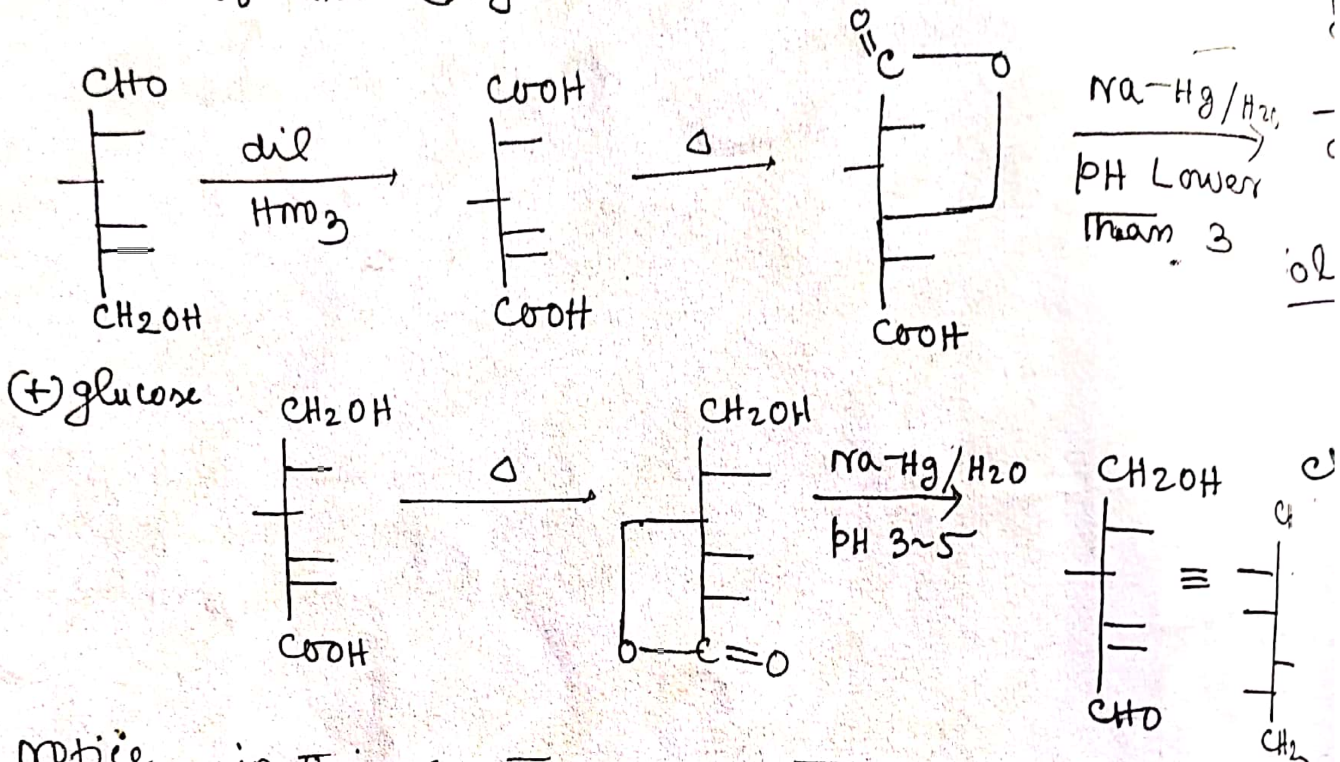
The procedure, Fischer used for interchanging the ends of the (+) glucose involves the following st



notice, in this synthesis that the second reduction with Na-Hg is carried out at pH 3~5. under these conditions, reduction of the lactone yields an aldehyde and not a primary alcohol.

| (+) gulo

Problem-1 Complete The following series of reactions

$$\begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CH_2OH\end{array} \xrightarrow[\Delta]{KHSO_4} ? \xrightarrow[\text{Saturated with dry HCl}]{\text{Excess } CH_3CH_2OH} ? \text{ (a chloro compound)} \xrightarrow[KOH/\Delta]{EtOH} ?$$

$$\xrightarrow[\text{alkaline } KMnO_4]{\text{Cold dil}} ? \xrightarrow[H_2SO_4]{\text{dil}} ?$$

Solution-1

$$\begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CH_2OH\end{array} \xrightarrow[\Delta]{KHSO_4} CH_2=CH-CH=O \xrightarrow[\text{EtOH, Saturated with dry HCl}]{\text{Excess}}$$

$$Cl-CH_2CH_2-CH(OEt)_2 \xrightarrow[\text{"elimination of HCl"}]{EtOH-KOH} CH_2=CH-CH(OEt)_2 \xrightarrow[\text{alk. } KMnO_4]{\text{Cold dil}}$$

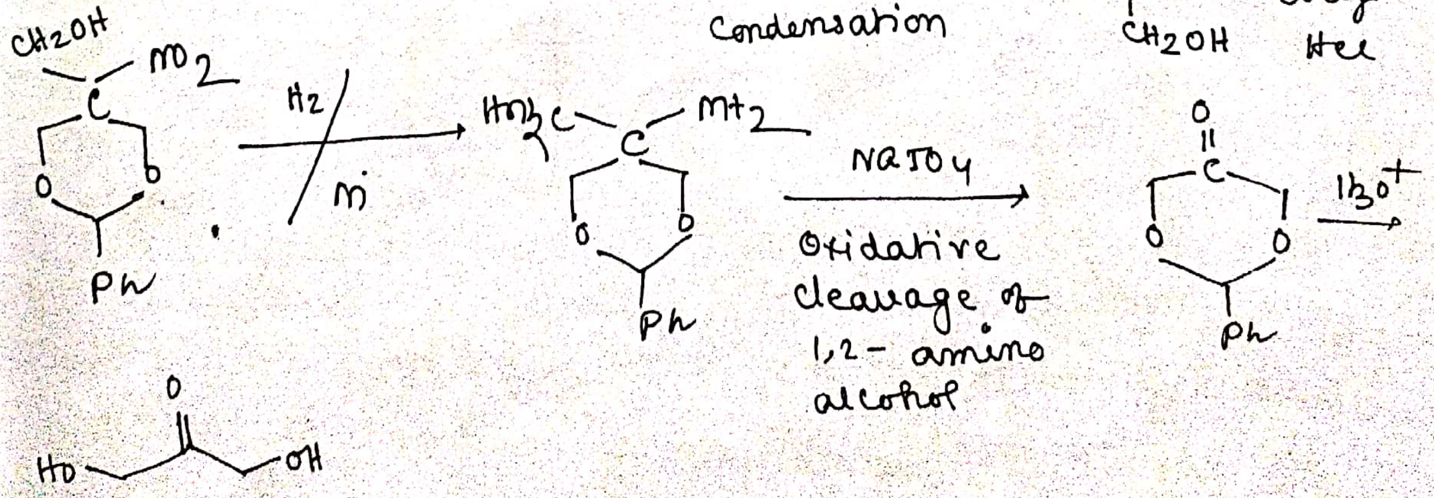
$$\begin{array}{l}CH_2-CH-CH(OEt)_2\\ \;|\qquad\;|\\ OH\quad OH\end{array} \xrightarrow[H_2SO_4]{\text{dil}} \begin{array}{l}OHCCH-CH_2\\ \quad\;|\qquad|\\ \quad OH\quad OH\end{array}$$

Problem-2

$$CH_3NO_2 + 3\,H_2C=O \xrightarrow{HO^-} ? \xrightarrow[\text{dry HCl}]{PhCHO} ? \xrightarrow[\text{Catalyst}]{H_2} ? \xrightarrow[\text{ii) } H^+]{\text{i) } NaIO_4} ?$$

Solution-2

$$CH_3NO_2 + 3\,H_2C=O \xrightarrow[\text{aldol Condensation}]{HO^-} \begin{array}{c}CH_2OH\\ |\\ HOH_2C-C-NO_2\\ |\\ CH_2OH\end{array} \xrightarrow[\text{dry HCl}]{PhCHO}$$



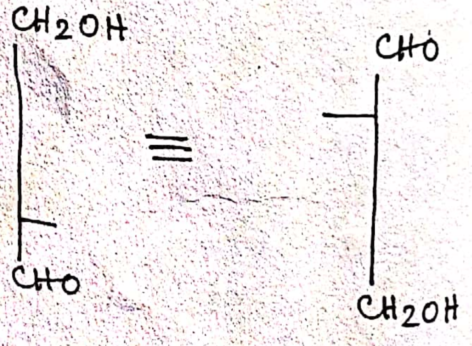
Problem – III

A, B and C are Three aldohexoses. A and B H$_2$/catalyst reduction yield the same alditol but different osazones when treated with phenyl hydr different osazones when treated with phenyl hydr whereas B and C yield same osazone but differ alditols. A, B and C are the members of D-fam Identify them.

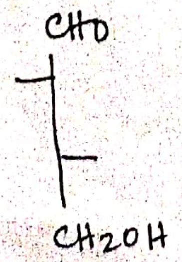
Solution – III

A and B on H$_2$/Ni reduction yield same al So they differ with the interchange of –CHO and – groups. now since A is a member of D-family, partial Configuration of A is

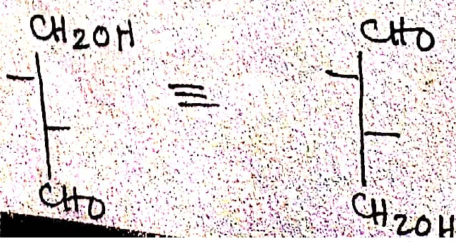
now since A and B differ with the Interchange of –CHO and –CH groups the partial Configuration of B: is



now 'B' is a member of D-family, the partial Configuration of 'B' is

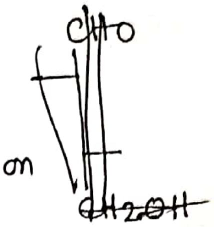


Consequently the partial Configurat of A is

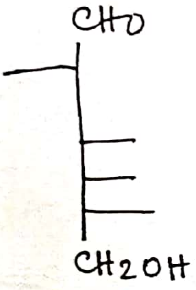


Thus the partial configurations of A and B are

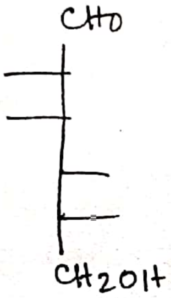
~~Thus the partial configurations of A and B are~~



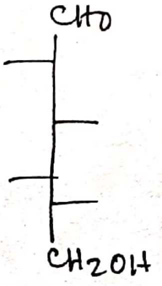
Now from this partial configuration we can have four possible configurations which are:



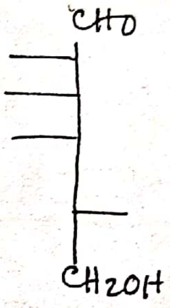
(I)



(II)

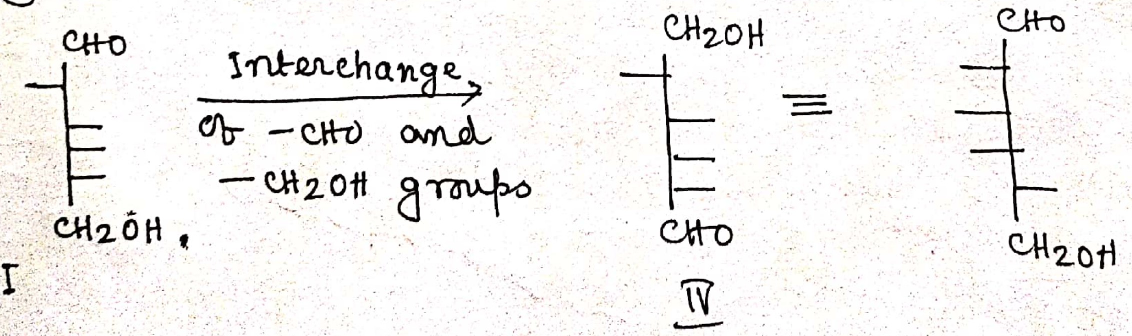


(III)



(IV)

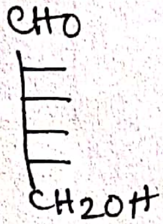
and of these one is (A) and another is (B). Now if we take a close look on I & IV we find that I and IV differ with the interchange of -CHO and -CH2OH groups:



Thus of I and IV one is (A) and another is (B). Obviously I and IV yield the different osazone.

Now 'B' and 'c' yield the same osazone. Thus (B and (C) are epimeric and they differ in chan in configuration at C-2. Thus if (I) is (A) then (IV (B) and consequently the configuration of 'c' is

Again if IV is (A) then I is B and consequently the configuration of is

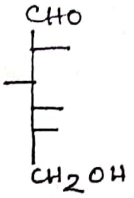


Problem-4

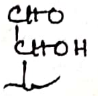
A compound (A) known to be a mon -methyl ether of D-glucose gives an os with phenyl hydrazine. The Killiani– Fischer syn yields two new methylated sugars, one of which b dil. HNO_3 oxidation yields an optically inactive mo methyl ether of an aldaric acid. Suggest the configu -ration of (A).

Solution-4:

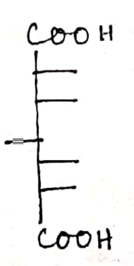
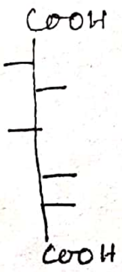
olution: The configuration of D-glucose is



The given compound (A) is the monomethyl ether of D-glucose. Thus the compound (A) may be 2, 3, 4, 5 or 6-O-methyl glucose. The compound A forms Osazone. Thus it contains the group

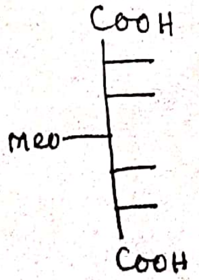

$CHO-CHOH-$

Thus the compound "A" is not 2-O-methyl glucose. Now K.F synthesis on D-glucose yields two aldoheptoses which on dilute HNO_3 oxidation yields

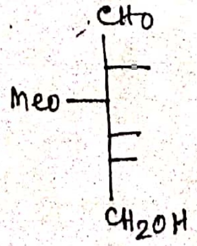

and


I II

Of these I is optically inactive and II is optically active. Now it is informed that the compound "A" the monomethyl ether of D-glucose on K.F. synthesis yields two new methylated sugars, one of which on dilute HNO_3 oxidation yields an optically inactive monomethyl ether of an aldaric acid. Obviously then the configuration of the aldaric acid is



Thus the configuration of A is



i.e. it is 3-O-methyl glucose

Problem 6:

(a) Aldaric acid from D-glucose undergoes lactonisation to two different γ-lactones. What are their structures.

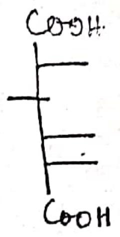
(b) How many γ-lactones are obtainable during the lac -tion of the aldaric acid from D-mannose? What a their structures?

(c) Whether (+) gulose is a member of D-family or L- -mily?

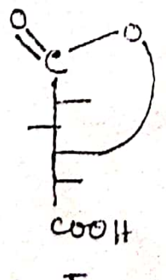
(d) Write down the configuration of D-galactose an L-galactose. How can you convert D-galactose to L -galactose?

Solution 6:

(a) Aldaric acid from D-glucose is

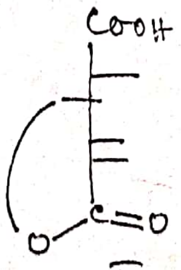


Thus two different γ-lactones from this aldaric ac



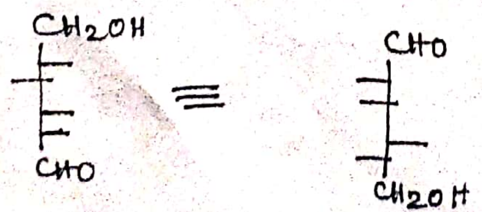
I

and

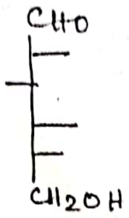


II

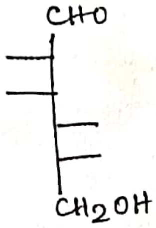
The γ-lactone I yields, L-gulose



nd The γ- Lactone II yields, D- glucose



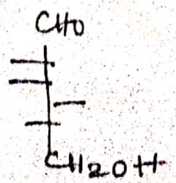
D- Mannose and D- Glucose differ with the change in Configuration at C2 - only. Thus the configuration of D-mannose is



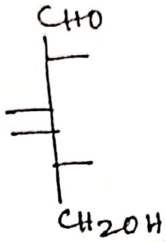
ow the aldaric acid from D- mannose is

ow Lactonisation may occur in two ways but yields ingle lactone which is

(+) gulose is a member of L- family



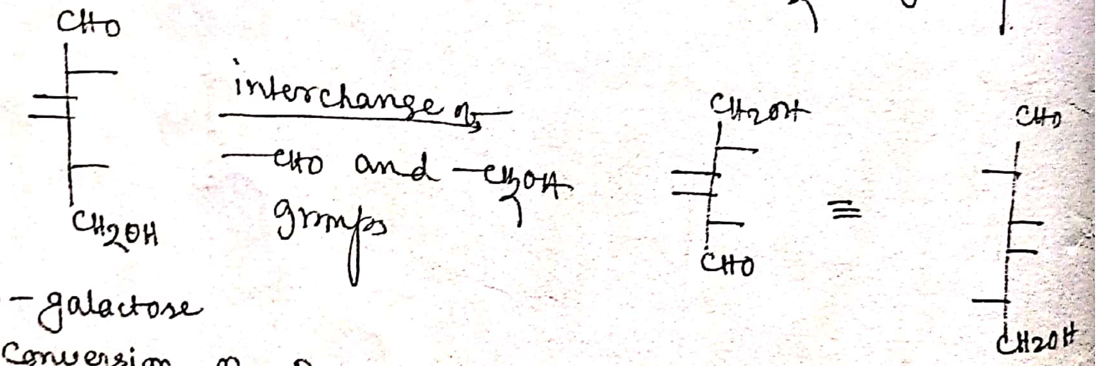
(d)



D-galactose

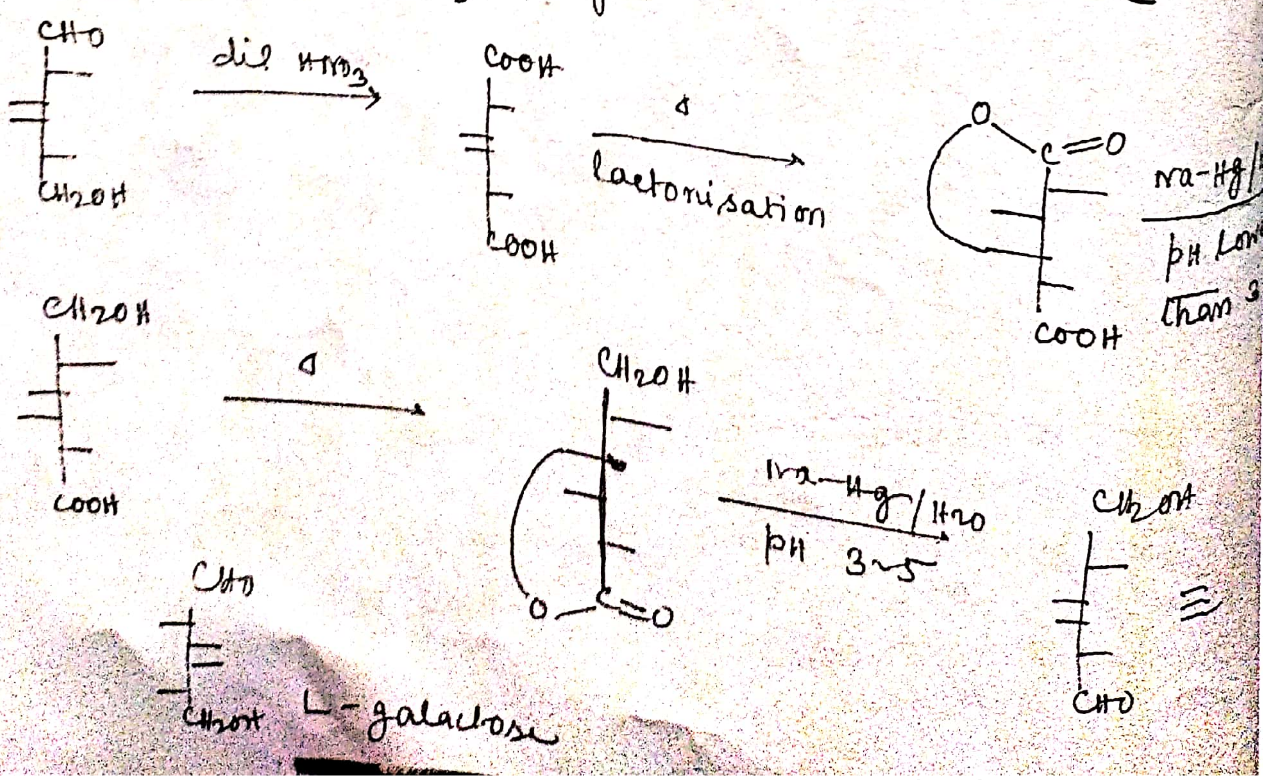
L-galactose

Now if we take a close look on the Configuratio D-galactose and L-galactose we find that they di with the interchange of $-CHO$ and $-CH_2OH$ groups.



D-galactose

Thus the Conversion of D-galactose to L-galactose involves the following steps: L-gal



L-galactose

CYCLIC STRUCTURE OF MONOSACCHARIDES

The open chain structure of D(+) glucose does not explain a number of observations. Some of these are given below.

[A] Glucose fails to undergo certain reactions typical of aldehyde.

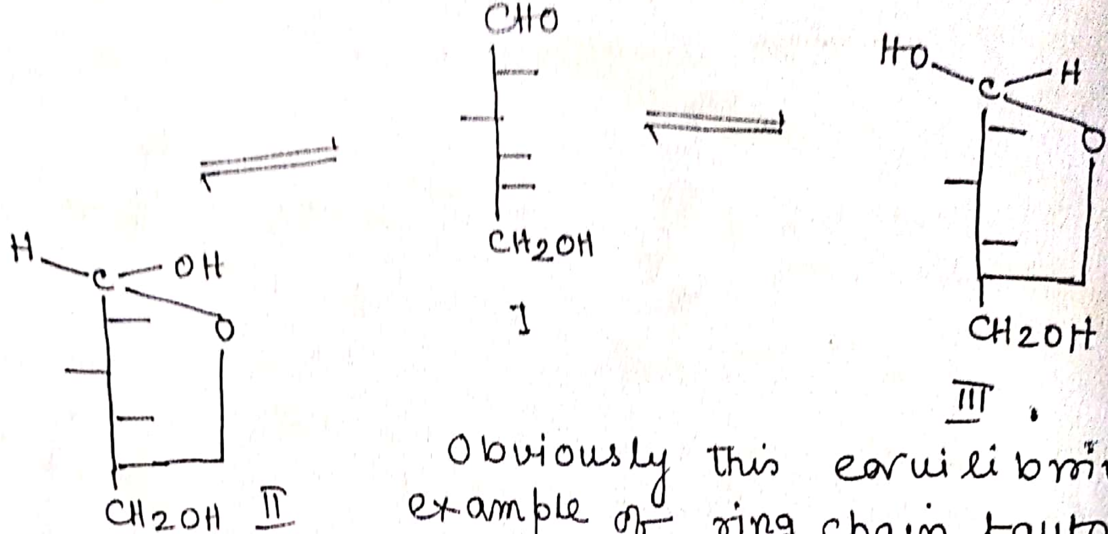
(i) Glucose does not give schiff's test for aldehyde
(ii) Glucose does not form an addition product with sodium bisulfite
(iii) Glucose pentaacetate does not react with hydroxyl amine to form oxime.

[B] D(+) glucose forms two isomeric methyl-D-glucosides on treatment with MeOH/HCl

[C] Aldehydes normally form acetals by combination with two molecules of a monohydric alcohols, glucose combine with one molecule of alcohol

[D]. Natural D(+) glucose is dextrorotatory and has a specific rotation of $[\alpha]_D = +112^\circ$ in aqueous solution, when this aqueous solution is allowed to stand at room temperature, the sp. rotation gradually decreases and finally becomes static at $[\alpha]_D = +52.5^\circ$. This phenomenon is known as mutarotation. Aldohexose structure of D(+) glucose with rigid chiral centres can not account for this phenomenon.

To explain this, (+) glucose in aq. solution is considered to be the equilibrium mixture of I, II & III

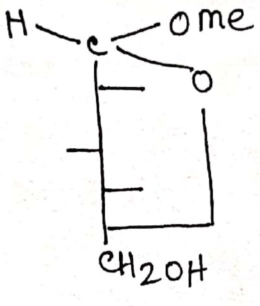


Obviously this equilibrium is example of ring chain tautomeris now with this we can explain above facts in the following way.

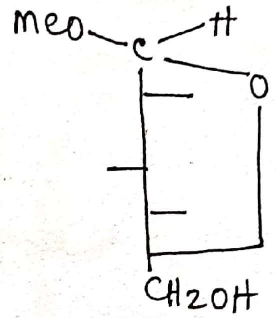
(a) The typical aldehyde reactions of (+) glucose—cyanohydrin formation, the osazone formation, the Br_2/H_2O oxidation — are presumably due to small amount of open chain form, which regained as fast as it is consumed. The concentration of this open chain structure however, too low (less than 0.5%) for certain reversible aldehyde reactions like bisulph addition and the schiff's test.

(b) The two forms of (+) glucose are II & III — wh are diastereoisomeric with the change in configuration at C_1. So these have different mps and sp. rtn. Again when either form dissolved in water we get an equilibriu mixture of I, II & III and thus mutarotat results.

(c) now II & III are intermolecular hemiaceta corresponding to the reaction between the aldehyde group and C-5 hydroxyl group of the open chain structure-1. So for the formation of acetal only one methoxy group will be introduced. So, two isomeric products during the treatment with MeOH / dry HCl on (+) glucose are



(A)

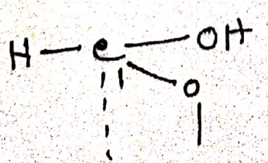


(B)

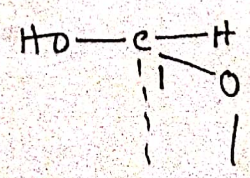
α and β- Anomer : All common monosaccharides exist in two forms: either six membered cyclic hemiacetals or hemiketals or, five membered cyclic hemiacetals or hemi ketals. These are diastereoisomeric called **ANOMERS**. The two stereoisomeric ring-forms of a sugar are often referred to as anomers.

Now the question is which one is α-anomer and which one is β anomer? C. S. Hudson made the following proposal.

Of an α, β pair of sugars in the D-series, the α-anomer, which has the higher dextro-rotation has the hydrogen to the left; the β-anomer consequently has the hydrogen atom to the right.



α- anomer



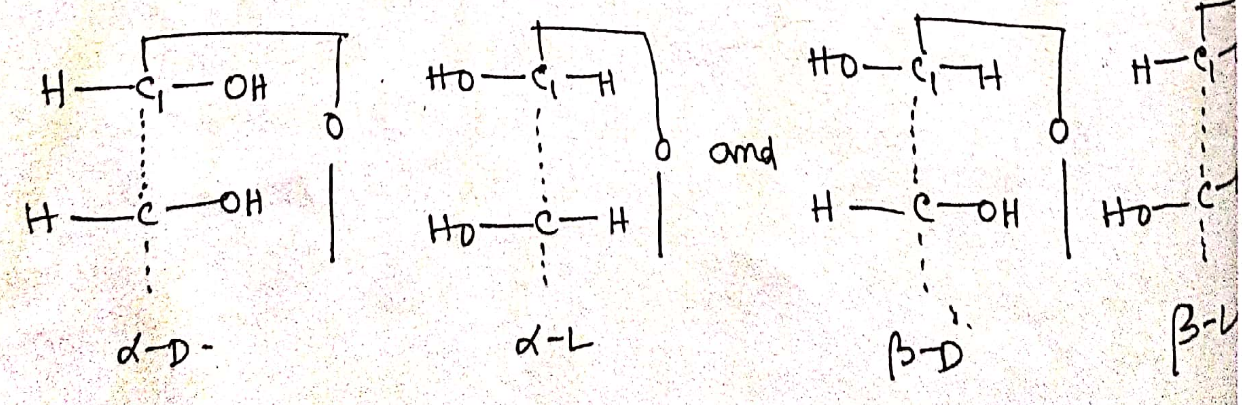
β-anomer

Thus, α-D(+) glucose is the anomer with the s rotation +111°, and β-D(+)-glucose is the anomer with the specific rotation +19.2°.

If the D-sugar has a negativ rotation, then, according to the emperical rule, β-anomer has the higher negative rotation (i.e. less ⊕ve rotation). Thus, α-D(−) fructose is the ano with the specific rotation −20°, and the β-anomer −

In the L-sugars, the α-anomer the one with the higher laevorotation, and the other β-anomer; thus the α-forms (and the β-forms) of D- and L-series are enantiomers.

It has been pointed out abo that the two anomers of a D-sugar are enantio of the corresponding two anomers of the L-sugar. This means that the configurations at C-1 are al mirror images, and consearuently the configuration C-1 in an α-D-aldose (C_1—H to the left) is identical that of the β-L-aldose (C_1—H also to the left).



Glycosides: Sugars, in their ring-forms, react with a molecule of an alcohol to form the acetal derivative, which is known under the generic name of glycoside: Those of glucose are known as glucosides; of fructose, fructosides, etc. The hydroxyl group produced at the oxo group by ring formation is known as the glycosidic hydroxyl group. The non-sugar part of a glycoside is known as the agycon (or aglycone).

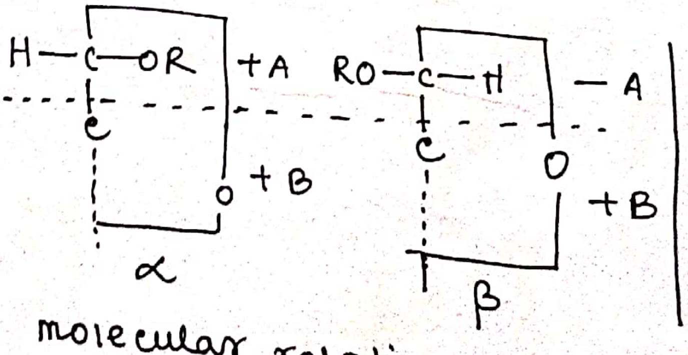
Hudson's isorotation rules:

Hudson applied the rule of optical superposition to carbohydrate chemistry, and his first application was to the problem of the configuration of C-1 in the anomers of aldoses. Hudson pointed out that the only structural difference between the α- and β- anomers (of sugars and glycosides) is the configuration of C-1. Thus representing the rotation of this terminal group as A and that of the rest of the molecule as B, and then taking the α-anomer as the one with the higher ⊕ve rotation (in the D- series) we have,

Rule of Optical Superpos

when a compound contains or more chiral centres, the optical rotatory power of molecules is the algebr of the contributions of eac centre. This rule is base the assumption that the co -bution of each chiral cen is independent of the o chiral centres present. assumption however is usu satisfactory only when th chiral centres are far a

A more satisfactory the Rule of Shift or th Displacement Rule. If chiral molecules A and are changed in the same structurally to give A' an then the differences in molecular rotations (A and (B' are of same s



molecular rotation of the α-anomer

$+A$

molecular rotation of the β-anomer

$-A+$

Thus in every pair of α and β- anomers the following rules will hold.

Rule 1 : The sum of the molecular rotations (2B) will be a constant value characteristic of a particular sugar and independent of the nature of R.

Rule 2: The difference of the molecular rotations (2A) will be a constant value characteristic of R.

In the sugars, however, the rotation of C-1 is affected only to a small extent by changes in the rest of the molecule, and vice versa. This is illustrated in the following table, from which it can be seen that the sum of the molecular rotations (2B) for various pairs of glucopyranoside anomers is fairly constant

C-1	M_α	M_β	$M_\alpha + M_\beta = 2B$
—OH	+202	+34	+236
—OMe	+309	−66	+243
—OEt	+314	−69.5	+245.5

These isorotation rules have been used to ascertain which of an anomeric pair of glycosides is α and which is β, and to determine the type of glycosidic link in disaccharides and polysaccharides.

Problem : A certain sugar and its methyl glycoside can be isolated in both α and β-anomeric forms. Also the ring structure of the glycoside is known to be present in the pyranose form. How could you ascertain ~~form~~ from rotation data whether or not the parent sugar also exists in pyranose form.

Solution: A monosaccharide and its glycosides c
Several chiral centres. The molecular rotation of Th
Compounds is the sum of each of the individual r
-tions of the asymmetric Carbons. Thus for an αD-
aldohexose in pyranose form having five chiral

$$[M_s]_\alpha = A + B + C + D + E$$

Where A represents the rotation for anomeric Carbon. Thus for the β-anomer

$$[M_s]_\beta = -A + B + C + D + E$$

Now for α-glycoside in pyranose form:

$$[M_g]_\alpha = A' + B + C + D + E$$

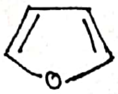
Where A′ represents the rotation for anomeric Carbon. Thus for the β-anomer of glycoside in pyranose form

$$[M_g]_\beta = -A' + B + C + D + E$$

Therefore, if the α and β-anomeric forms the glycosides and their parent monosaccha are all in pyranose forms the sum $[M]_\alpha + [M]_\beta$ will be the same for the monosaccharide and its glycosides.

Pyranose and Furanose form

Five membered cyclic anomer is known as furanose and six membered cyclic anomer is known as pyranose. These names comes from the names of the oxygen containing heterocycles furan and pyran

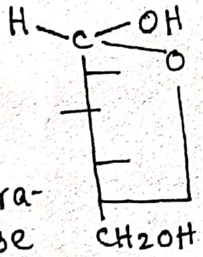


Furan

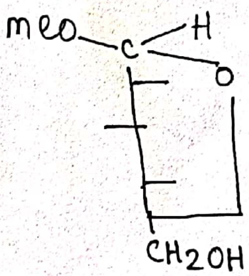
When a monosaccharide is treated with ROH | dry HCl we get a cyclic acetal or ketal with the introduction of –OR group in place of anomeric hydroxyl group. These are known as glycosides:

If it is six membered one it is called pyranoside.
If it is a five membered one it is called furanoside.

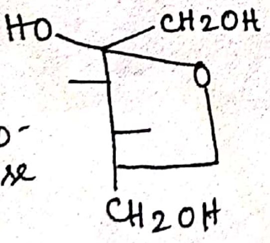
Thus;



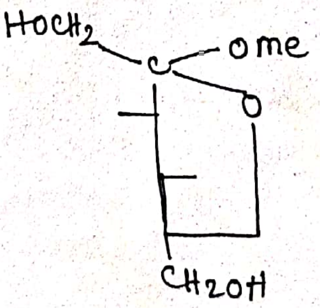
α-D-glucopyra-nose



β-methyl-D-glucopyranoside

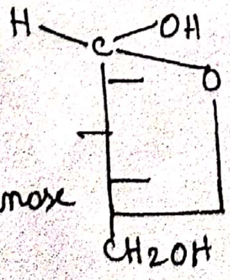


β-D-fructo-furanose



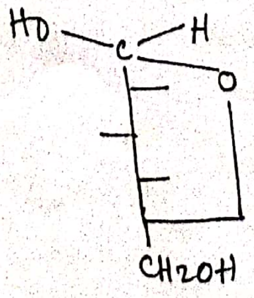
α-methye-D-fructofuranoside.

Now we have two glucopyranoses



-D-glucopyranose

Ⓐ

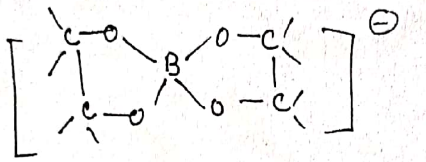


Ⓑ

β-D-glucopyra-nose

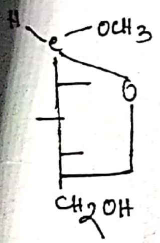
for The two forms (i) one with m.p. 146° and sp. rotation +112°
(ii) Another with m.p. 150° and sp rotation +19°

(A) is α-D-glucopyranose and B is β-D-glucopyranose. Now the question is how can we prove it? we know that cis-glycol with boric acid forms a highly conductive solution due to the formation of following complex

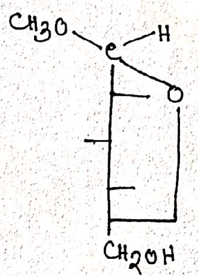


Now when (A) is added to boric acid the conductivity of the solution is very high which gradually decreases. Thus (A) is α-anomer as here C_1 & C_2 hydroxyl groups are cis orientation where as B is β-anomer as here C_1 & C_2 hydroxyl groups are in trans orientation.

Now we have two methyl glucopyranosides



α-methyl-D-glucopyranoside
(x)



β-methyl-D-glucopyranoside
(y)

of the two forms (i) one with mp 165°C sp. rotation +158° (x)
(ii) Another with mp 107°C sp. rotation −33° (y)

(x) is α-anomer and (y) is β-anomer. How can we prove it?

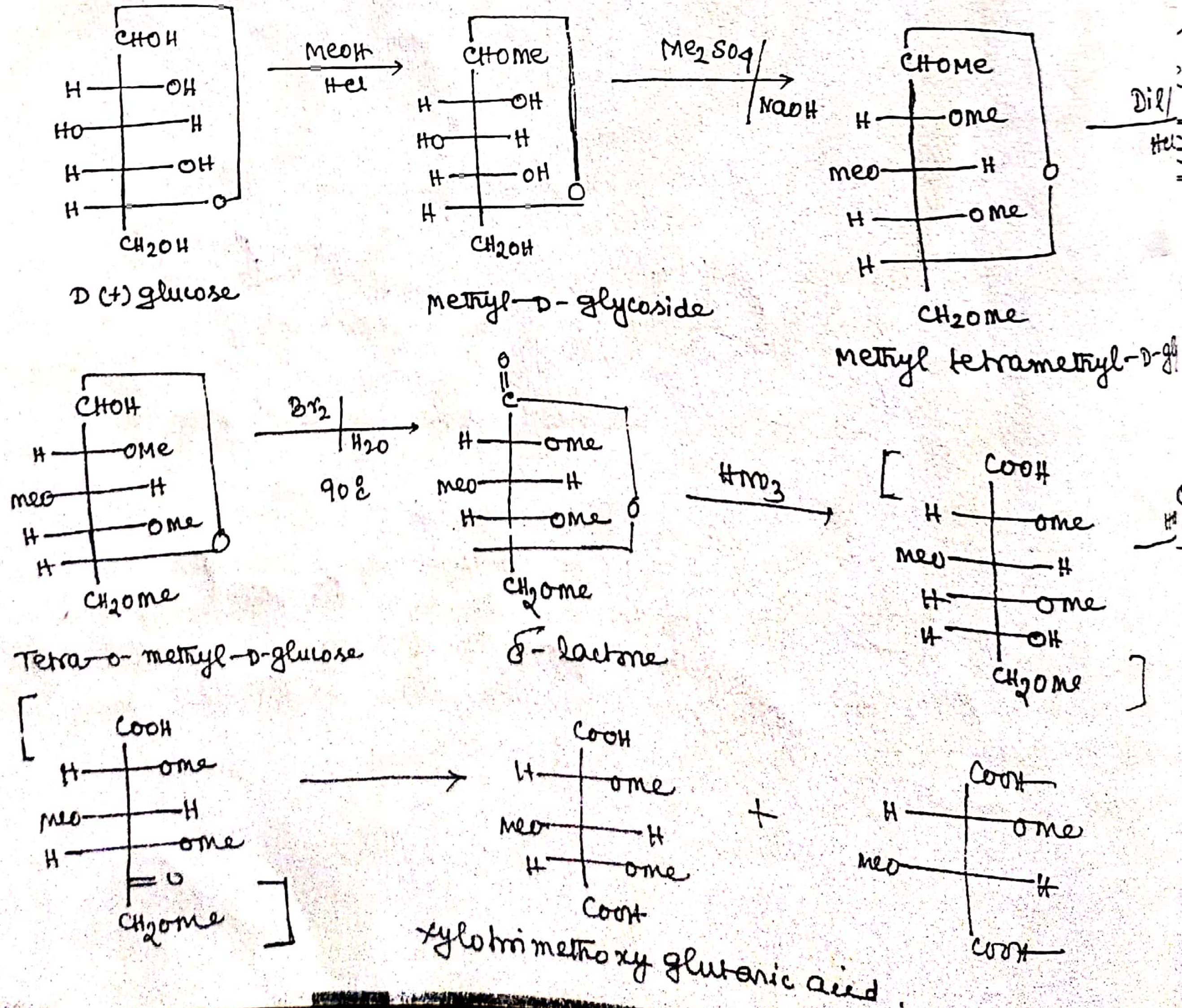
Fischer Enzymatic method:

The method is based upon the specificity of certain enzymes in promoting the hydrolysis of glycosides. The enzyme maltase effects the hydrolysis of only the methyl α-D-glu- oside, while the enzyme emulsin effects the hydrolysis of only methyl β-D-glucoside. Thus maltase and emulsin are wn as α and β-glucosides respectively.

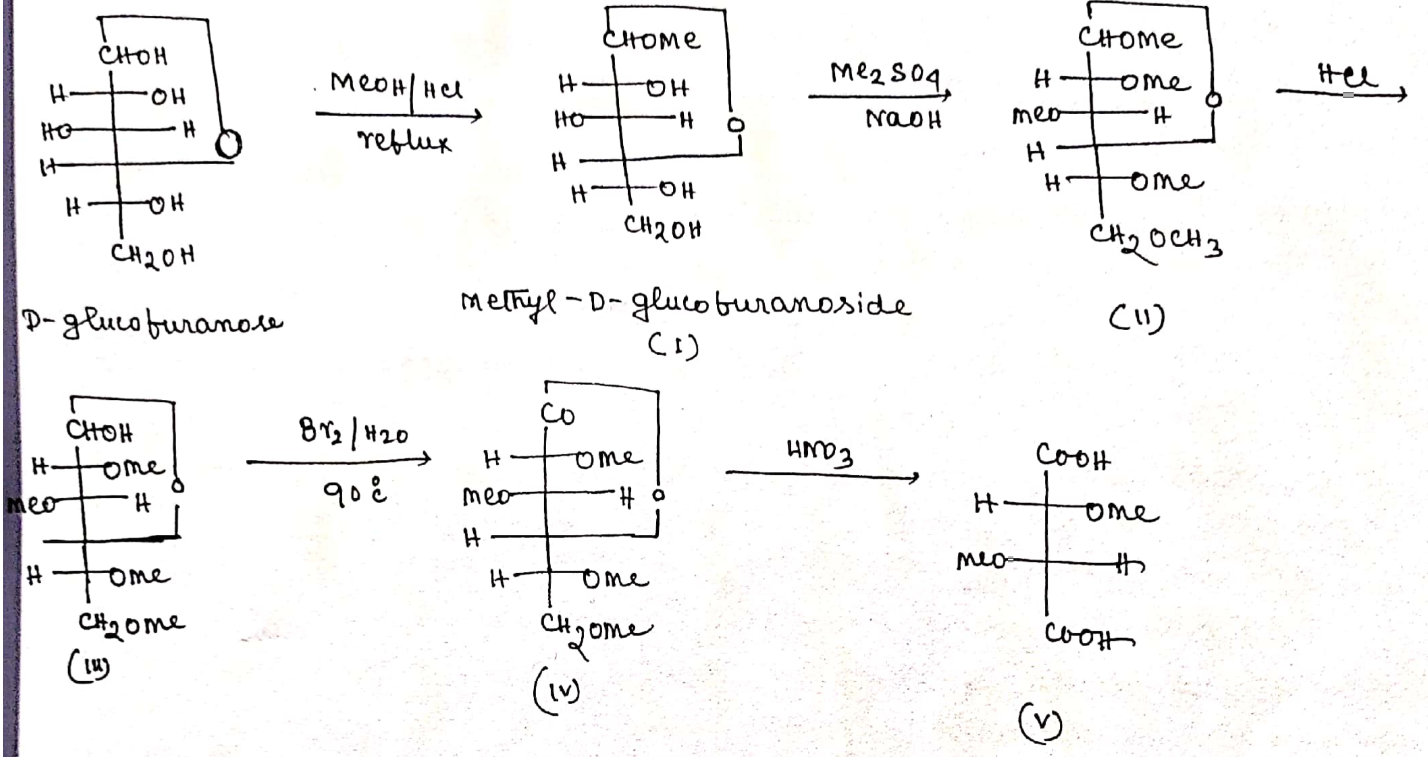
DETERMINATION OF RING SIZE

Haworth's method: Pyranose structure

D(+) glucose is refluxed in MeOH/HCl, the product is methyl glycoside. It is then methylated with Me_2SO_4/NaOH to get me tetramethyl-D-glycoside. This on hydrolysis with dilute HCl, gi tetramethyl-D-glucose. Tetramethyl-D-glucose on oxidation wi bromine in aqueous medium produces a lactone, whic further oxidation with HNO_3 gives xylotrimethoxy glutaric acid: active dimethoxy succinic acid. In actual experiment trim glutaric acid has been isolated as one of the products oxidation. The isolation of this product conclusively establis the location of ketonic group at C_5. It must, therefore, be position C_5 that is involved in the hemiacetal ring of original β-D-glucose.



Furanose structure



D-glucofuranose

Methyl-D-glucofuranoside (I)

(II)

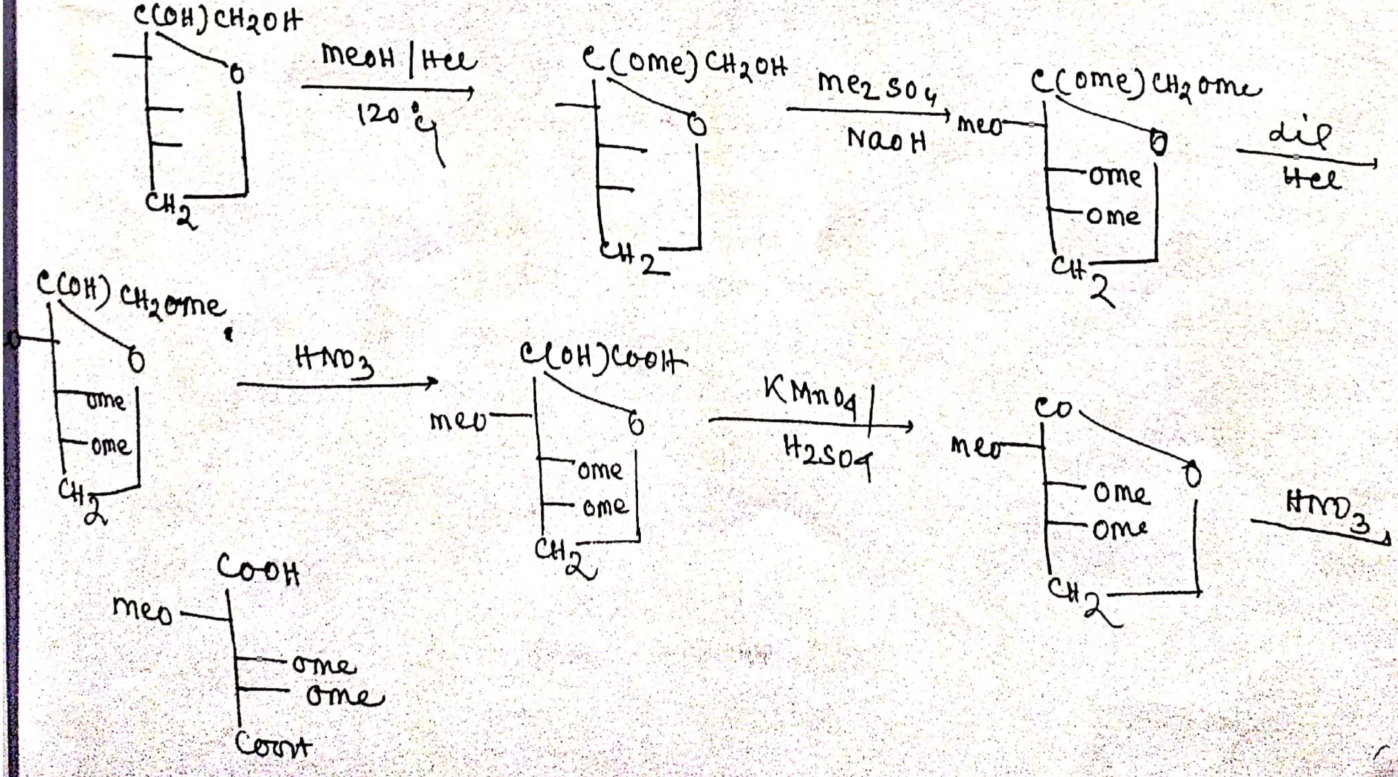
(III)

(IV)

(V)

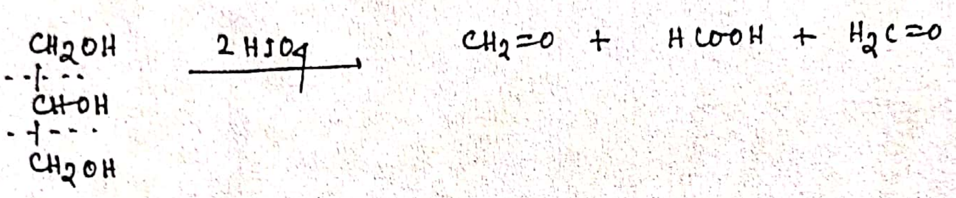
The compound (V) is the only compound of known structure and is therefore the key to the determination of the size of the ring in the sugar. working backward we may conclude that D(+) glucose has the furanose structure.

D(-) Fructopyranose

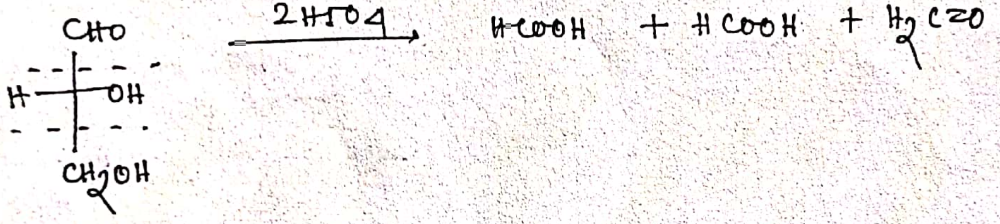


OXIDATION BY $NaIO_4$ AFTER THE FORMATION OF METHYL GLYCOSIDES: Hudson's method:

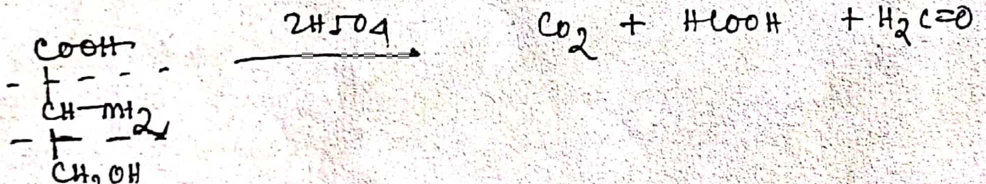
This method is based on the fact that periodic splits the compounds having hydroxyl groups, oxo groups, amino on the adjacent carbons: Thus:



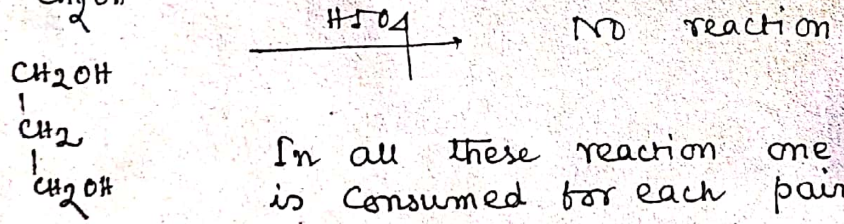
$$CH_2OH-CHOH-CH_2OH \xrightarrow{2\,HIO_4} CH_2=O + HCOOH + H_2C=O$$



$$CHO-CH(OH)-CH_2OH \xrightarrow{2HIO_4} HCOOH + HCOOH + H_2C=O$$



$$COOH-CH(NH_2)-CH_2OH \xrightarrow{2HIO_4} CO_2 + HCOOH + H_2C=O$$



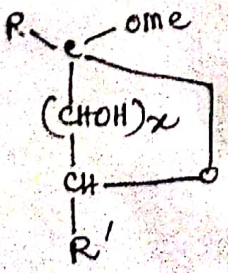
$$CH_2OH-CH_2-CH_2OH \xrightarrow{HIO_4} \text{No reaction}$$

In all these reaction one equivalent of HIO is consumed for each pair of adjacent gro

Thus by estimating the periodic acid consumed and from the nature of products the structure of the compound can ascertained.

Thus in the Hudson's method after the formation methyl glycoside i.e. after locking the ring the product is treated with $NaIO_4$. Obviously then from the consumption of the number of moles of $NaIO_4$ and from the nature the product it is possible to determine the ring size.

Thus;



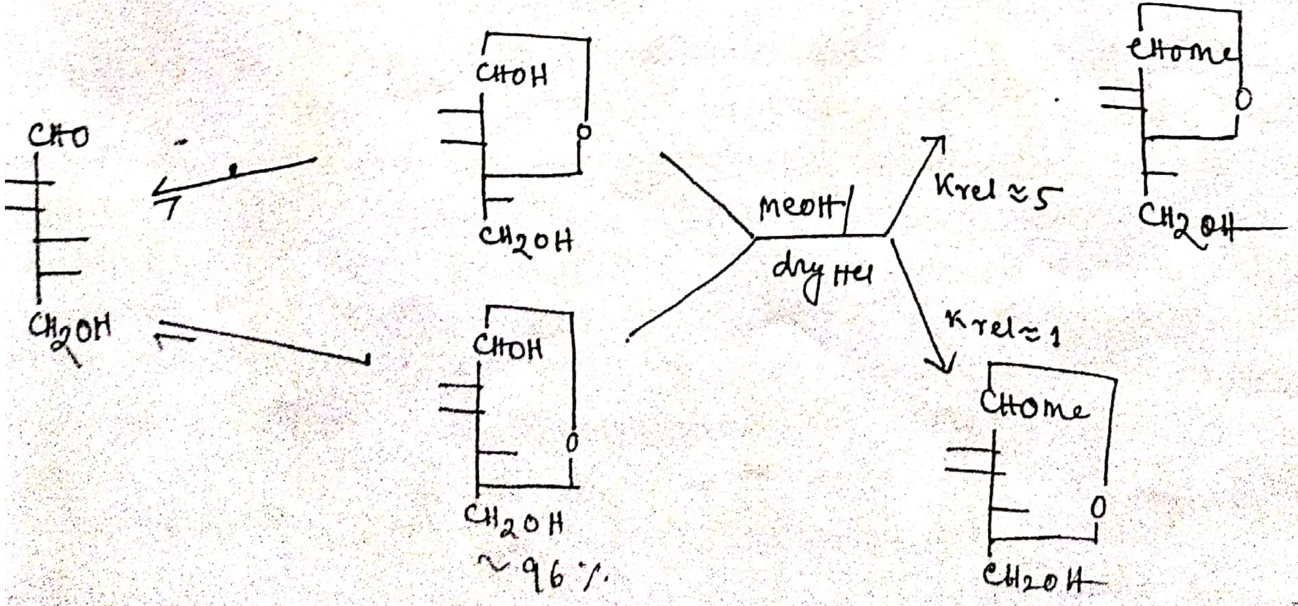
	x	HIO_4	H_2CO	HC
$R = R' = H$	3	2	X	1M
$R = CH_2OH$, $R' = H$	3	2	X	1M
$R = H$, $R' = CH_2OH$	3	2	X	1M

6- membered ring

	x	HIO_4	$H_2C=O$	$HCOOH$
R= H R'= -CH_2OH	2	1	✗	✗
R = CH_2OH = R'	2	1	✗	✗
R = CH_2OH R'=H	2	1	✗	✗
R = H R' = -$CHOHCH_2OH$	2	2	2 mole	✗

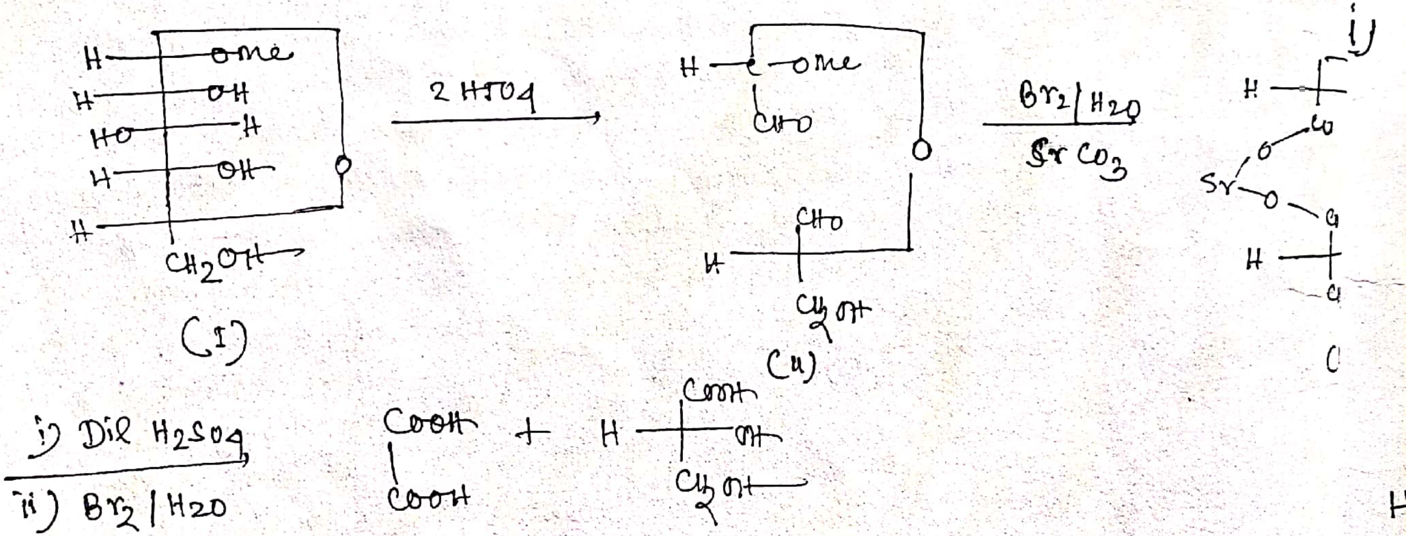
5- membered ring

In our study so far we have noted that during the determination of ring size of a monosaccharide we have locked the ring through the formation of methyl glycoside. Again during the formation of methyl glycoside the ring is locked either in pyranoside form or in furanoside form depending upon the reaction condition. Actually five membered ring formation is kinetically controlled and six membered ring formation is thermodynamically controlled. Thus strictly speaking the above ring size determination is actually the ring size determination of methyl glycoside of monosaccharide rather than the ring size determination of a monosaccharide itself. However most common monosaccharides exists in the pyranose form at equilibrium. Thus, D- Mannose for example, for example, cyclizes to methyl furanoside about 5 times faster than the pyranoside is formed even though the six membered ring accounts for over 96% of the equilibrium mixture.



The Configuration about C_1 and C_5 is the same in methyl pyranosi of all α-D-hexoses: Proff

Hudson subjected methyl α-D-glycoside (I) to HIO_4 or and found that two molecules of HIO_4 were consumed and o molecule of HCOOH was produced. But the most important is the dialdehyde (II). Dialdehyde was then oxidise with Br_2/H_2O presence of $SrCO_3$ then a crystalline strontium salt (III) wa formed. Hydrolysis of (III) with dil H_2SO_4 followed by furthe oxidation with Br_2/H_2O gave oxalic acid and D(-) glyc acid (IV). Isolation of (II), (III), (IV) along with HCOOH and acid confirm that the ring in the methyl α-D(+) glucos a six membered ring.



It is interesting to note that all methyl pyranosides of normal type aldohexoses undergo simil type of HIO_4 oxidation resulting in the formation of sa products. This facts confirm that all these α-pyra-sides have six membered ring and also have iden configuration at C_1 and C_5 carbon atoms :- Formation of same dialdehyde (II) is practically important be it has two chiral centres which are originated from anomeric carbon atom (C-1) and the carbon atom of the parent glycosides.