Course Code: CHEM3014
Course Name: Organic Chemistry V

Unit: 4
(Carbohydrate)
(Lecture-Part 3)

For
B.Sc. (Honours)
Semester: VI

By

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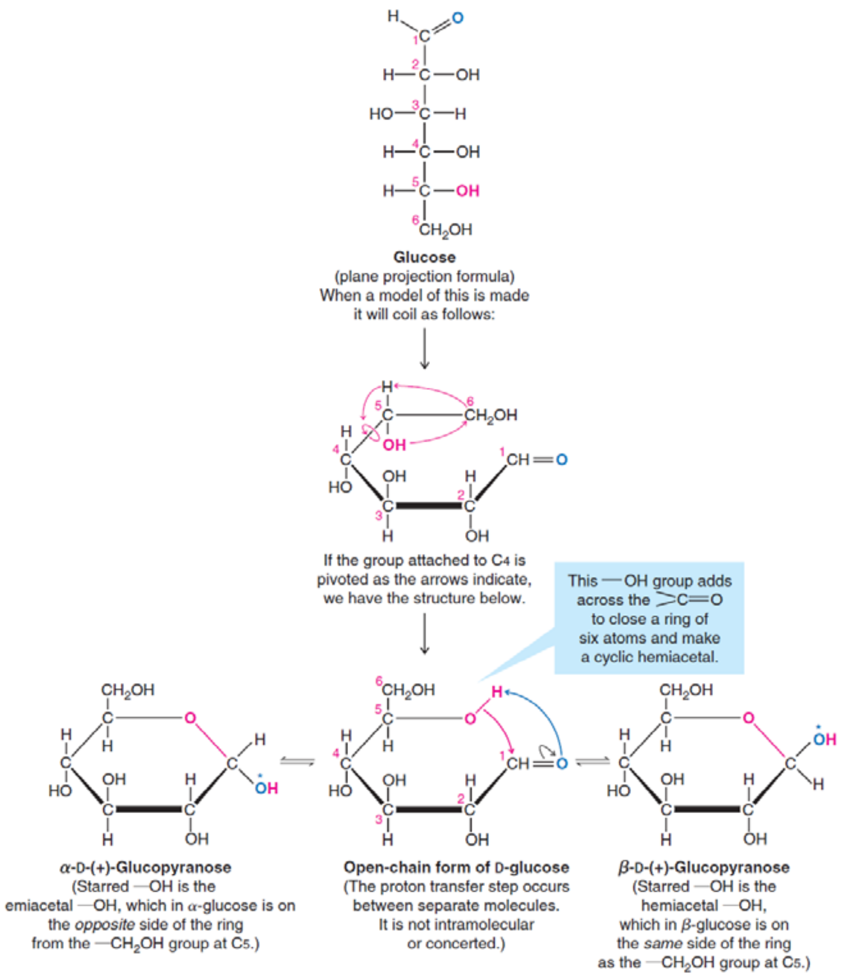
Conversion of Open-Chain to Cyclic structure of Monosaccharide

- *The open chain form has been found to be in equilibrium with the cyclized hemiacetal forms in case of monosaccharide. Example of cyclization of glucose has been shown below.*



Glucose
(plane projection formula)
When a model of this is made
it will coil as follows:

If the group attached to C4 is
pivoted as the arrows indicate,
we have the structure below.

This —OH group adds
across the >C═O
to close a ring of
six atoms and make
a cyclic hemiacetal.

α-D-(+)-Glucopyranose
(Starred —OH is the
emiacetal —OH, which in α-glucose is on
the *opposite* side of the ring
from the —CH_2OH group at C5.)

Open-chain form of D-glucose
(The proton transfer step occurs
between separate molecules.
It is not intramolecular
or concerted.)

β-D-(+)-Glucopyranose
(Starred —OH is the
hemiacetal —OH,
which in β-glucose is on
the *same* side of the ring
as the —CH_2OH group at C5.)

Figure 1: Example of cyclization of glucose

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Anomer Formation During Cyclization

- *As it can be seen in previous slide, that during cyclization, the -OH group present at C-5 could approach to the CHO group which is planar from two different faces. After this nucleophilic addition step, a new chiral centre generates. Overall it results into the formation of two diastereomers* **α-D-(+)-glucopyranose and β-D-(+)-glucopyranose** *which differ only at one carbon centre.*

- ***Anomer**: These diastereomers differing only at the hemiacetal or acetal carbon are called **anomers**, and the hemiacetal or acetal carbon atom is called the **anomeric carbon atom.** Therefore after cyclization two anomers generated which are **α and β anomers** depending on the orientation of OH group at C1 carbon.*

- *Before we move to the next part, in first point **term 'pyranose'** was used so let's have a look at it.*

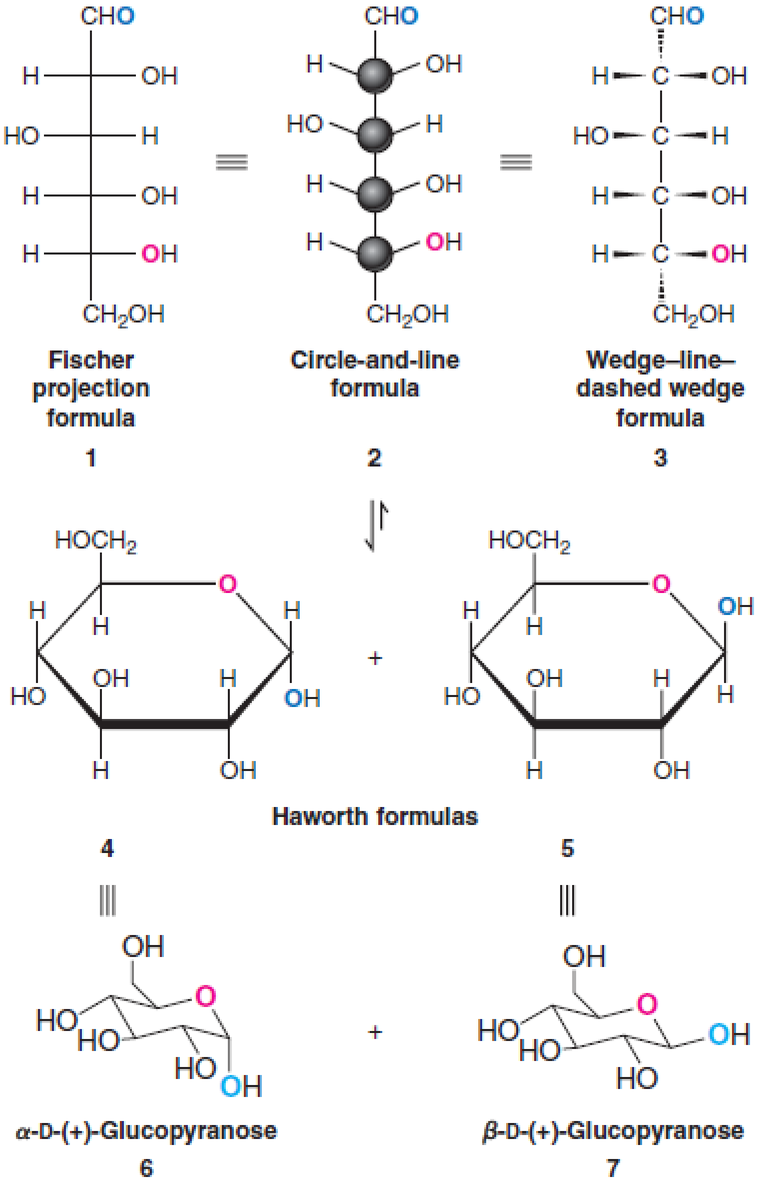
Pyran **Furan**

Figure 2: Structure of pyran and furan ring

- ***Pyranose**: If the monosaccharide ring is six membered similar to pyran, the compound is called a **pyranose.***

- ***Furanose:** if the ring is five membered similar to five membered furan ring, the compound is designated as a **furanose.***

Different ways/Formula to represent open chain and cyclic form



Fischer projection formula 1

Circle-and-line formula 2

Wedge–line–dashed wedge formula 3

Haworth formulas 4 5

α-D-(+)-Glucopyranose 6

β-D-(+)-Glucopyranose 7

When we draw the cyclic forms of a D sugar in the orientation shown in Figs. 4 or 5, the α-anomer has the OH trans to the CH_2OH group and the β-anomer has the OH cis to the CH_2OH group.

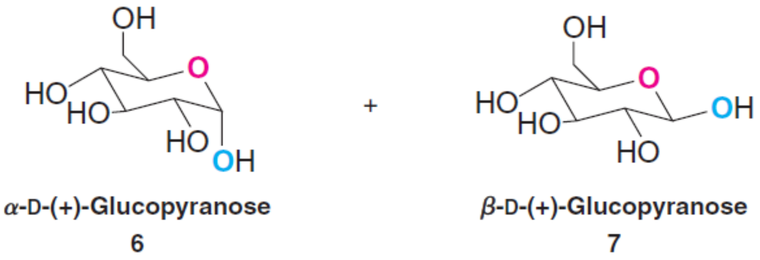
Figure 3: ***Different formula to represent open chain and cyclic forms.***

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Chair Conformation of Monosaccharides

- *X-ray cyclic hemiacetal forms of D-(+)-glucose using analysis have demonstrated that the actual conformations of the rings are the chair forms represented by conformational formulas* ***6 and 7 in Fig. 4. Similar to what we have studied for*** *conformations of cyclohexane .*

- *Similar to cyclohexane where bulky group generally occupies equatorial position, in the β-anomer of D-glucose all of the large substituents, OH and CH_2OH, are equatorial. In the α-anomer, the only bulky axial substituent is the OH at C1.*



α-D-(+)-Glucopyranose
6

β-D-(+)-Glucopyranose
7

Figure 4: Two anomers of D-(+)-Glucose

- *If you don't specify the configuration at anomeric carbon whether α or β then it could be represented as follows:*

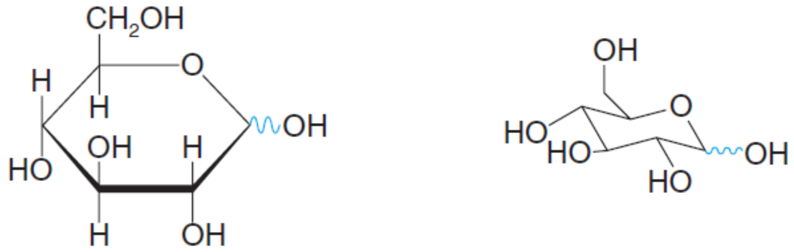


Figure 5: Representation of cyclcized form without specifying configuration at anomeric carbon

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Mutarotation

- Before moving to this part, the question is *how did one confirm that two different anomers generates during the cyclic hemiacetal formation* ?

- **Evidences to support these two forms are as follows**:

- Both α and β-forms have been isolated.

- Ordinary D-(+)-glucose has a melting point of 146°C. However, when D-(+)-glucose is crystallized by evaporating an aqueous solution kept above 98°C, a second form of D-(+)-glucose with a melting point of 150°C can be obtained.

- When the optical rotations of these two forms are measured, they are found to be significantly different, but when an aqueous solution of either form is allowed to stand, **its rotation changes**.

- The specific rotation of one form decreases and the rotation of the other increases, until both solutions show the same value.

- A solution of ordinary D-(+)-glucose (mp 146°C) has an initial specific rotation of +112, but, ultimately, the specific rotation of this solution falls to +52.7.

- A solution of the second form of D-(+)-glucose (mp 150°C) has an initial specific rotation of +18.7, but, slowly, the specific rotation of this solution rises to +52.7.

Continued…

Mutarotation

- This change in specific rotation from +112 and +18.7 toward an equilibrium value +52.7 is called **mutarotation.**

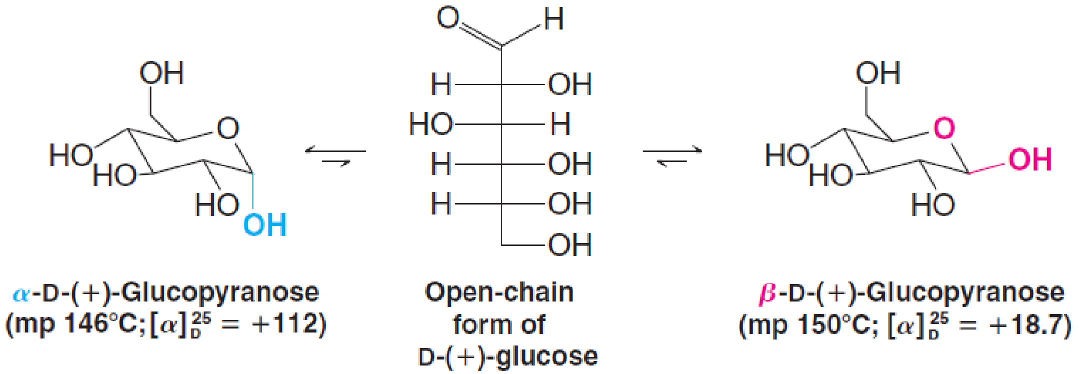


Figure 6: Equilibrium among open chain and two cyclized forms.

- X-Ray analysis has confirmed that **ordinary D-(+)-glucose has the α configuration at the anomeric carbon atom** and that the higher melting form has the *β* configuration.

- In solution, the **presence of open chain form is very less compared to the cyclic hemiacetal** forms as the solutions of D-(+)-glucose give **no observable UV or IR absorption band for a carbonyl group**.

- **solutions of D-(+)-glucose give a negative test with Schiff's reagent**—a special reagent that requires a relatively high concentration of a free aldehyde group (rather than a hemiacetal) in order to give a positive test.

- These percentages, **36% *α* anomer** and **64% *β* anomer**, are in accord with a greater stability for *β*-D-(+)-glucopyranose.

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Distribution of Two Different Anomers

- These percentages, **36% *α* anomer** and **64% *β* anomer**, are in accord with a greater stability for *β*-D-(+)-glucopyranose.

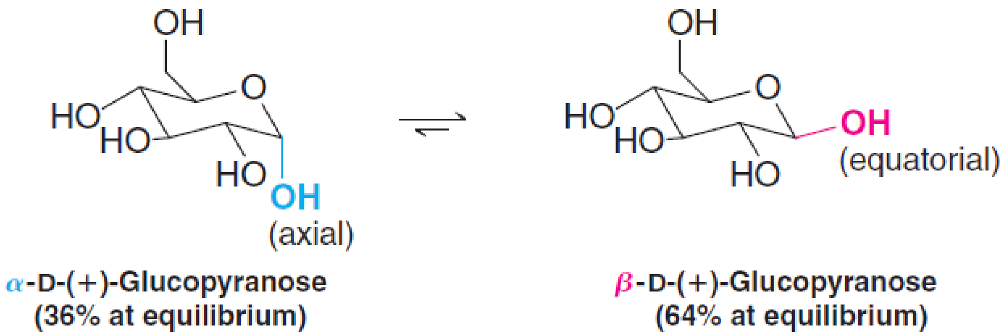


Figure 7: Distribution of two anomers at equilibrium.

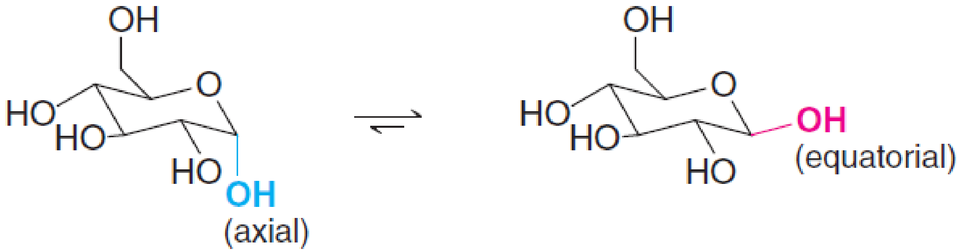
Question: How do you explain the greater stability of *β*-D-(+)-glucopyranose?

Answer: If you recall the axila and equatorial chair forms of cyclohexane, then in general the bulky groups occupy equatorial position rather than axial to avoid 1,3-diaxial interactions. Therefore in case of two anomers of glucose also, the *β*-D-(+)-glucopyranose is present in higher amount as in this case all the groups except H occupy equatorial position which make it more stable than the ***α* anomer .**

Can we generalize that β anomer will always be more stable than its α counterpart?

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Stability of Different Anomers

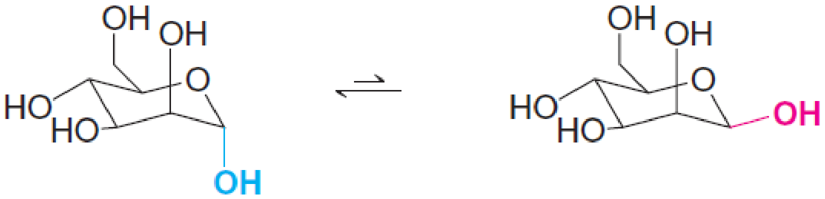


α-D-(+)-Glucopyranose
(36% at equilibrium)

β-D-(+)-Glucopyranose
(64% at equilibrium)

Figure 7: Distribution of two anomers at equilibrium.

- **β anomer of a pyranose is not always the more stable.** For example, in case of D-mannose, the equilibrium favors the *α* anomer, and this result is called an ***anomeric effect.***



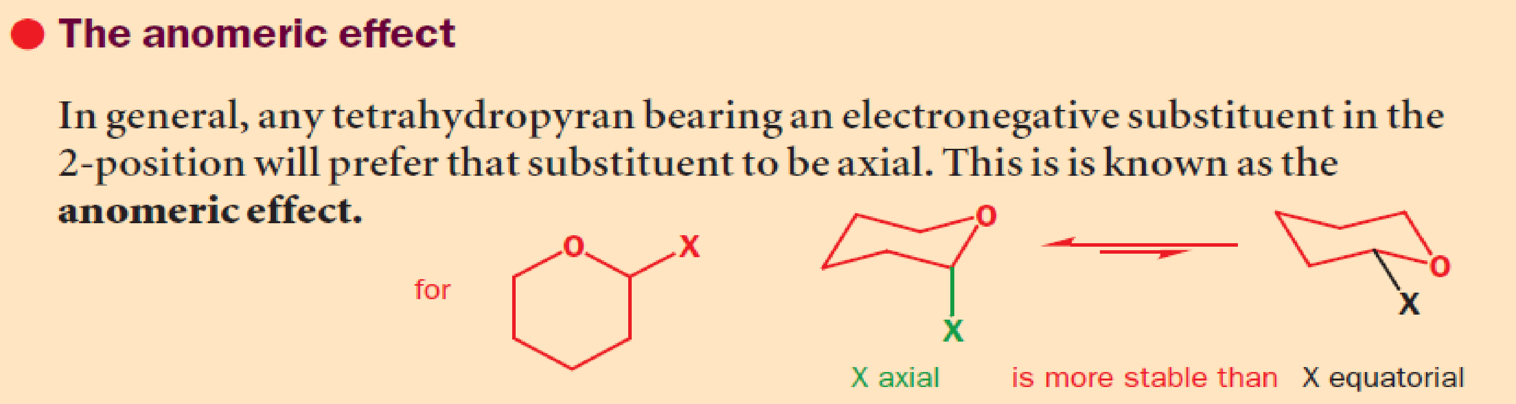
α-D-Mannopyranose
(69% at equilibrium)

β-D-Mannopyranose
(31% at equilibrium)

Figure 8: Distribution of two anomers of D-mannose at equilibrium.

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Anomeric Effect



The anomeric effect

In general, any tetrahydropyran bearing an electronegative substituent in the 2-position will prefer that substituent to be axial. This is is known as the **anomeric effect.**

- *An amide is more stable (less reactive) than a ketone because the p orbital of the N and the low-lying C=O p* of the carbonyl can lie parallel—they can overlap and electron density can move from nitrogen into the C=O bond, weakening C=O. (Evidence for this comes from the lower IR stretching frequency of an amide C=O, among other things.)*

- *Similarly, C–X bonds also have low-lying antibonding orbitals—the C–X σ*—so it is expected that molecule would be more stabilized if an adjacent heteroatom could donate electrons into this orbital like in case of amide. Take the generalized tetrahydropyran in the box above, for example, with X = Cl, say. This molecule is most stable if an oxygen lone pair can overlap with C–Cl σ*, like this.*

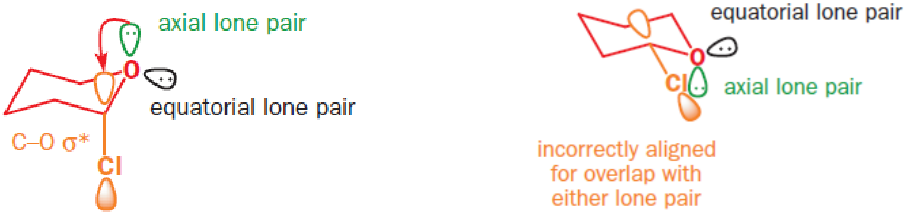


Figure 9: Explanation for Stabilization through anomeric effect.

Picture adapted from Chapter 42, ‘Organic Chemistry’; Publisher: Oxford University Press; 2nd edition; Authors: Jonathan Clayden , Nick Greeves , Stuart Warren.

Continued…

Anomeric Effect

- *The anomeric effect could be explanied by using applying the concept of hyperconjugation.*

- *An **axially oriented orbital associated with nonbonding electrons of the ring oxygen can overlap with a σ* orbital of the axial exocyclic C-Ohemiacetal bond.***

- *This effect is similar to that which causes the lowest energy conformation of ethane to be the anti conformation.*

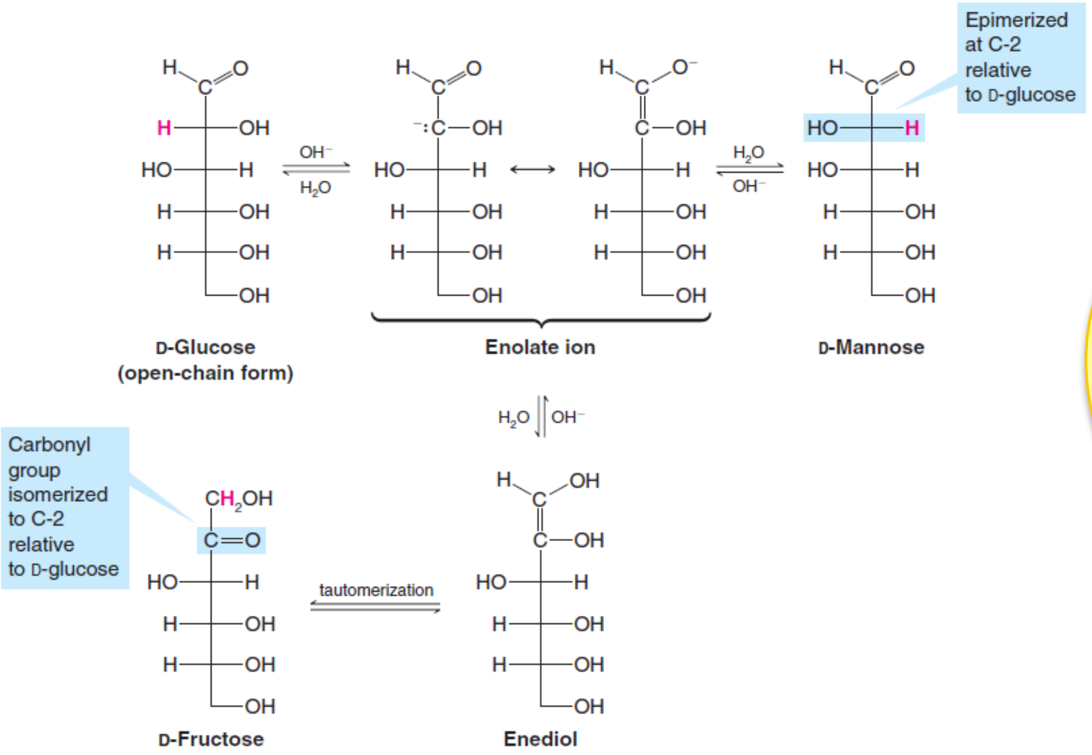
- *An anomeric effect will frequently cause an electronegative substituent, such as a hydroxyl or alkoxyl group, to prefer the axial orientation.*

Now we will be moving towards the reactions of carbohydrates

Enolization, Tautomerization, and Isomerization

- ***Lobry de Bruyn–Alberda van Ekenstein transformation***:

Under basic reaction condition monosaccharides such as glucose isomerized into their epimer such as D-mannose and different isomer such as D-fructose. Reaction proceeds through a series of enolizations and keto–enol tautomerizations that lead to isomerizations. This type of reaction is called the Lobry de Bruyn–Alberda van Ekenstein transformation after the two Dutch chemists who discovered it in 1895.



For example, when D-glucose containing calcium hydroxide is allowed to stand for several days, a number of products can be isolated, including D-fructose and D-mannose.

Figure 10: Iosmerization of D-Glucose to D-Mannose and D-Fructose

(Picture adapted from *Chapter No. 22, 'Organic Chemistry' (10th edition) by T. W. G. Solomons and C. B. Fryhle.)*

Glycoside formation

- *When a small amount of gaseous hydrogen chloride is passed into a solution of D-(+)-glucose in methanol, a reaction takes place that results in the formation of anomeric methyl acetals:*

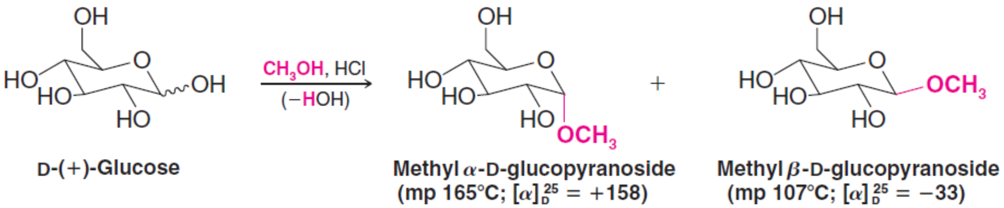


Figure 11: Glycoside formation reaction

- *Carbohydrate acetals are generally called* ***glycosides*** *and an acetal of glucose is called a glucoside. (Acetals of mannose are mannosides, acetals of fructose are fructosides, and so on.)*

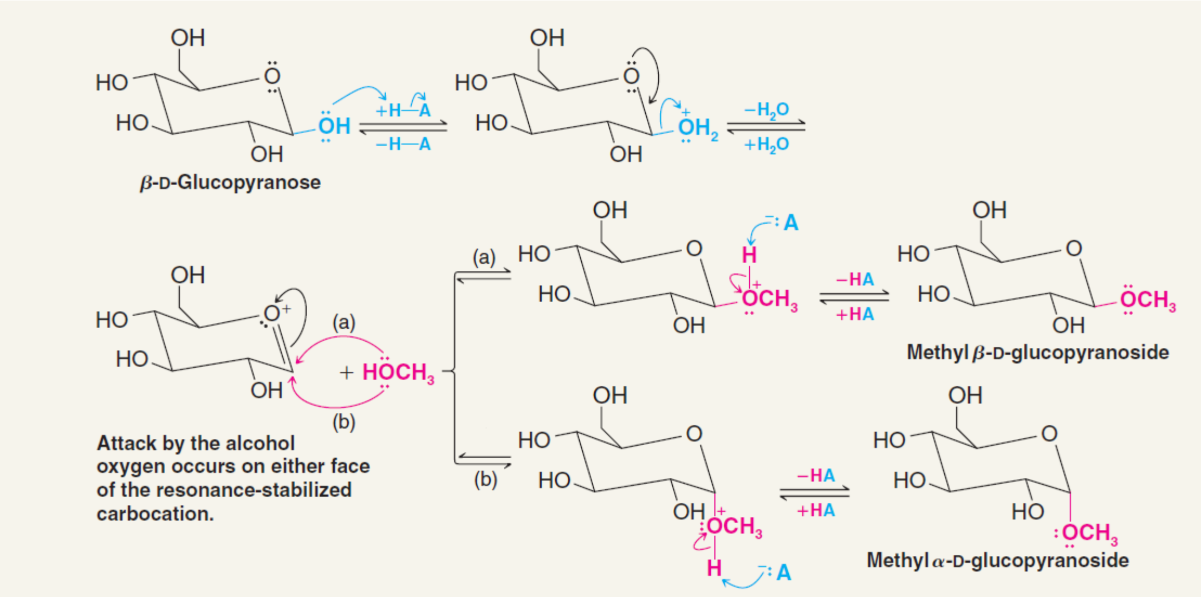


Figure 12: Mechanism of Glycoside formation

Chapter 22, Organic Chemistry (10th edition); Publisher: John Wiley & Sons, Inc. Authors: T. W. G. Solomons and C. B. Fryhle.

Stability of Glycosides under different reaction conditions

- *Glycosides are **stable in basic solutions** because they are acetals.*

- *But under acidic condition, glycosides undergo hydrolysis to produce a sugar and an alcohol . The alcohol obtained by hydrolysis of a glycoside is known as an **aglycone**.*

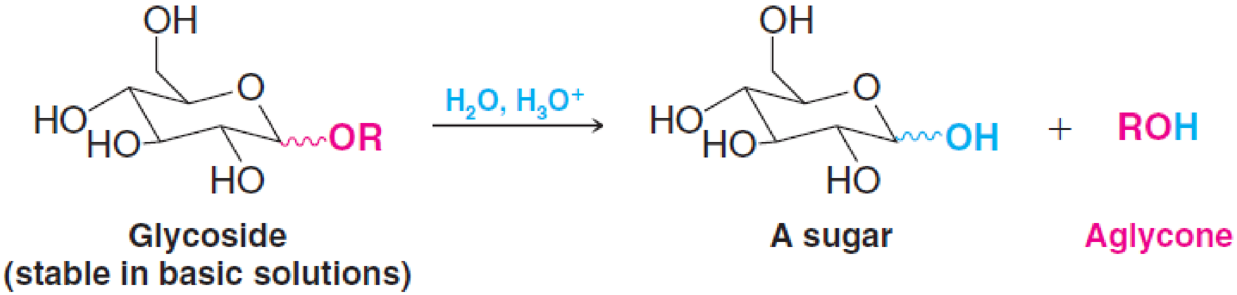


Figure 13: Hydrolysis of Glycoside to form aglycone

- *For example, when an aqueous solution of methyl β-D-glucopyranoside is made acidic, the glycoside undergoes hydrolysis to produce D-glucose as a mixture of the two pyranose forms (in equilibrium with a small amount of the open-chain form)*

Chapter 22, Organic Chemistry (10th edition); Publisher: John Wiley & Sons, Inc. Authors: T. W. G. Solomons and C. B. Fryhle.

Mechanism for hydrolysis of Glycosides under acidic condition

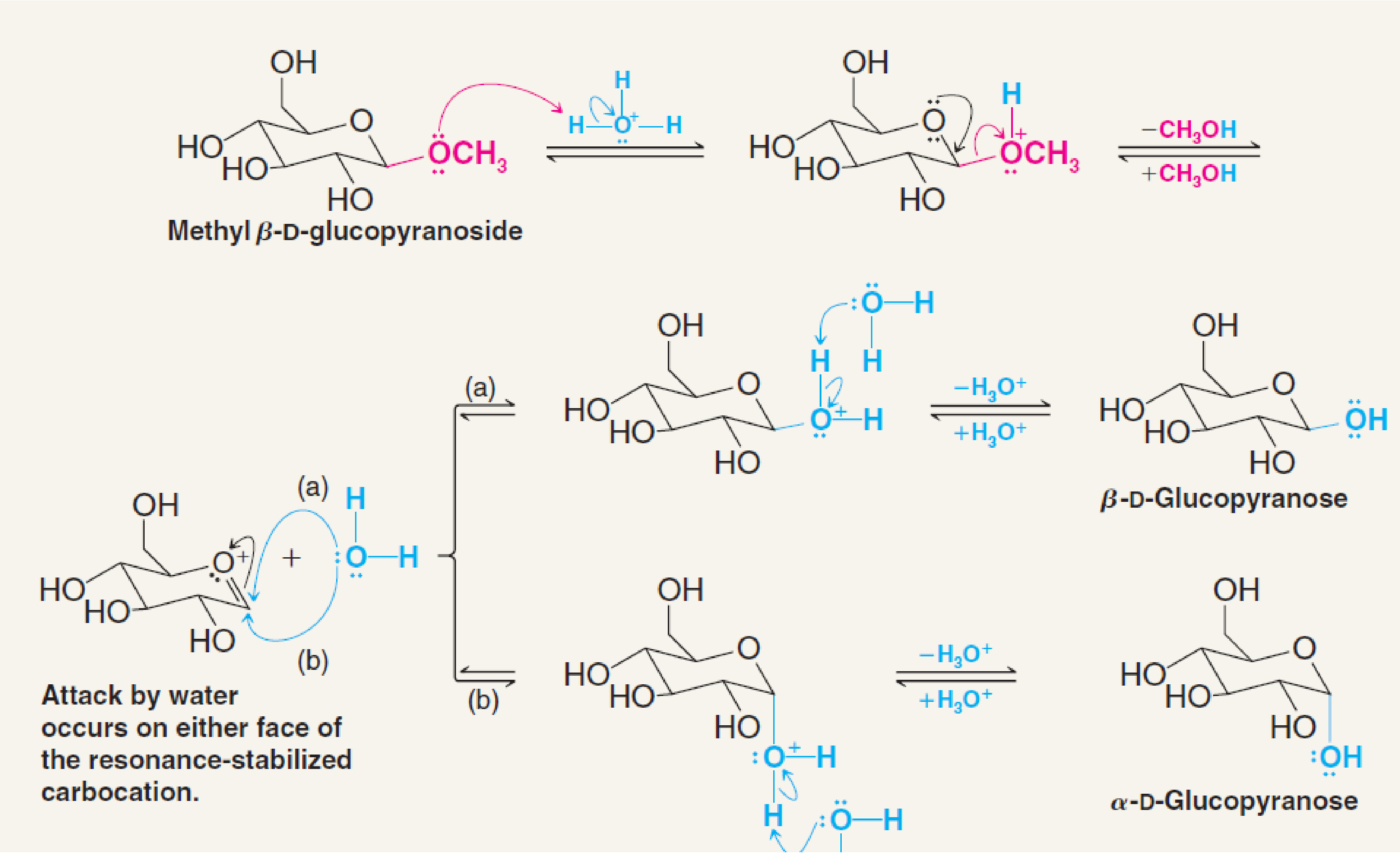


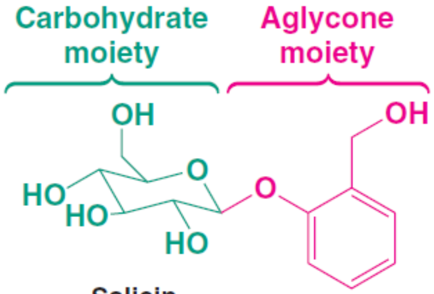
Figure 14: Mechanism for hydrolysis of Glycoside under acidic condition

Chapter 22, Organic Chemistry (10th edition); Publisher: John Wiley & Sons, Inc. Authors: T. W. G. Solomons and C. B. Fryhle.

Examples of Glycosides in nature

- Glycosides may be as simple as the methyl glucosides that we have just studied or they may be considerably more complex. Many naturally occurring compounds are glycosides.

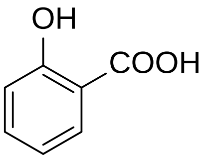
- For example ***salicin****, a compound found in the bark of willow trees:*



Salicin

Figure 15: Structure of salicin, a natural glycoside

- *Salicin can be converted to salicylic acid, which in turn can be converted into the most widely used modern analgesic, aspirin.*



Aspirin

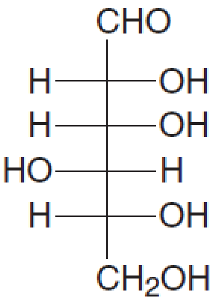
Figure 16: Structure of Aspirin

Chapter 22, Organic Chemistry (10th edition); Publisher: John Wiley & Sons, Inc. Authors: T. W. G. Solomons and C. B. Fryhle.

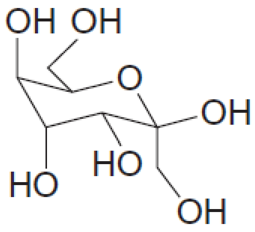
Assignments

- *Draw the α and β-pyranose form of (a) in its lowest energy chair conformation, and a Fischer projection for the compound (b) given below.*

(a)



(b)



- *Draw conformational formulas for α-D-allopyranose, β-D-allopyranose.*

- *In neutral or basic solutions, glycosides do not show mutarotation. However, if the solutions are made acidic, glycosides show mutarotation. Explain*

- *What products would be formed if salicin were treated with dilute aqueous HCl? Outline a mechanism for the reactions involved in their formation.*

- *How would you convert D-glucose to a mixture of ethyl α-D-glucopyranoside and ethyl β-D-glucopyranoside? Show all steps in the mechanism for their formation.*

References

- *Student may also consult following study materials and books:*

1. *Chapter 22, Organic Chemistry (10th edition); Publisher: John Wiley & Sons, Inc. Authors: T. W. G. Solomons and C. B. Fryhle.*

2. *Chapter 16, 'Organic Chemistry'; Publisher: Oxford University Press; 2nd edition; Authors: Jonathan Clayden , Nick Greeves , Stuart Warren.*

Rest of the topics of this unit will be discussed in next part of the lecture.

Stay Happy, Healthy and Safe!