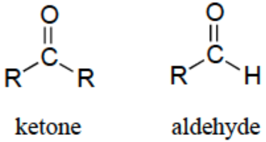
Bio-organic chemistry

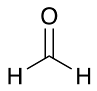
Lecture 9

Reactions directly at the Carbonyl group with acyl substituents

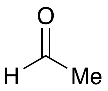


Reactivity of Carbonyl Groups - Summary

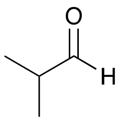
Steric Effects



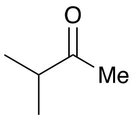
formaldehyde



acetaldehyde



isobutyraldehyde



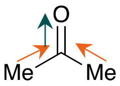
3-methylbutan-2-one

The less crowded the electrophile, the more reactive

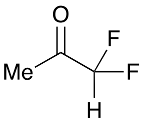
➔ Aldehydes are more reactive than Ketones

Question: How easy can a reactant access the carbon?

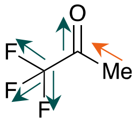
Electronic Effects



propan-2-one



1,1-difluoropropan-2-one



1,1,1-trifluoropropan-2-one

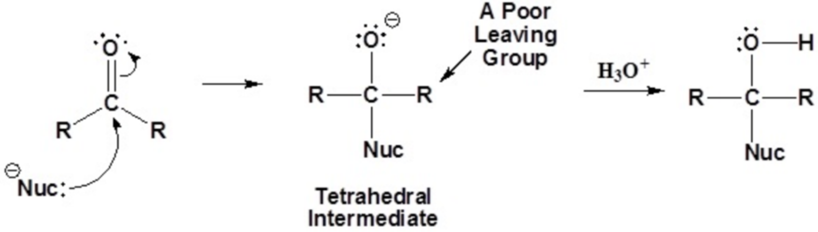
The more positive the electrophile, the more easily it will react.

➔ Electron withdrawing groups increase reactivity
➔ Electron pushing groups reduce reactivity

Question: How stable is the positive charge on the carbon?

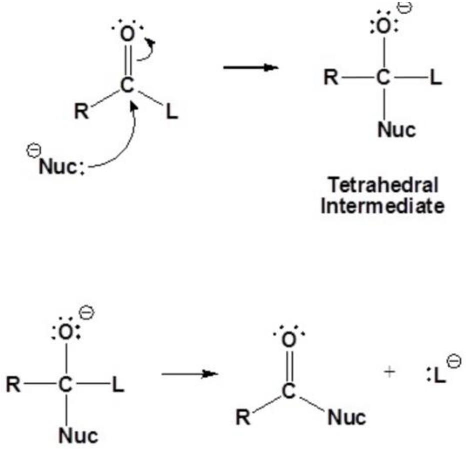
Comparing nucleophilic additions and nucleophilic substitutions

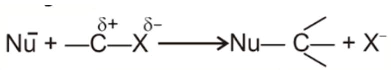
Addition



-pi bond reacts with a nucleophile leading to the diseapearence of a double bond and the creation of a new sigma bond

Substitutions

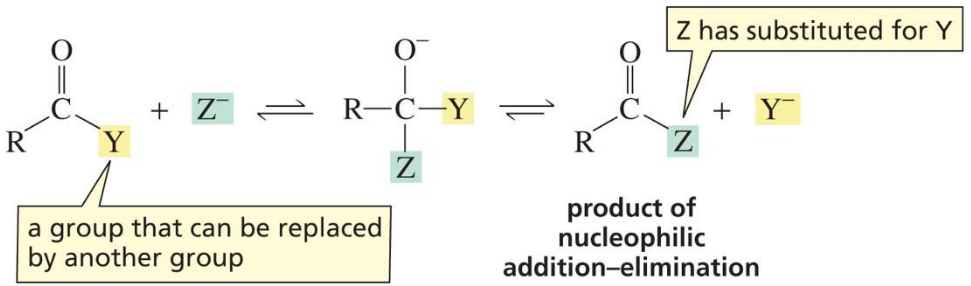




$$\mathrm{Nu}^- + -\overset{\delta+}{\mathrm{C}}-\overset{\delta-}{\mathrm{X}} \longrightarrow \mathrm{Nu}-\mathrm{C} + \mathrm{X}^-$$

-Leaving group leaves

Aldehydes and Ketones React Differently Than Do Carboxylic Acid Derivatives

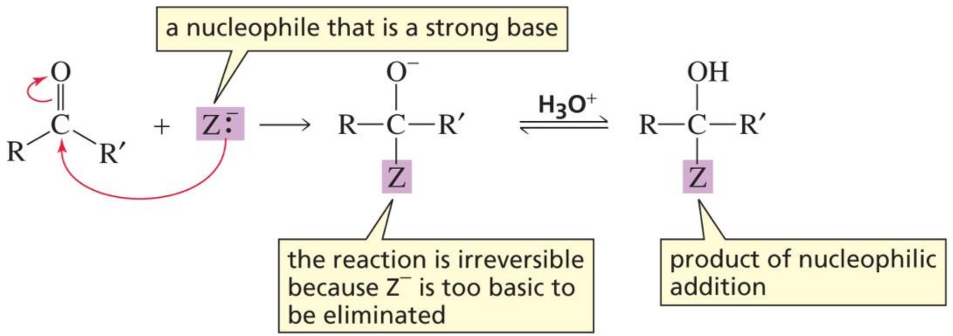


Z has substituted for Y

a group that can be replaced by another group

product of nucleophilic addition–elimination

In a carboxylic acid derivative, Y^- can leave. Addition–elimination is observed.



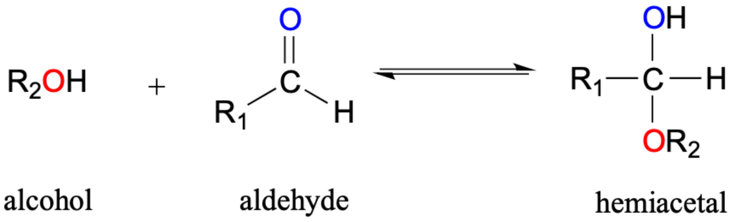
a nucleophile that is a strong base

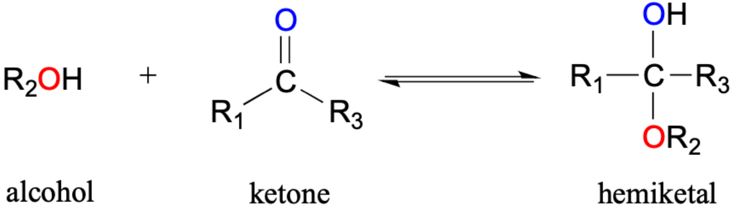
the reaction is irreversible because Z^- is too basic to be eliminated

product of nucleophilic addition

In aldehydes and ketones, neither alkyl nor hydride groups can leave. Addition is observed.

Hemiacetals and hemiketals for carbohydrate chemistry





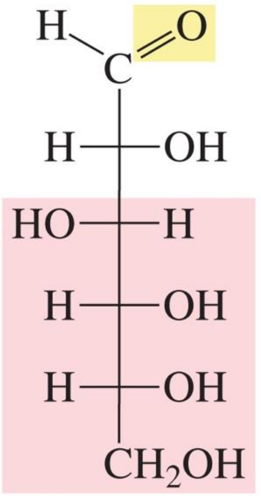
-hemi means half - in different contexts we can have the addition of a second alcohol

Biochemical mechanism of hemiacetal formation:

-reversible reaction

- The important point to learn is where are the positive and negative groups that drive the reaction

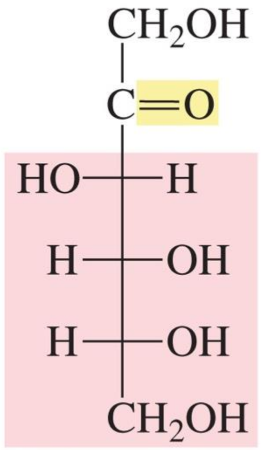
Carbohydrates are Polyhydroxy Aldehydes or Polyhydroxy Ketones



Fischer projection

D-glucose

a polyhydroxy aldehyde



Fischer projection

D-fructose

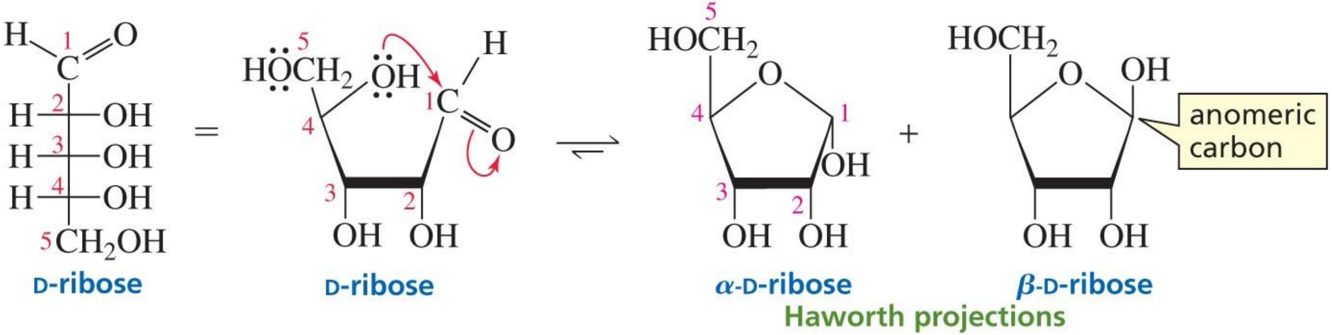
a polyhydroxy ketone

molecular formula = $C_n(H_2O)_n$

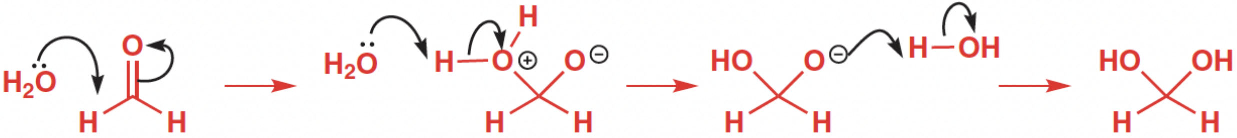
The structures of glucose and fructose differ only at the top two carbons.

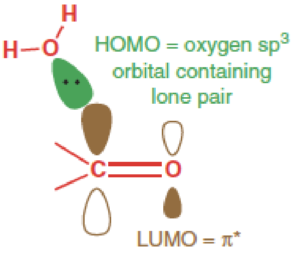
Monosaccharides Form Cyclic Hemiacetals

Haworth projection



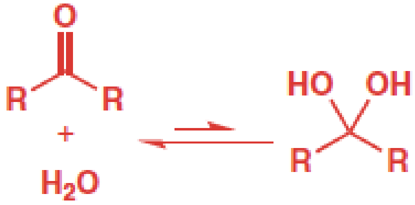
Addition of water to aldehydes and ketones





orbitals involved in the addition of water

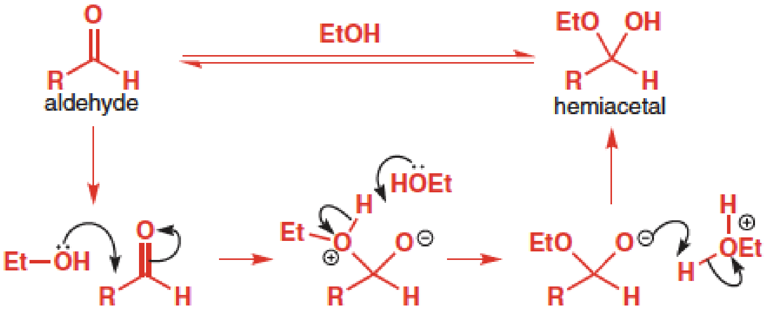
*The addition of water is an **equilibrium**. Usually only significantly found for aldehydes and not for ketones!*
*-> **Steric and electronic effects***

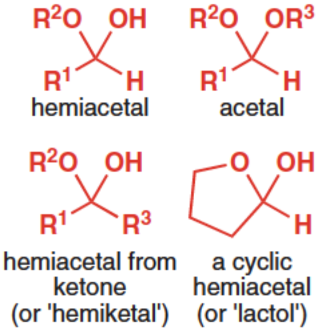


Let’s take a look at the reaction of alcohols with ketones/aldehydes

Hemiacetals from reaction of alcohols with aldehydes and ketones

Alcohols add to carbonyl groups

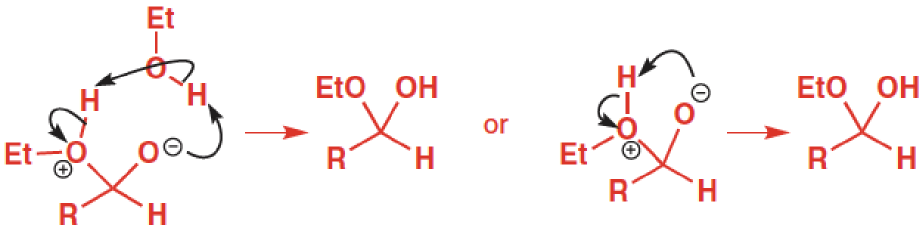




names for functional groups

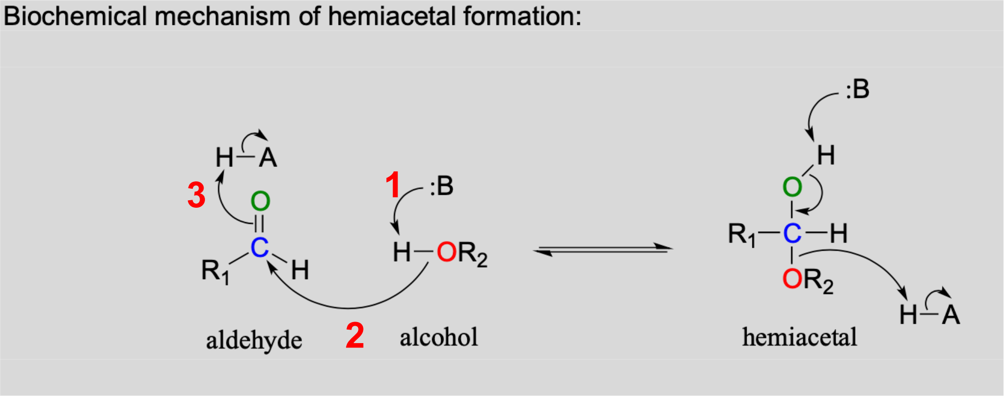
One proton has to be transferred from one oxygen to another – How exactly, we can only guess

two more (and equally correct) mechanisms for proton transfer between the oxygen atoms:



Many times, reaction mechanisms are not fully proven

Let’s take a look at the mechanism



Biochemical mechanism of hemiacetal formation:

Remember – let’s search for the most negative and positive species which drive the attack or are neutralized

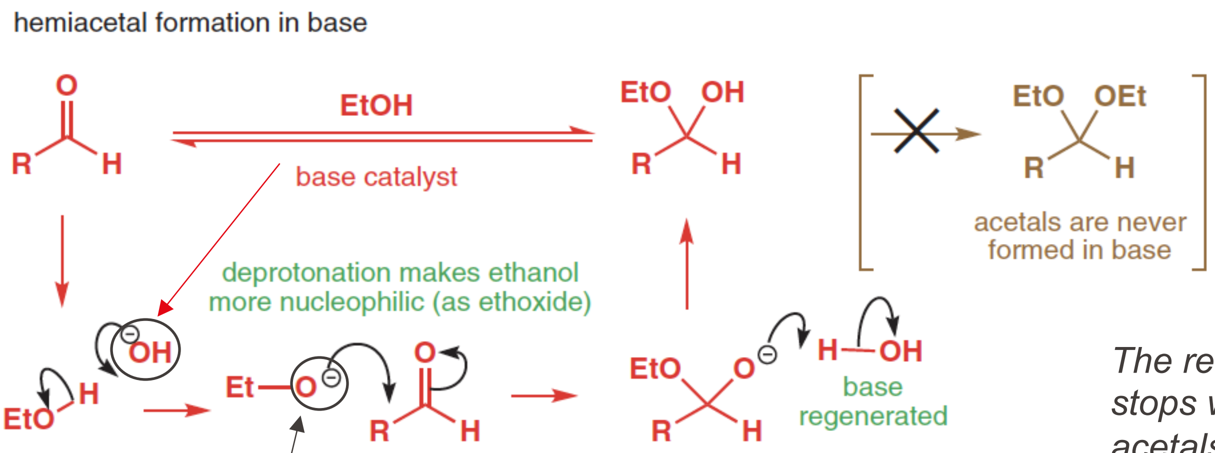
1 - Base activates the alcohol extracting a proton and creating a negative charge ($^{-}OR_2$)

2 – Nucleophilic attack to the electrophilic carbon ($^{-}OR_2$) forming a tetrahedral intermediate

3 – Nucleophilic attack to the acidic proton to form the alcohol

Base Catalysis of hemiacetal and hydride formation

The first step is now deprotonation of the ethanol by hydroxide

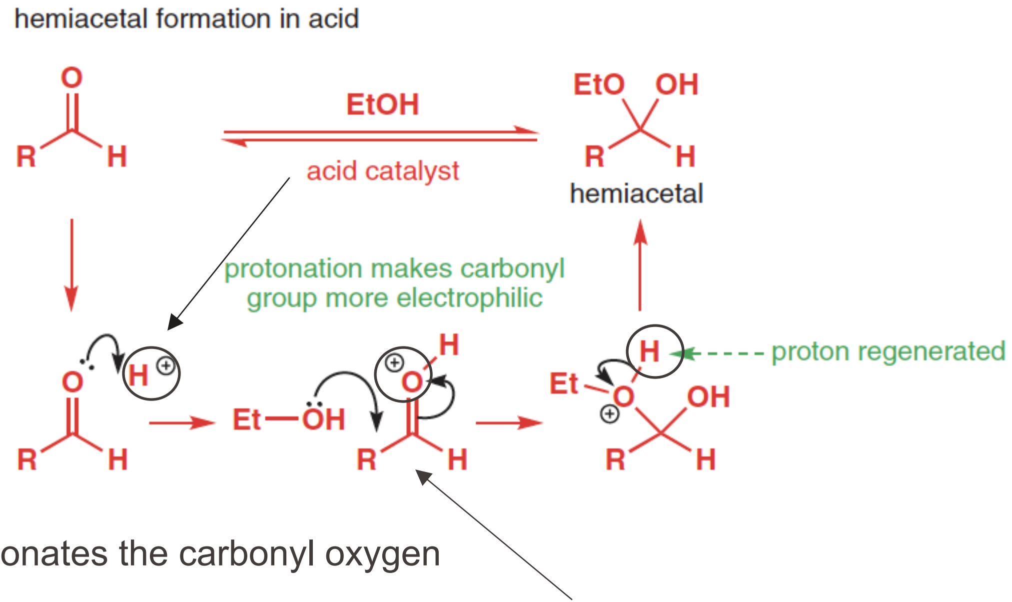


The reaction in base always stops with the hemiacetal—acetals never form in base

The negative charge makes it much more nucleophilic -> reacts faster

Acid Catalysis of hemiacetal and hydride formation

The first step is now protonation of the carbonyl group's lone pair



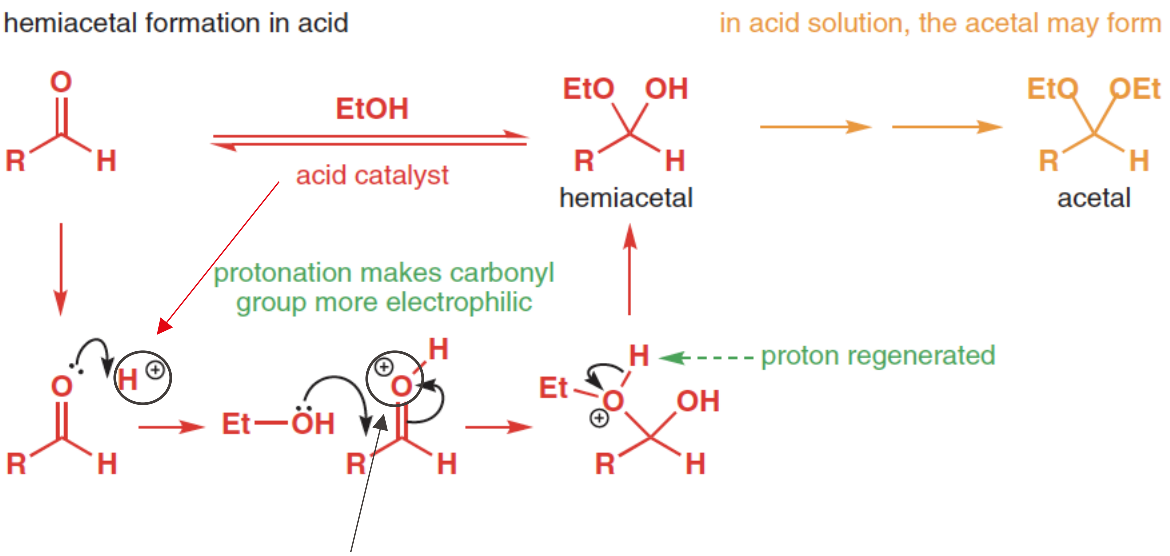
-Acid protonates the carbonyl oxygen

-Positive charge makes the carbon more electrophilic – reacts faster

-Proton is attacked by the deprotonated acid (e.g. A^-)

Acid Catalysis of hemiacetal and hydride formation

The first step is now protonation of the carbonyl group's lone pair

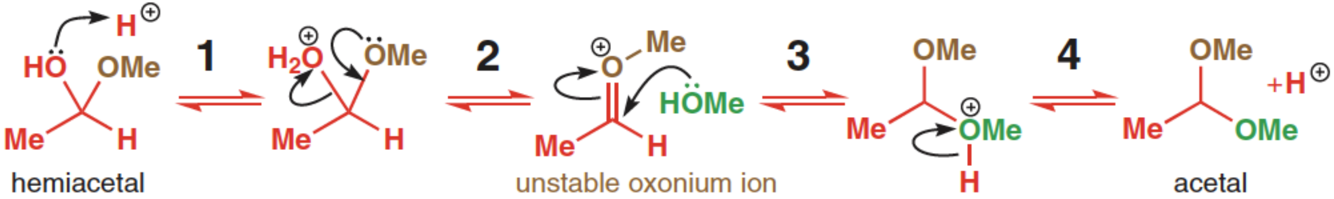


In acid it is also possible for the hemiacetal to react further with the alcohol to form an acetal

The positive charge makes it much more electrophilic
-> reacts faster

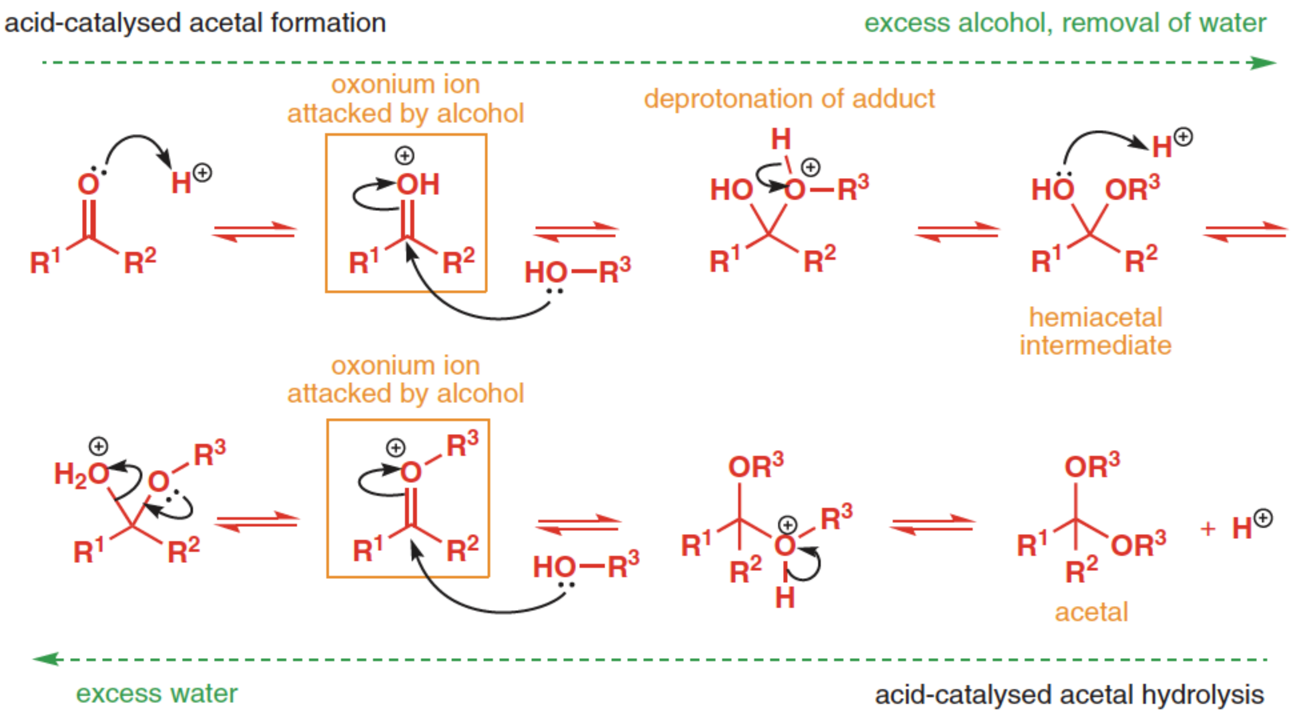
Formation of Acetals under acidic conditions

acid-catalysed acetal formation from hemiacetal



1. ***Protonation****: Acidic conditions protonate the hydroxyl group of the hemiacetal, forming an oxonium ion. Making the hydroxyl a good leaving group*
2. ***Elimination****: Loss of a water molecule occurs, leading to the generation of an unstable oxonium ion, characterized by high reactivity.*
3. ***Nucleophilic Addition****: Addition of an alcohol molecule (like methanol) occurs, breaking the π bond of the oxonium ion, resulting in a new intermediate.*
4. ***Deprotonation****: A proton transfer happens, leading to the loss of a proton and the formation of the desired acetal. This acetal contains two -OR groups on the same carbon atom.*

The formation of Hemi-/Acetals is a controllable equilibrium

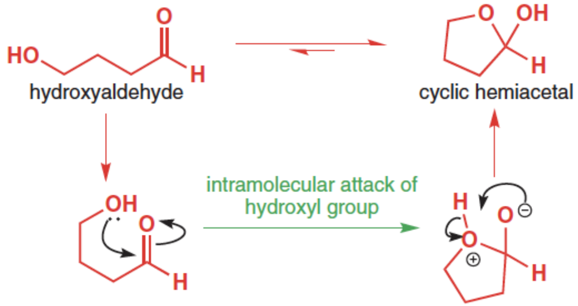


With aqueous acid, the hydrolysis of acyclic acetals is very easy. Not in basic conditions!

Intramolecular cyclization can stabilize hemiacetals

Hemiacetal formation is reversible, and hemiacetals are stabilized by the same special structural features as those of hydrates

Stability depends on size of the ring:
Five and six-membered rings are free from strain

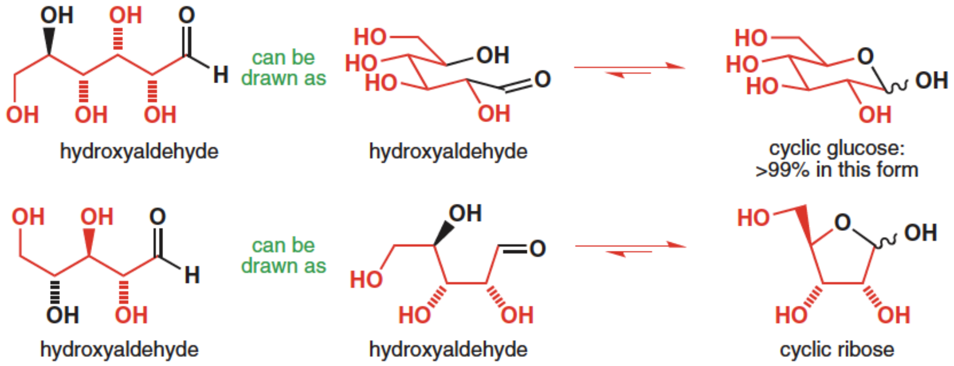


hydroxyaldehyde

cyclic hemiacetal

intramolecular attack of hydroxyl group

Stability depends on size of the ring:
Five and six-membered rings are free from strain



hydroxyaldehyde

can be drawn as

hydroxyaldehyde

cyclic glucose: >99% in this form

hydroxyaldehyde

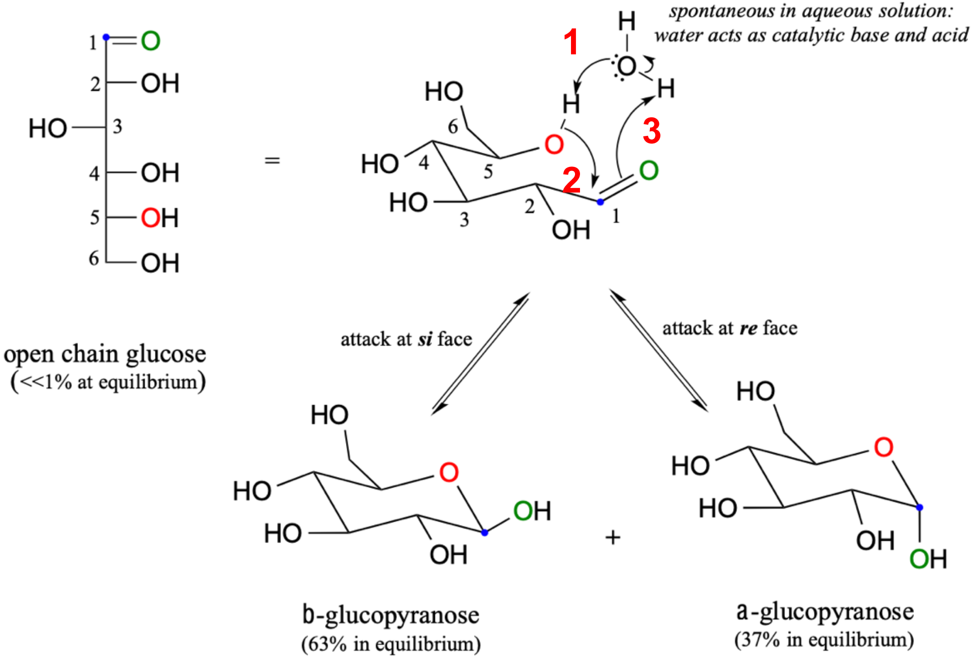
can be drawn as

hydroxyaldehyde

cyclic ribose

>99% of glucose is cyclic in solution

Sugars as intramolecular hemiacetals and hemiketals

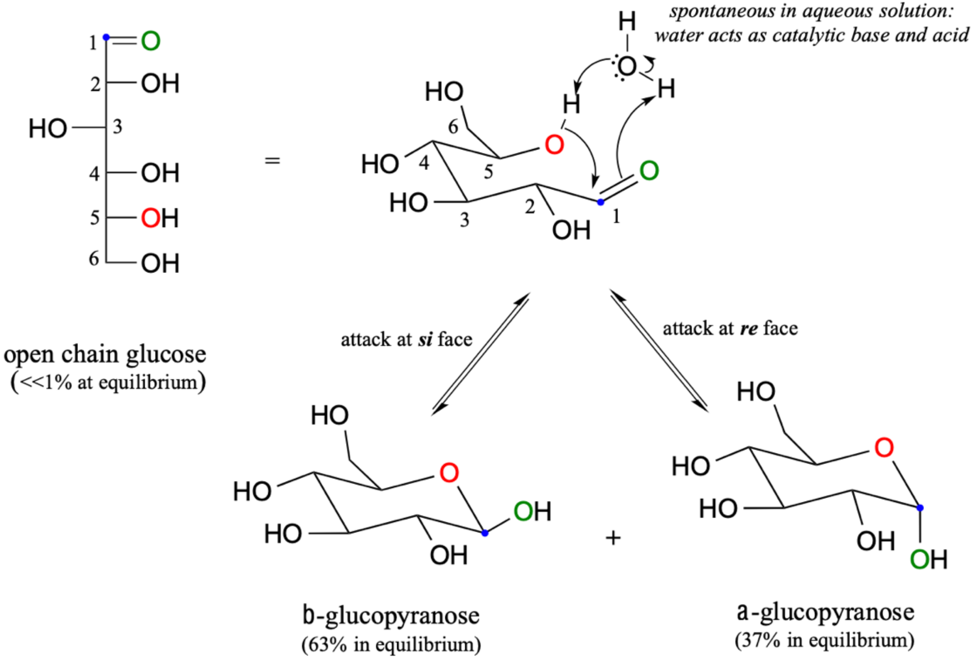


-Water attacks alcohol group forming a RO^- and an H_3O^+

-Attack to the electrophilic carbonyl carbon

-Negative species formed in the carbonyl oxygen that attacks the

Sugars as intramolecular hemiacetals and hemiketals



spontaneous in aqueous solution: water acts as catalytic base and acid

attack at ***si*** face

attack at ***re*** face

open chain glucose
(<<1% at equilibrium)

b-glucopyranose
(63% in equilibrium)

a-glucopyranose
(37% in equilibrium)

Notice the product isomers

-In sugars these are called anomers

-The relative proportion is determined by the relative stability

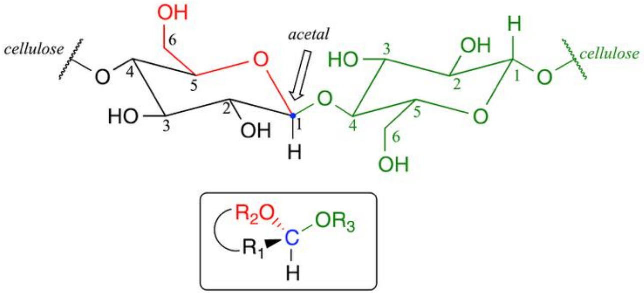
-They are referred to beta and alpha

-Which one is axial and which one equatorial ?

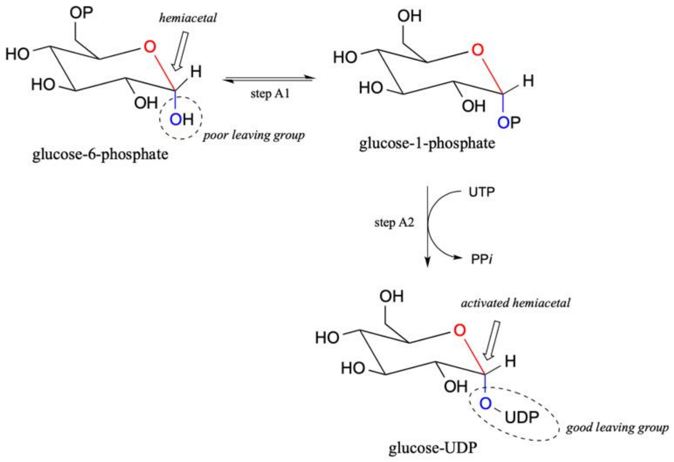
Formation and breaking of Glycosidic bonds in sugars

Glycosyltransferases: These enzymes catalyze the **formation** of **glycosidic bonds** by transferring sugar moieties, enabling the creation of acetal linkages crucial in the synthesis of complex carbohydrates.

Glycosidases: These enzymes facilitate the **breakdown** of **glycosidic bonds** through hydrolysis, cleaving acetal linkages and releasing simple sugar units, essential for digestion and nutrient absorption in biological systems.



First we get a good leaving group



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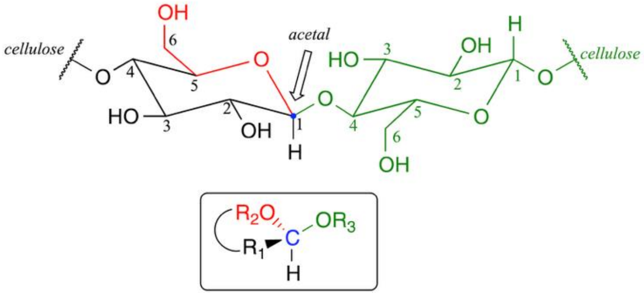
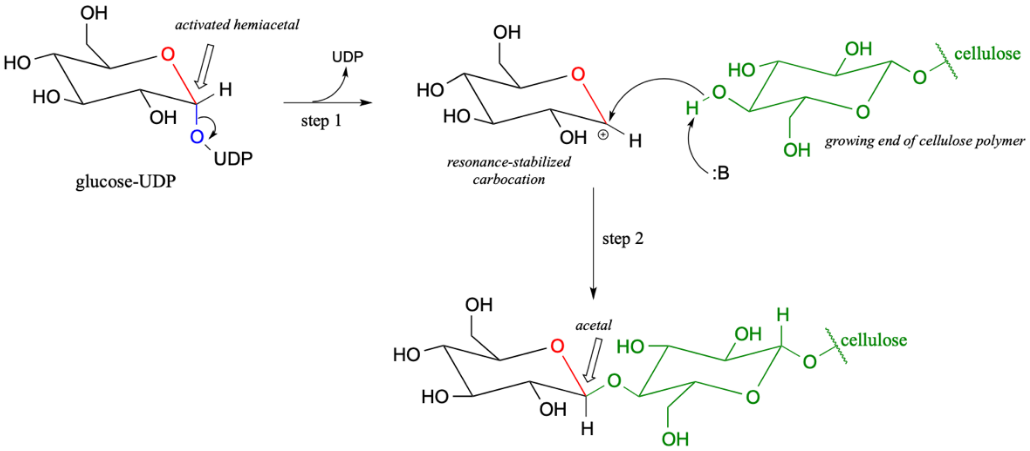
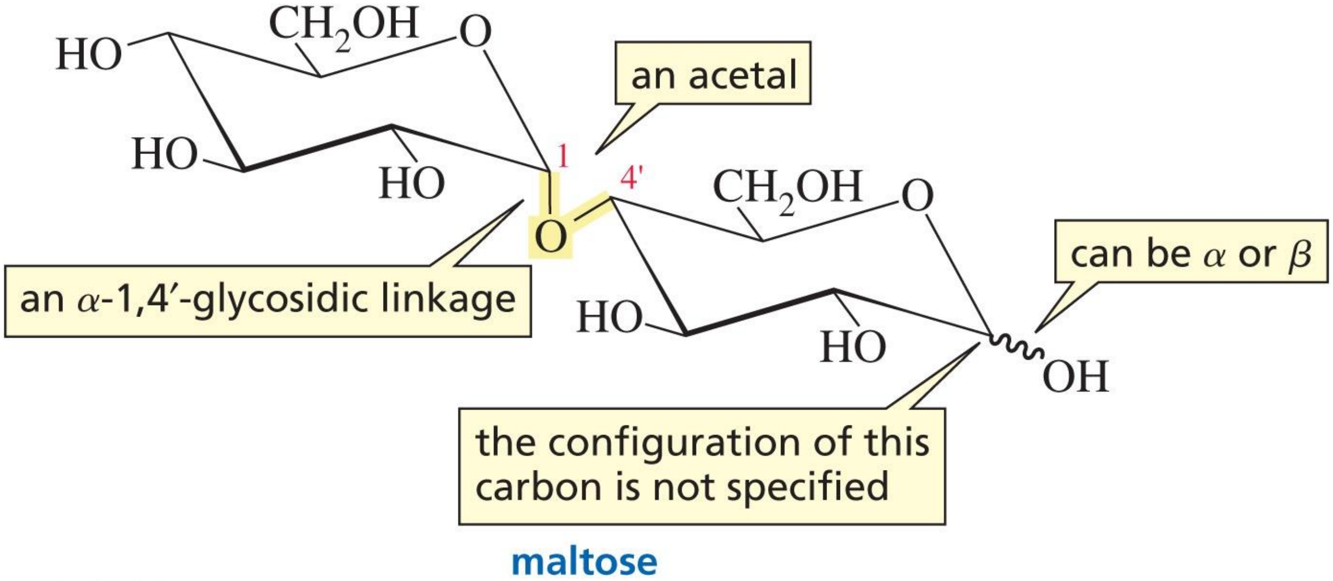


Second an acetal bond is formed

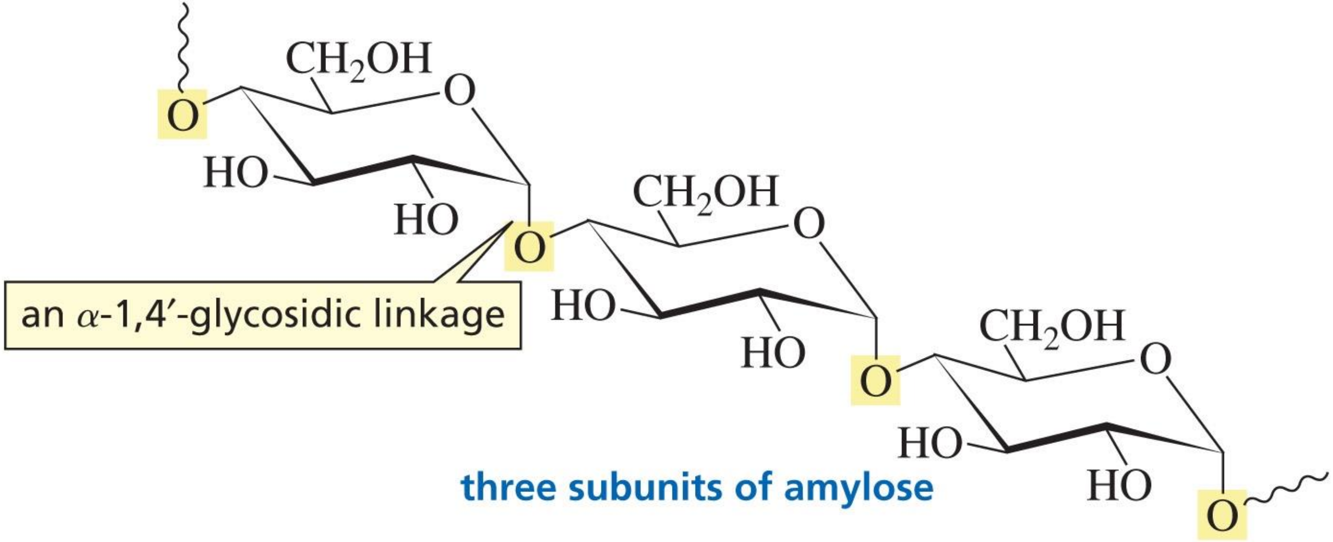


Maltose



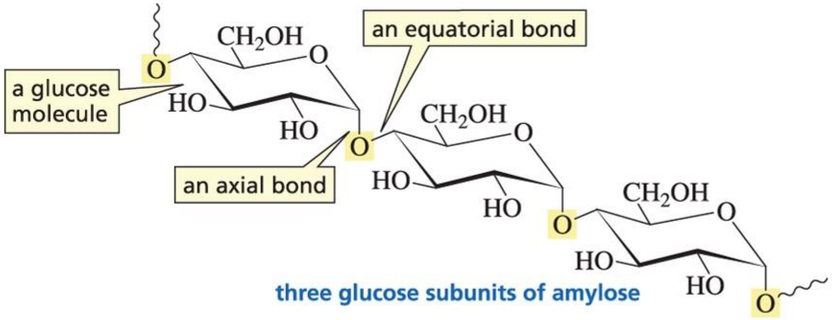
Maltose is a disaccharide.

Amylose



About 20% of starch is amylose.

The Only Difference Between Starch and Cotton is an Equatorial Bond Versus an Axial Bond



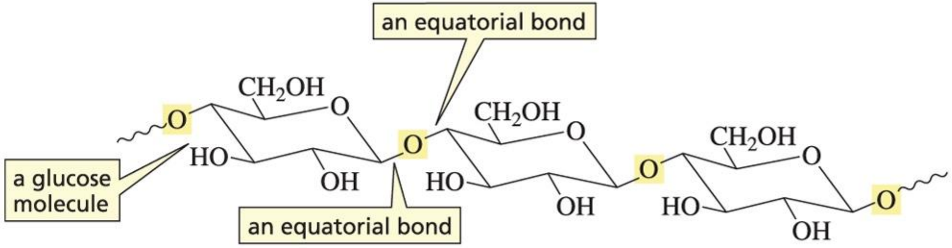
a glucose molecule

an equatorial bond

an axial bond

three glucose subunits of amylose

foods rich in starch



an equatorial bond

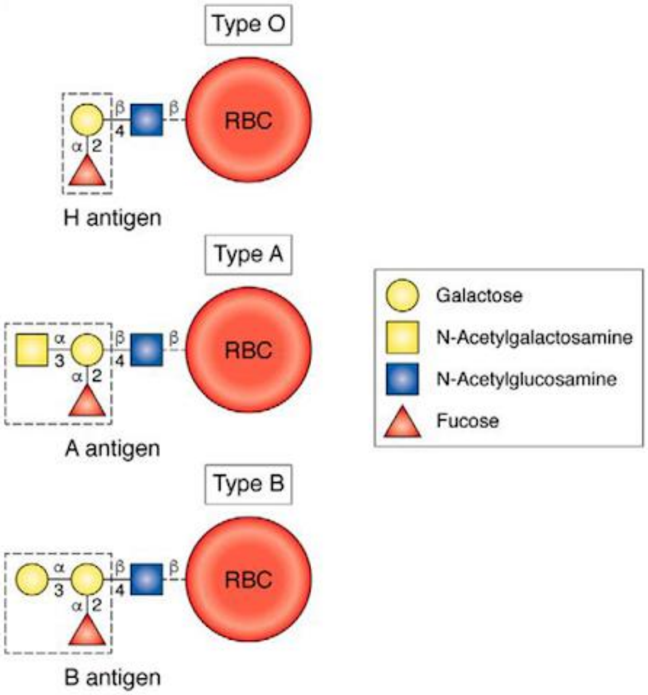
a glucose molecule

an equatorial bond

three glucose subunits of cellulose

cotton plant and cotton towel

How blood groups are defined



Antigens: ABO blood groups are based on the presence or absence of specific antigens (carbohydrate molecules) on the surface of red blood cells.

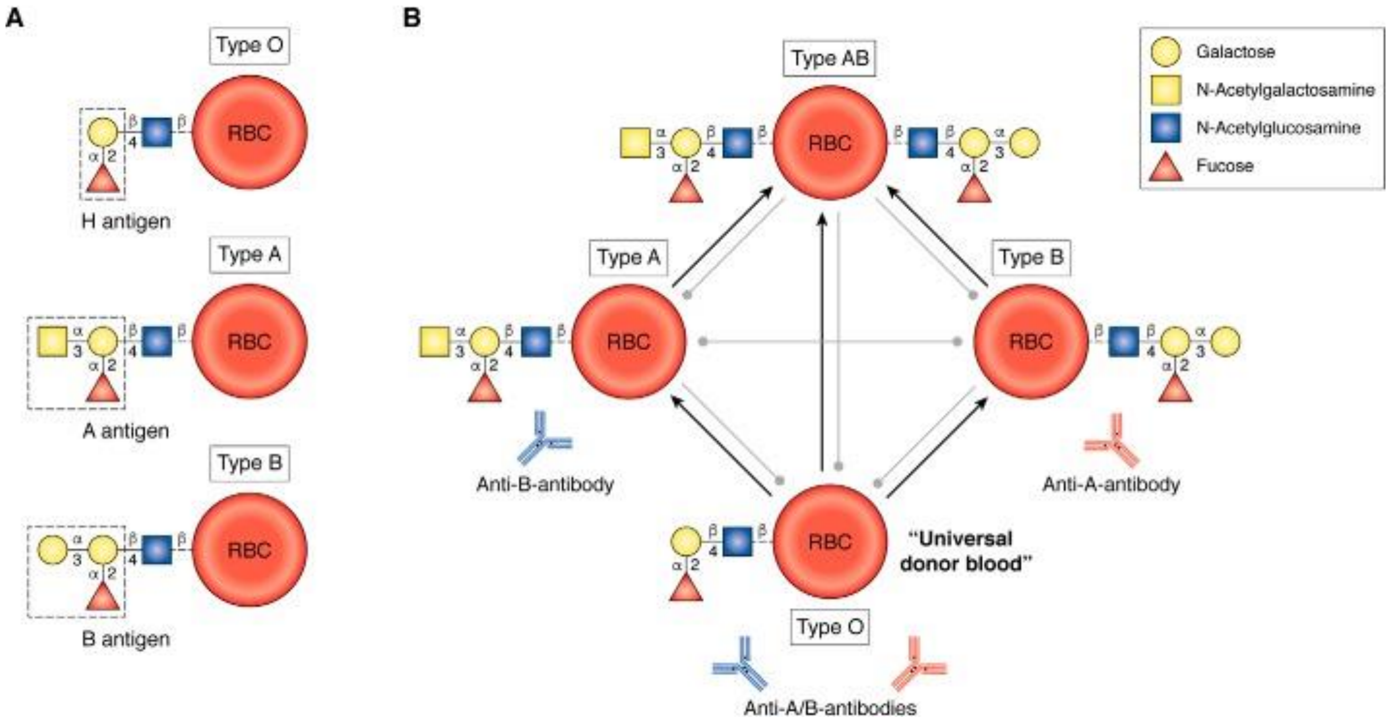
Antigen Types:

Blood Type A: Contains A antigens (oligosaccharides with N-acetylgalactosamine) on the red blood cell surface.
Blood Type B: Carries B antigens (oligosaccharides with galactose) on the red blood cell surface.
Blood Type AB: Exhibits both A and B antigens on the red blood cell surface.
Blood Type O: Lacks both A and B antigens on the red blood cell surface.

Genetic Basis: The ABO blood group system is controlled by the ABO gene, which encodes the glycosyltransferase enzymes responsible for adding specific sugars to the precursor oligosaccharide chains on red blood cells.

Rahfeld P, Withers SG, J Biol Chem. 2020 Jan 10;295(2):325-334.

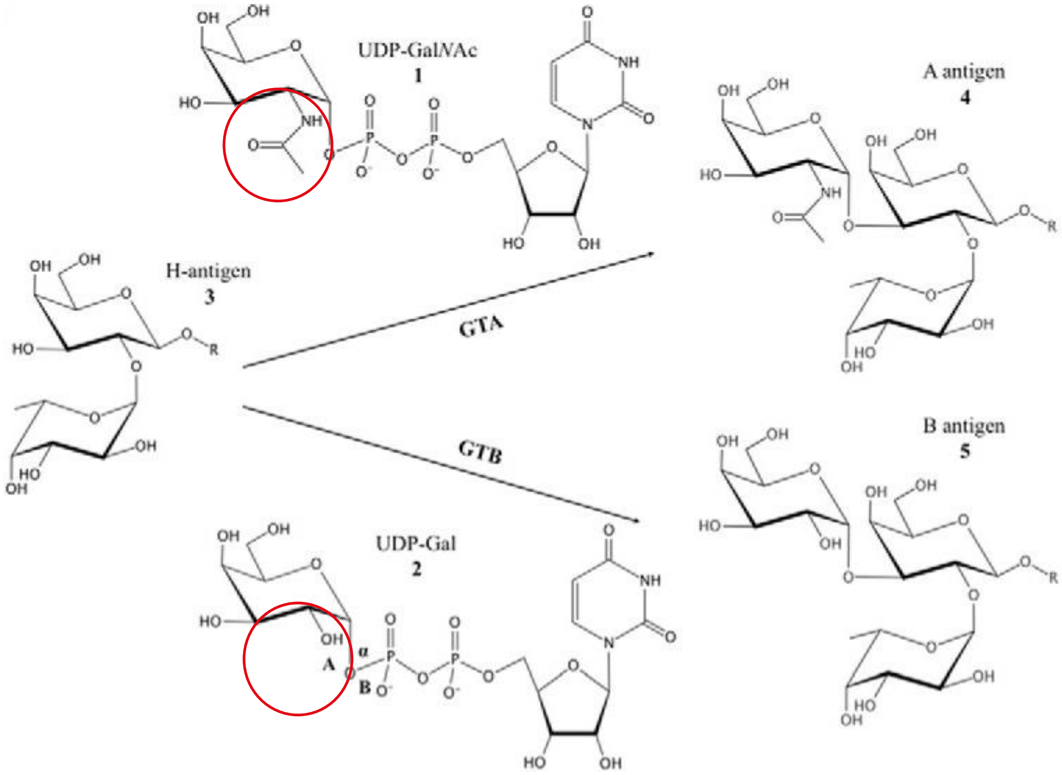
How blood groups are defined



Rahfeld P, Withers SG, J Biol Chem. 2020 Jan 10;295(2):325-334.

How blood groups are defined

Homologous glycosyltransferases **GTA** and **GTB** catalyze the final step in ABO(H) blood group A and B antigen synthesis through sugar transfer from activated donor to the H antigen acceptor

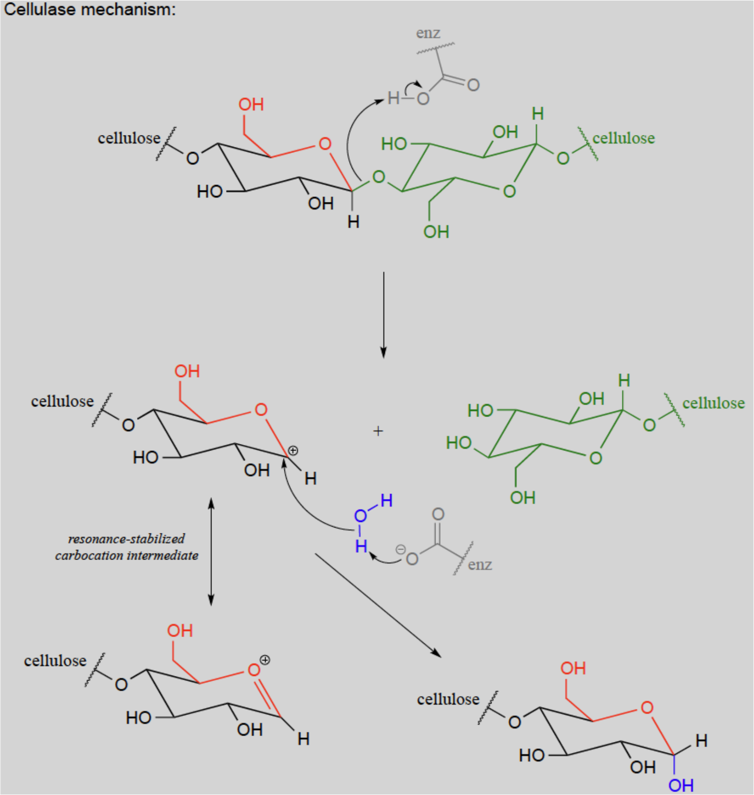


α-(1→3)-*N*-acetylgalactosaminyltransferase
Uses a UDP-GalNAc donor to convert the H-antigen acceptor to the A antigen

α-(1→3)-galactosyltransferase
Uses a UDP-galactose donor to convert the H-antigen acceptor to the B antigen

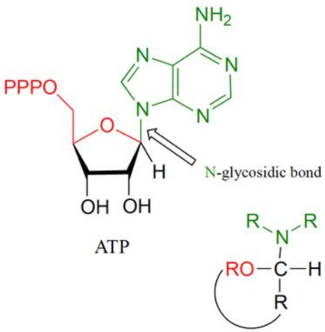
Hydrolosis of Glycosidic bonds

Cellulase mechanism:

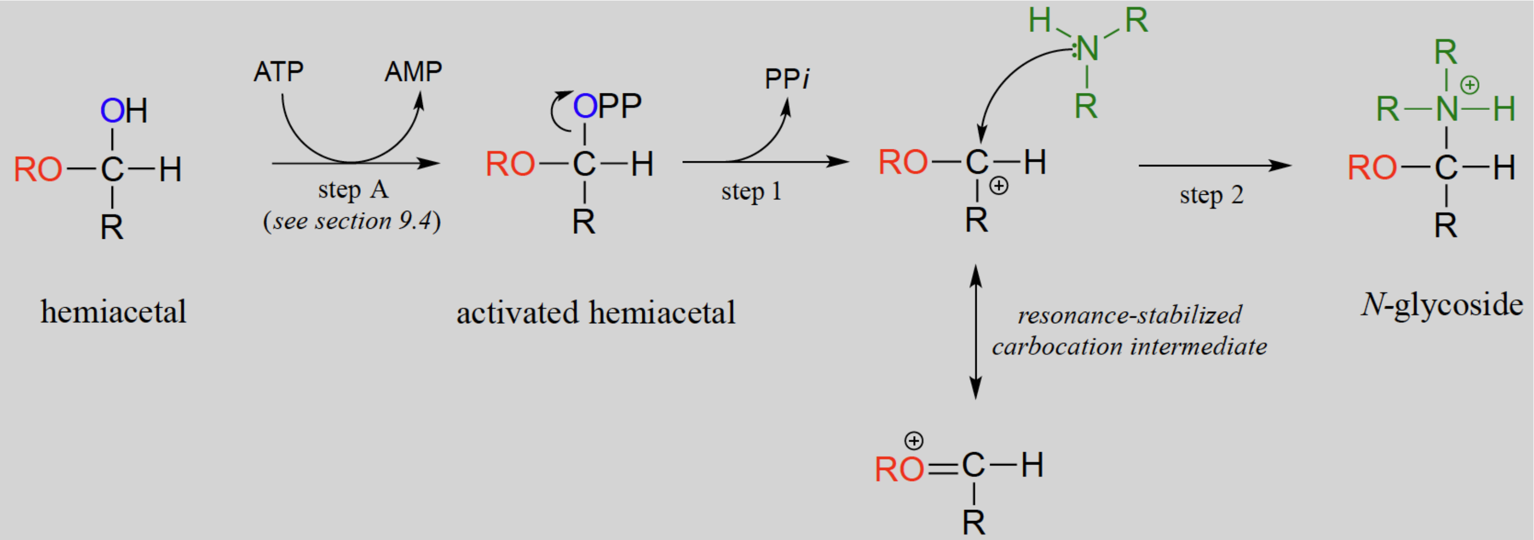


- Pandas primarily consume bamboo
- Pandas lack the enzymes required to digest cellulose on their own
  -> Rely on symbiotic microbes in their digestive tracts to break down cellulose.
- Studies on panda feces from Zoos, discovered over forty cellulose-digesting bacteria.
  -> Important for identification of novel enzymes needed for new foodstocks and bioorganic fuels
- These enzymes break down cellulose to individual glucose molecules

N- glycosidic bonds

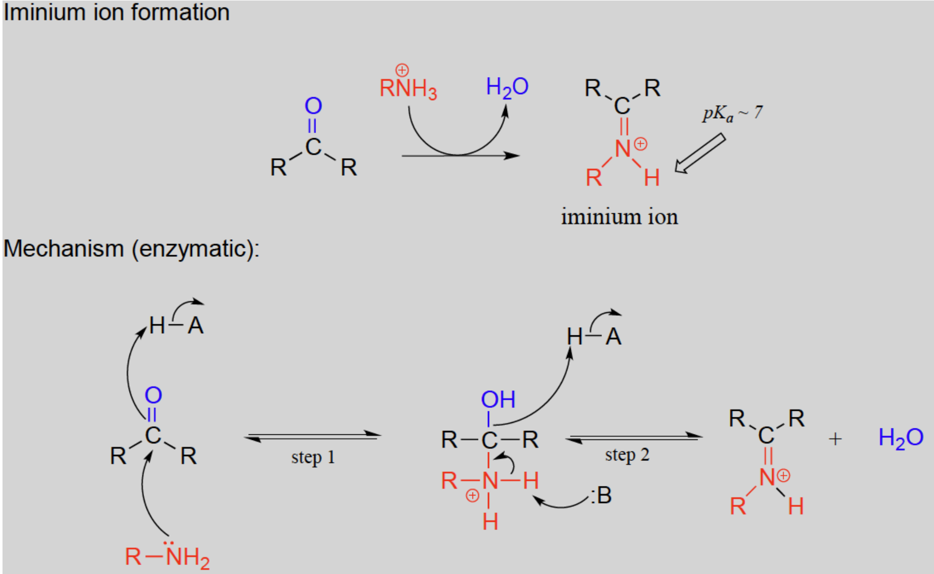


- Hemiacetals can form acetal or ketal bonds when reacted with alcohols, while reacting with amines results in N-glycosidic bonds.
- N-glycosidic bonds involve the anomeric carbon of a sugar linked to both an oxygen and a nitrogen atom from an amine.
- These bonds are vital in nucleosides and nucleotides, connecting the nitrogenous bases (A, G, C, T, U) to the sugar backbone in DNA and RNA.



Imines and iminium ions

Functional group in which the C=O double bond is replaced by a **C=N double bond** -> Also known as **Schiff-Base**



The conversion of an iminium **back to an aldehyde or ketone** is a **hydrolytic process** (bonds are broken by a water molecule), and mechanistically is simply the reverse of iminium formation

Nucleophilic Addition Step

- Amine's nitrogen attacks the carbonyl carbon, leading to hemiacetal/hemiketal formation.
- Forms an intermediate with the nitrogen bonded to the carbon, resembling early acetal/ketal formation.

Elimination of Oxygen

- Instead of a second amine attacking, nitrogen's lone pair displaces the oxygen from the carbon.
- Results in the displacement of a water molecule and the formation of a carbon-nitrogen double bond (C=N), creating an iminium ion.

Let’s take a look at a reaction

What to know

-Recognize aldehyde and ketone groups in organic biomolecules

-Explain the bonding picture for aldehyde and ketone groups

-Why the carbonyl carbon in aldehyde or ketone is electrophile

-Draw curved arrow mechanisms for the discussed reactions

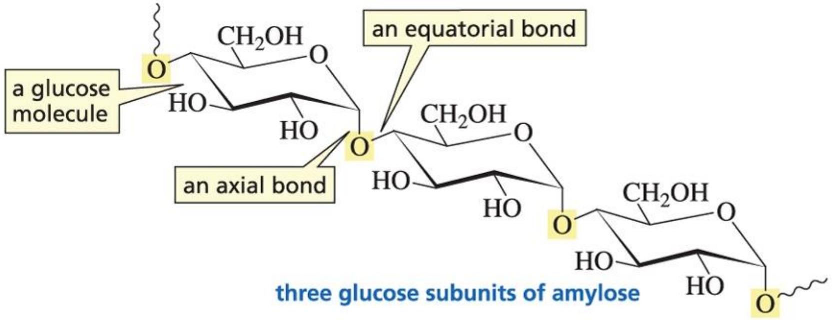
-Stereochemical considerations of a nucleophilic addition to aldehyde/ketone

-Mechanisms for formation of hemiacetal and acetal from aldehyde/ketone

-Mechanism of imines formation from aldehyde/ketone

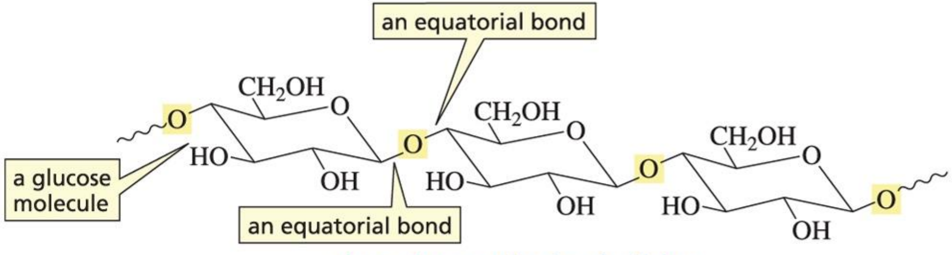
Questions ?

The Only Difference Between Starch and Cotton is an Equatorial Bond Versus an Axial Bond



three glucose subunits of amylose

foods rich in starch



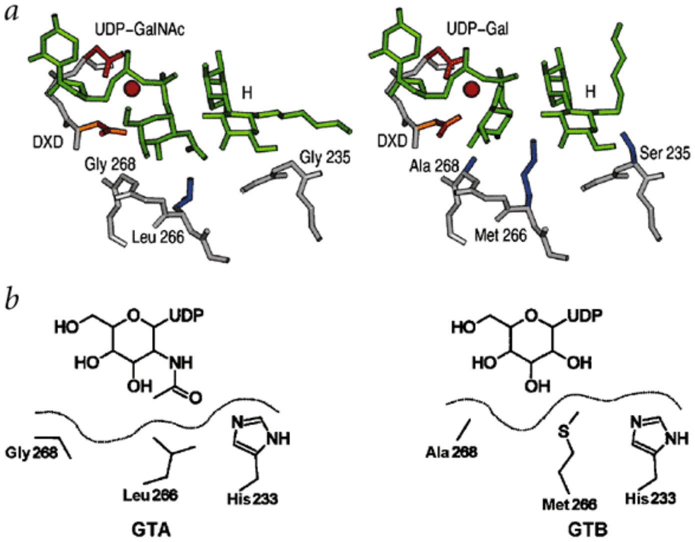
three glucose subunits of cellulose

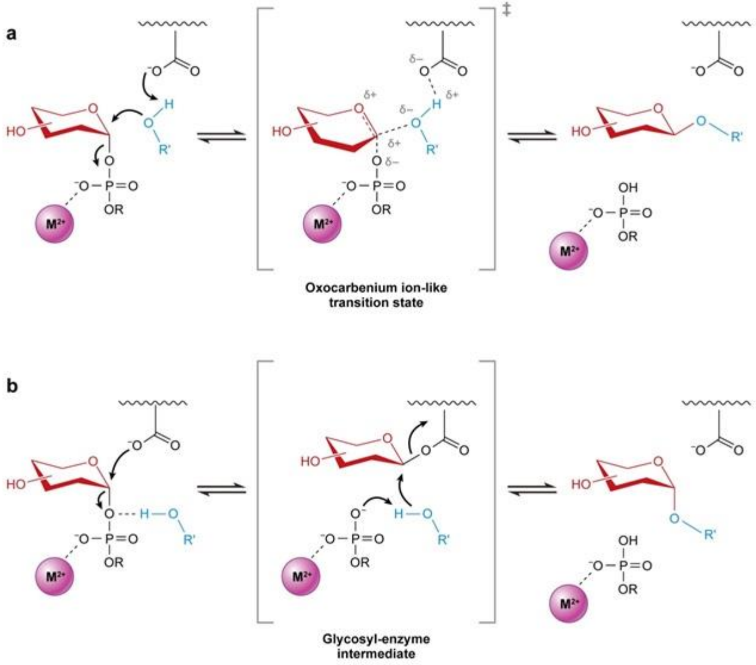
cotton plant and cotton towel

How blood groups are defined

But how can that work? Already discovered in 1901 by Karl Landsteiner, but the genetic basis later in 1990 defined by Fumiichiro Yamamoto and colleagues

Difference between GTA and GTB in 4 critical amino acids: Arg/Gly-176, Gly/Ser-235, **Leu/Met-266**, and **Gly/Ala-268**



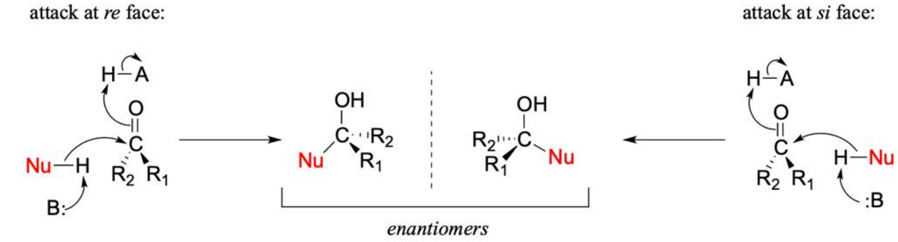


Hypothesis: GTB can easily exclude bulkier A donor (UDP-GalNAc) as the floor of the active site cleft contains the larger critical residues Met 266 and Ala 268 that restrict the space available to UDP-donor sugar moieties. In contrast, the smaller critical residues Leu 266 and Gly 268 in GTA form a larger active site cleft that would lack complementarity with the smaller B donor (UDP-Gal)

Patenaude, S., Seto, N., Borisova, S. *et al. Nat Struct Mol Biol* **9**, 685–690 (2002).
Yamamoto F, Clausen H, White T, Marken J, Hakomori S. Nature. 1990 May 17;345(6272):229-33

Stereochemistry on nucleophilic additions

-Distinguishing *re* and *si* faces in of the planar sp2 carbon



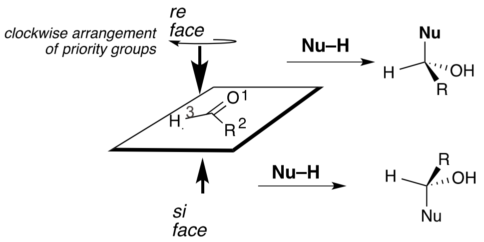
(assume R_1 is higher priority than R_2)

-Remember we go from an sp2 to sp3 configuration of the carbon

-If the R groups are not equivalent – a chiral center is created

-The configuration of the chiral center depends on the face that is attacked

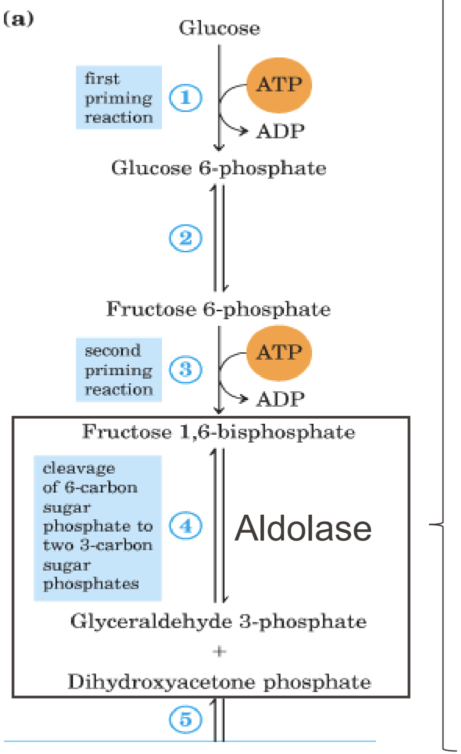
- Let's revise the faces assignment



Cahn-Ingold-Prelog

1) rank substituents:
    1) Higher molecular weight
    2) If identical move to next atom away from chiral center
    3) Multiple bonds count as two identical substituent atoms

Schiff-Base as common intermediates in enzymatic reactions



Reaction Mechanism

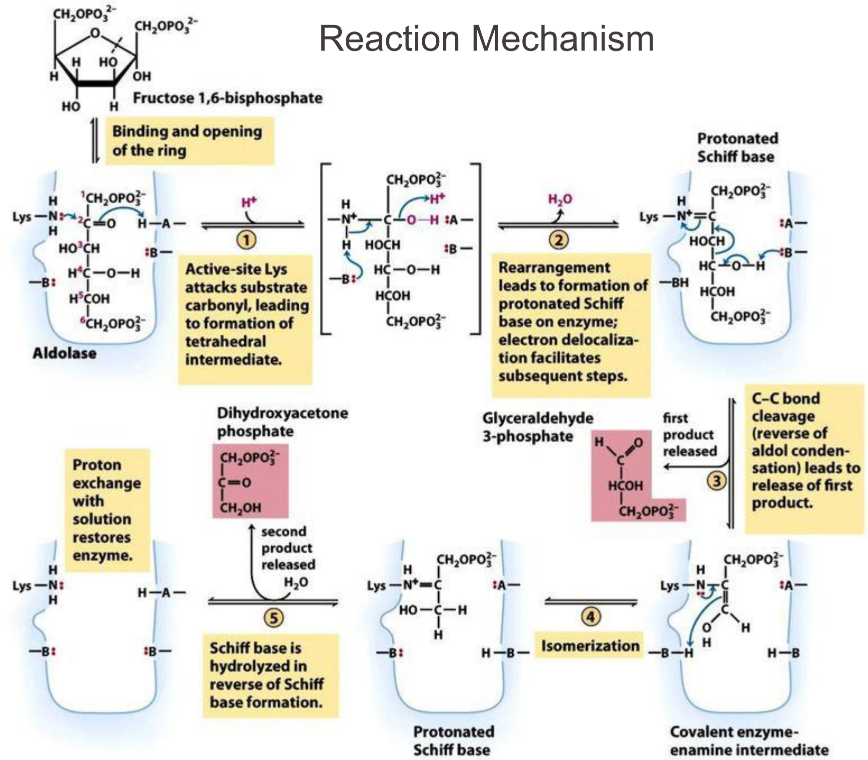


Figure 14-5
Lehninger Principles of Biochemistry, Fifth Edition