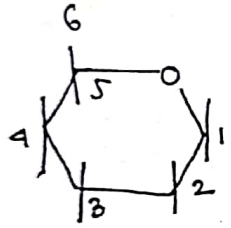
Haworth Representation and Conformational Analysis

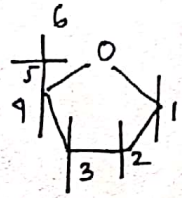
To obtain the Haworth Representation

(a) We have to modify the F.P.F in such a way that all the ring elements will be on the vertical line only.

(b) Now the molecule is tilted towards right to obtain it in the following form

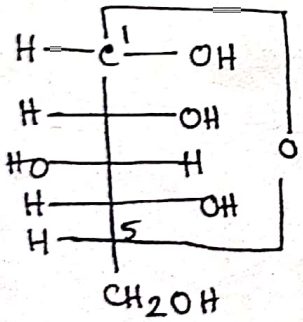


for pyranose or pyranoside

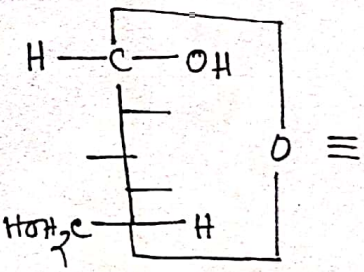


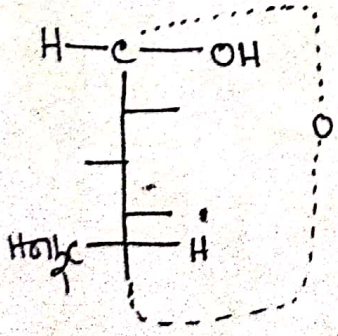
for furanose or furanoside

(i) α-D-glucopyranose

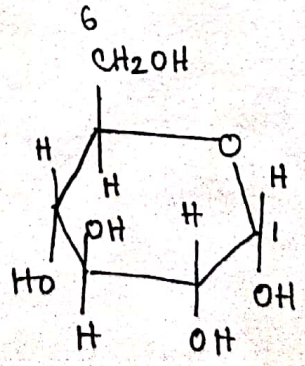


Double interchange at C_5 so that ring elements are only on the vertical line

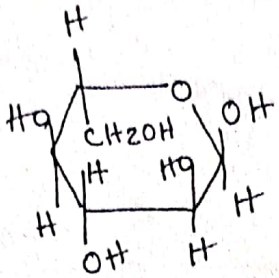




tilted towards right



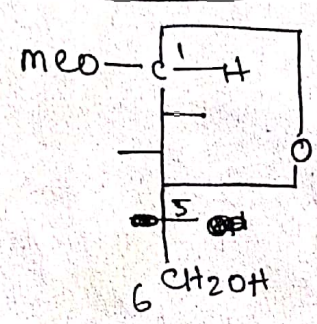
The pyranose forms of the L-sugars are obtained by the same process. The result is the mirror image of the corresponding D-sugar



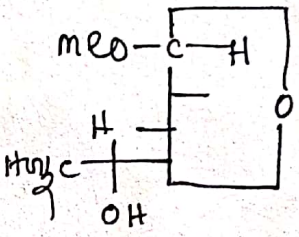
α-L-glucopyranose

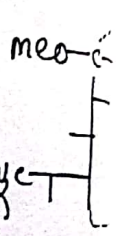
In a similar manner Haworth proposed a five-membered ring for β-sugars.

(ii) β-D(+)-glucofuranoside

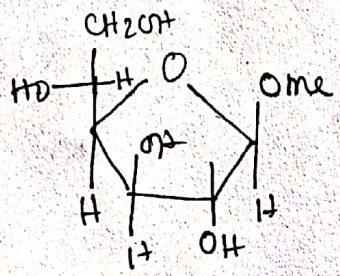


Double interchange at the C4 atom

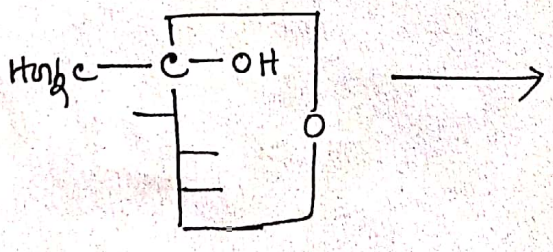


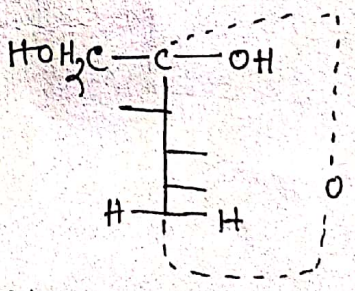


Tilted towards right

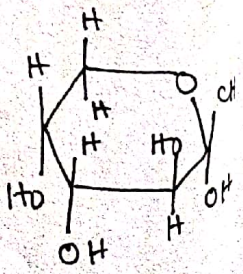


(iii) α-D-fructopyranose

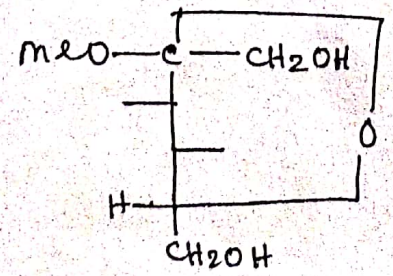




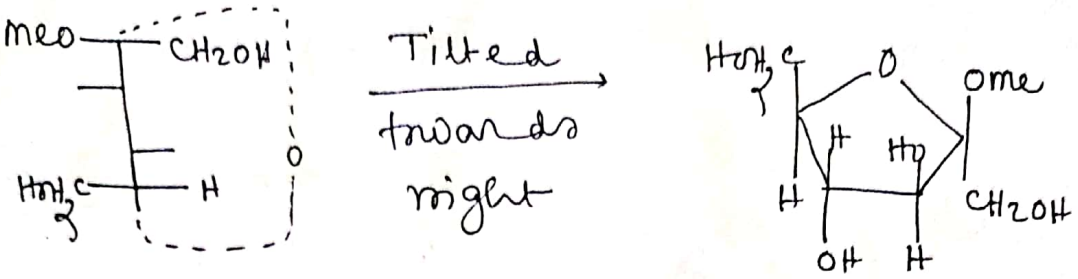
Tilted towards right



(iv) methyl β-D(+) fructofuranoside

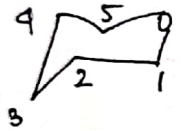


Double interchange at C4 atom

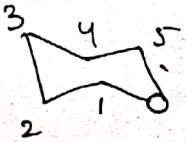


CONFORMATIONAL ANALYSIS

Two regular chair conformations of monosaccharides are suggested



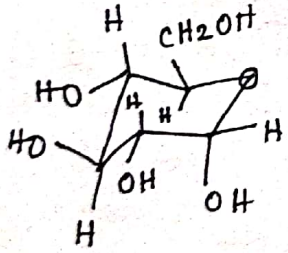
C1



1C

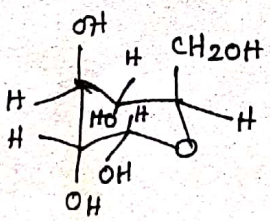
one is called normal chair (C1) and another is called reverse or inverted chair conformations.

Two regular chair conformations of α-D-glucopyranose are:



C1 form

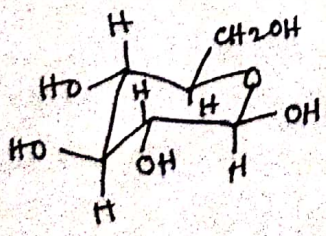
and



1C form

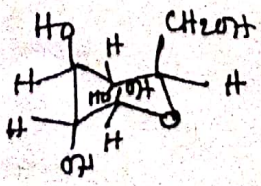
one is obtained from the other via flipping.

Again, two regular chair conformations of βD-gluco-pyranose are



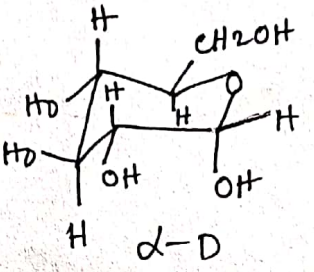
C1-type

and



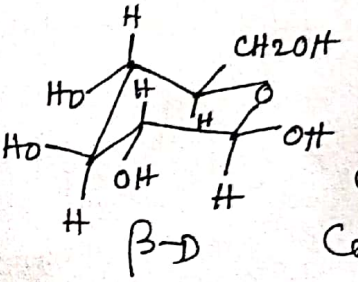
1C-type

Now axial hydroxyl group and axial $-CH_2OH$ gro
-increases the instability of the molecule. Thus, in
case 1c type conformations are less stable than c1
conformations. So the preferred conformations of α-D-g
pyranose and β-D-glucopyranose are;



α-D

and



β-D

respectiv
which are
c1 type
conformati

various methods are used to study conformational
analysis of the monosaccharides. one method inv
the estimation of the instability rating of the vario
conformations. This is done by the use of instabil
factors.

(a) The chain conformation is usually prefe
to the boat (or twist boat) whenever both
structurally possible.

(b) Axial hydroxyl groups (or any substitu
other than hydrogen) increase the instability
the molecule. Each axial hydroxyl group resu
in one instability unit.

(c) 1,3- interactions involving axial hydroxyl
result in 0.5 instability unit.

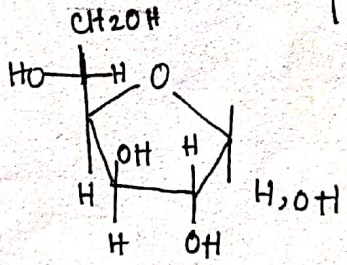
(d) An axial $-CH_2OH$ group (at C-5) results in
instability unit if only axial hydrogens a
on C-1 and C-3. If an axial substituen
other than hydrogen is on C-1 or C-3, the
instability factor is 2.5 units.

This situation is referred to as the Delta-2 ($\Delta 2$) condition or the $\Delta 2$ instability factor. Its origin is not fully understood, but it appears to be due to dipole interaction.

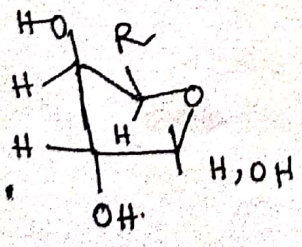
Now in α-D-glucopyranose C2, C3, C4-hydroxyl groups and $-CH_2OH$ group are at equatorial positions where as anomeric hydroxyl group is at axial position. But in β-D-glucopyranose all the hydroxyl groups and $-CH_2OH$ group are at equatorial positions. Thus β-anomer is more stable than α-anomer in the case of D-glucopyranose.

α/β-D glucofuranose

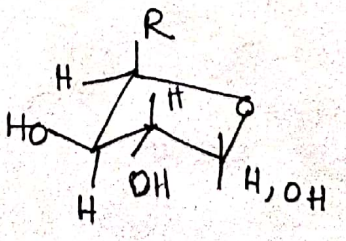
The complete Haworth representation of α/β-D glucofuranose is



Thus, two regular envelop conformations of α or β-D glucofuranose are



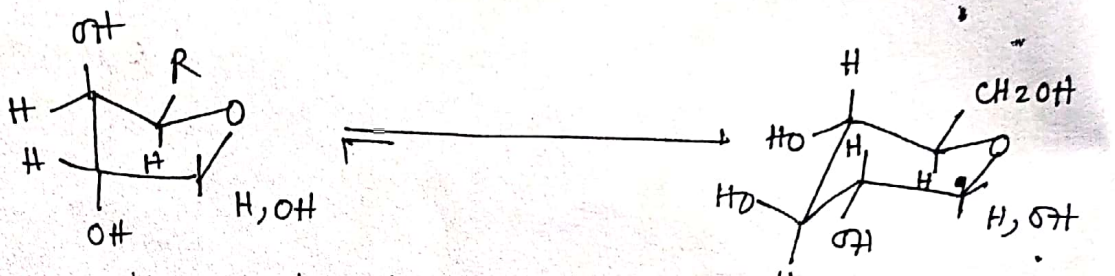
and



$R = -CH(OH)-CH_2OH$

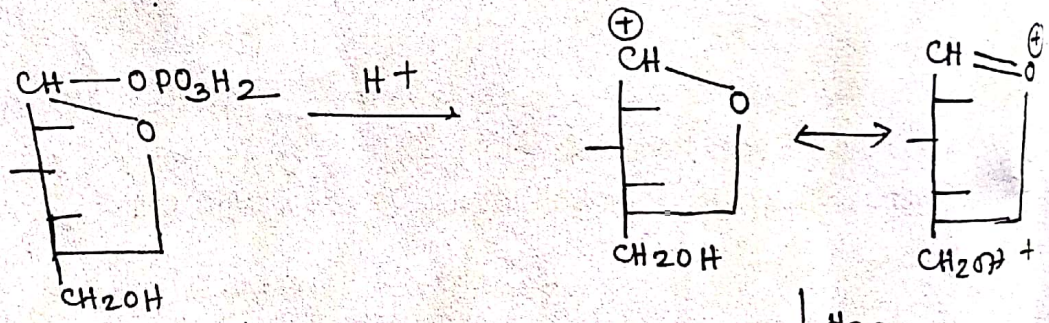
Obviously first one is preferred as the bulkiest group R occupies the equatorial position. Let us consider the furanose and pyranose forms of D(+) glucose in solution. Keeping aside the anomeric hydroxyl group.

in each case we can see that in envelope confor, the C-2 and C-3 hydroxyl groups are at axial po but in chair conformation all the large groups and $-CH_2OH$ are at equatorial positions. Hence it anticipated that furanose form will be less stab than pyranose form and so the equilibrium wi lie far to the right.

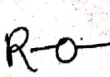


Problem: On dilute acid, hydrolysis of D-glucose-1-pho differs from ordinary alkyl esters of its type ($ROPO_3H$) in two ways: it is abnormally fast it takes place with cleavage of carbon-oxygen bo Can you suggest an explanation for its unusual behaviour?

Solution:

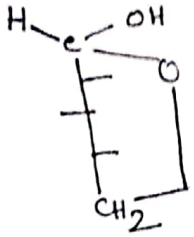


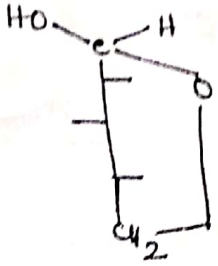
The hydrolysis is S_N1 like with the intermediate formation of highly stable carbo-cation through the cleavage of carbon-oxygen bond.

But the hydrolysis of ordinary ester  via a common mechanistic cours through the cleavage of RO bond. Thus we have the said behaviour.

xylose:

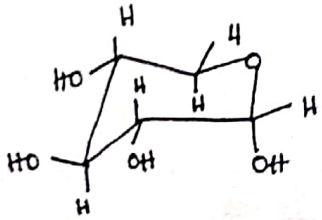
Let us take a close look on the Configuration of α and β-D-xylopyranose:



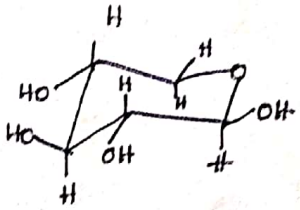


Obviously these are Configurationally allied with α-D-glucopyranose and β-D-glucopyranose broom C-1 to C-4 respectively

Thus the preferred Conformations of α and β-D xylopyranose are

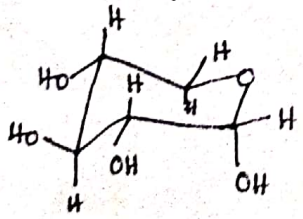


and



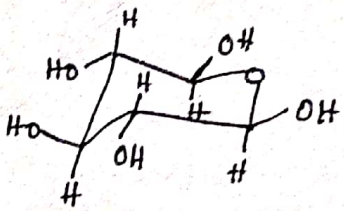
respectively which are C-1 type Conformations.

By analogy with D-glucopyranose we can say that β-anomer is more stable than α-anomer. So here during mutarotation β-anomer predominates:



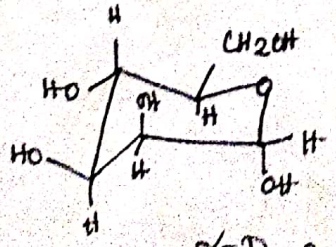
~29%

Aqueous medium ⟹

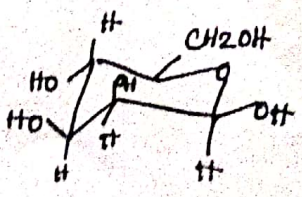


71%

Mannose: D-mannose and D-glucose differ in change in Configuration at C2 only.



and

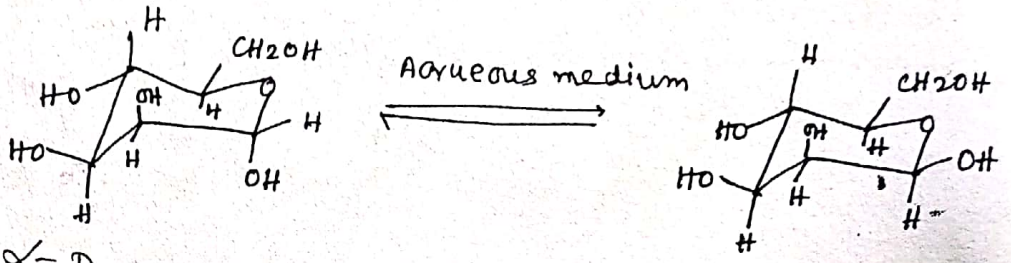


α-D-mannopyranose

β-D-mannopyranose

C-1 type Conformations.

By analogy with D-glucopyranose we do expect that β-D-L-
mannopyranose is more stable than α-D-mannopyran-
But here during mutarotation α-anomer predom-
over β-anomer in equilibrium.

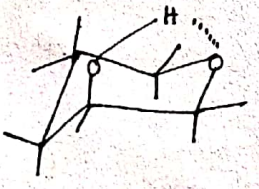


α-D-mannopyranose ~ 64 %

β-mannopyranos- ~ 36 %

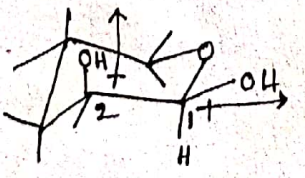
Thus α-anomer is more stable than β-anomer. Th-
can be explained in the following way:

(a) With C-2 axial hydroxyl group we have the foll-
type intramolecular hydrogen bonding.



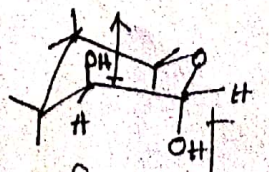
Thus with C-2 axial hydroxy-
group the system is not
so unstable as one can
expect

(b) In β-anomer here there is a dipolar repulsio-
between C1–O and C2–O bonds.



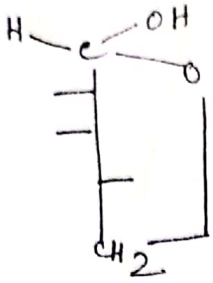
This is often referred to a-
⊲2 instability factor.

But such a dipolar repulsion is reduced in α-
anomer

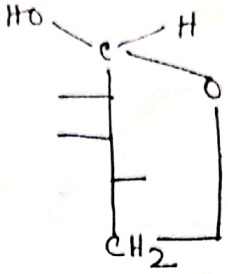


(c) When anomeric hydroxyl group is at axial posi-
it has got extra stability — The anomeric effect

L-Lyxose:

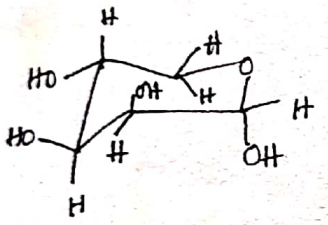


α-D- lyxopyranose

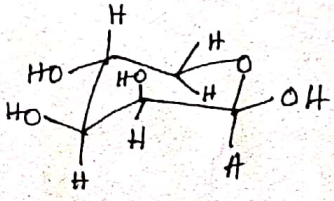


β-D- lyxopyranose

These are Configurationally allied with that of α-D-mannopyranose and β-D- mannopyranose from C-1 to C-4 respe-ctively. Thus the preferred Conformations of α-D- lyxopyra-nose and β-D- lyxopyranose are

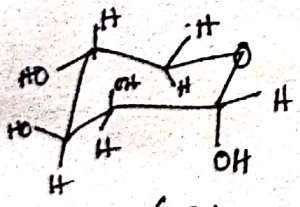


and



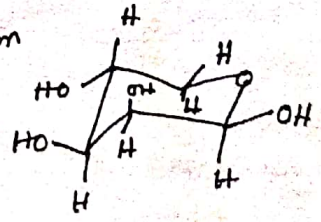
respectively which are C1 type Conformations.

Now by analogy with D-mannopyranose we can say that α- anomer is more stable than β-anomer here. So during mutarotation α- anomer predominates.



α-D- ~69%

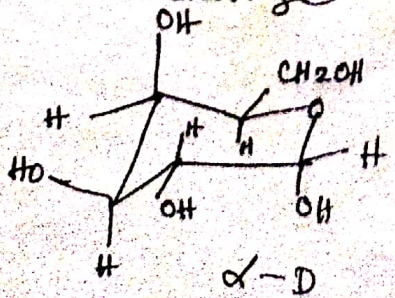
Aqueous medium



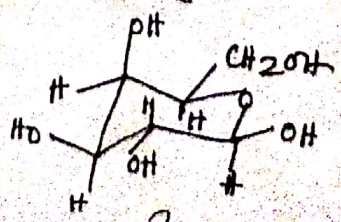
β-D- ~31%

D-Galactose

D-galactose and D- glucose differ with the change in Configuration at C4 only.



α-D

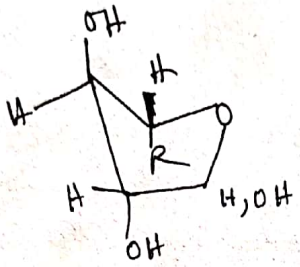


β-D-

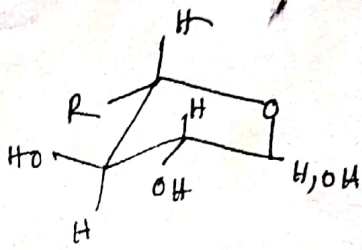
C-1 type Conformation

obviously β-anomer is more stable than α-anomer

now two regular envelope conformations of α or β-D-galactopyranose are



and

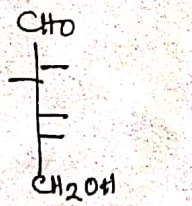


where

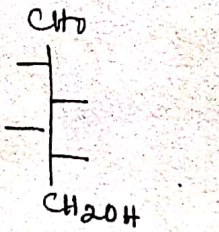
R = H

Obviously second one is preferred one as here the C-2 and C-3 hydroxyl groups and bulky R group are at the equatorial position

D-Iodose D-iodose differs with the change in configuration C-2, C-3 and C-4 with respect to D-glucose

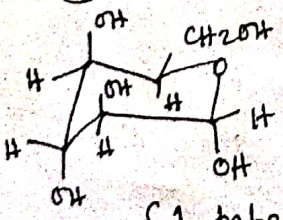


D-glucose

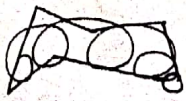


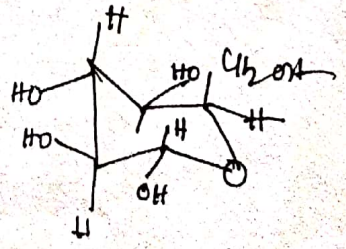
D-iodose

α-D-iodopyranose



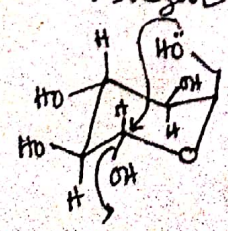
C1 type



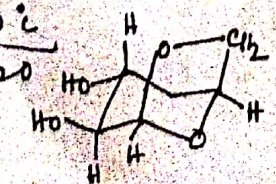


1C type

obviously 1C type conformation is preferred one for α-D-iodopyranose. Thus at 100°C D-iodopyranose exists as 1,6 anhydro sugar in 86% because of conformational rigid- orientation of $-CH_2OH$ and anomeric hydroxyl group in α-anomer. obviously 1,6-anhydrosugar is an intermediate glycoside.



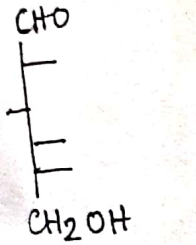
100°C / $-H_2O$



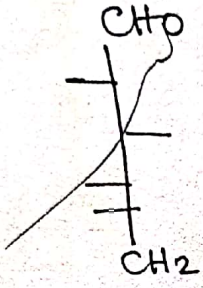
1,6-anhydrosugar

Problem: Draw the preferred conformation of β-L-glucopyranose.

Solution: The configuration of L-glucose is the mirror image of D-glucose

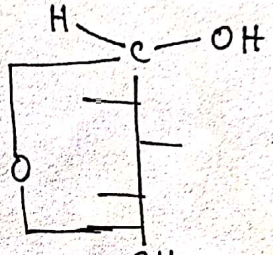


D-glucose

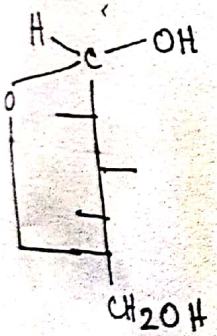


L-glucose

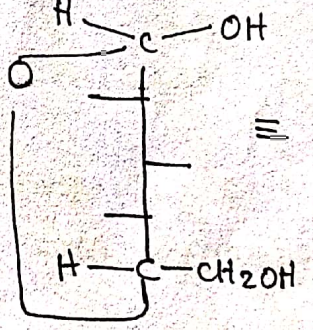
The configuration of β-L-glucopyranose is



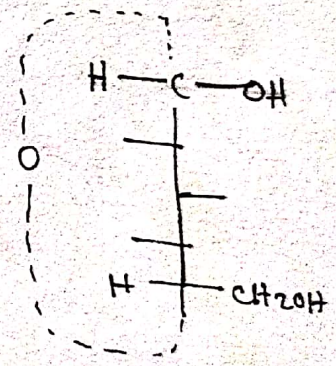
Let us draw the Haworth Representation



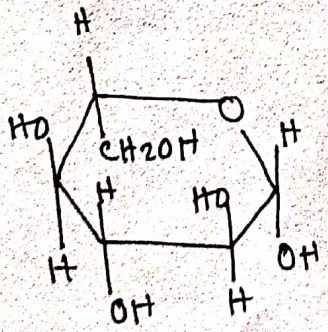
Double exchange at C5 so that ring elements are only on the vertical line



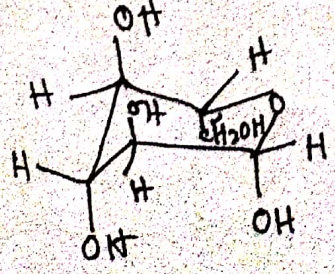
≡



tilted towards right

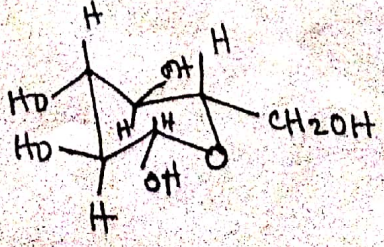


Now two pyranose regular chair conformations of β-L-glucopyranose are



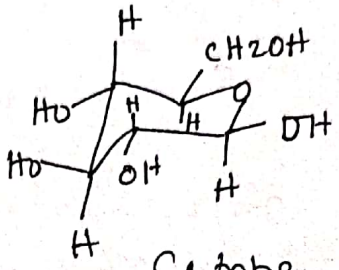
C1-type

and



1C type

Obviously here the preferred conformation is ... one. now the preferred conformation of β-D-glu... ranose is

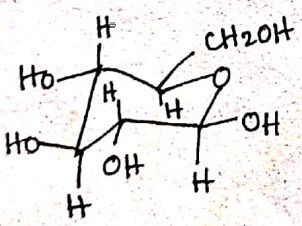


^1C type.

It might be noted ... L-sugar may be dr... as the mirror image ... D-sugar, but now ... mirror image of a ... sugar is the ^1C-L-sug...

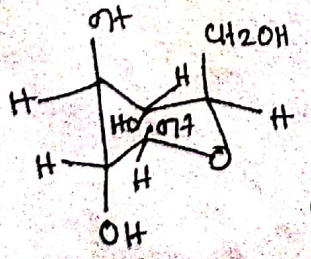
Problem: 4 The chair conformation of β-D-gluc... in which all hydroxyl groups are axial ... not as unfavourable as we might expect fro... axial-axial non bonded interactions? What favou... factor can account for the decreased instabili...

Solution: The preferred chair conformation of ... -glucopyranose is

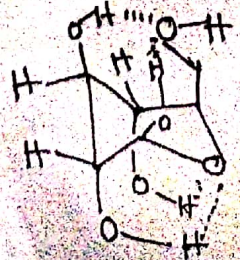


in which the hydroxyl groups and ... $-CH_2OH$ group are at equatorial po...

now the flipped conformation is



in which the hydroxyl groups ... $-CH_2OH$ are at axial position. So ... we do expect the axial-axial non bonded interactions. But here we ... the following type of intramolecular hydrogen b...

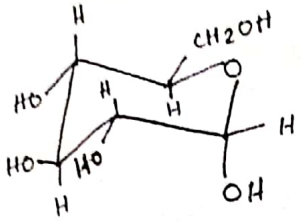


Problem: Why do aldoses react with Fehlings solution and $PhNHNH_2$ but not with $NaHSO_3$

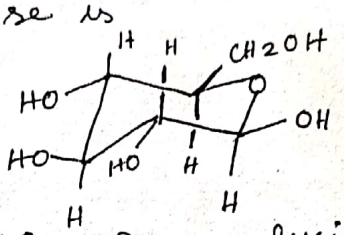
Solution: These reactions are typical for the $-CHO$ group, which means that the open chain aldehyde form is in equilibrium with the cyclic hemiacetal form. Since Fehling's and osazone reactions are irreversible, the equilibrium shifts to restore the low concentration (0.02%) of the aldehyde as it is depleted through reaction, and eventually all the aldose reacts. Bisulphite addition is reversible and enough aldehyde remains in equilibrium with the bisulfite adduct to satisfy the equilibrium with the hemiacetal form. Consequently, there is no noticeable reaction.

THE ANOMERIC EFFECT

The preferred conformation of α-D-glucopyranose is



and the preferred conformation of β-D-glucopyranose is

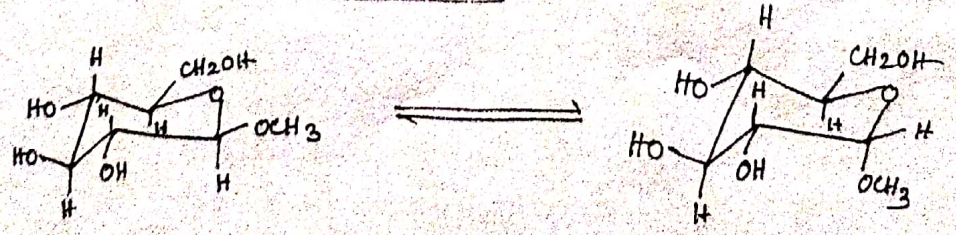


Now the rules of conformational analysis tell us that substituted cyclohexane with higher number of substituents at equatorial positions are usually more stable as with a axial substituent there will be two gauche butane type or 1,3-diaxial interactions. Thus we do expect that β-D-glucopyranose is more stable than α-D-glucopyranose and during mutarotation of β-D-glucopyranose should be present in higher amount than α-D-glucopyranose in equilibrium i.e.

This is actually observed in practice.

However the reverse situation is observed when the anomeric hydroxyl group is replaced by alkoxy group or acetoxy group or halogen. Let us consider the following examples

A. <u>methyl-D-glucopyranoside</u>



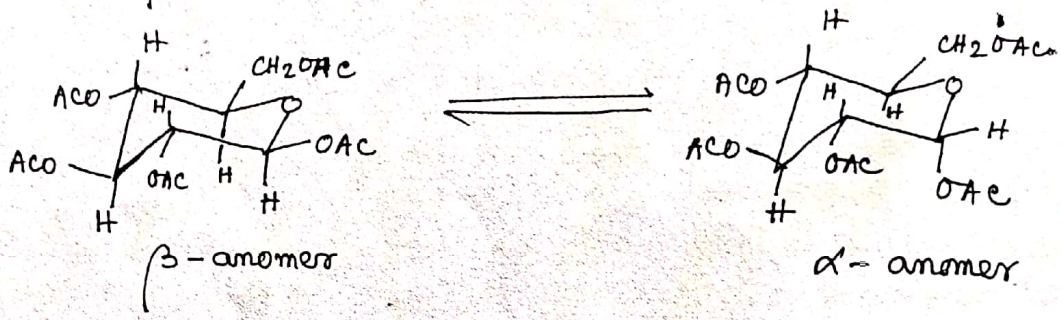
β-anomer

α-anomer

in anhydrous acidic methanol:

α-anomer: ~ 67 % / Equilibrium Constant ≈ 2
β-anomer: ~ 33 %

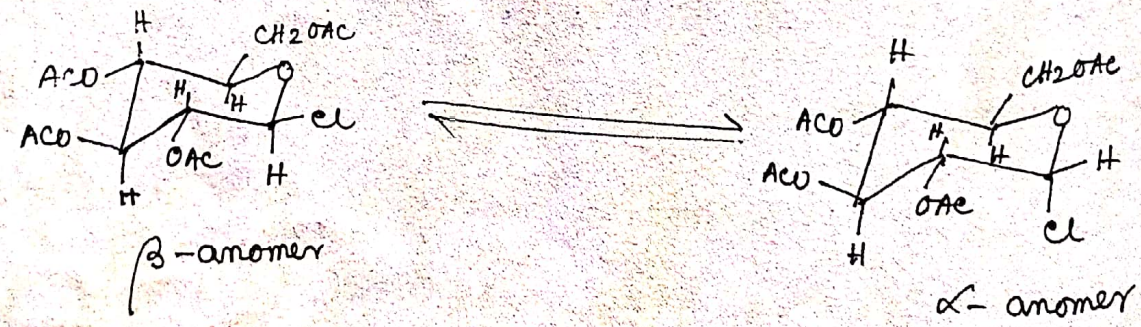
B. Glucose pentaacetate.



in 50% acetic acid : acetic anhydride, 0.1 M H_2SO_4

α-anomer ~ 86 %
β-anomer ~ 14 % / Equilibrium Constant ≈ 6

C. Tetra-o-acetyl-D-glucopyranosyl chloride



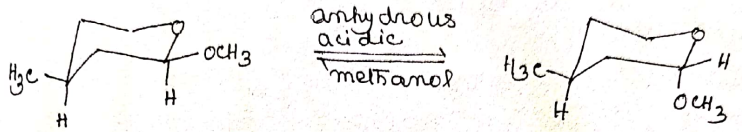
in acetonitrile solution

α-anomer ≈ 94 %
β-anomer ≈ 6 % / Equilibrium Constant ≈ 15.66

The above tendency of an electron withdrawing anom
group to be at axial position is not limited to
Carbohydrates but carries over to simpler ring syste

such as 2- substituted tetrahydropyrans and substituted dioxanes. Let us consider the following examples:

A. 2- methoxy – 4- methyl tetrahydropyran:



~ 35 % ~ 65 %

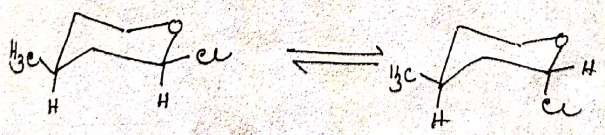
B. 2- methoxy- 6- methyl tetrahydropyran

Equilibrium Constant:

= 3·4 in CCl_4

= 1·8 in acetonitrile

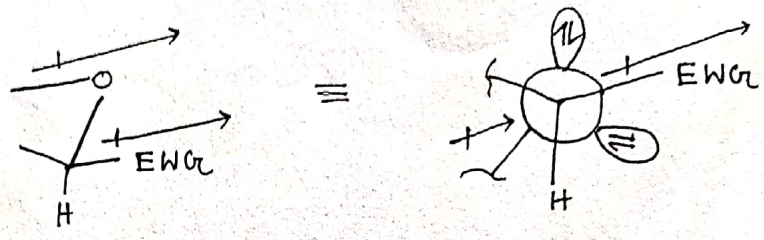
C. 2- Chloro – 4- methyl tetrahydropyran



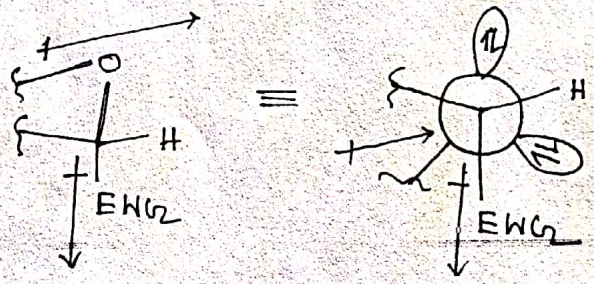
Equilibrium Constant ≈ 32 (in pure liquid state at 40°C)

The above unexpected preference of electron withdrawing group to be at axial position is known as Anomeric Effect. Such a preference can be explained in the following ways.

(a) When the electron withdrawing group is at the eq
-torial position there is a strong dipolar repu
as shown below

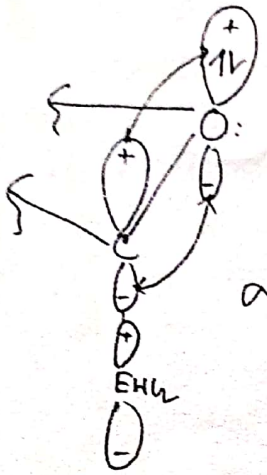


But such a dipolar repulsion is reduced when the el
withdrawing group is at axial position



Now we do expect that the above dipolar repulsion i
equatorial form can be reduced in polar solvents. Th
in aqu. medium; a polar one, the dipolar repulsion in
β-D- glucopyranose is reduced i.e. anomeric effect is outw
As a result with D-glucose during mutarotation in aq.
β-anomer predominates. Again we have α-anomer of
-glucopyranose is 50% in non- aqueous methanol where
dielectric constant is lesser.

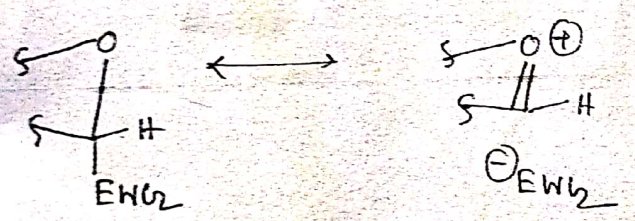
(b) From the molecular orbital view point the anome
effect is expressed as resulting from interaction
the lone pair of electrons on oxygen and σ* orbit
associated the bond C—EWG. Such an interac
only possible when the electron withdrawing group i
the axial position as shown below:



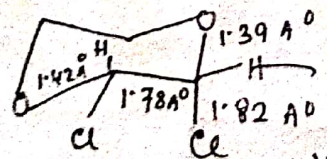
n on bonding electrons of Oxygen: HOMO

σ^* orbital of C–EWG bond: LUMO

In resonance picture such interaction can be represented by using the following canonical forms:

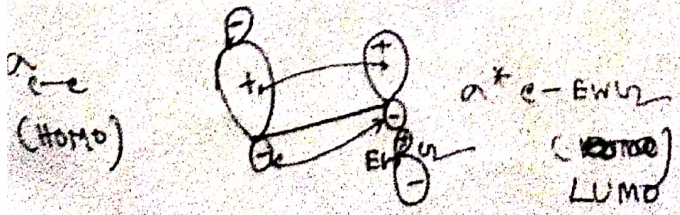


Obviously such interactions leads to an increase in C–EWG bond length and decrease in C–O bond length. Thus we have the following observations about the bond lengths in crystalline cis-2,3-dichloro-1,4-dioxane



Again the above type of interaction is more pronounced when the substituent is a stronger electron withdrawing group as there will be a close matching in energy of l.p. of electrons and of σ^* orbital associated with C–EWG bond.

In this connection it may be informed that as HOMO not only the lone pair of electrons but also the σ_{C-C} or σ_{C-H} may be involved i.e. of the following type



Again as LUMO not only σ^*_{C-EWG} but also σ^*_{C-C} or σ^*_{C-H} may be involved.

DISACCHARIDES

Disaccharides are the simplest and most important oligosaccharides. In general these are sweet testing, crystalline, water-soluble substances, easily hydrolysed by enzymes and dil. mineral acids to two monosaccharide units. Hydrolysis of ~~dich~~ disaccharides into two monosaccharides is the characteristic reaction of all the disaccharides. In the formation of a disaccharide molecule, at least one monosaccharide unit is linked to the other through the glycosidic Carbon (C_1). As far as the point of the Linkage of the second monosaccharide is Concerned it has been observed that it might either be a C_1, C_4 & C_6.

SUCROSE : STRUCTURE DETERMINATION

1. Sucrose on hydrolysis by acid or enzyme invertase to an equimolecular mixture of D(+) glucose and D(-) fructose, which thus constitute the two monosaccharide units of Sucrose.

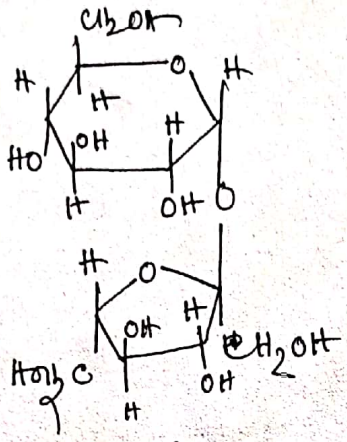
2. Sucrose is a non reducing sugar. Thus both the glucose and fructose must be linked via their reducing groups.

3. Sucrose is hydrolysed by the enzyme maltase, thus indicating the α-link is present. Again the glucose which is formed by hydrolysis of sucrose shows downward mutarotation. It therefore indicates that α-glucose is present in sucrose. There is an enzyme invertase which hydrolyzes methyl-β-fructofuranosides, and it has been found that it also hydrolyses sucrose. This suggest that fructose is present in sucrose in the β-form.

Oxidation of sucrose with periodic acid Confirms its structure. Three molecules of periodic acids are Consumed and one molecule of formic acid is produced. Consumption of 3-moles of HIO_4 indicates presence of six membered ring of a monosaccharide and five membered ring of another in sucrose.

formation of one mole of HCOOH confirms, it is the glucose which is six membered and fructose which is five membered.

So the structure of sucrose is



INVERSION OF SUCROSE

Hydrolysis of sucrose to D-glucose and fructose is very interesting in two ways. Firstly, the dextrorotatory sucrose gives the laevorotatory product on hydrolysis. The reason being the sucrose with $[\alpha]_D^t = +66.5°$, on hydrolysis gives an equilibrium mixture of glucose, $[\alpha]_D^t = +52.5°$ and fructose $[\alpha]_D^t = -92°$. Now as the specific rotation value of fructose is high as compared to glucose as well as parent compound sucrose, the mixture after hydrolysis will be, on the whole laevorotatory. Furthermore, since the direction of rotation is reversed (or inverted), the mixture of sugars formed on hydrolysis with a specific rotation of $-20°$ is known as invert sugar. Thus invert sugar is the equimolecular mixture of D-glucose D-fructose obtained on hydrolysis of sucrose.

$$C_{12}H_{22}O_{11} \xrightarrow[\text{or invertase}]{H_2O/H^+} \underset{\text{D-glucose}}{C_6H_{12}O_6} + \underset{\text{D-fructose}}{C_6H_{12}O_6}$$

Sucrose

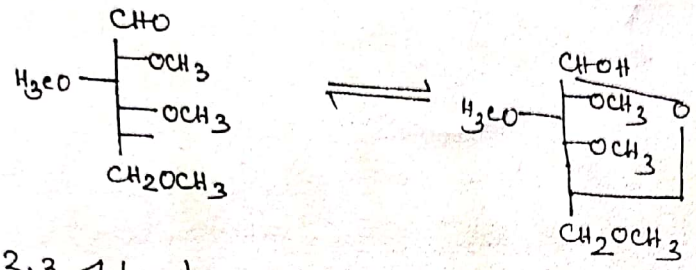
$[\alpha]_D = +66.5°$

$[\alpha]_D = +52.5°$

$[\alpha]_D = -92°$

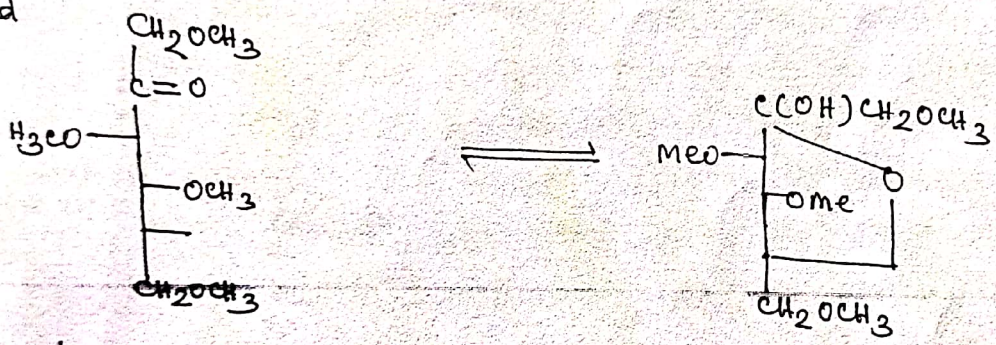
Sucrose structure (Contd.)

Methylation of sucrose gives an octamethyl derivative that, on hydrolysis yields:



2,3,4,6-tetra-o-methyl glucose

and



1,3,4,6-tetra-o-methyl fructose

This confirms the pyranose ring structure for glucose and furanose ring structure for fructose.

The specific rotation of invert sugar is one half the sum of those of the individual monosaccharides:

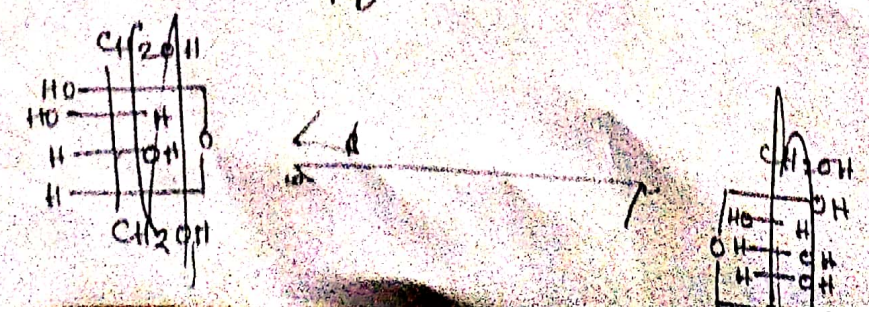
$$\frac{1}{2}\left[+52.5^{\circ}+(-92^{\circ})\right] \approx -20^{\circ}$$

It is also interesting to note that the sucrose after hydrolysis is more sweeter than the sucrose itself. The reason being the presence of fructose in invert sugar which is the sweetest of all the sugars. This also explains why honey (containing a large proportion of invert sugar, that is formed by the hydrolysis of honey by the saliva of bees), is sweeter than sucrose. The relative sweetness of the common sugars as determined practically by taking the sucrose as arbitrary standard value of 100 are given below

Sugar	Relative Sweetness	Sugar	Relative Sweetness
Sucrose	100	D-xylose	40
D-fructose	173	Maltose	32
Invert sugar	123	D-galactose	32
D-glucose	74	Lactose	16

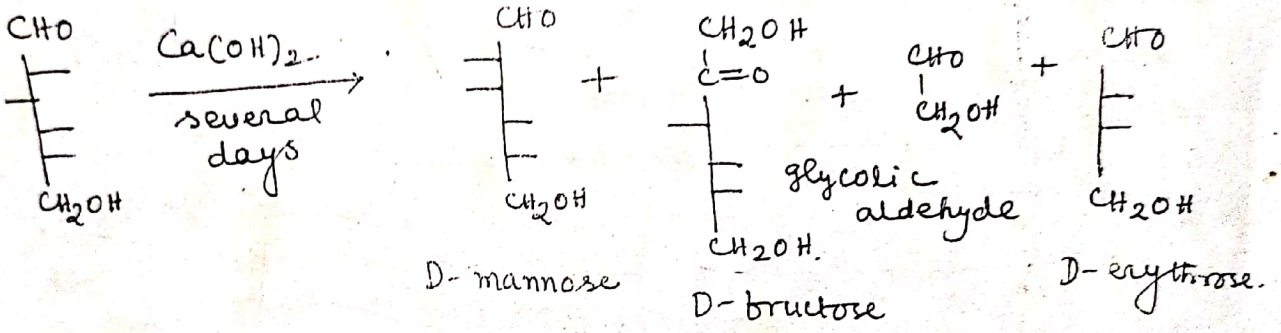
Secondly, hydrolysis of sucrose gives first of all α-D(+)-glucopyranose and β-D(-) fructofuranose, but the latter is unstable and immediately changes into the stable

D(-)-fructopyranose.

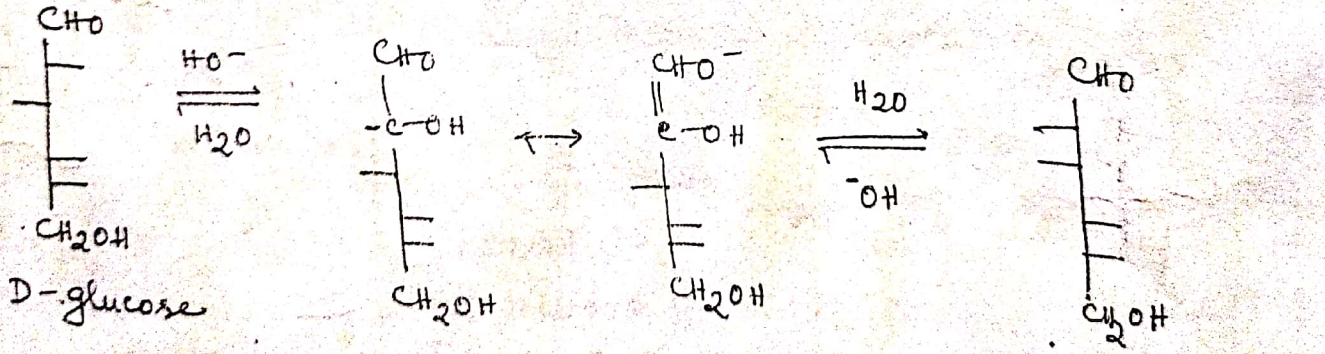


REACTION WITH BASE

On presence of base aldoses and ketoses rapidly equilibriate to a mixture of monosaccharides. If D-glucose is treated with aqueous calcium hydroxide and the solution is allowed to stand for several days, a mixture of products results, including D-mannose, D-fructose, glycolic aldehyde and D-erythrose.

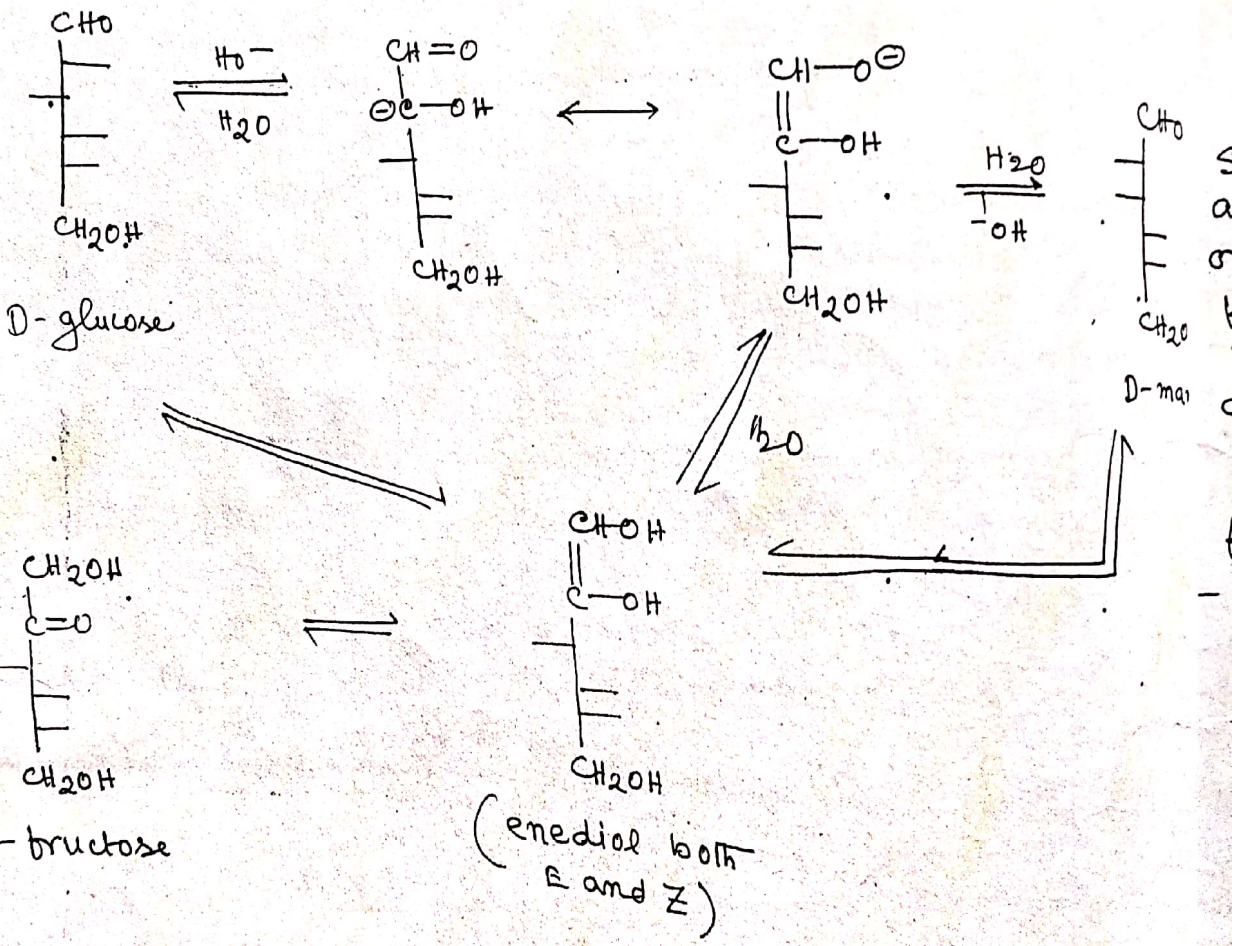


This transformation is an example of the Lobry-de Bruyn-Alberda van Ekenstein Reaction. Here D-mannose results from the reversible formation of an enolate ion:



Obviously protonation of this enolate ion at one base gives back D-glucose and protonation at other base gives D-mannose. This conversion of D-glucose to D-mannose is called epimerisation.

now protonation of the enolate ion at oxygen giv
a new enol, called an enediol. Because the enediol ac
has a hydroxyl group at both ends of the doubl cy
bond, it is the enol not only of the two aldos
but also of D-fructose. Thus the enediol
tautomerises to D-fructose:



Again glycolaldehyde and D-erythrose result from a reverse aldol condensation.