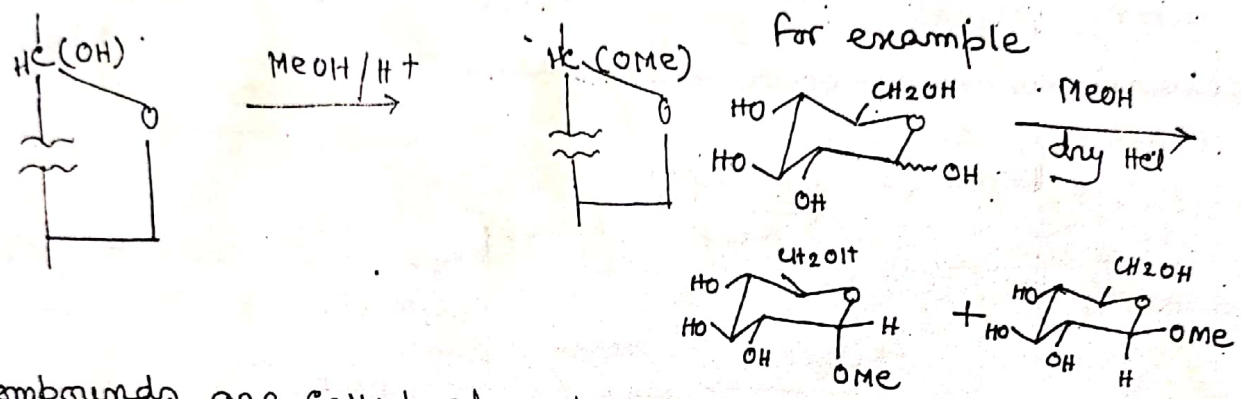
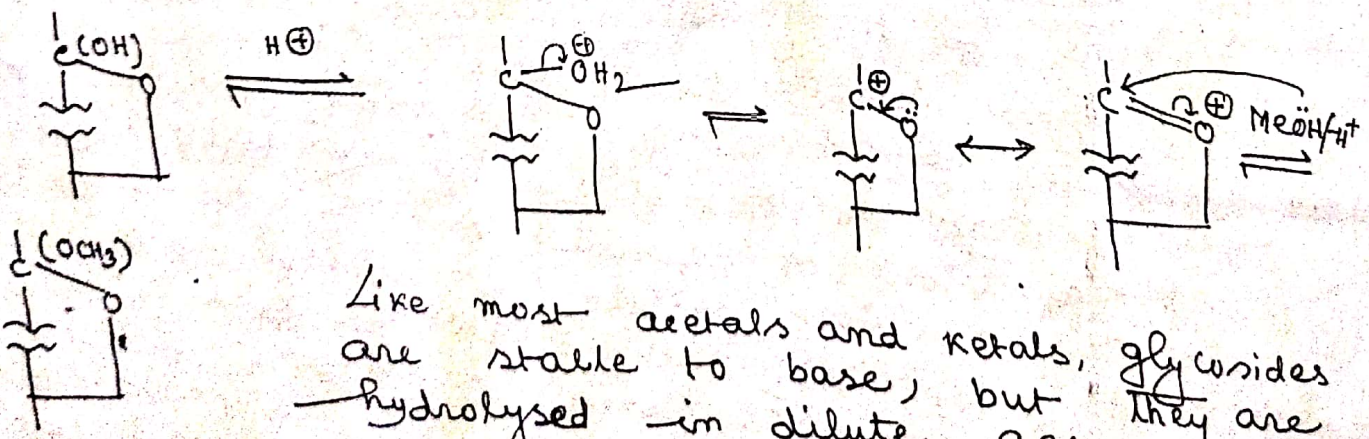
REACTION WITH ALCOHOLS

Monosaccharides react with alcohols under acidic conditions to yield cyclic acetals for aldoses and cyclic ketals for ketoses.

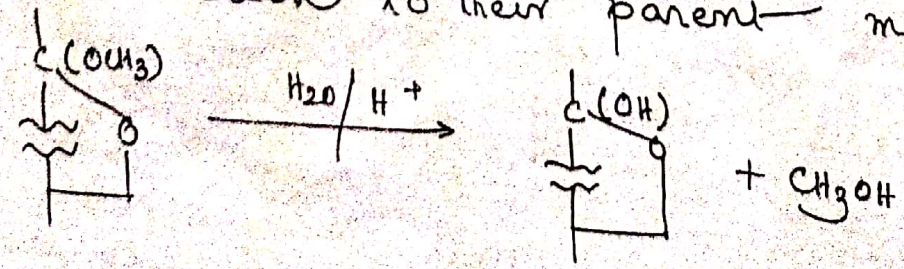


Such compounds are called glycosides. These are special type of acetals or ketals in which one of the oxygens of the acetal or the ketal linkages is the ring oxygen. During glycoside formation the ring size may be five membered or six membered which depends on the nature of monosaccharides and the reaction condition.

Glycoside formation, like acetal or ketal formation is catalysed by acid and involves the intermediate formation of highly stable carbocation.

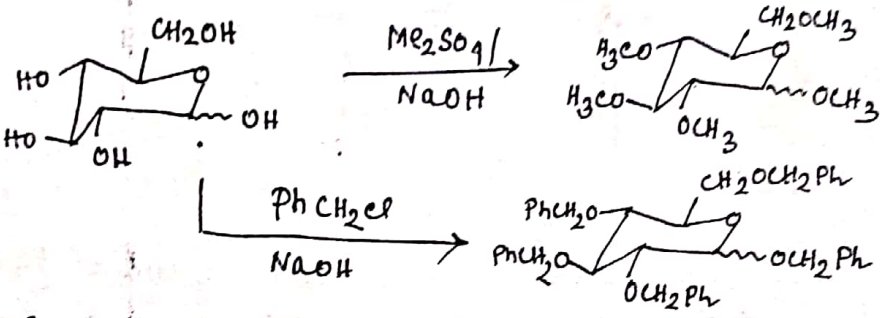


Like most acetals and ketals, glycosides are stable to base, but they are hydrolysed in dilute aqueous acid back to their parent monosaccharides.

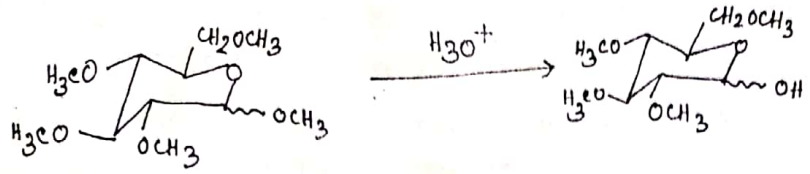


ETHER FORMATION:

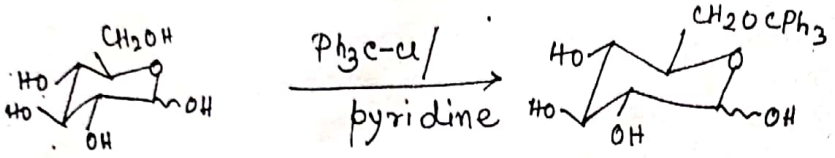
In the presence of Concentrated base, mo-saccharides are converted into ethers by reactive alk-lating agents. Dimethyl sulphate; methyl iodide and benz chloride are frequently used for this purpose. Thus;



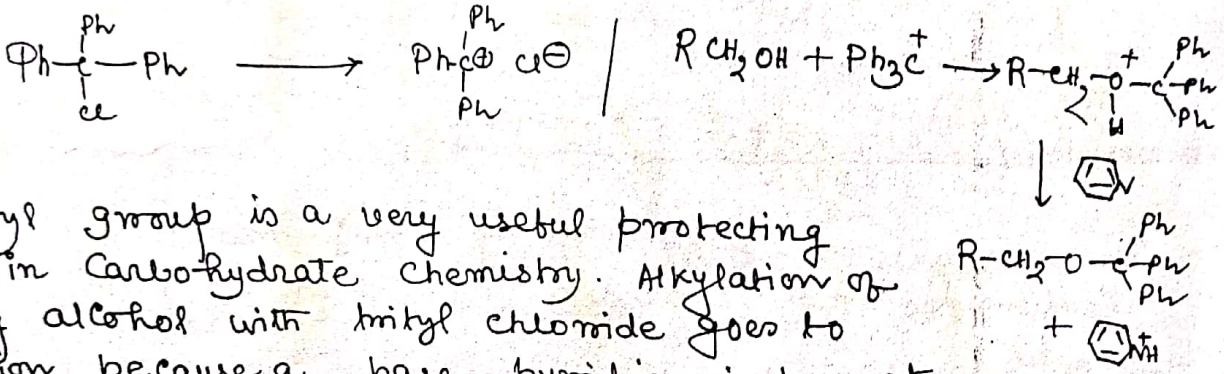
These reactions are the examples of the Williamson et synthesis. With most alcohols this reaction reauires a base stronger than ^-OH to form the Conjugate ba alkoxide. The hydroxyl groups of monosaccharide are therefore more acidic ($pK_a \times 12$) than that of ordinary alcohols. The higher acidity of the hydr-xyl groups of monosaccharides is attributable the inductive effect of the many neighbouring oxygens in the molecule and intramolecular hydrogen bonding stabilisation of alkoxide ic by the neighbouring hydroxyl groups. It is interesting that little or no base Catalysed epimerisation or degradation is observed here in this reaction despite the strongly basic Condition used. Evidently alkylation of the hydroxyl gr at the anomeric Carbon is much faster. It i important to distinguish the ether at anomer Carbon from the other ether groups in the alkylated monosaccharide. The ether at the ano meric Carbon is the part of glycosidic linkage and therefore hydrolysed in dilute aqueous acid. The other ethers are ordinary ethers and do not hydrolyse under these conditions.



When a monosaccharide is treated with trityl chloride in pyridine, trityl group is introduced selectively as an ether at primary hydroxyl group as it is less sterically hindered.

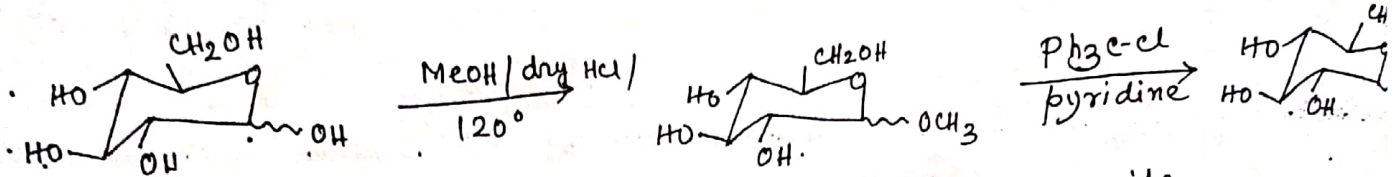


Reaction proceeds via an S_N1 pathway with the involvement of highly stable carbocation which is tertiary as well as benzylic one.



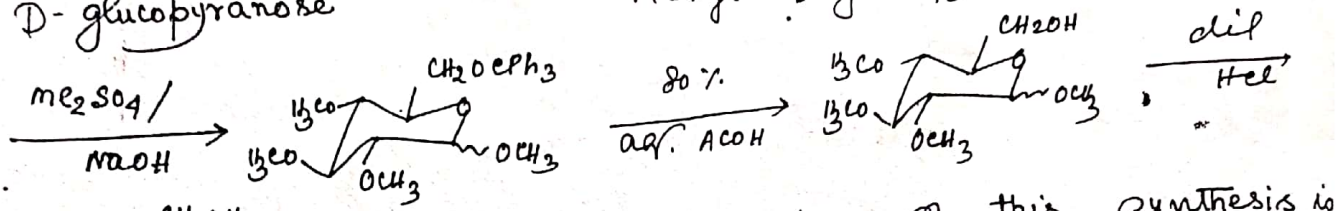
The trityl group is a very useful protecting group in carbohydrate chemistry. Alkylation of primary alcohol with trityl chloride goes to completion because a base pyridine is present to consume the liberated HCl. In the presence of acid, however, trityl ethers are readily cleaved by a mechanism that is essentially the reverse of the alkylation mechanism. Standard conditions for removal of the trityl group are either hydrogen bromide in acetic acid or 80% aqueous acetic acid. The latter conditions are especially useful because they do not affect most benzylic ethers. ~~On the other hand~~

Let us consider the following sequence of reactions which shows how a trityl group can be used as protecting group during the synthesis of 2,3,4-tri-o-methyl-D-glucopyranose.



D-glucopyranose

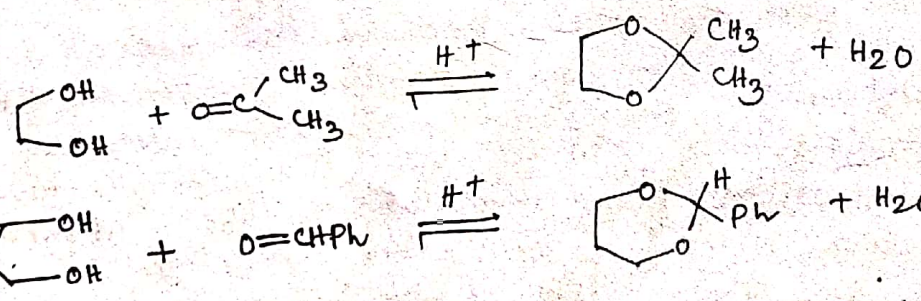
Methyl-D-glucopyranoside



Obviously the object of this synthesis is to alkylate all hydroxyl groups except those at Carbon-1 and Carbon-6.

ACETAL AND KETAL FORMATION

A dihydroxy Compound reacts with Carbonyl Compound under acidic condition to yield an acetal or ketal.



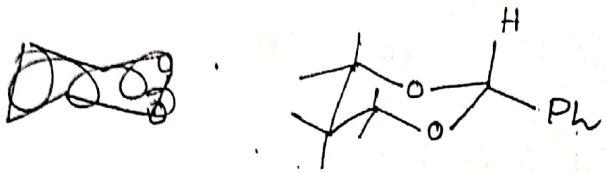
Now obviously monosaccharide and their derivatives act as sources of dihydroxy Compound. e.g;

(a) with benzaldehyde six membered cyclic acetal is formed ——— such a derivative is called — benzylidene derivative

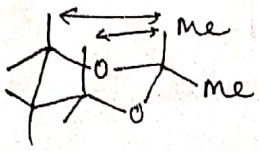
(b) with acetone five membered cyclic ketal is formed ——— such a derivative is known as isopropylidene derivative

This can be explained in the following way;

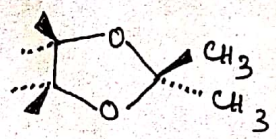
Since acetal/ketal formation is reversible in nature we do expect the formation of more stable product. Now six membered ring system is more stable than five membered one. Thus with benzaldehyde we get six membered ring acetal in which the phenyl group is at equatorial position.



Now with acetone in six membered ring there will be strong 1,3-diaxial interactions as at least one methyl will be at axial position.

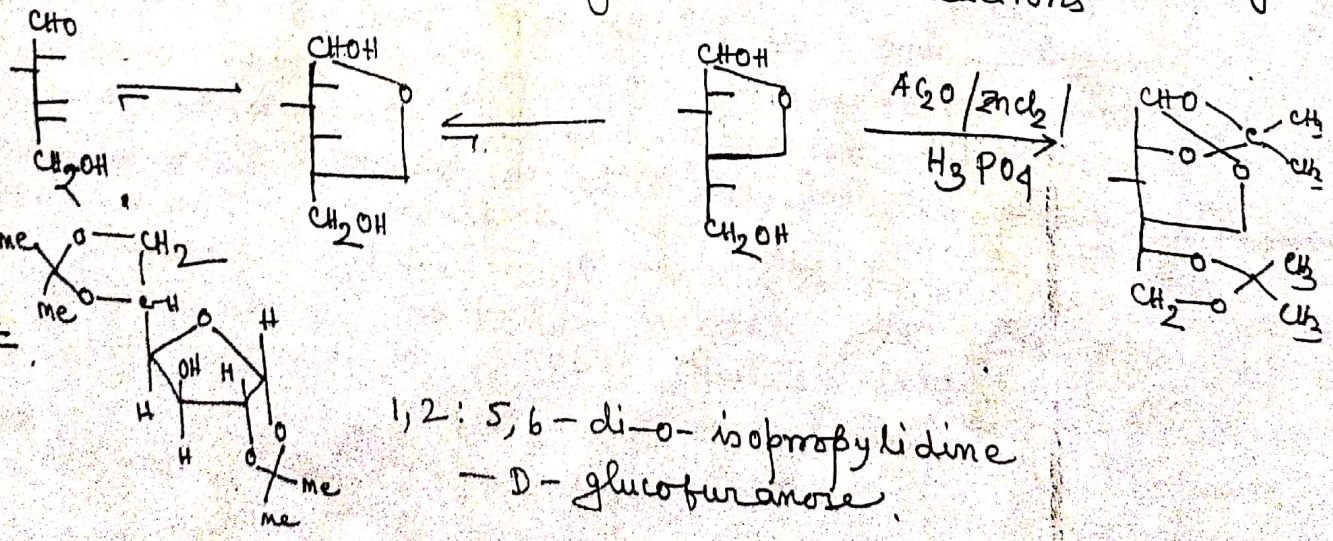


So with acetone we get five membered ring ketal

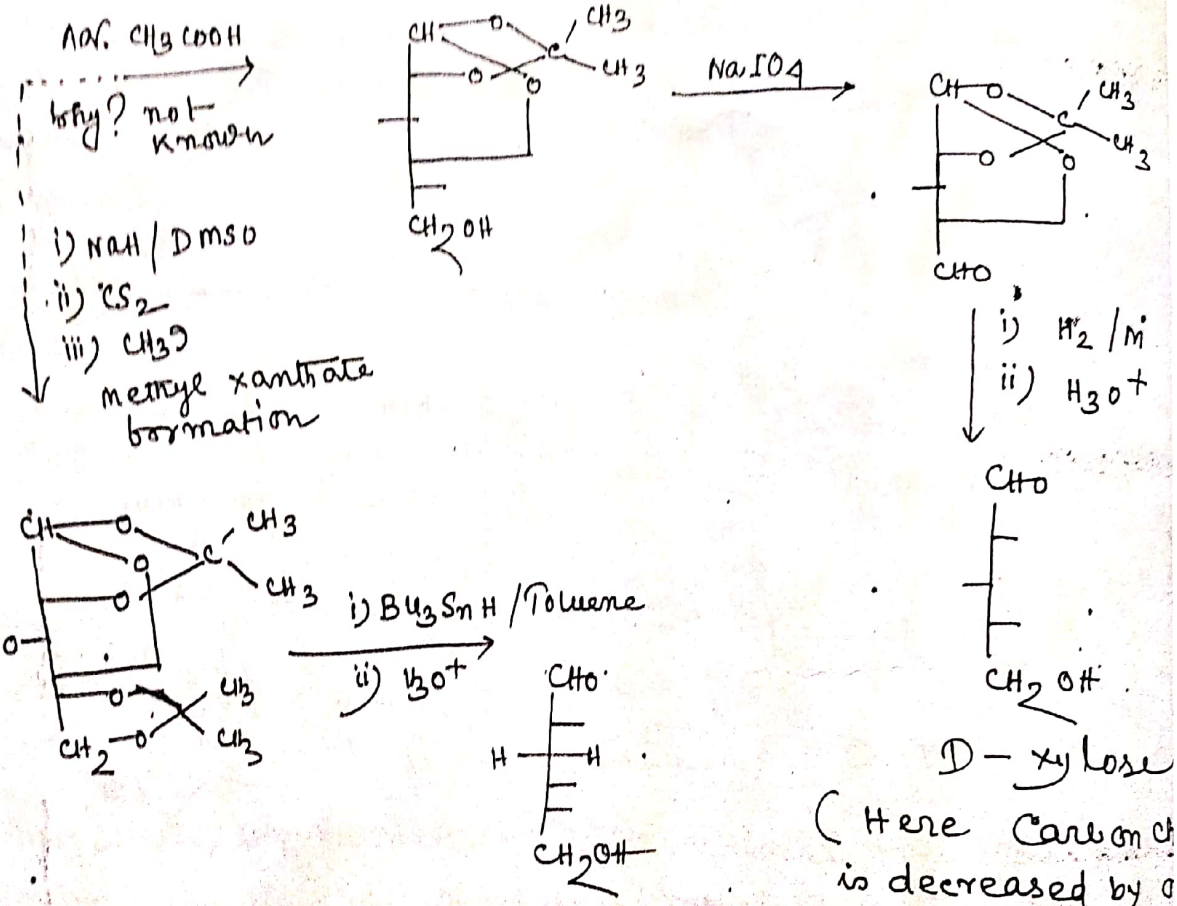


The acetal or ketal formation is used to block the hydroxyl groups of sugars and to carry out further reactions at other sites. Acetone nucleus or benzaldehyde nucleus can be removed via dilute acid treatment. Again benzaldehyde unit can be removed via hydrogenolysis. Let us consider the following series of reactions

(a)



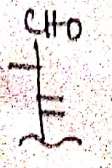
1,2 : 5,6 – di–o– isopropylidine – D – glucofuranose.



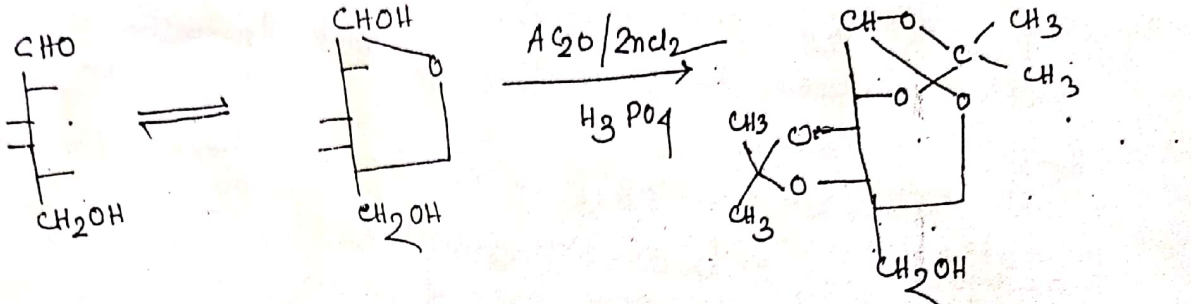
(Here Carbon ch
is decreased by o
unit from botto

As a result of much experimental work of the l
-going type, it has been found that acetone usua
Condenses with cis-hydroxyl groups on adjacent Ca
atoms, Condensation occuring in such a way as t
favour the formation of the diisopropylidine deriv
Because of this majority of aldoses form furanose
rather than pyranose derivatives. The reason
is not certain, but a widely accepted explan
is that the strain in two fused five mem
rings is less than that in fusion of a five
with a six ~~Six~~membered ring

However aldoses with D-ara
Configuration or L-arabino Configuration



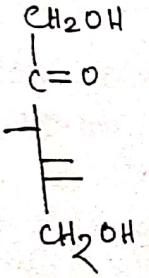
at C_2, C_3 and C_4 do react to give pyranose derivatives. Thus with D-galactose we have the following observation.



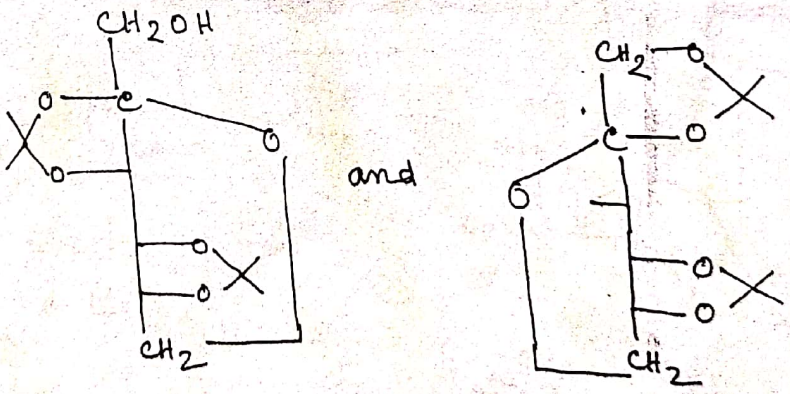
D-galactose

1,2:3,4 di-o-isopropylidine-D-galactopyranose.

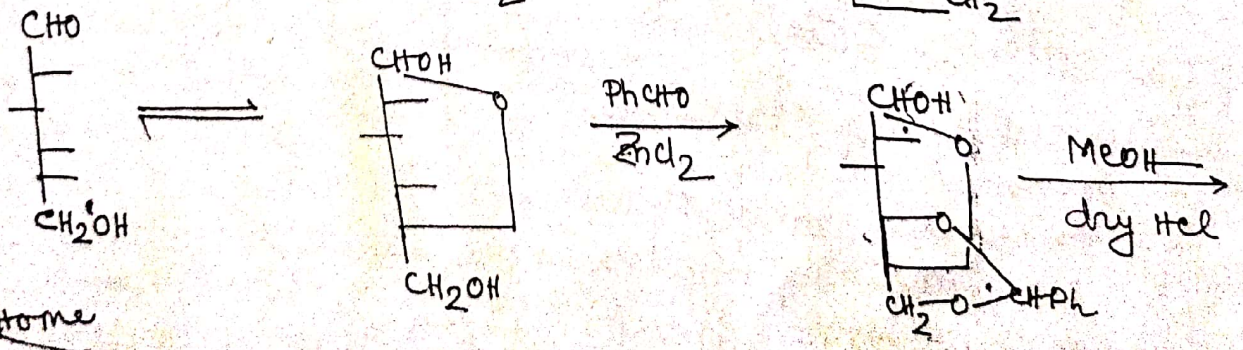
Again D-fructose



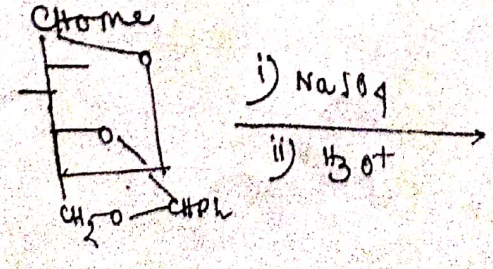
Can form two diisopropylidine derivative having pyranose ring.



(b)



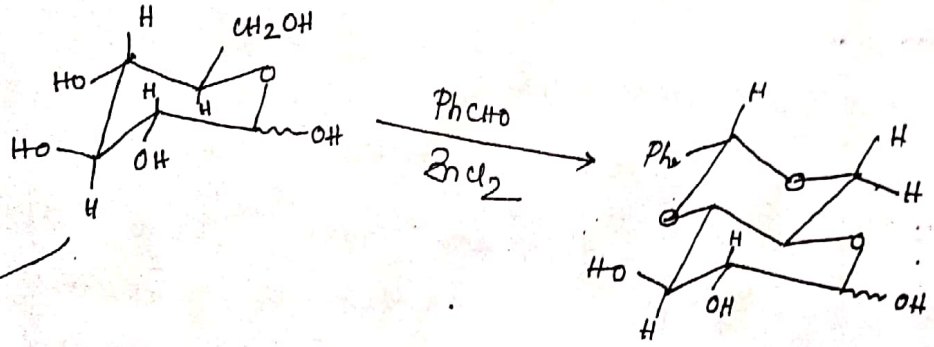
4,6-o-benzylidine-D-glucopyranose



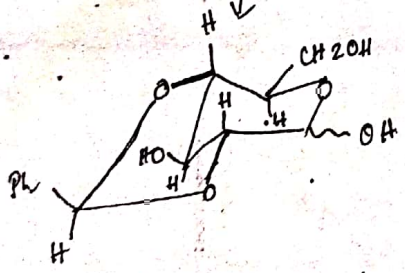
D-erythrose

(Here the Carbon chain is decreased by two units from the above)

Now during the formation of benzylidine derivati
C_4 and C_6 hydroxyl groups which are in 1,3 - relati
are involved but not C_2 and C_4 - hydroxyl group
Why? This can be explained from conformationa
analysis as obvious from the following figure:



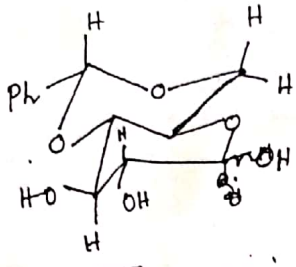
In such strain: $-CH_2OH$ group can not rotate for whi
the 4,6 - cyclic acetal can
form with its ring in
stable chair conforma



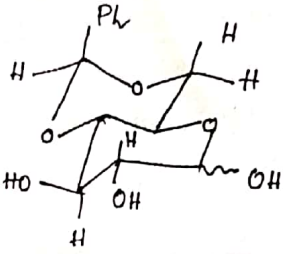
Highly strained;
acetal ring contains a
transoid bond in six
membered ring system —
1,3 - diequatorial arrangement
of hydroxyl groups can not
be bridged with a single
Carbon

Problem: In principle, two separable cyclic 4,6 - ac
can form when benzaldehyde reacts with D - glucos
Give their structures. only one of the two aceta
usually forms; which is it? why is the other comp
not formed in appreciable amount?

Solution: Two possible 4,6-cyclic acetals are



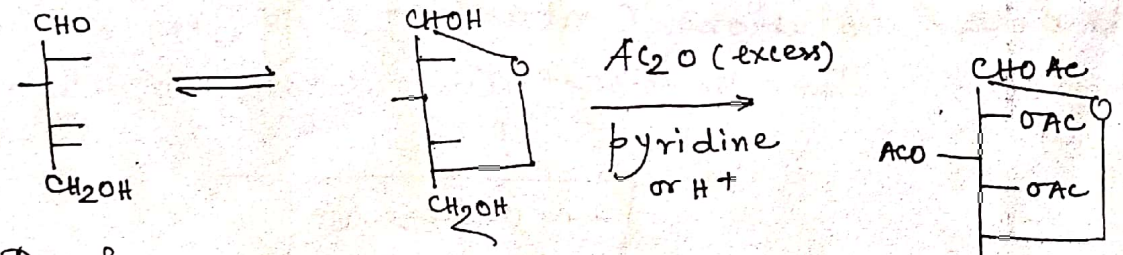
and



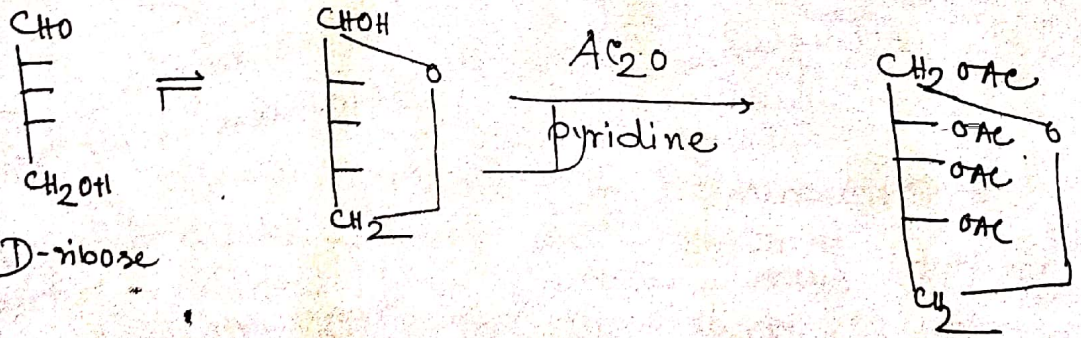
Obviously in first one Ph group is at the equatorial position and in second one Ph group is at the axial position. Now acetal formation is a reversible reaction. So we do expect the formation of more stable acetal. Thus first one is expected to be the actual product.

ESTER FORMATION

The hydroxy groups of a sugar, like those of other alcohols, can be esterified. Thus:

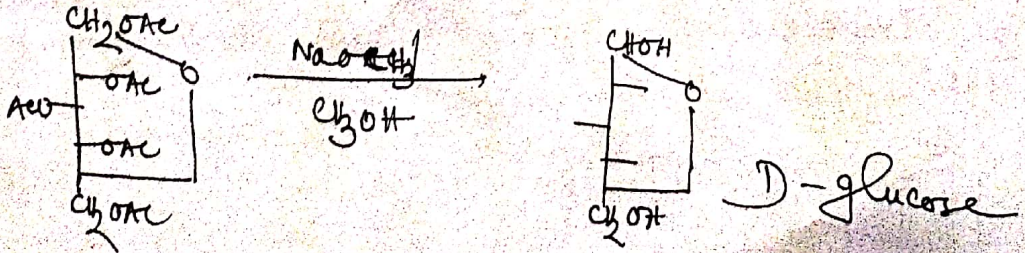


D-glucose



D-ribose

These ester can be saponified in base or removed by transesterification with an alkoxide such as methoxide



D-glucose

Oxidation of monosaccharides:

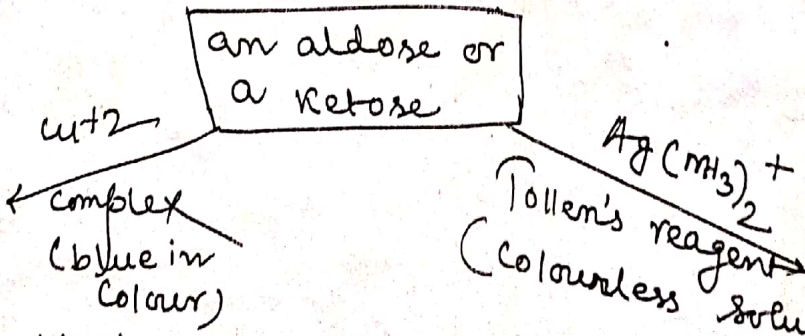
The most important oxidation methods are

(i) Benedict Solution, Fehling's solution and Tollen's Reag
(ii) Bromine Water (iii) Dilute nitric acid iv) Periodic

Each of these reagents produces a different usually specific effect when it is allowed to rea with a monosaccharide.

Oxidation by Benedict / Fehling's solution and Tollen's Re

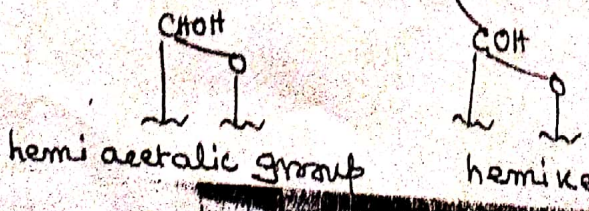
Benedict Solution is an alkaline solution containing a cupric citrate complex. Simil Fehling's solution is an alkaline solution conta a cupric tartarate complex. Tollen's reagent is alkaline solution containing $Ag(NH_3)_2^+$. These three reagents can oxidise an aldose or a ketose:



Cu_2O + oxidation products (brick red ppt)

Ag + oxidation products (mirror or grey ppt.)

Sugars that give positive tests with these reage are known as Reducing sugars, and Carbohydrates Contain a hemiacetalic group or hemi ketalic group positive tests.



hemi acetalic group hemiketalic group.

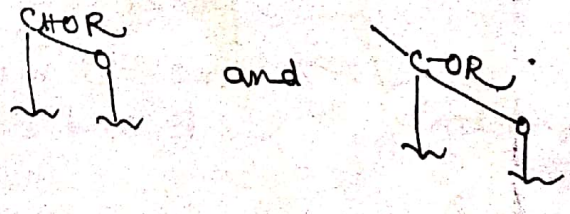
In aqueous solution these hemiacetals or hemiketals exist in equilibrium with relatively small, but not insignificant, concentrations of monocyclic aldehydes or α-hydroxy ketones. It is the latter that undergoes the oxidation, perturbing the equilibrium to produce more aldehyde or α-hydroxy ketone, which undergoes oxidation and so forth, until one reactant is exhausted.

Carbohydrates that contain only acetal or ketal groups do not give positive tests with Benedict's Solution or Fehling's Solution or Tollen's Reagent and they are called 'non-reducing sugars'. This is due to the fact that acetals or ketals do not exist in equilibrium with aldehydes or α-hydroxy ketones in the basic medium of the test reagents.

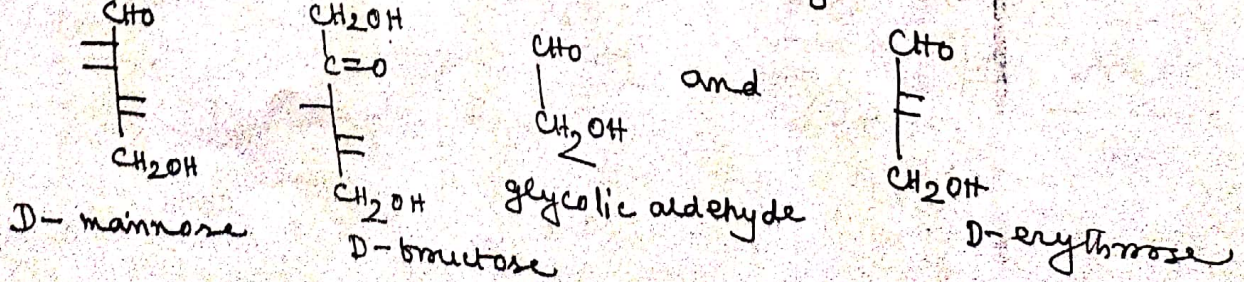
Thus,

Reducing Sugars:

Non-reducing sugars



Problem-1 If D-glucose is treated with aqueous $Ca(OH)_2$ and the solution is allowed to stand for several days, a mixture of products results, including

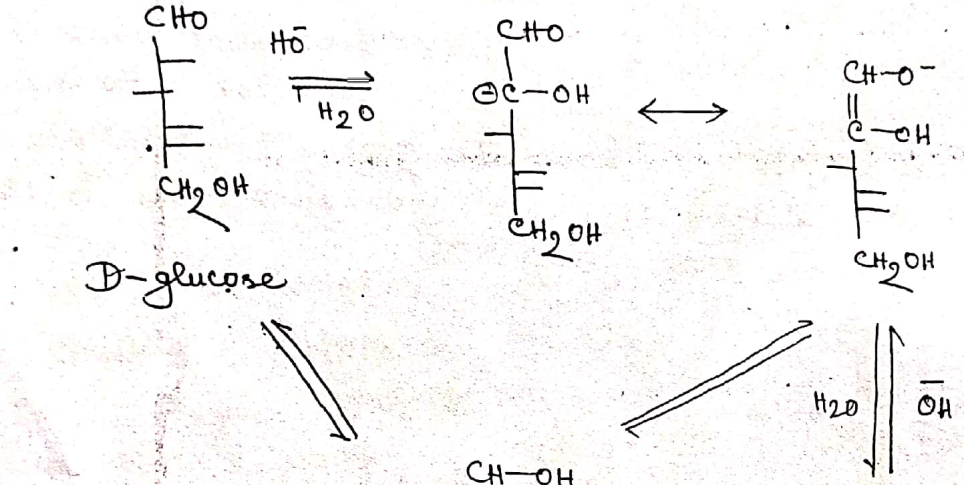


D-mannose, D-fructose, glycolic aldehyde, D-erythrose

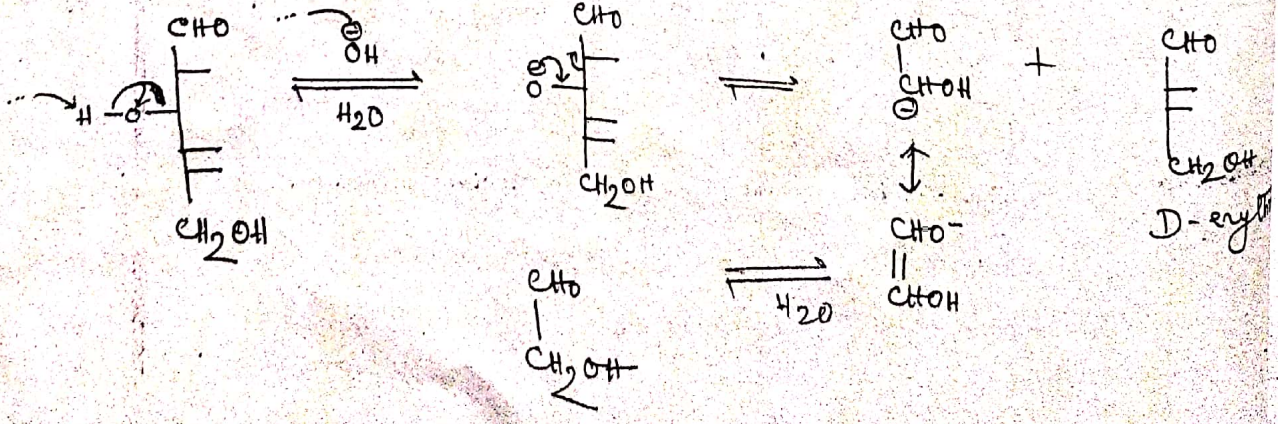
Problem-2 Why D(-) Fructose gives Tollen's test

Solution-1

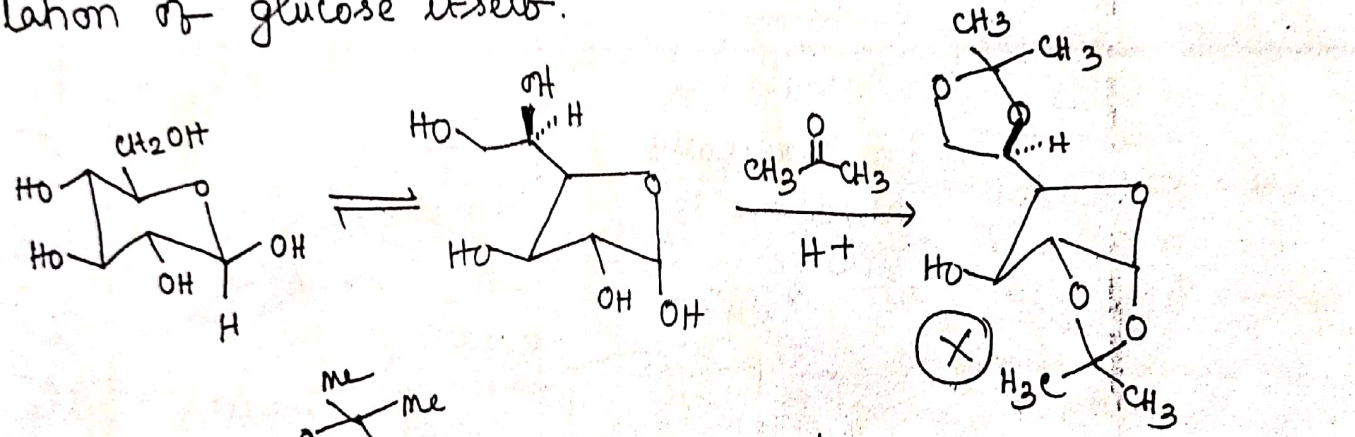
D- Mannose and D- fructose formation p via cyclisation in the following way



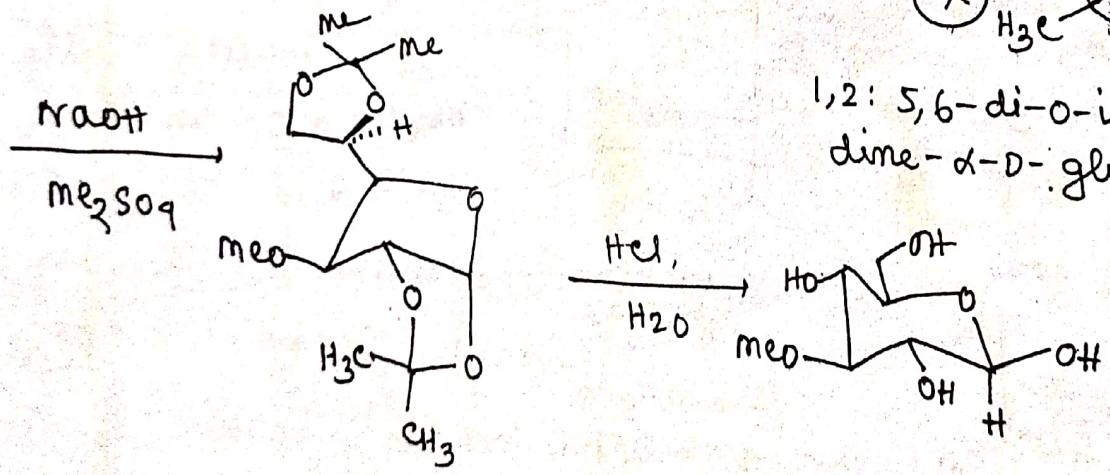
Again the glycolic aldehyde and D-. erythrose re from reverse aldol condensation



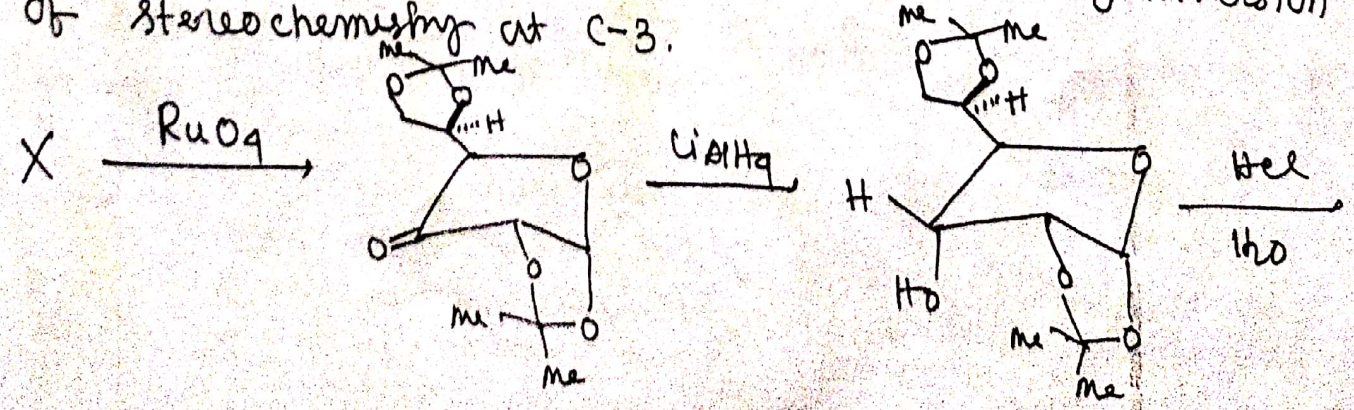
The cyclic acetals and ketals serve the useful function of protecting either two or four of the -OH groups normally present in the free sugar. The acetal groups are sensitive to acid, but are relatively stable to ~~reduced~~ neutral and basic conditions. Reactions may be carried out on the remaining -OH groups, and the protecting groups may then be removed by mild acid hydrolysis. An example is the synthesis of 3-O-methyl glucose, a feat that cannot be accomplished by selective methylation of glucose itself.

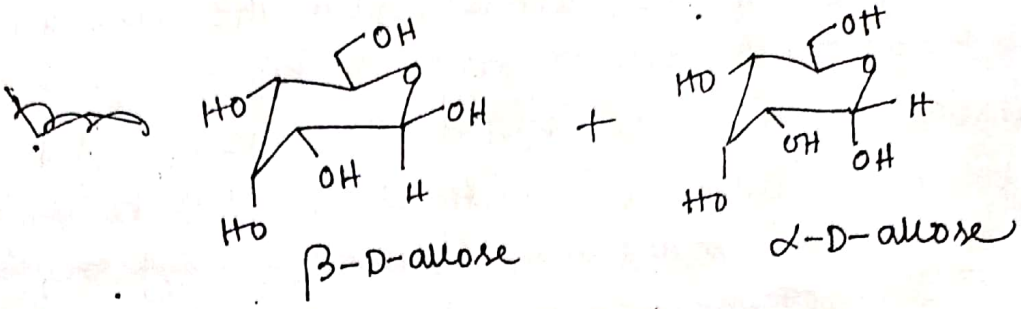


1,2 : 5,6-di-O-isopropylidine-α-D-glucofuranose.

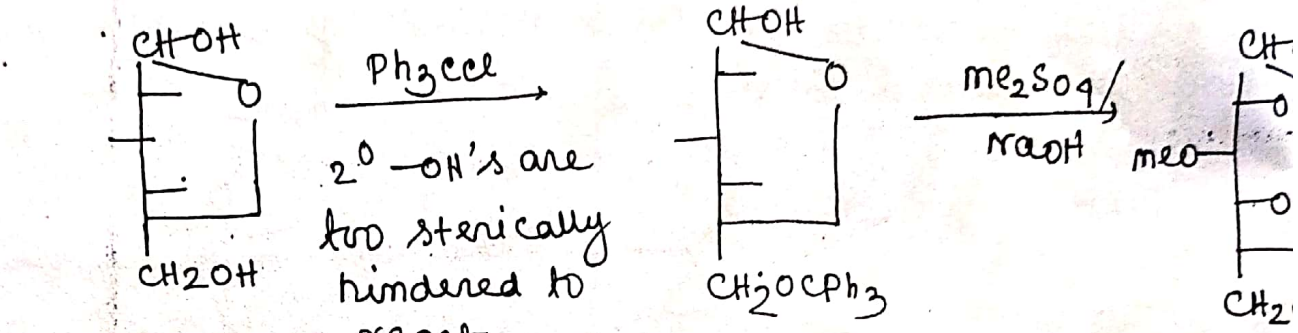


Another example is the following, which shows how D-glucose can be converted into D-allose by inversion of stereochemistry at C-3.



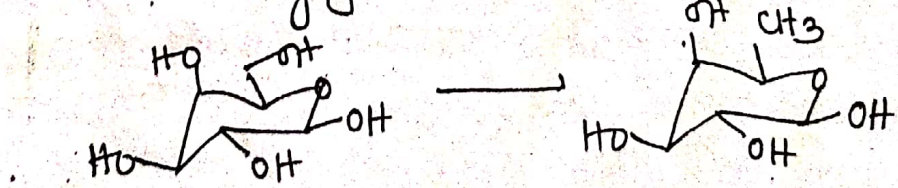


Synthesis of 2, 3, 4 – trimethyl aldopyranoside

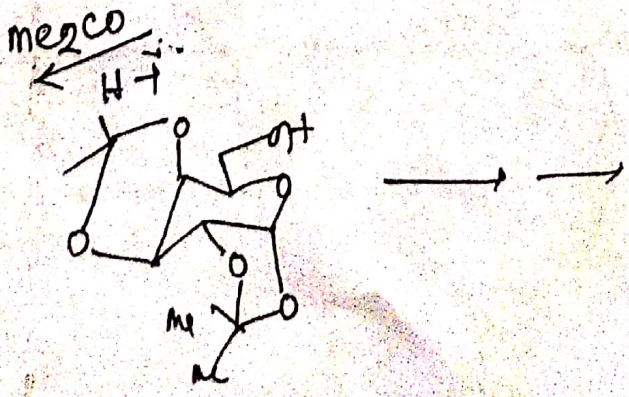


The facile hydrol
of the –O– trityl gr
proceeds through th
formation of the very
stable carbocation Ph3C

Problem: Suggest a method for the synthesis of 6-deoxygalactose from galactose.



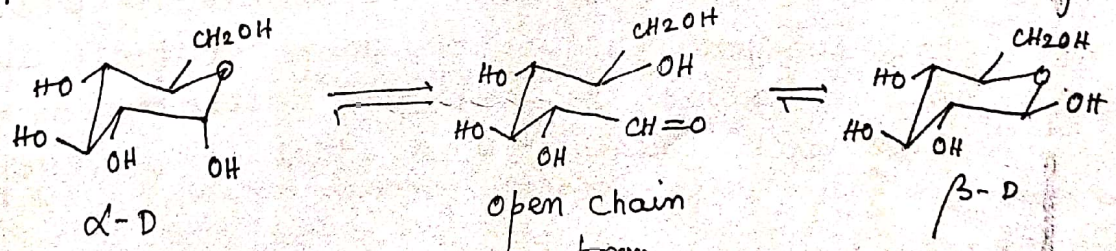
6-deoxy galactose



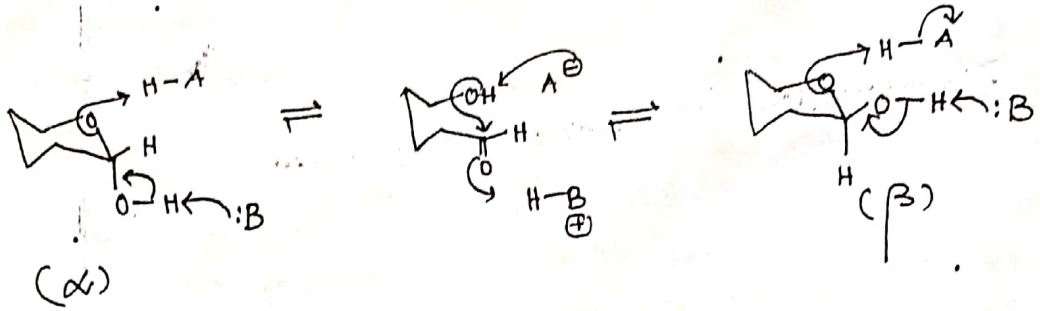
MUTAROTATION.

When a crystalline monosaccharide is dissolved in water the optical rotatory power of the solution gradually changes until it reaches a constant value, e.g. when crystalline α-D-glucose (prepared from cold aqueous solution by crystallization below 50°C) is dissolved in water its initial specific rotation of +112° falls gradually and becomes constant at +52.5°. A second form of glucose β, (crystallised) from water above 95°C) possess an initial specific rotation about +19°, gradually rises to the equilibrium value of +52.5°. This change of sp. rotation with time is called mutarotation (muta ≡ change). A similar phenomenon occurs whenever pure anomer of any other reducing sugar is dissolved in aqueous solution.

The mutarotation of glucose is caused by the conversion of the α and β-D-glucopyranose to an equilibrium mixture containing mainly the two six membered anomers along with small amount of open chain form.

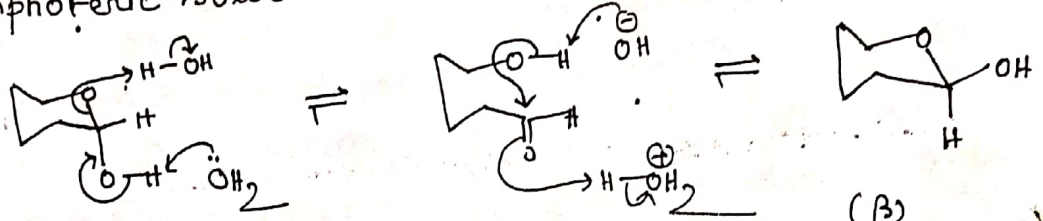


Mechanism: It has been observed that in pyridine soln or in cresol solution mutarotation does not occur but much rapid in a mixture of two i.e., mutarotation requires the presence of both an acid and a base or an amphoteric solvent e.g. H_2O. Thus mutarotation is an example of generalised acid base catalysis and following pathway is thus suggested.



(α) (β)

· In Amphoteric solvent:



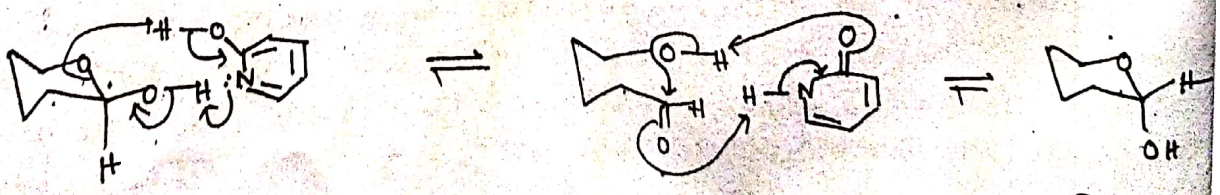
(α) (β)

. The above mechanistic Course of mutarotation is supp -ted by the following facts.

(a) Mutarotation shows third order kinetics; first orde each in substrate, base and acid

(b) Mutarotation in benzene solution in presence of hydroxy pyridine is far more rapid (compare to the rate observed in benzene solution in presen of pyridine and phenol) and that the reaction or is two.

This is due to the functionating of 2-hydro pyridine both as an acid and a base and proce the mechanism via lower energy cyclic T.S.



[β] open chain [α]

Problem: ① α-anomer of D-glucopyranose: sp. rt. +112°
β-anomer of D-glucopyranose: sp. rt. +19°

Now when either form is dissolved in water sp. rt. value changes to constant value of 52.7°. What is the % of α and β anomers of D-glucopyranose? (neglect the % of open chain form.)

Problem ②: Propose another mechanism of mutarotation in aqueous solution. How can you disprove it?

Solution 1 Say α-D-glucopyranose is x %
and β-D-glucopyranose is y %

Thus in equilibrium mixture

$$(x+y) \times 52.7 = x \times 112 + y \times 19$$

or $52.7y - 19y = 112x - 52.7x$

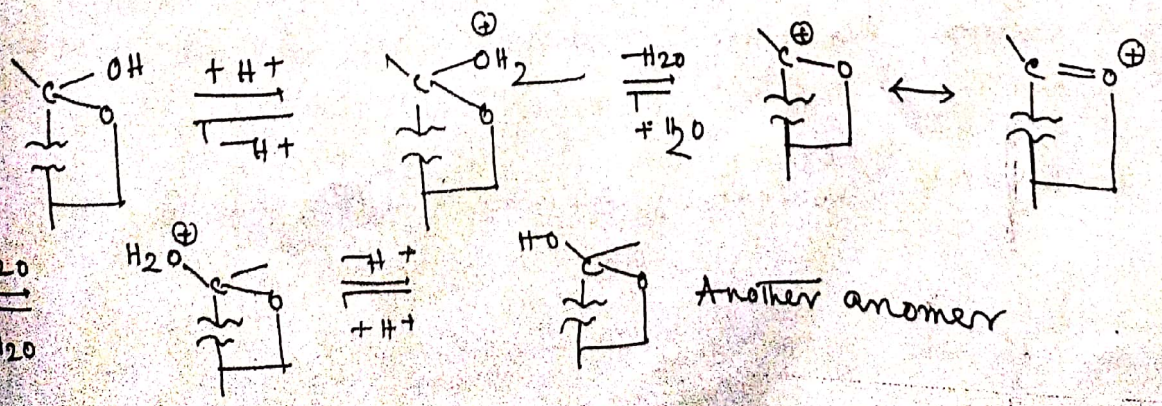
or $33.7y = 59.3x$

$$\therefore \frac{x}{y} = \frac{33.7}{59.3}$$

$$\therefore \%\ \alpha\text{-D-glucopyranose} = \frac{100 \times 33.7}{33.7+59.3}\ \% = 36.23\%$$

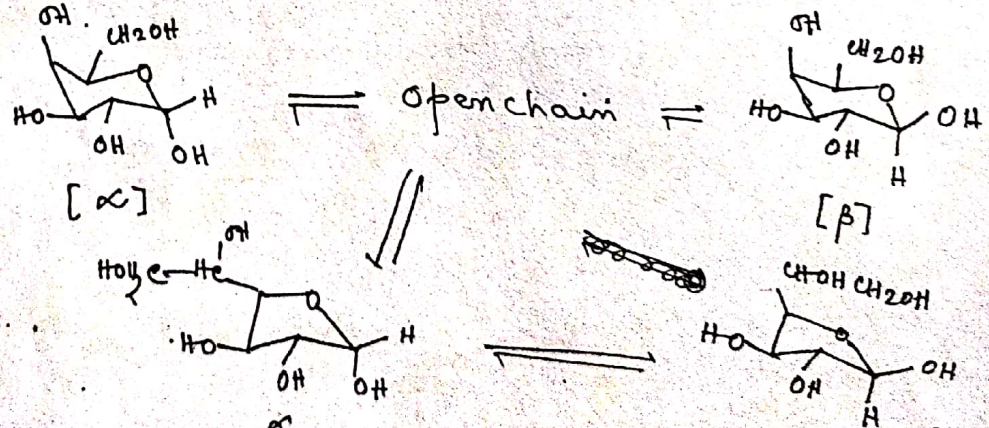
$$\text{and } \%\ \beta\text{-D-glucopyranose} = \frac{100 \times 59.3}{33.7+59.3}\ \% = 63.76\%$$

Solution 2 : Another resonable mechanism for mutarotation in aqueous solution is



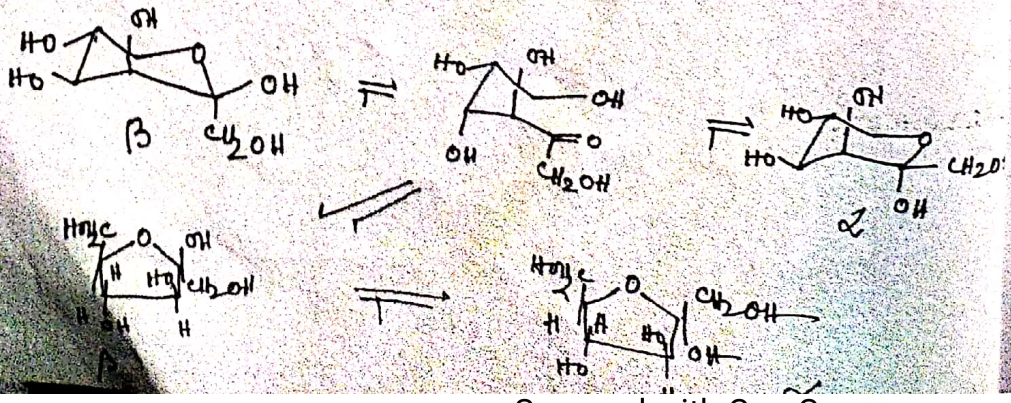
This mechanism is reasonable as the intermediate -Cation is highly stabilised through resonance. As to this mechanism every time a molecule undergoes mutarotation it must incorporate a molecule of from solvent. Thus solvent water must be incorpor into the sugar at least as fast as mutarotation place. But the mutarotation of glucose is 30 times a as the incorporation of O^{18} into the sugar from isot labelled solvent H_2O^{18}. Obviously this observation ruled the above mechanism.

Abnormal Mutarotation: Abnormal mutarotation are by those sugars whose 5 & 6 mem rings are closer in stability. Examples are ribose, ar galactose, talose, D-fructose. The variation of rotation irregular eg: with galactose

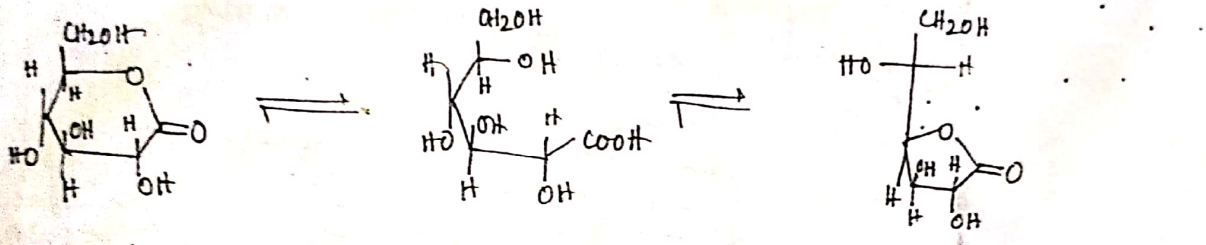


Pyranose structure is destabilised by one —OH at α position (C-4, here).

D-fructose



Mutarotation can also occur due to structural change of a molecule when dissolved in suitable solvent. for example, when δ-gluconolactone $[\alpha]_\lambda^t = +63.5°$ is dissolved in water, its rotation gradually changes to +12°. Similar result is observed when γ-gluconolactone having $[\alpha]_\lambda^t = +67.8°$ is dissolved in water. This is explained on the basis of the following dynamic equilibrium involving structural change that comes into existance in aqueous medium.

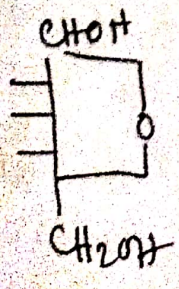


$[\alpha]_\lambda^t = +63.6°$ $[\alpha]_\lambda^t = -6.7°$ $[\alpha]_\lambda^t = +67.8°$

Equil^m. $[\alpha]_\lambda^t = +12°$

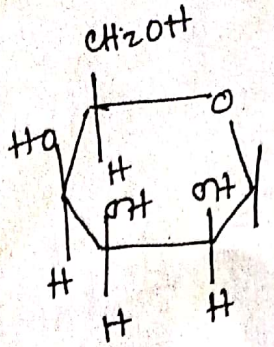
Problem: Do you expect abnormal mutarotation curve for D-talose? which aldopentose is homomorphous with D-talose? what is your expectation regarding the mutarotation curve?

Solution: The abnormal mutarotation curve is expected only when both furanose and pyranose forms are present in appreciable amounts at equilibrium. Let us consider the case of D-talose. Now the configuration of D-talose in the cyclic form is

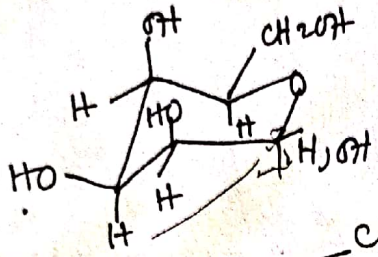


Hydro

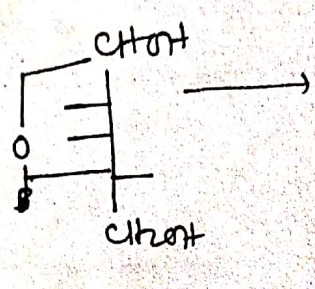
Haworth projection



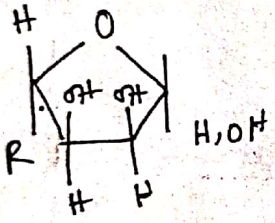
of D-talopyranose is

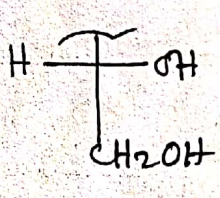


Let us try to carry out the Conformational analysis of D-talopyranose.

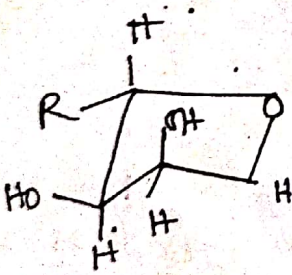


tilted towards right



where R ≡ 

The preferred Conformation of D-talofuranose is



The above Conformational analysis indicates that in the case of D-talose There will be an appreciable amount of furanose and pyranose forms in solution as these two forms have similar stabilities. Thus D-talose is expected to show the abnormal mutarotation curve.

Now the aldopentose which is homomorphic with D-talose is

L-ribose. Just like D-talose we do expect the abnormal mutarotation curve for L-ribose.

Glucose

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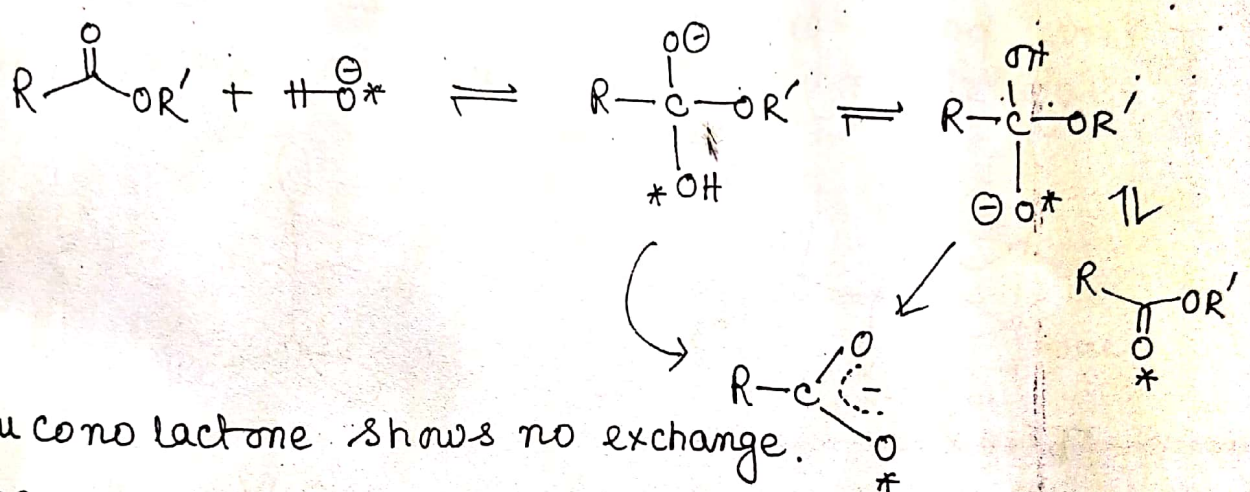
Hydrolysis of gluconolactone

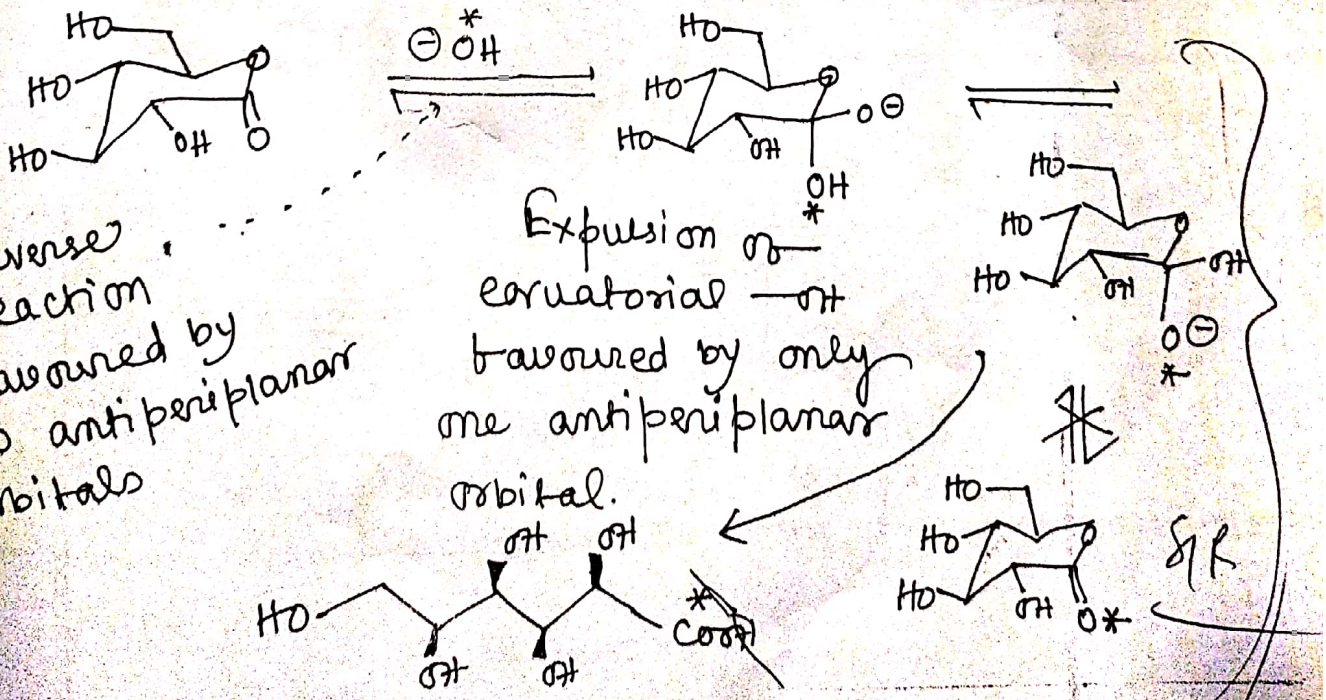
During hydrolysis of gluconolactone oxygen exchange with the solvent does not occur

Simple acyclic esters usually undergo isotopic exchange at a rate that is competitive with hydrolysis. This occurs through the tetra-hedral addition intermediate

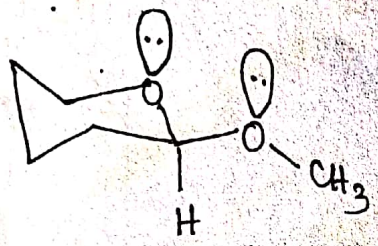


Gluconolactone shows no exchange.

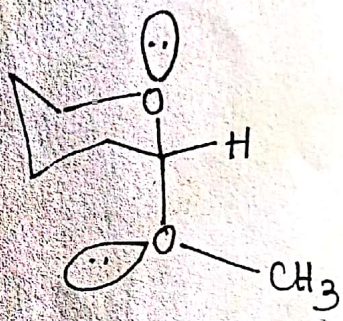
The reason is that the tetrahedral intermediate is formed and breaks down stereoselectively. Even though proton exchange can occur in the tetrahedral intermediate, the anomeric effect leads to preferential loss of the axial oxygen.



Isomers with equatorial 2-alkoxy (hydroxy
are more reactive than those with axial 2
(-OH) groups. The greater reactivity of the eq
isomers is the result of the alignment of
lone pairs on both the endocyclic and
exocyclic oxygen to assist in hydrogen a



Two lone-pairs orbitals are in antiperiplanar arrangement



only one lone-pa orbital are in antiperiplanar arrange ment

Mutarotation curve