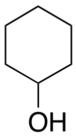
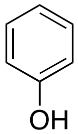
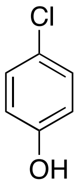
Acidity of alcohols



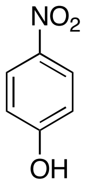
cyclohexanol
$pK_a = 18$



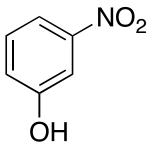
phenol
$pK_a = 10$



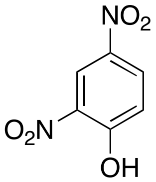
4-chlorophenol
$pK_a = 9.3$



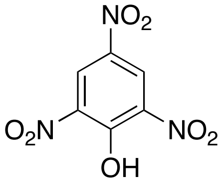
4-nitrophenol
$pK_a = 7$



3-nitrophenol
$pK_a = 9.3$



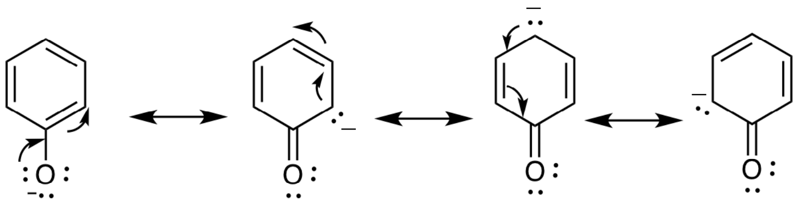
2,4-dinitrophenol
$pK_a = 4.5$



2,4,6-trinitrophenol
picric acid
$pK_a = 0.5$

What is the influence of substituents? inductive & resonance

As the pK_a values above show, phenol is 10^8 more acidic than cyclohexanol.

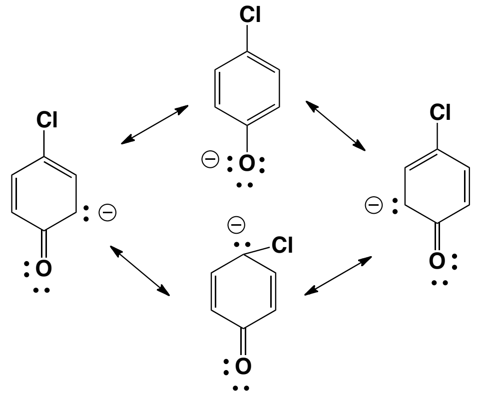


Phenol has a pK_a value of 10 (given this information, you should immediately recognize that it is more much acidic (about 6 orders of magnitude) than water (pK_a 15.7) and methanol (pK_a 16) since it has lower pK_a value). As phenol is more acidic, this means that its conjugate anion is more stable. The phenoxide anion is stabilized through resonance (shown above). It has 4 resonance forms, and therefore, more ability to spread the negative charge and be stabilized.

Where does the equilibrium lie for ionization of phenol to phenoxide and a proton (H^+) ?

Answer: It lies far to the left (not ionized). Even though phenol is 10^6 more acidic than water, its pK_a of 10 tells you that the acidity constant is 10^{-10} or that only one part in 10^{10} is ionized; the rest exists as phenol with H attached to oxygen.

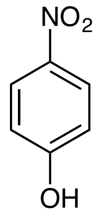
Example: Chlorophenol



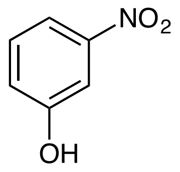
Is the anion more or less stabilized compared to phenol?

Answer: More stabilized. The chlorine atom is electron withdrawing and stabilizes the negative charge at the *para* position through the inductive withdrawing effect. However, it also has a weak resonance donating effect. The inductive effect of chlorine wins over resonance effect in this case (contrast this with electrophilic aromatic substitution where the resonance donating effect wins out against the inductive effect).

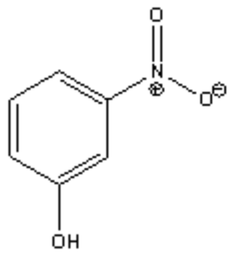
Example: *para*- and *meta*-nitrophenol



p-nitrophenol
pKa=7.2

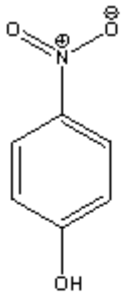


m-nitrophenol
pKa=9.4



m-nitrophenol

VS

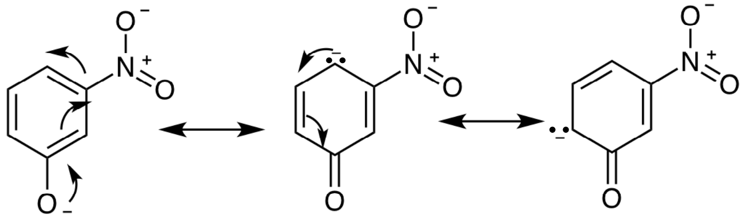


p-nitrophenol

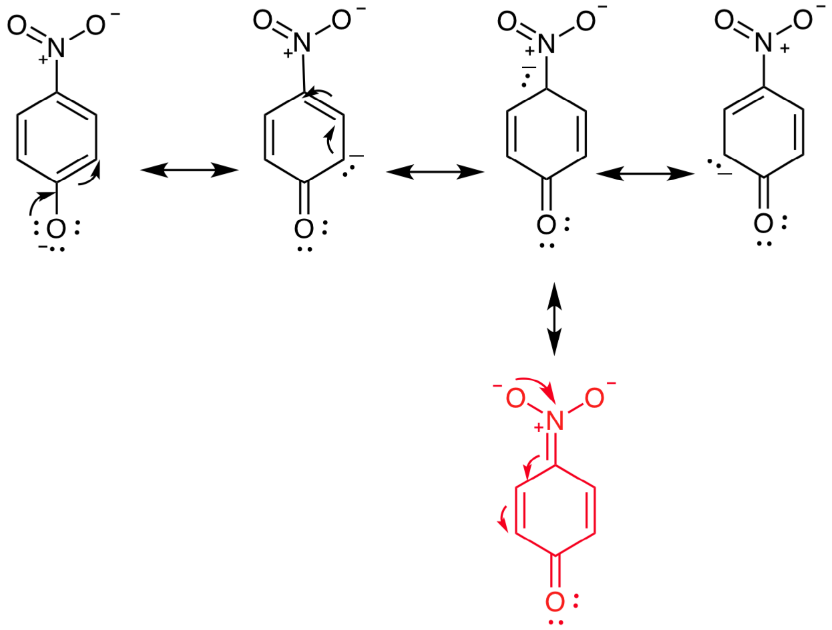
p-nitrophenol has a pK_a value of 7.2, whereas *m*-nitrophenol has a pK_a value of 9.3

Which one is more acidic? Answer: *p*-nitrophenol
Why? (Think about conjugate anion stabilization and resonance forms).

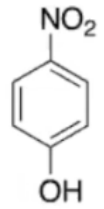
Resonance forms for *m*-nitrophenoxide anion:



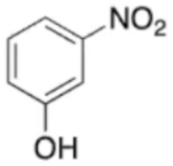
Resonance forms for *p*-nitrophenoxide anion:



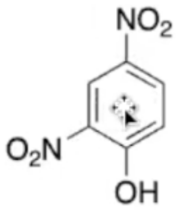
The nitro group offers an additional resonance form for *p*-nitrophenol that is not possible for *m*-nitrophenol (we are able to drive electrons all the way in to the nitro group for the *para*- substituted nitrophenol). Since there is an additional reasonable resonance form, the *p*-nitrophenol pK_a 7.2 is about 100 times (10^2) more acidic than the *m*-nitrophenol with pK_a 9.3 (pK_a 9.3-7.2 = 2.1 pK_a units)



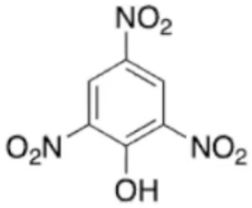
4-nitrophenol
$pK_a = 7$



3-nitrophenol
$pK_a = 9.3$



2,4-dinitrophenol
$pK_a = 4.5$

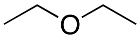


2,4,6-trinitrophenol
picric acid
$pK_a = 0.5$

If there are two nitro groups in the *ortho* and *para* positions of the phenoxide anion, the pK_a of the phenol (2,4-dinitrophenol) drops to 4.5. If three nitro groups are attached, the pK_a of the phenol becomes even lower (2,4,6-trinitrophenol has a pK_a of approximately 0.5). This is because *ortho* and *para* positions are where the negative charge of the resonance form can be located, and addition of a nitro group is able to offer more stabilization. This phenomenon is not observed for the *meta* position.

Ethers

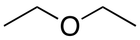
An ether is a substance that has two organic groups bonded to the same oxygen atom, R-O-R’, where R and R’ can be the same or different, but cannot be carbonyl (C=O), or H directly attached. The organic groups may be alkyl, aryl, or vinylic, and an ether can either be an open chain or a ring. Perhaps the most well known ether is diethyl ether, a familiar substance that has been used medically as an anesthetic, and is used industrially as a solvent.



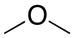
diethyl ether

Naming Ethers

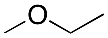
Two systems for naming ethers are allowed by IUPAC rules. Simple ethers with no functional groups are named by identifying the two organic substituents and adding the word *ether* as in the below examples.



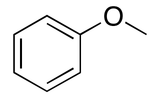
diethyl ether
or ethyl ether
or ether



dimethyl ether
or methyl ether



ethyl methyl ether

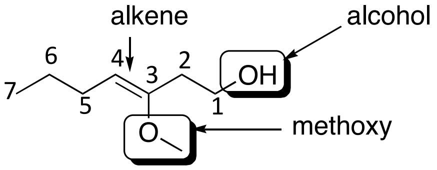


anisole
methyl phenyl ether

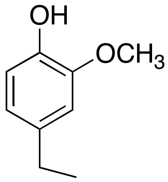
Naming Rule:
Drop ane add oxy: e.g. methyl to methoxy

If other functional groups are present, the ether part is considered to be an alkoxy substituent (-OR).

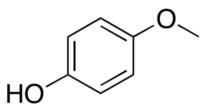
For example, the parent name for the below structure is an alcohol.



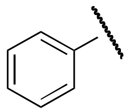
(*Z*)-3-methoxyhept-3-en-1-ol
(*Z*)-3-methoxy-3-hepten-1-ol



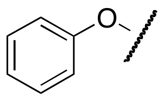
Cockroach sex pheromone
2-methoxy-4-ethylphenol
4-ethyl-2-methoxyphenol



4-methoxyphenol
methyl *p*-hydroxyphenyl ether

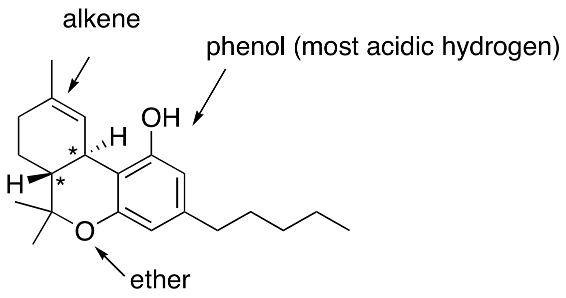


phenyl group



phenoxy group

Example: THC



Tetrahydrocannabinol
(THC)

Functional groups
- Alkene
- Alcohol
- Aromatic
- Ether
- Alkyl

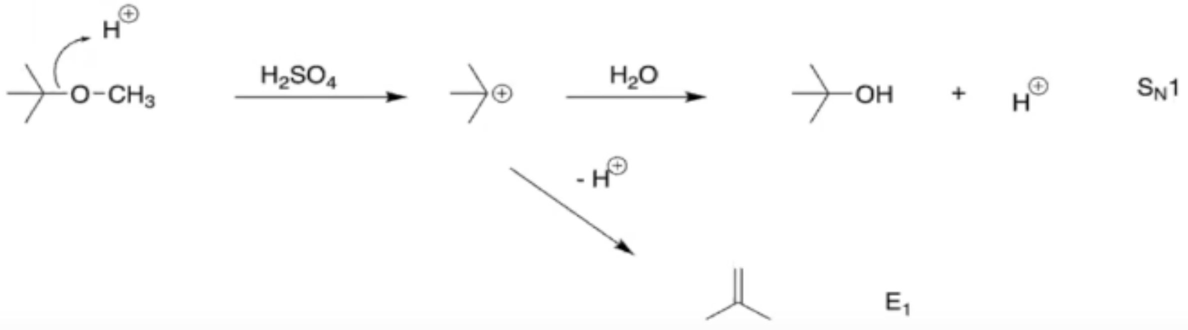
# of stereogenic centers = 2

You should be able to identify different functional groups in a large molecule like THC, and be able to find stereogenic centers and identify the configurations. If treated with Br_2, which double bond will react? *Answer:* Top one (The non-aromatic alkene).

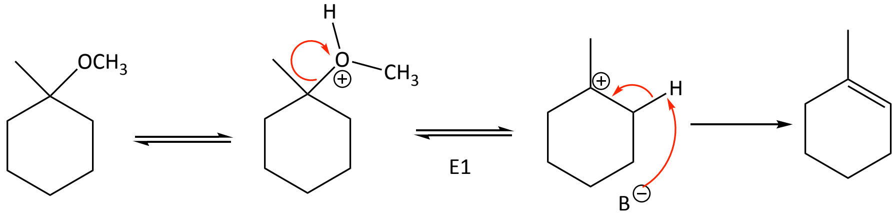
Ethers: Properties
1. Intermediate polarity - usually have dipoles & can accept hydrogen bonds
2. Not miscible with water - very slight solubility
3. Good solvents for many organic compounds
4. Less dense than water $\rho < 1.0$ - floats on water
5. Usually chemically unreactive - inert to base or weak acid - can react with very strong acid

Elimination to alkenes - discussed previously
Reverse of addition reaction requires strong acid

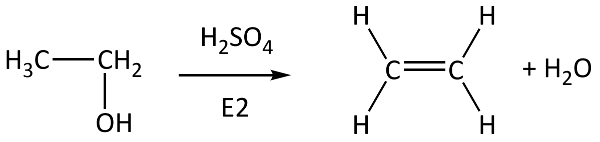
Example:



Example:

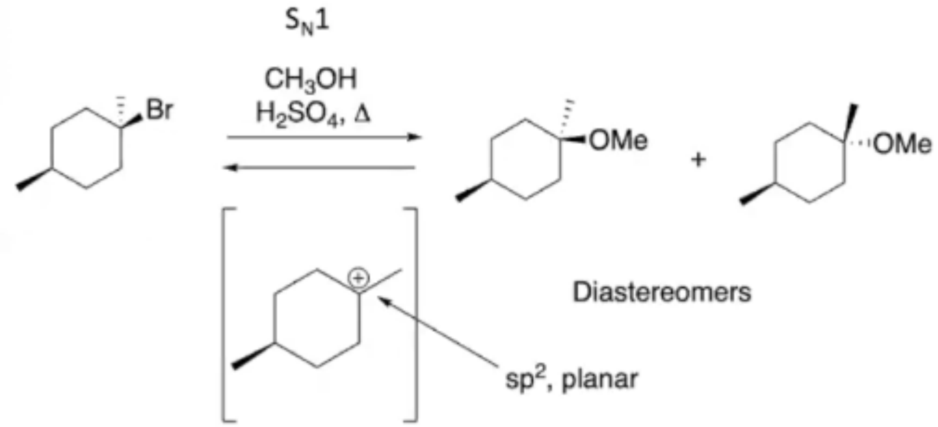


Example:

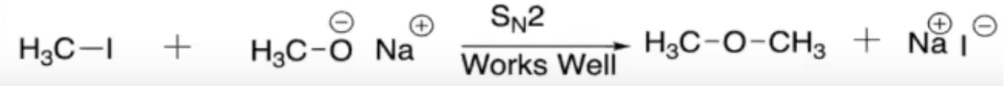


Substitution to alcohols or alkyl halides - discussed previously

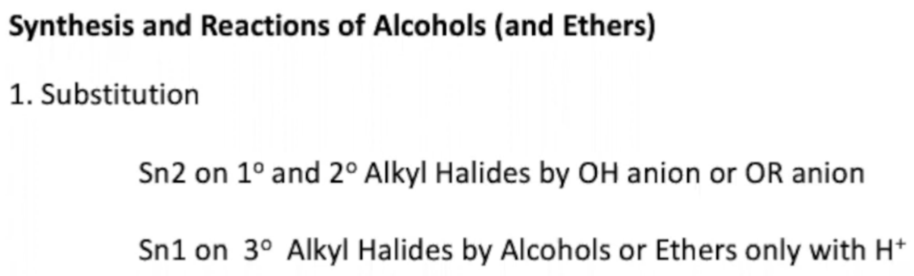
- Substitution reversible – reverse of synthesis of ethers
- Requires strong acid



S_N2 Reaction to Convert Alkyl Halide to Ethers – NOT reversible without strong acid



$$H_3C{-}I \;+\; H_3C{-}\overset{\ominus}{O}\ \overset{\oplus}{Na} \xrightarrow[\text{Works Well}]{S_N2} H_3C{-}O{-}CH_3 \;+\; \overset{\oplus}{Na}\ \overset{\ominus}{I}$$



Synthesis and Reactions of Alcohols (and Ethers)

1. Substitution

Sn2 on 1° and 2° Alkyl Halides by OH anion or OR anion

Sn1 on 3° Alkyl Halides by Alcohols or Ethers only with H$^+$

2. Addition to Alkenes of HOH or HOR with H+ or Halohydrin Rxn (X_2 and HOH or HOR)

3. Oxidations of Alkenes to Diols with $KMnO_4$ (cold) or OsO_4

4. Epoxidation of Alkenes to Epoxides (oxiranes = 3 membered ring ethers) with peracids

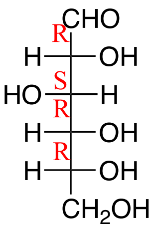
5. Elimination of Alcohols or Ethers to Alkenes with H^+ E1 (3°) and E2 (1° and 2°)

6. Addition Rxns to Carbonyls (C=O) – NOT COVERED in the course

Carbohydrates (also known as sugars or saccharides) – See Handout

Approximately 0.02% of the sun’s energy is used on this planet for photosynthesis in which organisms convert carbon dioxide (CO_2) and water (H_2O) to D-glucose ($C_6H_{12}O_6$) and oxygen (O_2). About 4 x 10^{11} metric tons of carbon dioxide are converted to glucose annually by plants, and glucose (as a subunit) is the most abundant organic compound on the planet. Learn the structure of D-glucose shown below.

$$CO_2 + H_2O \xrightarrow{h\nu} C_6H_{12}O_6 + O_2$$



Glucose (also called dextrose)

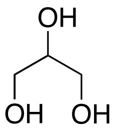
Carbohydrates occur in every living organism. The sugar in starch in food and the cellulose in wood, paper, and cotton, are carbohydrates. Modified carbohydrates form part of the coating in living cells, other carbohydrates are found in the DNA that carries genetic information, and still others are used in medicine.

The term carbohydrate is used to refer to a broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Carbohydrates are also known as saccharides.

The general formula for a carbohydrate is approximated as $C_NH_{2N}O_N$. The number of carbons in the carbohydrate chain is also given special nomenclature.

3 carbons – Triose
4 carbons – Tetrose
5 carbons - pentose
6 carbons – hexose

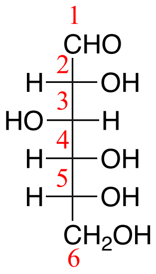
Example:



Glycerol

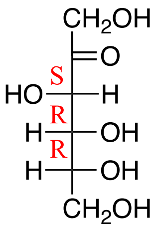
(a triose)

Carbohydrates can further be classified as either aldoses or ketoses. The –ose suffix is used to identify the carbohydrate, and the aldo- and keto- prefixes identify the nature of the carbonyl group. For example, glucose is an aldohexose, a six carbon aldehyde sugar; fructose is a ketohexose, a six carbon keto sugar; and ribose is an aldopentose, a five carbon aldehyde sugar. The most commonly occurring sugars are either aldopentoses or aldohexoses.



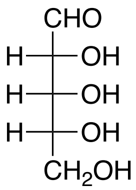
D-Glucose
(an aldohexose)

C5 = R-configuration = D



D-Fructose
(a ketohexose)

Reducing sugar

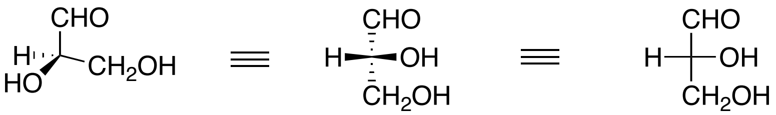


D-Ribose
(an aldopentose)

Reducing sugar

Configuration of Sugars: Fischer Projections

Fischer projections depict the stereogenic centers on a flat page surface. A Fischer projection is represented by two crossed lines, in which the horizontal line represents bonds coming out of the page, and the vertical lines represent bonds going into the page. By convention, the carbonyl is placed at or near the top of the Fischer projection. Shown below is the Fischer projection of (R)-glyceraldehyde.

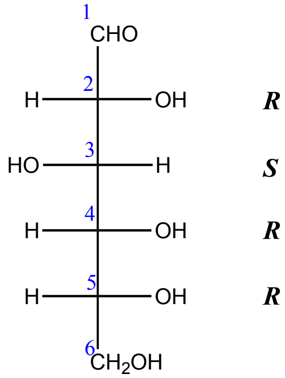


(R)-glyceraldehyde

Fischer projection of
(R)-glyceraldehyde

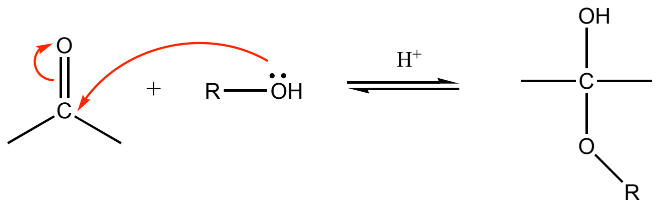
- If highest numbered stereogenic center is **R** → **D-sugar**
- If highest numbered stereogenic center is **S** → **L-sugar**

D-glucose has the structure shown below (you must know its structure). It is an aldohexose (“aldo” since it contains aldehyde functionality and “hexose” since it is a six carbon sugar, numbered on structure).

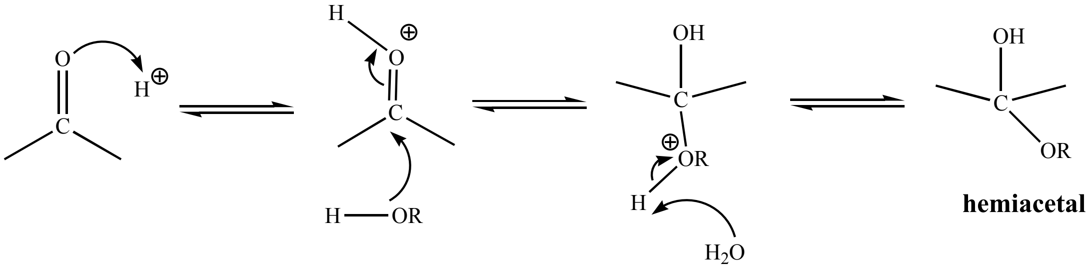


It contains 4 stereogenic carbons (C2, C3, C4 and C5). The highest numbered stereogenic center tells you whether it is a D (if it is R configuration at that stereogenic center) or an L (if it’s S configuration at that stereogenic center) sugar. For glucose, the highest numbered stereogenic center is C5. It has an R configuration. By convention, it is designated as a “D” sugar. Configurations of other stereogenic centers are also shown next to the structure.

Carbohydrates- Hemiacetal Formation



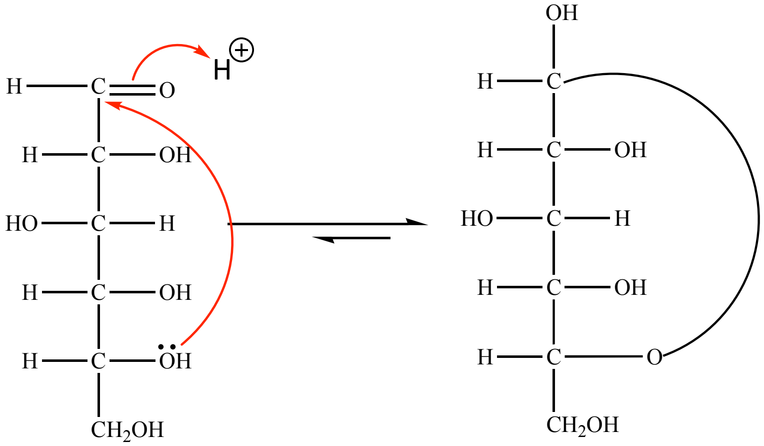
Mechanism



In nature, formations of 5- and 6-membered rings are favored, and if possible, a molecule will form such a ring when it can.

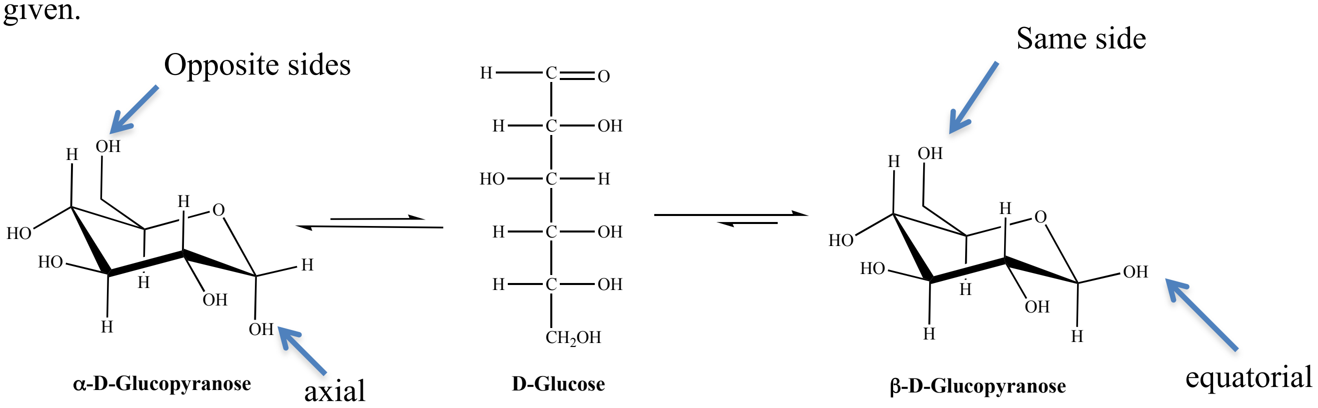
In sugars, the cyclic forms with 5-membered rings are called furanoses, and 6-member rings are called pyranoses. For most aldohexoses, the five membered furanose and six-membered pyranose can be formed. However, with D-glucose the six-membered pyranose usually predominates.

For example, glucose can react internally to form a hemiacetal (an intramolecular cyclization).



D-Glucose **hemiacetal**

The molecule exists predominantly in the cyclic form; however, it is still in equilibrium with a small amount of the acyclic form. The cyclic 6-membered rings exist in energy minimum chair forms (shown in figure below). This is also depicted in the handouts given.



Opposite sides

Same side

axial

equatorial

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

trans or *α*
(pyran = 6-membered ring)

cis or *β*
(pyran = 6-membered ring)

The cyclic forms are indicated in the name by combining the simple name of the sugar with “furanose” or “pyranose” to indicate the size of the ring. Therefore, glucose in its 6-membered ring form is called glucopyranose.

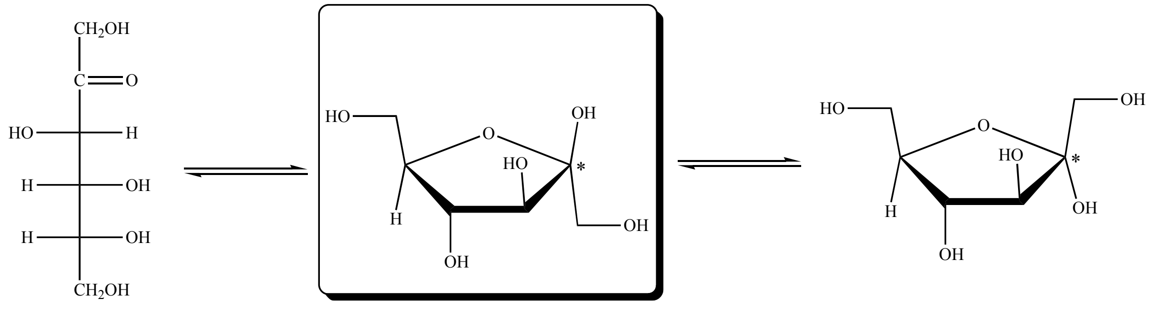
The intramolecular cyclization reaction creates a new stereogenic carbon that can be either R or S configuration, with OH group in equatorial or axial position. The terms ***α*** and ***β*** refer to position of OH at C1 relative to CH_2OH group of C6.

When the OH group attached to C1 is down relative to the CH_2OH group that is up (they are *trans* to each other), The configuration is ***α***. When they are on the same side (both are up), the configuration is ***β***.

The two stereoisomers are interconverting structural isomers called **anomers**. They differ only in stereochemistry at C1 position, which is known as the **anomeric carbon**.

- The ***α*** and ***β*** anomers can equilibrate through the linear form.

Formation of a 5-membered ring is possible for D-glucose, but exists predominantly as the 6-membered ring. Fructose exists predominantly as 5-membered ring.



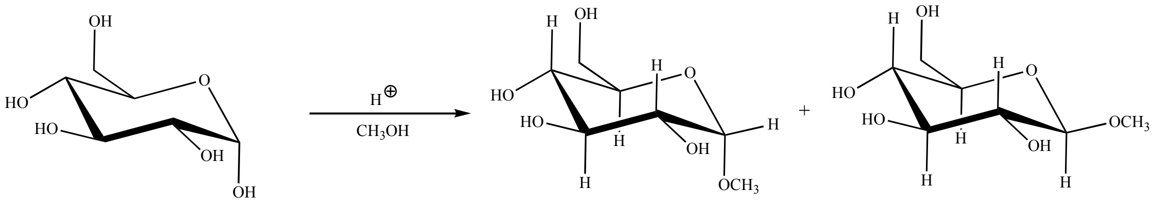
D-Fructose **D-β-Fructofuranose** **D-α-Fructofuranose**

D-fructose is a ketohexose ("keto" since it contains ketone). Its cyclized form, D-fructofuranose is a hemiacetal since the anomeric carbon (marked by asterisk) has a free OH group and a OR group attached. An easy way to find the anomeric carbon is to find a carbon with 2 oxygen atoms attached directly.

Is the fructofuranose highlighted in box an ***α*** or ***β*** *sugar?*

Answer: It is ***β***. The rule is to find the CH_2OH group (not on the anomeric carbon) and the OH substituent of the anomeric carbon, and see ff they are on the same or opposite side. Since the OH and the CH_2OH group are on the **same** side as each other, the ring is ***β***.

Acetal formation

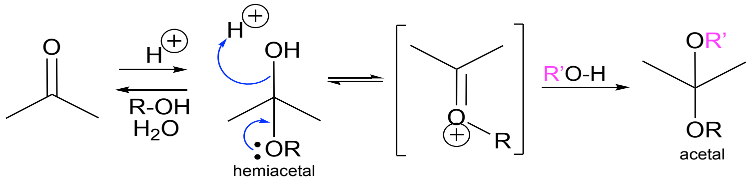


α-D-Glucopyranose **α-D-Glucopyranoside (favored)** **β-D-Glucopyranoside (minor)**

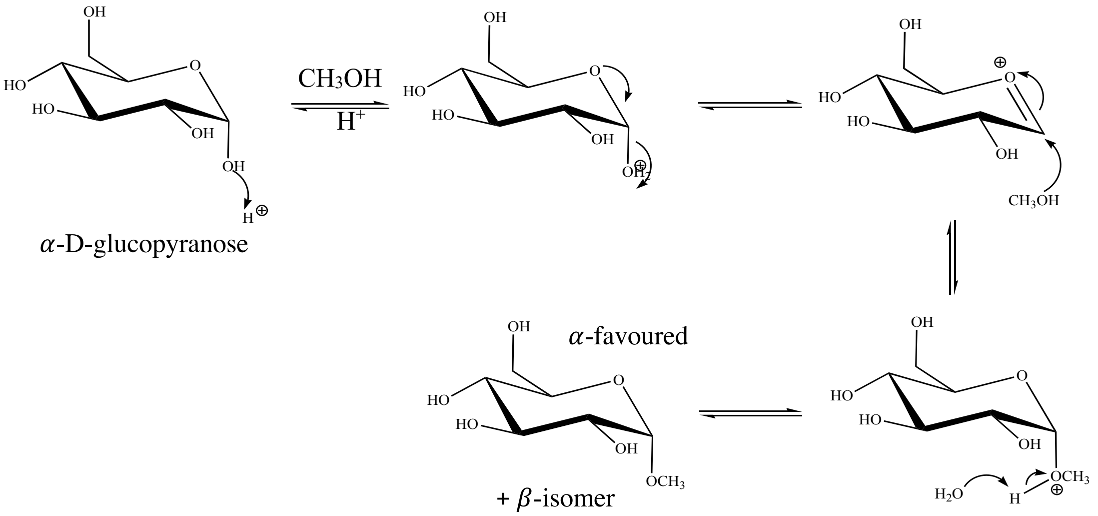
Treatment with dilute acid and alcohol converts only the OH at the anomeric position into an acetal called a glycoside. Specific glycosides are named by replacing the "ose" of the simple sugar's name with "oside". When glucopyranose is reacted, its product is called glucopyranoside.

The ***α*** anomer with the methoxy group in axial position is favored due to the anomeric effect (details about the anomeric effect is beyond the scope of this class).

Reaction:

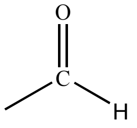


Mechanism:

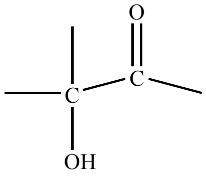


Reducing and non-reducing sugars

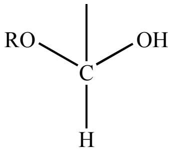
Usually, reducing sugars contain one of the three functional groups:



aldehyde



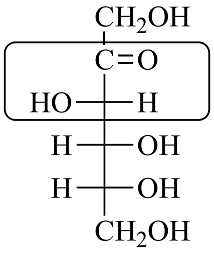
α-hydroxyketone



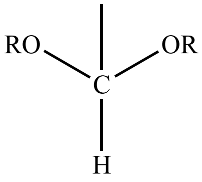
hemiacetal

Non-reducing sugars do NOT contain the above functionality, but may contain acetal

Example:



D-Fructose



acetal

Fructose is the sweetest sugar of all (sweetness index 180)

Is it a reducing or non-reducing sugar? It is reducing since it contains a α-hydroxyl ketone group in open form and the cyclized form is a hemiacetal at anomeric position.

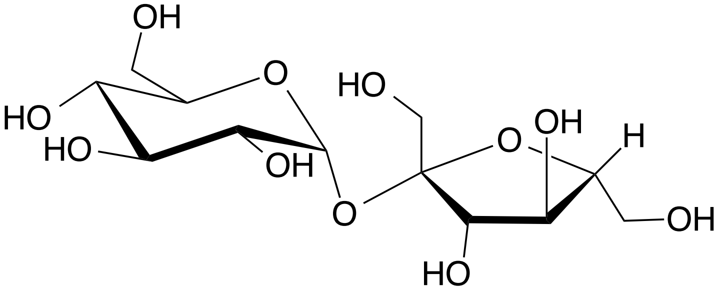
Polysaccharides = polymers of sugars

Disaccharides = 2 sugar linked
Trisaccharides = 3 sugar linked
Tetrasaccharides = 4 sugar linked
.
Oligosaccharides = Polysaccharides

Table Sugar (Sucrose):

Is it a reducing or non-reducing sugar?

Non-reducing acetal



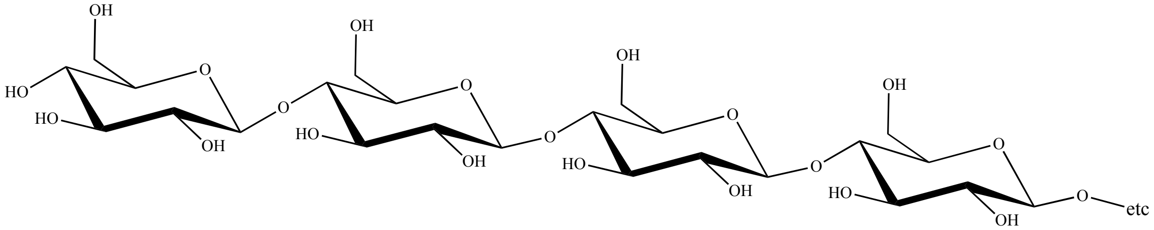
Structure in video incorrect in placement of OH groups on 5 membered ring

α–D-Glucopyranosyl-β–D-Fructofuranoside

Does this molecule have anomeric carbons ? Yes - two

Oligosaccharides = Polysaccharides

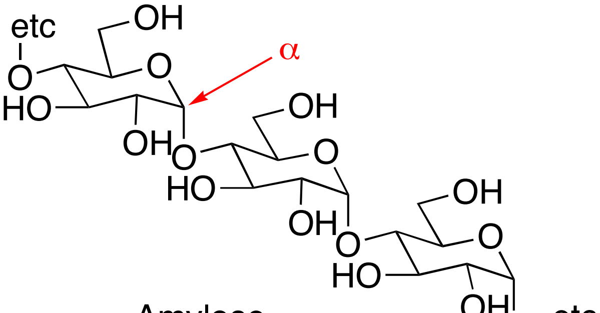
Example: Cellulose; β-(1,4) linked D-glucose polymer



Cellulose is a polymer of simple repeating monosaccharide units (D-glucose).

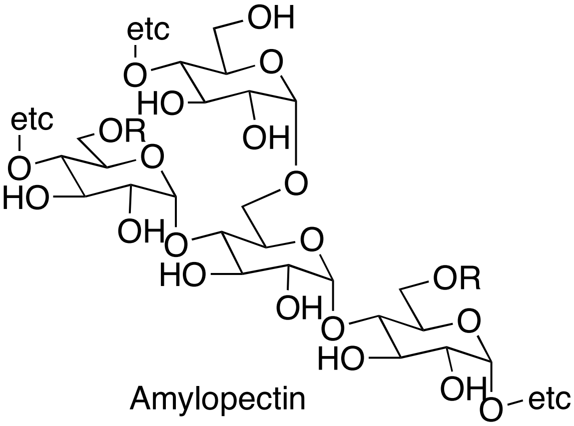
Many mammals cannot digest cellulose directly. Ruminants such as cows or goats have bacteria in their stomach to break it down to its simpler unit. The bacteria have a cellulose hydrolysis enzyme called cellulase which we do not have. Humans cannot metabolize these β linkages.

Example: Amylose; α-(1,4) linked D-glucose polymer



Amylose
(starch)

In contrast, amylose is a polysaccharide with α linkage between each monosaccharide units. Humans can digest amylose. Starch is comprised of approximately 20% amylose.
Example: Amylopectin



Amylopectin

Amylopectin is the other component in starch (~ 80%), which is similar to glycogen.