also digest grasses and hay because β-glucosidase-containing microorganisms are present in their alimentary systems.

D-Chitin:

Chitin is a polysaccharide that also occurs widely in nature-notably, in the shells of arthropods (for example, lobsters and crabs). Crab shellis an excellent source of nearly pure chitin.



Chitin is a polymer of *N*-acetyl-D-glucosamine (or, as it is knoun systematically, 2-acetamido-2-deoxy-D-glucose). Residues of this carbohydrate are connected by β-1,4-glucosidic linkages within the chitin polymer. *N*-Acetyl-D-glucosamine is liberated when chitin is hydrolyzed in aqueous acid. Stronger acid brings about hydrolysis of the amide bond to give D-glucoseamine hydrochloride and acetic acid.



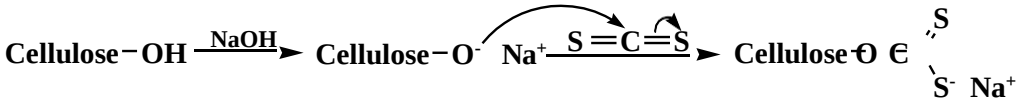
***N*-acetyl-D-glucosamine**
(2-acetamido-2-deoxy-D-glucose)

D-glucosamineHCl salt
2-amino-2-deoxy-D-glucose)

Glucosamine and *N*-acetylglucosamine are the best-known examples of the **amino sugars.** A number of amino sugars occur widely in nature. Amino sugars linked to proteins(glycoproteins) are found at the outer surfaces of cell membranes, and some of these are responsible for blood-group specificity.

Textile Fibers from Cellulose:

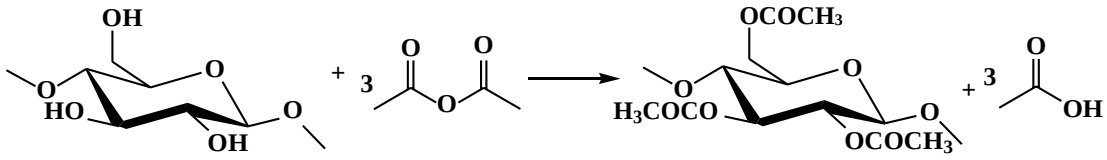
Cotton is almost pure cellulose. Both rayon and acetate rayon are made from chemically modified cellulose and were the first commercially important synthetic textile fibers. In the production of rayon, cellulose-containing materials are treated with carbon disulfide, CS_2, in aqueous sodium hydroxide. In this reaction, some of the OH groups on a cellulose fiber are converted to the sodium salt of a xanthate ester, which causes the fibers to dissolve in alkali as aviscous colloidal dispersion.



Cellulose
(insoluble in water)

Sodium salt of xanthate ester
(a viscous colloidal suspension)

The solution of cellulose xanthate is separated from the alkali insoluble parts of wood and then forced through a spinneret, a metal disc with many tiny holes, into dilute sulfuric arid to hydrolyze the xanthate ester groups and precipitate regenerated cellulose. Regenerated cellulose extruded as a filament is called viscose rayon thread. In the industrial synthesis of acetate rayon, cellulose is treated with acetic anhydride.



Acetylated cellulose is then dissolved in a suitable solvent, precipitated, and drawn into fibers known as acetate rayon. Today, acetate rayon fibers rank fourth in production in the United States, surpassed only by Dacron polyester, nylon, and rayon.

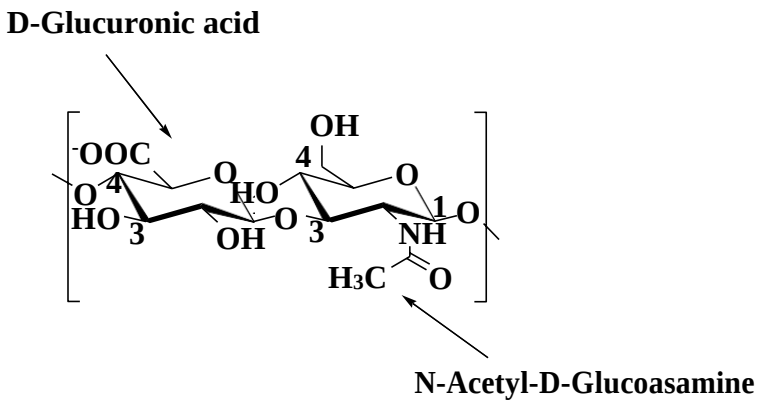
Acidic Polysaccharides:

Acidic polysaccharides a group of polysaccharides that contain carboxyl groups and/or sulfuric ester groups play important roles in the structure and function of connective tissues. There is no single general type of connective tissue. Rather, there are a large number of highly specialized forms, such as cartilage, bone, synovial fluid, skin, tendons, blood vessels, intervertebral disks, and cornea. Most connective tissues are made up of collagen, a structural protein, in combination with a variety of acidic polysaccharides that interact with collagen to form tight or loose networks.

1. Hyaluronic Acid

Hyaluronic acid is the simplest acidic polysaccharide present in connective tissue. It has a molecular weight of between $l0^5$ and 10^7 g/mol and contains from 3000 to 100,000 repeating units, depending on the organ in which it occurs. It is most abundant in embryonic tissues and in specialized connective tissues such as synovial fluid, the lubricant of joints in the body, and the vitreous humor of the eye, where it provides a clear, elastic gel that maintains the retina in its proper position.

The repealing disaccharide unit in hyaluronic acid is D-glucuronic acid linked by β-1,3-glycosidic bond to *N*-acetyl-D-glucosamine.

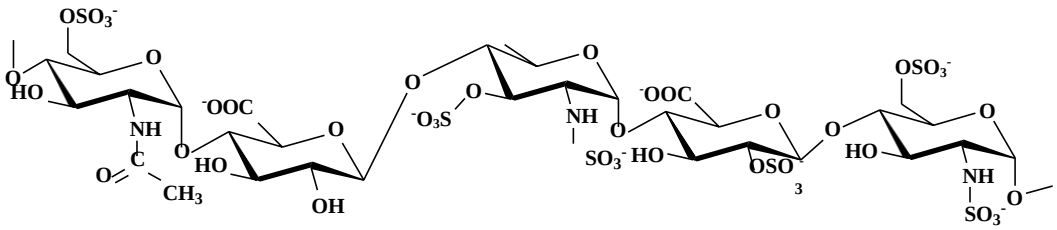


The repeating unit of hyaluronic acid

2. Heparin

Heparin is a heterogeneous mixture of variably sulfonated polysaccharide chains, ranging in molecular weight front 6000 to 30,000 g/mol. This acidic polysaccharide is synthesized and stored in mast cells of various tissues, particularly the liver, lungs, and gut. Heparin has many biological functions, the best known and understood of which is its anticoagulant activity. It binds strongly to antithrombin III, a plasma protein involved in terminating the clotting process.

The repeating monosaccharide units of heparin are N-acetyl-D-glucosamine, D-glucuronic acid, D-glucosamine, and L-ioduronic acid bonded by a combination of α-1,4- and β-1,4-glycosidic bonds.



Starch can be separated into two fractions given the names amylose and amylopectin. Amylose is a linear polymer of up to 4000 units of D-glucopyranose joined to α-1,4-glycosidic bonds. Amylopectin is a highly branched polymer of D-glucopyranose joined by α-1,4-glycosidic bonds and at branch points, by α-1,6-glycosidic bonds. Glycogen, the reserve carbohydrate of animals, is a high branched polymer of D-glucopyranose joined by α-l,4-glycosidic bonds and at branch

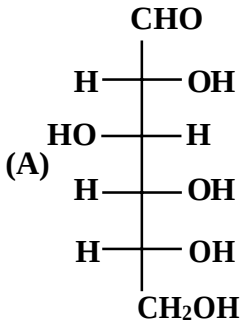
points, by α-1,6-glycosidic bond. Cellulose the skeletal polysaccharide plants, is a linear polymer of D-glucopyranose joined by β-1,4-glycosidic bonds. Rayon is made from chemically modified and regenerated cellulose. Acetate rayon is made by acetylation of cellulose.

The carboxyl and sulfate groups of acidic polysaccharides are ionized to COO^- and SO_3^- at the pH of body fluids, which gives these polysaccharides net negative charges.

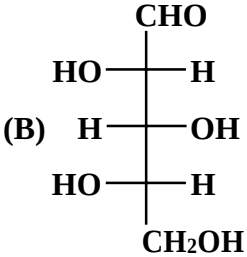
Problems:

Monosaccharides:

1. Explain the meaning of the designations D and L as used to specify the configuration of monosaccharides.
2. How many chiral centers are present in D-glucose? In D-ribose?
3. Which carbon of an aldopentose determines whether the pentose has a D or L configuration?
4. How many aldooctoses are possible? How many D-aldooctoses are possible?
5. Which compounds are D-monosaccharides? Which are L-monosaccharides?



(A)



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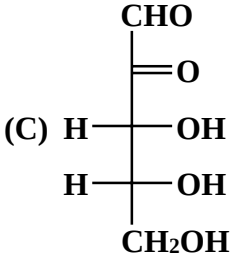


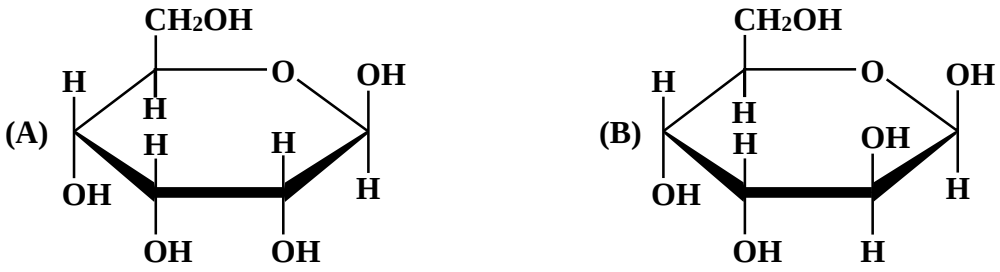
(C)

6. Write Fischer projections for L-ribose and L-arabinose.

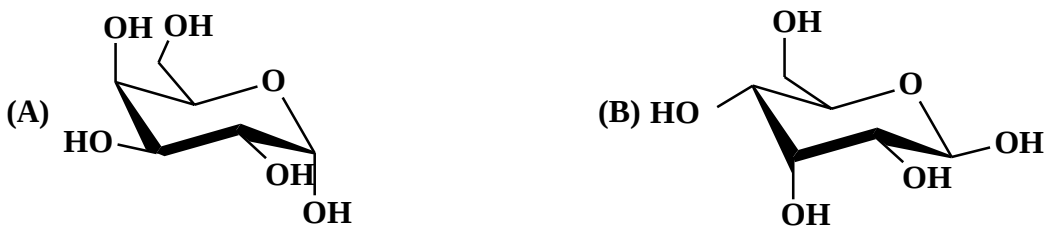
7. What is the meaning of the prefix deoxy- as it is used in carbohydrate chemistry?
8. Give L-fucose (Chemical Connections: “A, B, AB, and O Blood Group Substances”) a name incorporating the prefix deoxy that shows its relationship to galactose.
9. 2,6-Dideoxy-D-altrose, known alternatively as D-digitoxose, is a monosaccharide obtained on hydrolysis of digitoxin, a natural product extracted from foxglove (Digitalis purpurea). Digitoxin is used in cardiology to reduce pulse rate, regularize heart rhythm, and strengthen heart beat. Draw the structural formula of 2,6-dideoxy-D-altrose.

The Cyclic Structure of Monosaccharides:

10. Define the term anomeric carbon. In glucose, which carbon is the anomeric carbon?
11. Define the terms (a) pyranose and (b) furanose.
12. Which is the anomeric carbon in a 2-ketohexose?
13. Are α-D-glucose and β-D-glucose enantiomers? Explain.
14. Convert each Haworth projection to an open-chain form and then to a Fischer projection. Name the monosaccharide you have drawn.



15. Convert each chair conformation to an open-chain form and then to a Fischer projection. Name the monosaccharide you have drawn.



16. Explain the phenomenon of mutarotation with reference to carbohydrates. By what means is it detected?
17. The specific rotation of α-D-glucose is +112.2.
    a) What is the specific rotation of α-L-glucose?
    b) When α-D-glucose is dissolved in water, the specific rotation of the solution changes from +112.2 to +52.7. Does the specific rotation of α-L-glucose also change when it is dissolved in water? If so, to what value does it change?

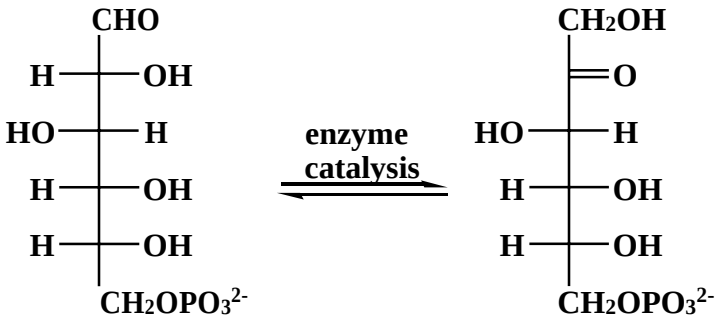
Reactions of Monosaccharides:

18. Draw Fischer projections for the product(s) fanned by reaction of D-galactose with the following. In addition, state whether each product is optically active or inactive.

a- $NaBH_4$ in H_2O	***b- H_2/Pt***	***c- HNO_3 warm***
d- $Br_2/H_2O/CaCO_3$	***e- H_5IO_6***	***f- $C_6H_5NH_2$***

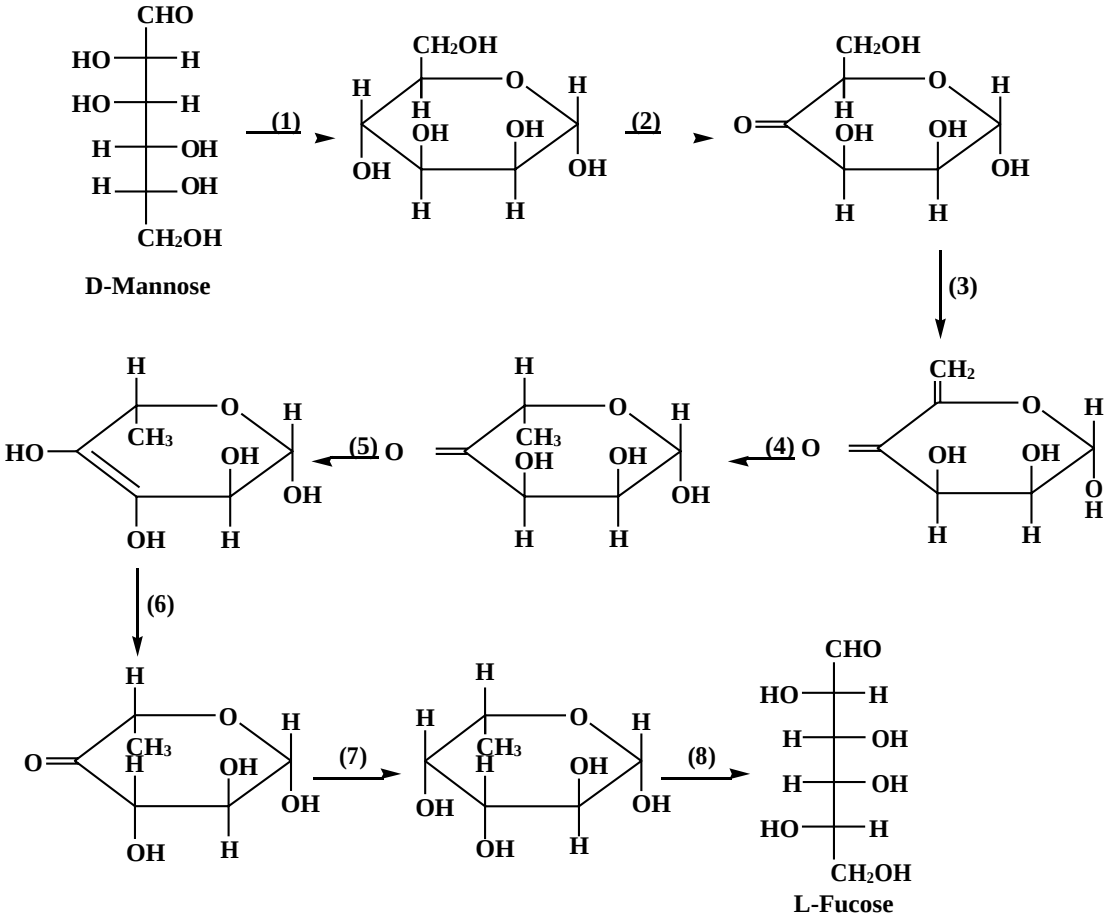
19. Repeat Problem 18 using D-ribose.
20. An important technique for establishing relative configurations among isomeric aldoses and ketoses is to convert both terminal carbon atoms to the same functional group, This can be done either by selective oxidation or reduction. As a specific example, nitric acid oxidation of D-erythrose gives meso-tartaric acid. Similar oxidation of D-threose gives (2S,3S)-tartaric acid. Given this information and the fact hat D-erythrose and D-threose are diastereomers, draw Fischer projections for D-erythrose and D-threose. Check your answers against Table 25.
21. There are four D-aldopentoses (Table 25-1). If each is reduced with $NaBH_4$, which yield optically active alditols? Which yield optically inactive alditols?
22. Name the two alditols formed by $NaBH_4$ reduction of D-fructose.

23. One pathway for the metabolism of D-glucose 6-phosphate is its enzyme catalyzed conversion to D-fructose 6-phosphate. Show that this transformation can be accomplished as two enzyme-catalyzed keto-enol tautomerisms.



D-Glucose 6-Phosphate **D-Fructose 6-Phosphate**

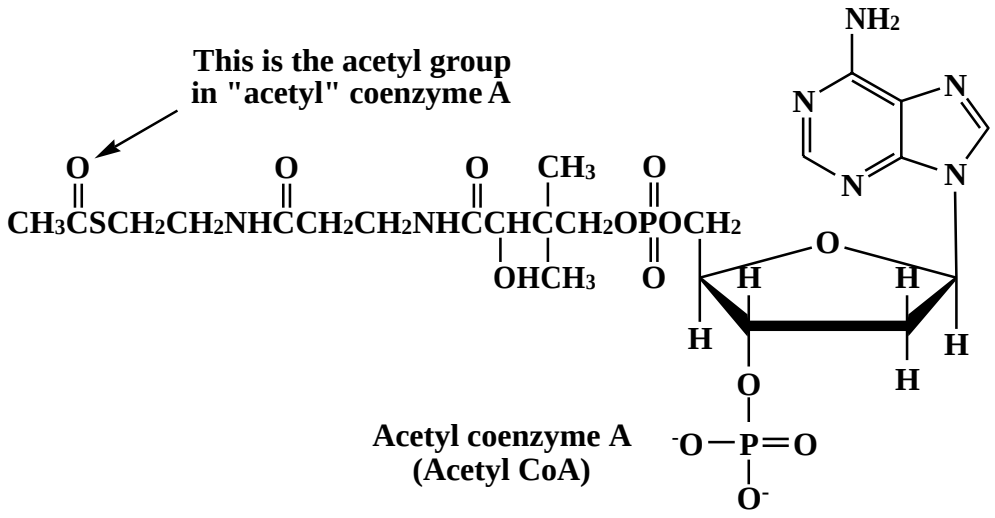
24. L-Fucose, one of several monosaccharides commonly found in the surface polysaccharides of animal cells, is synthesized biochemically from D-mannose in the following eight steps.



a) Describe the type of reaction (that is, oxidation, reduction, hydration, dehydration, and soon) involved in each step.

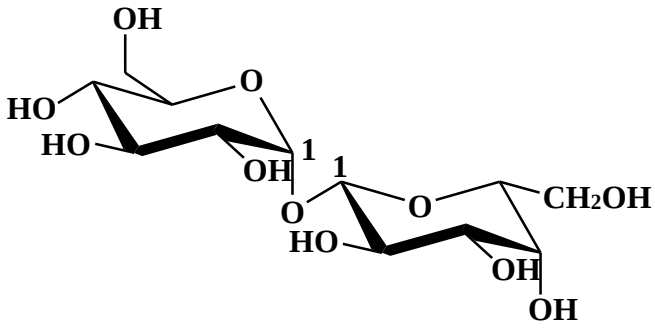
b) Explain why this monosaccharide derived from D-mannose now belongs to the L-series.

25. What is the difference in meaning between the terms glycosidic bond and glucosidic bond?
26. Treatment of methyl β-D-glucopyranoside with benzaldehyde forms a six-membered cyclic acetal. Draw the most stable conformation of this acetal. Identify each new chiral center in the acetal.
27. Vanillin (4-hydroxy-3-methoxybenzaldehyde). The principal component of vanilla, occurs in vanilla beans and other natural sources as a β-D-glucopyranoside. Draw a structural formula for this glycoside, showing the D-glucose unit as a chair conformation.
28. Hot water extracts of ground willow and poplar bark are an effective pain reliever, Unfortunately, the liquid is so bitter that most persons refuse it. The pain reliever in these infusions is salicin, β-glycoside of D-glucopyranose and the phenolic -OH group of 2-(hydroxymethyl) phenol. Draw a structural formula for salicin, showing the glucose ring as a chair conformation.
29. Draw structural formulas for the products formed by hydrolysis at pH 7.4 (the pH of blood plasma) of all ester, thioester, amide, anhydride, and glycoside groups in acetyl coenzyme A. Name as many of the products as you can.



Disaccharides and Oligosaccharides:

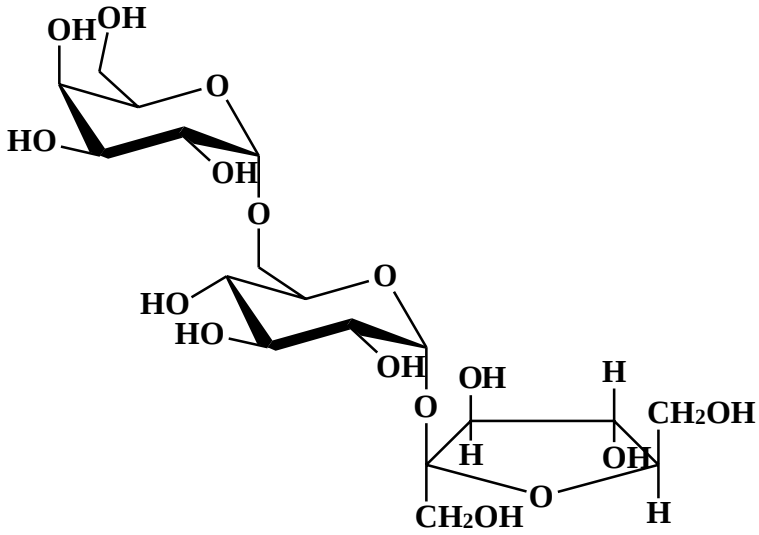
30. In making candy or sugar syrups, sucrose is boiled in water with a little acid, such as lemon juice. Why does the product mixture taste sweeter than the starting sucrose solution?
31. Trehalose is found in young mushrooms and is the chief carbohydrate in the blood of certain insects. Trehalose is a disaccharide consisting of two D-monosaccharide units, each joined to the other by an α-1,1-glycosidic bond.



Trehalose

a) Is trehalose a reducing sugar?
b) Does trehalose undergo mutarotation?
c) Name the two monosaccharide units of which trehalose is composed.

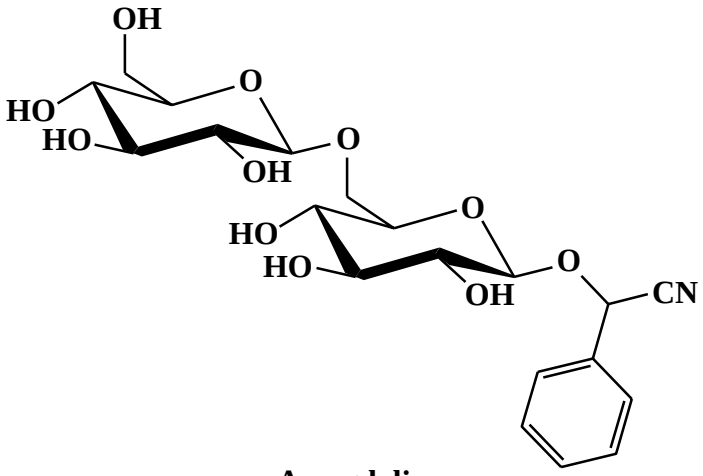
32. The trisaccharide raffinose occurs principally in cottonseed meal.



Raffinose

a) Name the three monosaccharide units in raffinose.
b) Describe each glycosidic bond in this trisaccharide.
c) Is raffinose a reducing sugar?
d) With how many moles of periodic acid will raffinose react?

33. Amygdalin is a toxic component in the pits of bitter almonds, peaches, and apricots.
    a) Name the two monosaccharide units in amygdalin and describe the glycoside bond by which they are joined.
    b) Account for the fact that on hydrolysis of amygdalin in warm aqueous acid liberates benzaldehyde and HCN.



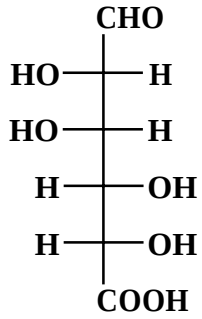
Amygdalin

Polysaccharides:

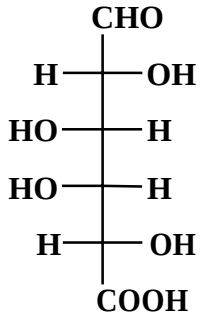
34. What is the difference in structure between oligo- and polysaccharides?
35. Why is cellulose insoluble in water?
36. Consider N-acetyl-D-glucosamine.
    a) Draw a chair conformation for the α- and β-pyranose forms of this monosaccharide
    b) Draw a chair conformation for the disaccharide formed by joining two units of the pyranose form of N-acetyl-D-glucosamine by a β-1,4-glycosidic bond. If you drew this correctly, you have the structural formula for the repeating dimer of chitin, the structural polysaccharide component of the shell of lobster and other crustaceans.
37. Propose structural formulas for the following polysaccharides.

a) Alginic acid isolated from seaweed is used as a thickening agent in ice cream and other foods. Alginic acid is a polymer of D-mannuronic acid in the pyranose form joined by β-1,4-glycosidic bonds.

b) Pectic acid is the main component of pectin, which is responsible for the formation of jellies from fruits and berries. Pectic acid is a polymer of D-galacturonic acid in the pyranose form joined by α-l,4-glycosidic bonds.

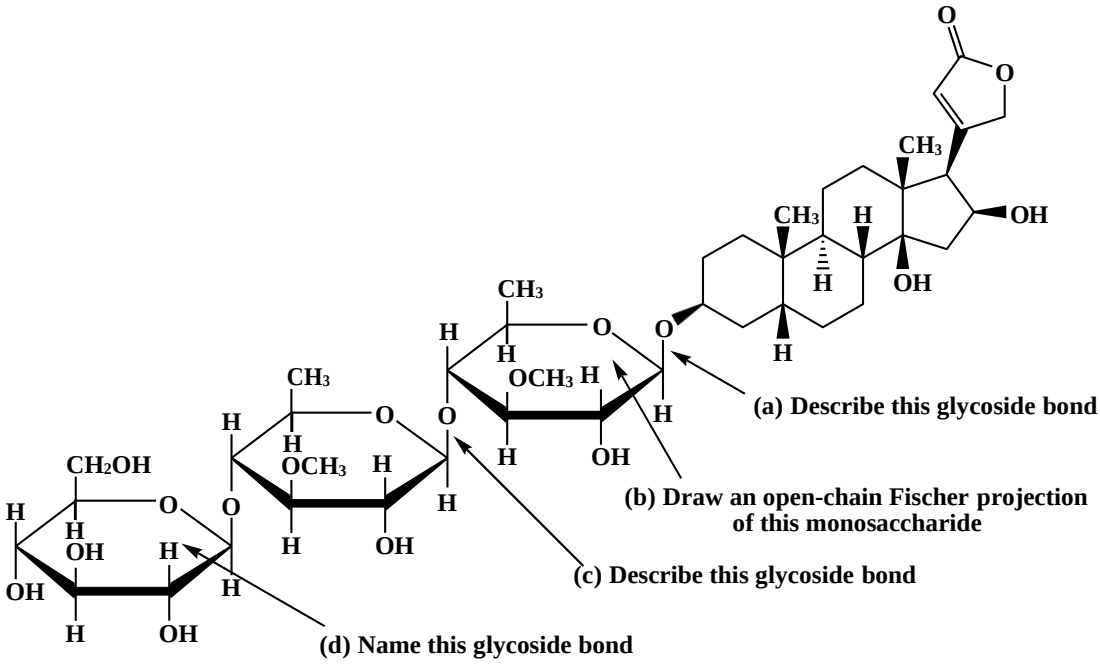


D-Mannuronic acid

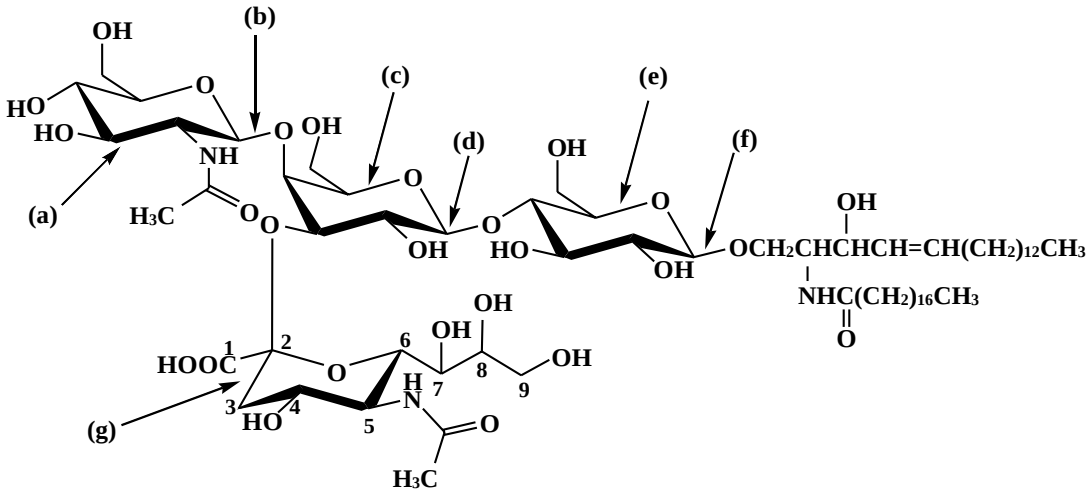


D-Galacturonic acid

38. Digitalis is a preparation made from the dried seeds and leaves of the purple foxglove. Digitalis purpurea, a plant native to southern and central Europe and cultivated in the United States. The preparation is a mixture of several active components including digitalin. Digitalis is used in medicine to increase the force of myocardial contraction and as a conduction depressant to decrease heart raw (the heart pumps more forcefully but less often).



39. Following is the structural formula of ganglioside GM_2, a macromolecular glycolipid (meaning that it contains lipid and monosaccharide units joined by glycosidic bonds).



In normal cells, this and other gangliosides are synthesized continuously and degraded by lysosomes, which are cell organelles containing digestive enzymes. If pathways for the degradation of gangliosides are inhibited, the gangliosides accumulate in the central nervous system causing all sorts of lift-threatening consequences. In inherited disease, of ganglioside metabolism, death usually occurs at an early age. Diseases of ganglioside metabolism include Gauchers disease, Niemann-Pick disease, and Tay-Sachs disease Tay-Sachs disease is a hereditary defect that is transmitted as an autosomal recessive gene. The concentration of ganglioside GM_2 is abnormally high in this disease because the enzyme responsible for catalyzing the hydrolysis of glycosidic bond (b) is absent.

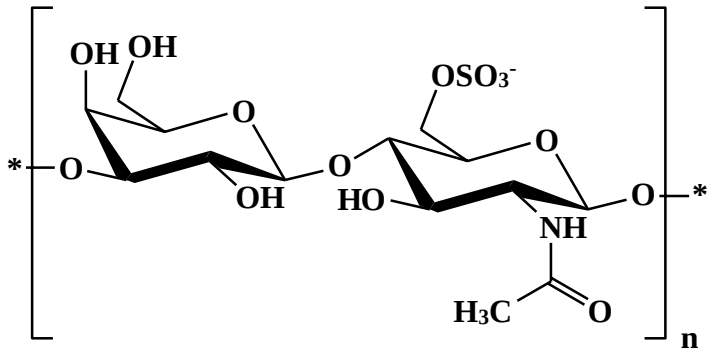
a) Name this monosaccharide unit.
b) Describe this glycosidic bond (α or β and between which carbons of each unit).
c) Name this monosaccharide unit.
d) Describe this glycosidic bond.
e) Name this monosaccharide unit.
f) Describe this glycosidic bond.

g) This unit is N-acetylneuraminic acid, the most abundant member of a family of amino sugars containing nine or more carbons and distributed widely throughout the animal kingdom. Draw the open-chain form of this amino sugar. Do not be concerned with the configuration of the five chiral centers in the open-chain form.

40. Hyaluronic acid acts as a lubricant in the synovial fluid of joints. In rheumatoid arthritis, inflammation breaks hyaluronic acid down to smaller molecules. Under these conditions, what happens to the lubricating power of the synovial fluid?

41. The anticlotting property of heparin is partly the result of the negative charges ii carries.
    a) Identify the functional groups that provide the negative charges.
    b) Which type of heparin is a better anticoagulant, one with a high or a low degree of polymerization?

42. Keratin sulfate is an important component of the cornea of the eye. Following is the repeating unit of this acidic polysaccharide.



    a) From what monosaccharides or derivatives of monosaccharides is keratin sulfate made?
    b) Describe the glycosidic bond in this repeating disaccharide unit.
    c) What is the net charge on this repeating disaccharide unit at pH 7.0?

43. Following is a chair conformation for the repeating disaccharide unit in chondroitin 6-sulfate. This biopolymer acts as the flexible connecting matrix between the tough protein filaments in cartilage. It is available as a dietary

supplement, often combined D-glucosamine sulfate. Some believe this combination can strengthen and improve joint flexibility.