

CHE 2060: Principles of Organic Chem



7. Nucleophilic carbonyl addition reactions

Introduction: How much panda power will your next car have?

7.1: Nucleophilic additions to aldehydes and ketones: an overview

7.1A: Remember aldehydes and ketones?

7.1B: Nucleophilic addition

7.1C: Stereochemistry of nucleophilic addition

7.2: Hemiacetals, hemiketals and hydrates

7.2A: Overview

7.2B: Sugars as intramolecular hemiacetals and hemiketals

7.3: Acetals and ketals

7.3A: Overview

7.3B: Glycosidic bond formation

7.3C: Glycosidic bond hydrolysis

7.4: N-glycosidic bonds

7.5: Imines and iminium ions

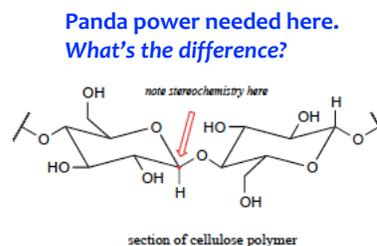
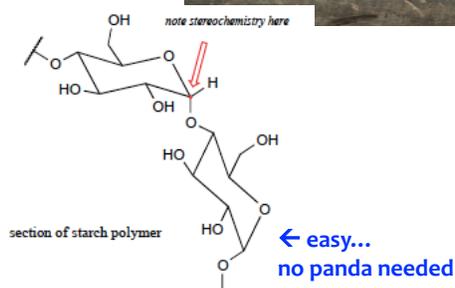
7.6: A look ahead: addition of carbon and hydride nucleophiles to carbonyls

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7. Nucleophilic addition to carbonyls



Introduction: Panda power?



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7. Nucleophilic addition to carbonyls



Big ideas:

1. Nucleophilic addition of alcohols to the carbonyl group of aldehydes and ketones produces hemiacetals and hemiketals, and addition of a second alcohol produces acetals and ketals.
2. This nucleophilic addition reaction plays a major role in carbohydrate chemistry.

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7. Nucleophilic addition to carbonyls



7.1: Nucleophilic additions to aldehydes and ketones – an overview

7.1A: Remember aldehydes and ketones?

7.1B: Nucleophilic addition

7.1C: Stereochemistry of nucleophilic addition

Resources for students:

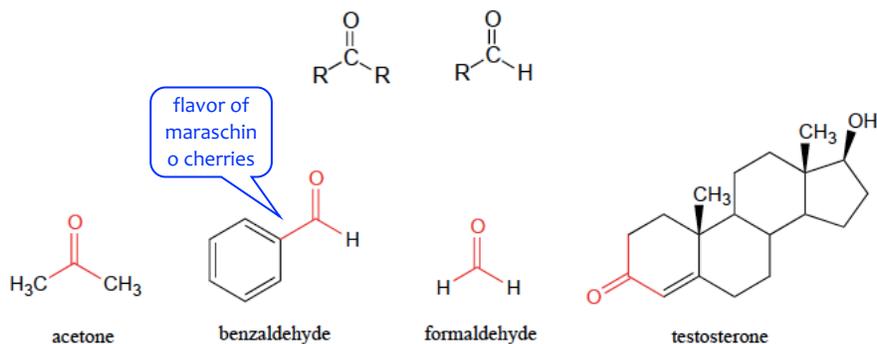
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Remember aldehydes and ketones?



This module focuses on the chemistry of **carbonyl groups**, carbons double bonded an oxygen atom and also bonded to two other atoms.

- We'll start with the **aldehyde** and **ketone** groups



How would you characterize the carbonyl group and these functional groups?

- What characteristics or properties will influence their reactivity?

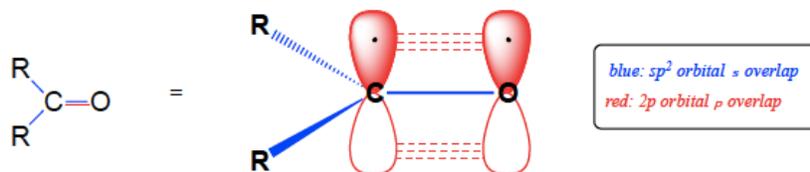
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Carbonyl groups are sp^2 hybridized



The **sp^2 hybridization** means:

- trigonal planar σ bonds
- π bond that is perpendicular to the σ bonds



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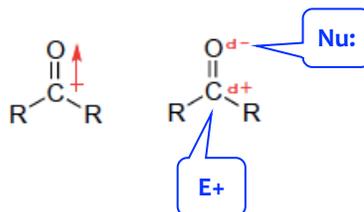
Carbonyl polarity and resonance



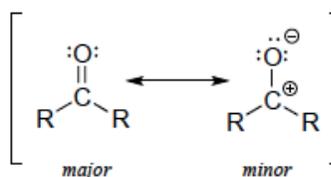
Other important characteristics?

Carbonyl groups are **polar** and have dipolar charges that give the group:

- E+ carbon
- Nu: oxygen



Carbonyl groups have **resonance** that both stabilizes the group and can increase its polarity.



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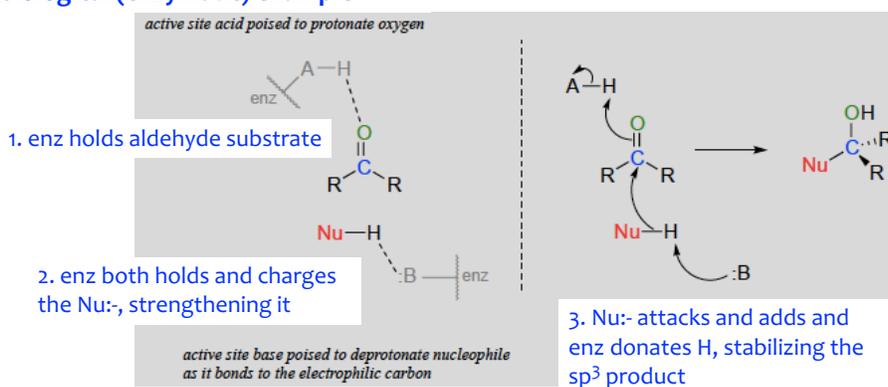
Carbonyl's E+ is a target for Nu: attack



Nucleophilic addition occurs when a powerful Nu: attacks the electrophilic carbon of the carbonyl group.

- The Nu: is added as a fourth substituent.
- The double (carbonyl) bond is destroyed.
- The charge of the carbonyl O is often negated when it bonds to a H atom.

biological (enzymatic) example



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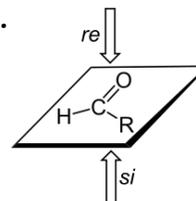
Stereochemistry



Carbonyls with two different substituents have **re and si faces**.

Re face: clockwise substituents have ↓ Cahn-Ingold-Prelog priority

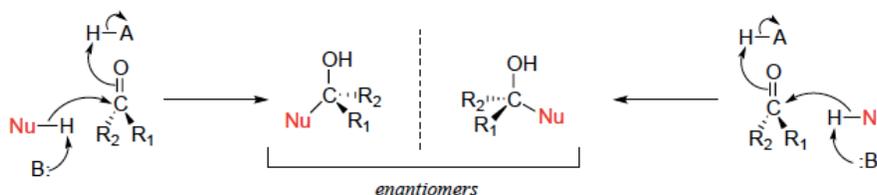
Si face: counter-clockwise substituents ↓ CIP priority



So Nu: addition to carbonyls produces sp^3 **products that will be chiral** if R_1 and R_2 are different.

attack at *re* face:

attack at *si* face:



(assume R_1 is higher priority than R_2)

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Can you?



- (1) Draw and distinguish between aldehydes and ketones?
- (2) Describe the characteristics of carbonyls that make this Nu: addition likely?
- (3) List and describe the general steps of a Nu: addition reaction to a carbonyl?
- (4) Describe and explain changes in hybridization and stereochemistry that occur during Nu: addition to carbonyls?

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7. Nucleophilic addition to carbonyls



7.2: Hemiacetals, hemiketals and hydrates

7.2A: Overview

7.2B: Sugars as intramolecular hemiacetals and hemiketals

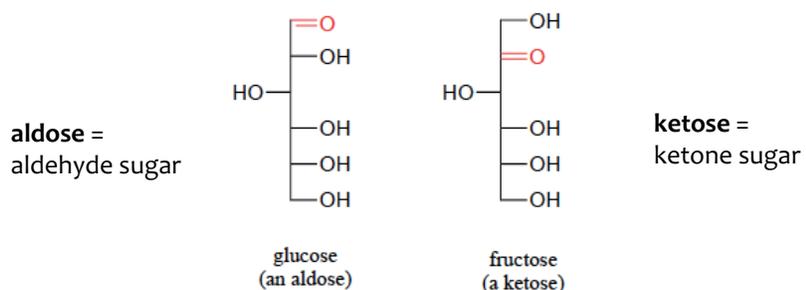
Resources for students:

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Aldehydes, ketones rule sugar reactions



Aldehydes and ketones, specifically their carbonyl groups, dominate the chemical and biochemical **reactions** of **sugars and starches**.



Glucose and fructose have the same molecular formulas.
What type of isomers are they?

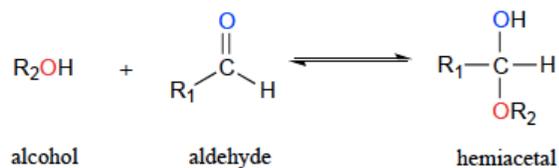
Structural or constitutional isomers: same molecular formula but different connectivity. Bonds must be broken and remade.

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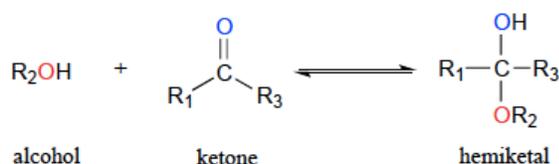
Hemiacetals and hemiketals



One of the most important examples of a nucleophilic addition reaction in biochemistry, and in carbohydrate chemistry in particular, is the **addition** of an **alcohol (Nu:)** to a **ketone or aldehyde (E+ carbonyl groups)**.



'Hemi' meaning half



Addition of another alcohol produces 'whole' **acetals** or **ketals**.

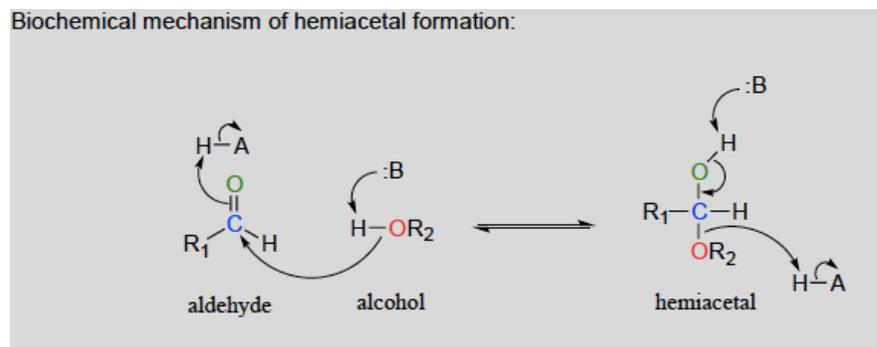
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Reversible Nu: addition mechanism



1. A base removes H from the alcohol strengthening the Nu:-
2. The ethoxide (R₂O⁻) Nu:- attacks carbonyl E+ (a kick in the crotch).
3. The carbonyl's π bond swings up and, acting as a Nu:-, attacks the weak acid, grabbing a H atom and becoming an OH group.

Biochemical mechanism of hemiacetal formation:



Because the **energy state** of the hemiacetal is greater than the energy state of the aldehyde, **equilibrium favors reactants for open-chain molecules**.

- However, **cyclic** hemiacetals have a lower energy level and **are favored**.

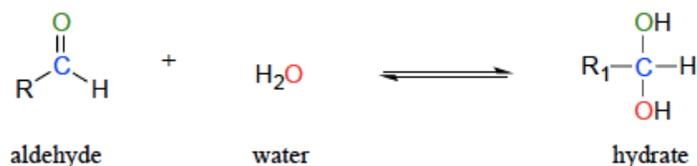
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Hydrate forms



Hydrate forms: created by addition of water (an alcohol) to aldehydes and ketones.

- In aqueous solutions, aldehydes and ketones take their hydrate forms.



For the sake of simplicity, we will draw aldehydes and ketones as we have been and not as their hydrate forms.

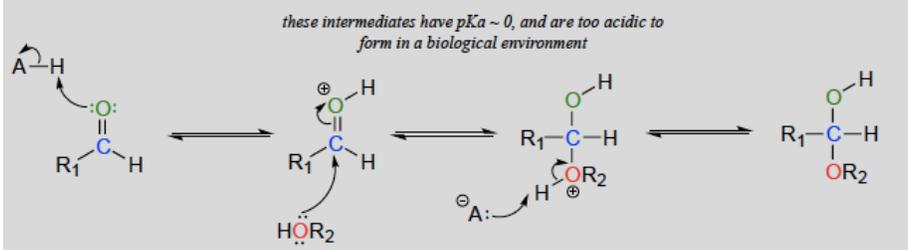
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Laboratory reactions are acid-catalyzed



In the organic lab, **strong acids** are used as **catalysts** to **strengthen the carbonyl carbon's E+** by enhancing polarization. This enhance the Nu: addition to aldehydes and ketones.

Acid-catalyzed hemiacetal formation (non-biological):



- Note that the strength of the acid catalyst and the intermediates wouldn't occur or function in biological systems.

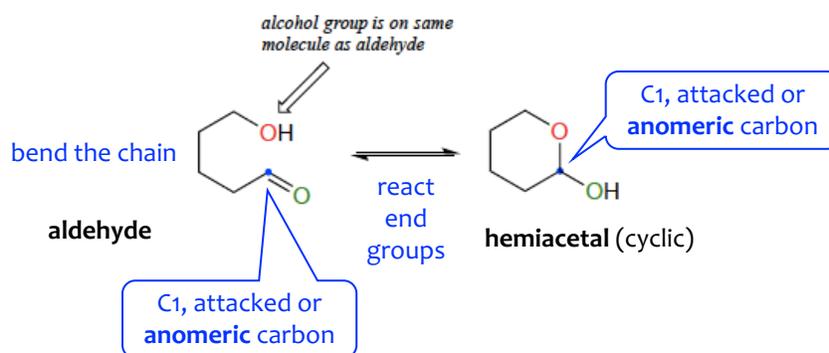
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Intramolecular reactions → cyclic



Sugars exist in both **open-chain** forms (shown on the previous slide) and **cyclic** forms shown here.

- In aqueous solutions open-chain and cyclic forms **interconvert** quickly by spontaneous, non-enzymatic, **intramolecular** reactions.
 - Cyclic forms **predominate** in aqueous solutions.

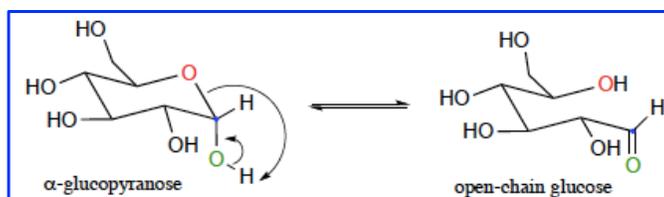


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Try this



Draw a mechanism for the interconversion of α -glucopyranose to the open-chain aldehyde form of glucose.



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Glucose is a cyclic hemiacetal



Glucose is a hemiacetal formed by intramolecular reaction of carbons 1 and 6.

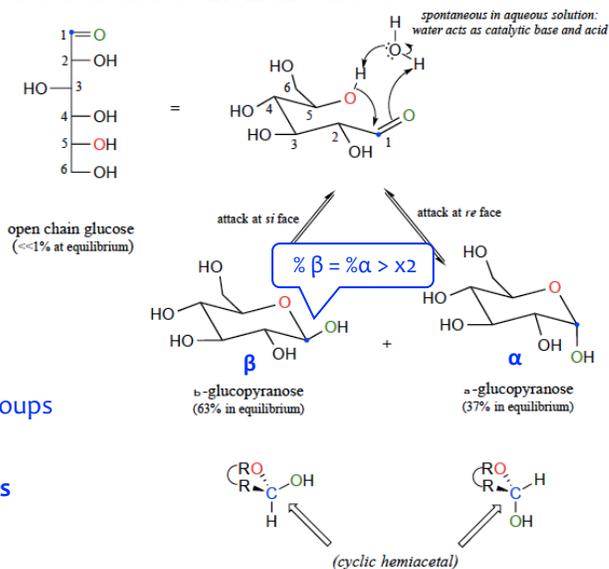
- For glucose, carbon 1 is the 'attacked' or **anomeric carbon**.

Two stereoisomers of the cyclic **glycopyranose** product are formed but the **β anomer** dominates.

Why?
Think about energy and stability!

In the **β anomer**, all OH groups are **equatorial**.

In the **α anomer**, **one OH is axial**.



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Fructose is a 6-atom cyclic hemiketal



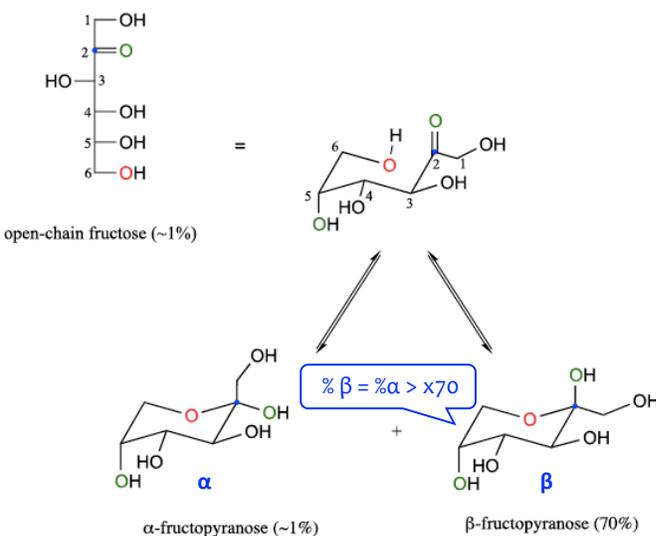
Fructose is a hemiketal formed by intramolecular reaction of carbons 2 and 6.

- For fructose, carbon 2 is the 'attacked' or **anomeric carbon**.

Given what you know about glucopyranose, why is the **β form** of fructopyranose even more strongly favored?

In the **α anomer**, **one bulky methoxy group (CH₂OH) is axial**.

In the **β anomer**, it is equatorial.



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Fructofuranose: a 5-atom cyclic hemiketal



You may have noticed that α and β -fructopyranose only add up to 71% of cyclic fructose. **Why?**

Because a different open to cyclic interconversion produces a 5-atom hemiketal ring, **fructofuranose**, with 2 carbons (rather than 1) outside of the ring.

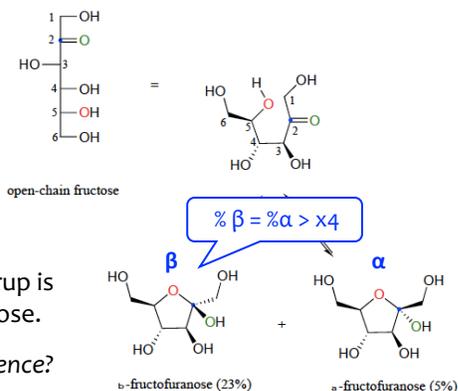
- Formed by intramolecular reaction of carbons 2 and 5.
- Carbon 2 is still the 'attacked' or **anomeric carbon**.

Again, why is the β form favored?

In the α anomer, there is more steric hindrance between the two bulky methoxy groups (CH_2OH).

β -fructopyranose (high-fructose corn syrup is much, much sweeter than β -fructofuranose.

Why would their structures make a difference?

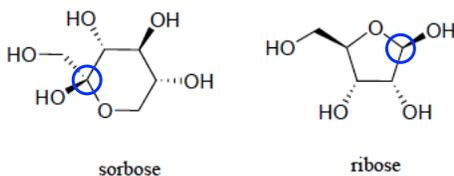


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Try this



Here are two other sugars that exist in equilibrium between open-chain and cyclic forms.



(a) Are they hemiacetals or hemiketals?

Sorbose is a hemiketal (the anomeric carbon isn't bonded to any H).

Ribose is a hemiacetal (the anomeric carbon is bonded to an H).

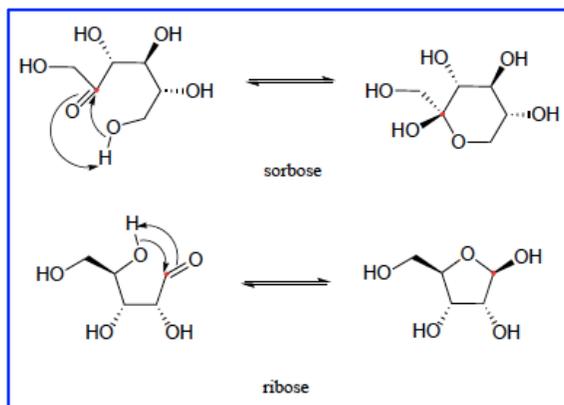
(b) Identify the anomeric carbons for each sugar. ○

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Try this



Draw the mechanisms for the intramolecular reactions that convert each to their open-chain forms.



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Can you?



- (1) Define the terms aldose and ketose?
- (2) Identify and draw the acid-catalyzed mechanism that converts aldehydes to hemiacetals and ketones to hemiketals?
- (3) Compare the energy states of aldehydes, hemiacetals and cyclic hemiacetals?
- (4) Describe and draw the hydrate forms of aldehydes and ketones?
- (5) Define the terms anomeric carbon and anomer? And locate anomeric carbons?
- (6) Draw the mechanism that closes open-chain sugars to form cyclic sugars?
- (7) Explain why one of the anomers, α or β is favored?
- (8) Compare and contrast the structures of glucose, fructose and fructofuranose?

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7. Nucleophilic addition to carbonyls



7.3: Acetals and ketals

7.3A: Overview

7.3B: Glycosidic bond formation

7.3C: Glycosidic bond hydrolysis

Resources for students:

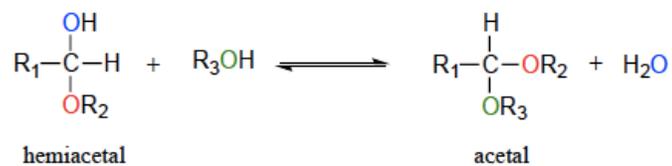
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Acetals



When **hemiacetals** react with **another alcohol** an OR group is substituted for the hemiacetal's OH group producing an **acetal**.

- So two molecules of alcohol must be used to go from aldehyde to acetal.
- The two alcohols can be either the same or different.

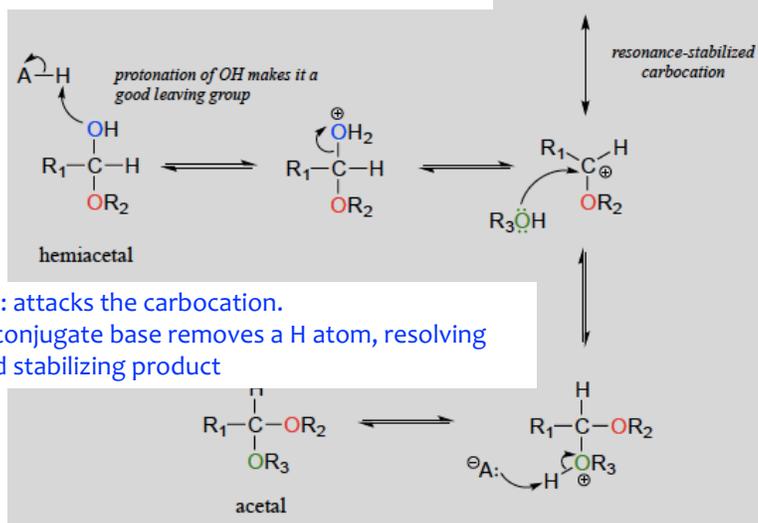


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Lab: acid-catalyzed SN1 rxn



1. Strong acid protonates the OH to make a good LG (H₂O).
2. LG leaves to form a carbocation.



3. Alcohol Nu: attacks the carbocation.
4. Catalyst's conjugate base removes a H atom, resolving charge and stabilizing product

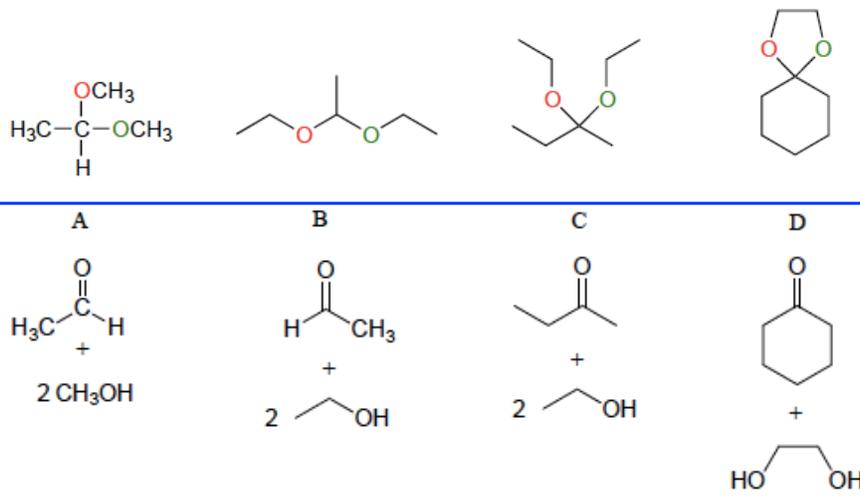
27

Try this



A–D are examples of simple, non-biological acetals or ketals.

- (a) Identify each as an acetal or ketal.
- (b) Draw the starting aldehyde or ketone **and** the starting alcohol for each.

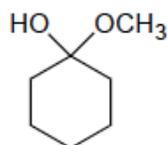


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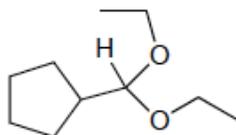
Try this



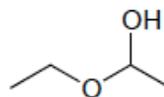
Identify each molecule as a hemiacetal, hemiketal, acetal, ketal, hydrate of an aldehyde or hydrate of a ketone.



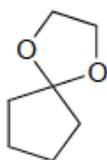
A
hemiketal



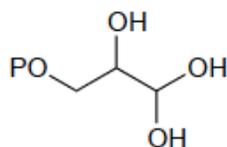
B
acetal



C
hemiacetal



D ketal



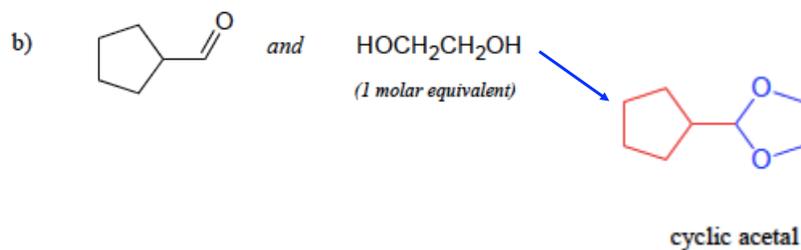
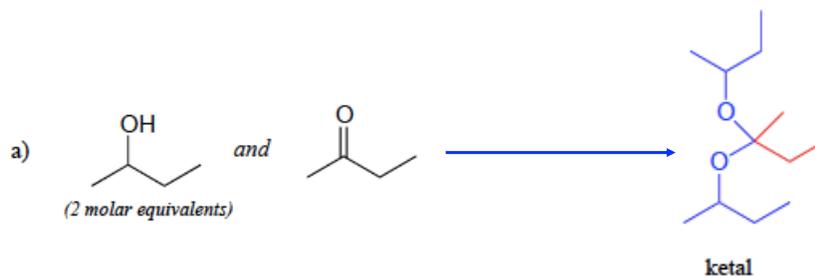
E hydrate of an aldehyde

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Try this



Draw the acetal or ketal product of each of these reactions.

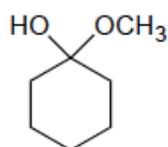


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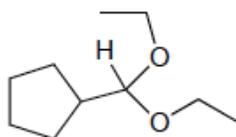
Try this



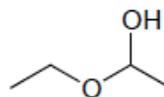
What combination of aldehyde (or ketone) and alcohol is needed to produce each of these molecules?



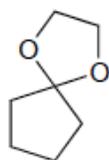
A



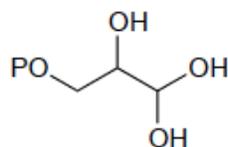
B



C



D



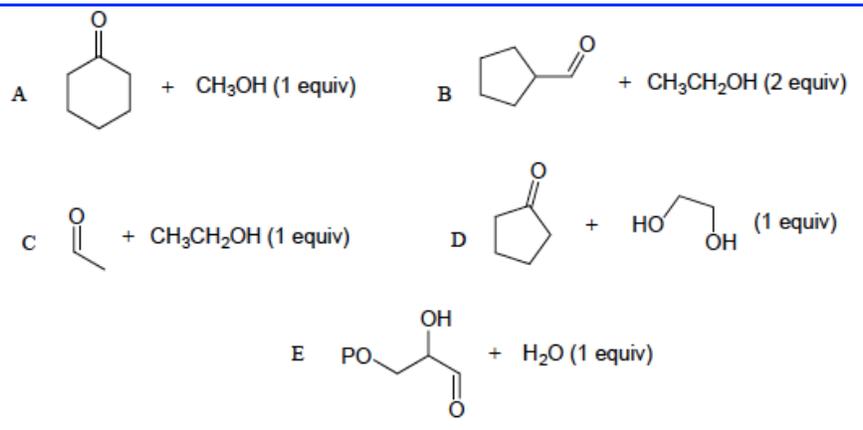
E

31

Try this



What combination of aldehyde (or ketone) and alcohol is needed to produce each of these molecules?



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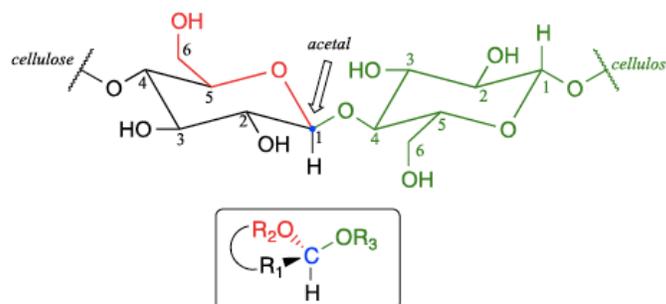
Glycosidic bond formation



Glycosidic bonds: the bonds formed between sugar monomers to form sugar polymers, aka polysaccharides

The bond shown here is called a **β -1,4 glycosidic bond or linkage** because:

- C1 of the first monomer (1)...
- ... is linked to C4 of the second monomer (4)...
- ... via a stereochemical β linkage (β)

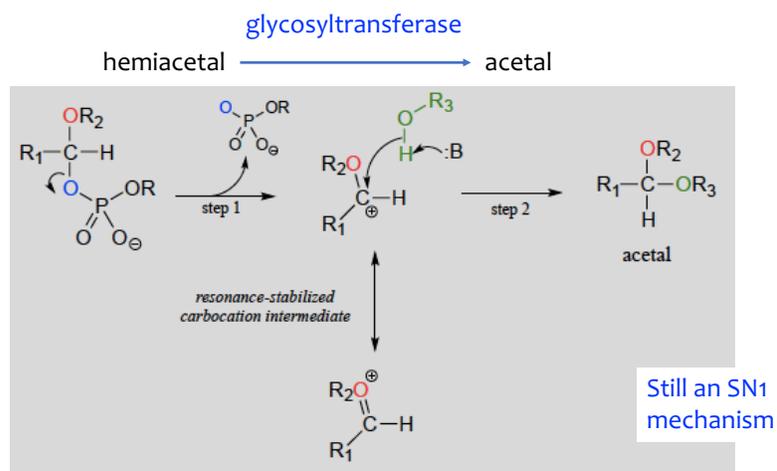


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Glycosyltransferase enzymes



In biological systems, **glycosyltransferase enzymes** are used to form the bonds or linkages between sugar monomers to form polysaccharides.



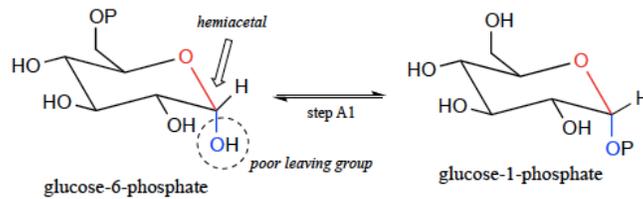
Note that in this biological, enzyme-catalyzed reaction addition of a phosphate group (**phosphorylation**), not a strong acid, is used to create a better LG.

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Glycosyltransferase mechanism (1)

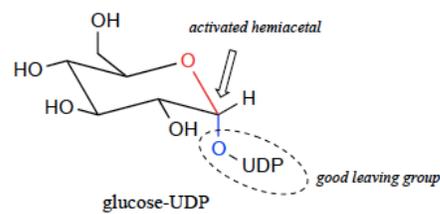
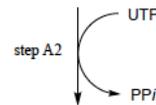
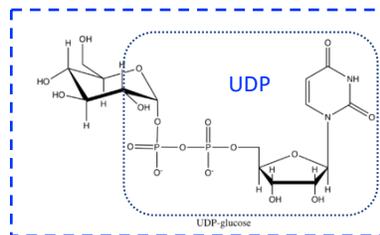


Step (1): phosphorylation to create a good LG



A1. Phosphate isomerization: OP moves from C5 to C1.

A2. UDP group replaces phosphate.



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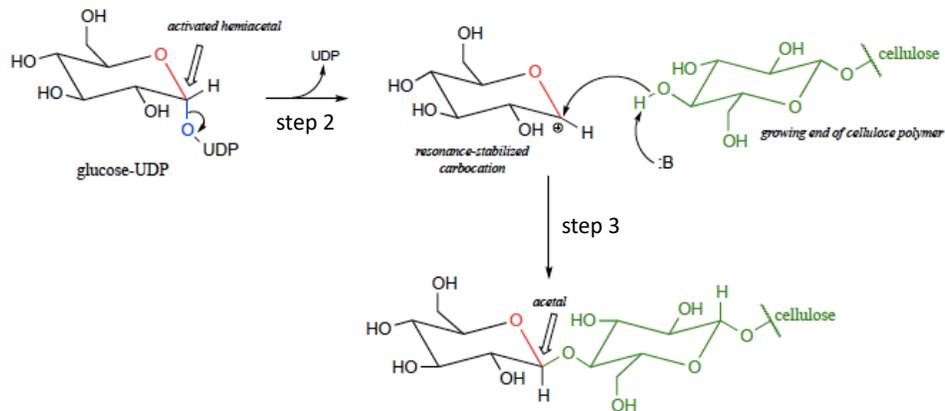
Glycosyltransferase mechanism (2, 3)



Step (2): UDP LG leaves, forming a carbocation intermediate

Step (3): alcohol Nu: is deprotonated to stronger Nu:-

Nu:- attacks the carbocation forming an inverted glycosidic linkage



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Converting acetals back to hemiacetals

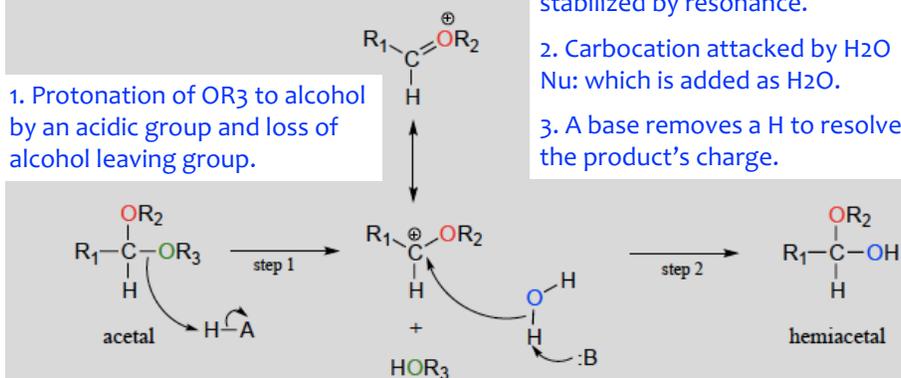


Acetals can be converted back into hemiacetals via an **SN1 reaction** that uses water as a reactant and releases an alcohol LG.

Hydrolysis: *the breaking of a bond using water as a reactant*

Mechanism for acetal hydrolysis (enzyme-catalyzed):

1. Protonation of OR₃ to alcohol by an acidic group and loss of alcohol leaving group.



Carbocation intermediate is stabilized by resonance.

2. Carbocation attacked by H₂O Nu: which is added as H₂O.

3. A base removes a H to resolve the product's charge.

For carbohydrates, this reaction is catalyzed by a **glycosidase enzyme**.

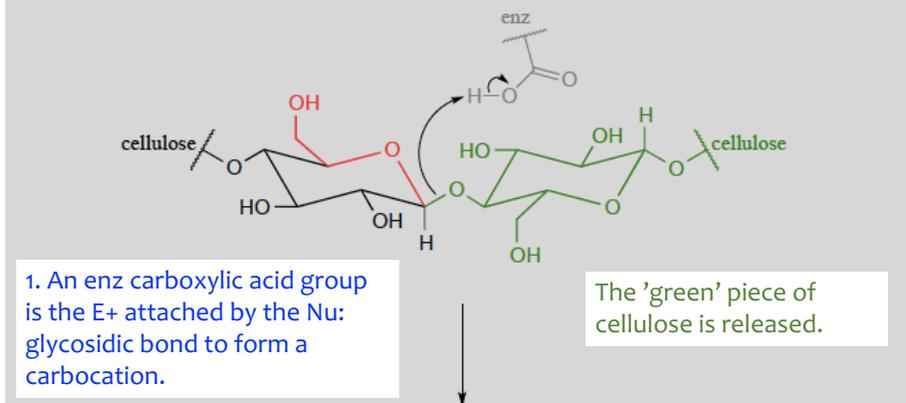
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Cellulose is tougher (1)



While many organisms (like us) can hydrolyze carbohydrates, **cellulose** is more difficult to break down into hemiacetals. Thus the challenge of produce **cellulosic ethanol** fuels rather than making ethanol from simple starches.

Cellulase mechanism:



1. An enz carboxylic acid group is the E⁺ attached by the Nu: glycosidic bond to form a carbocation.

The 'green' piece of cellulose is released.

For cellulose, this reaction is catalyzed by a **cellulase enzyme**.

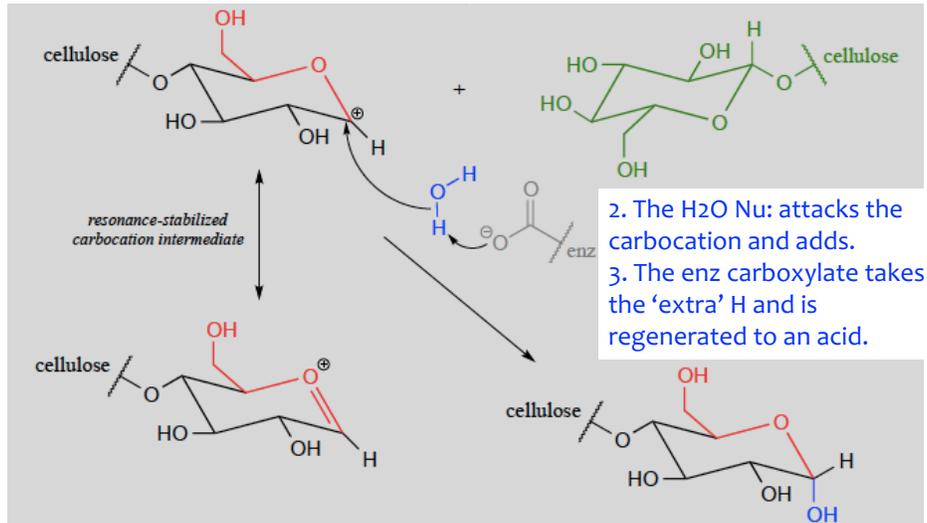
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Cellulose is tougher (2, 3)



Water is the Nu: again.

Note that the enzyme's carboxylic acid group is acting as a catalyst.



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Think about this



Polymerization of sugars into polysaccharides uses the high-energy UTP molecule (very much like ATP) to make the glycosidic bond. But hydrolysis of a polymerized glycoside bond to release a monomer does not require UTP.

Why?

It is a question of **entropy change**, which you should recall is a component of the Gibbs free energy change of a reaction.

Entropy: disorder or chaos

Stringing monomers together to create a polymer creates order and reduces entropy.

So, forming a new glycosidic bond reduces entropy which makes it less energetically favorable (it costs energy).

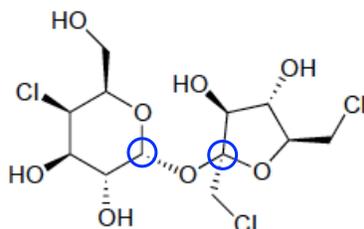
But, breaking a glycosidic bond increases entropy, making it more thermodynamically favorable.

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Try this



This is the structure of the artificial sweetener sucralose. Identify the anomeric carbon in each of the monomers of this disaccharide.



The anomeric carbons are bonded to two oxygen atoms.

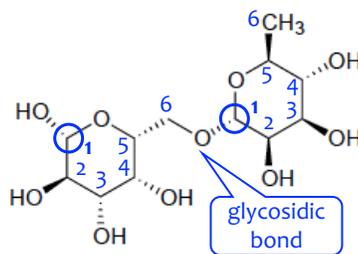
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Try this



This is the robinose, a disaccharide found in the 'Chenille plant' native to the Pacific islands.

- Identify the two anomeric carbons and the glycosidic bond.
- Using the same carbon numbering system as for glucose in the earlier figure, label carbon numbers (1 - 6) for each monosaccharide.
- Based on what you know of glycosidic bond-forming reactions in nature, propose a reasonable mechanism for the linking of the two monosaccharides, starting with the activated hemiacetal species, assuming that it is a UDP species as in the cellulose glycosidic bond-forming reaction.
- Draw the open chain form of each of the monosaccharides.

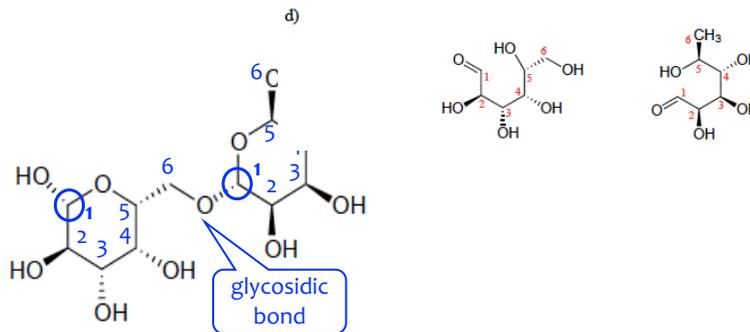
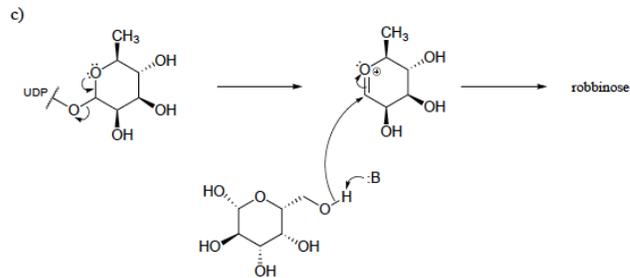


42

Try this (2)



robinose

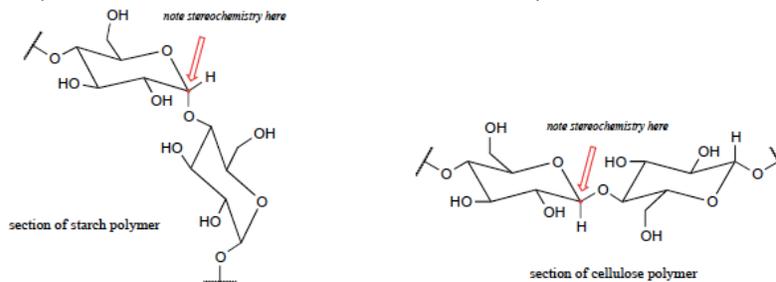


43

Try this



A structural feature of the cellulose polymer makes it inherently more resistant to enzymatic hydrolysis compared to starch.
 Explain. (Hint: think about intermolecular interactions.)



Notice that cellulose is a long straight polymer, while amylose is curved in shape. Because of its shape, cellulose forms ordered, rod-shaped crystals with tight packing between individual polymers - this makes the glycosidic bonds less accessible to cellulase enzyme. Amylose, with its curved shape, cannot pack closely and so forms a disordered, amorphous solid, making its glycosidic bonds more accessible to amylose enzymes. (Do an internet image search for 'cellulose microfibril structure')

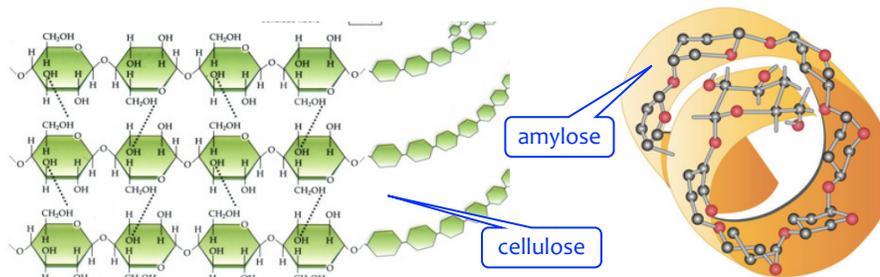
44

Try this (2)



A structural feature of the cellulose polymer makes it inherently more resistant to enzymatic hydrolysis compared to starch.

Explain. (Hint: think about intermolecular interactions.)



Notice that cellulose is a long straight polymer, while amylose is curved in shape. Because of its shape, cellulose forms ordered, rod-shaped crystals with tight packing between individual polymers - this makes the glycosidic bonds less accessible to cellulase enzyme. Amylose, with its curved shape, cannot pack closely and so forms a disordered, amorphous solid, making its glycosidic bonds more accessible to amylase enzymes. (Do an internet image search for 'cellulose microfibril structure')

45

Can you?



- (1) Draw the structure of acetals and ketals?
- (2) Distinguish between hemiacetal, hemiketal, acetal, ketal, hydrate of an aldehyde or hydrate of a ketone?
- (3) Identify and draw the acid-catalyzed mechanism of the reaction of 'hemis' with alcohol to produce acetals or ketals?
- (4) Predict and draw the products of reactions 'hemis' with alcohols?
- (5) Predict and draw the reactants needed to produce acetals and ketals?
- (6) Define the term glycosidic linkage?
- (7) Find the anomeric carbons of disaccharides or polysaccharides?
- (8) Describe the role of phosphorylation in formation of glycosidic linkages?
- (9) Draw the mechanism of hydrolysis of acetals and ketals back to 'hemis'?

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7. Nucleophilic addition to carbonyls



7.4: N-glycosidic bonds

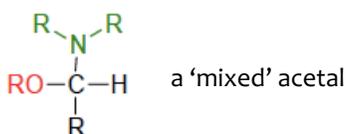
Resources for students:

47

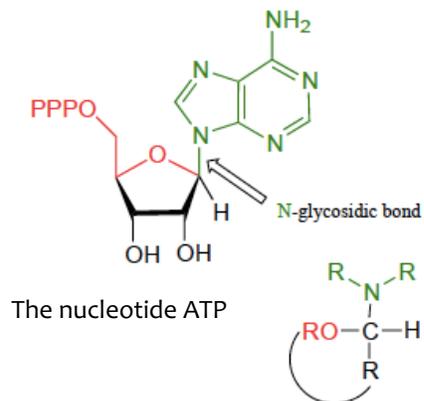
N-glycosidic bonds



N-glycosidic bond: formed when an amine, rather than a second alcohol reacts with a hemiacetal or hemiketal.



N-glycosidic bonds are found in **nucleotides** where they link one of the 5 bases (A, T, G, C, or U) to a ribose or deoxyribose sugar.



48

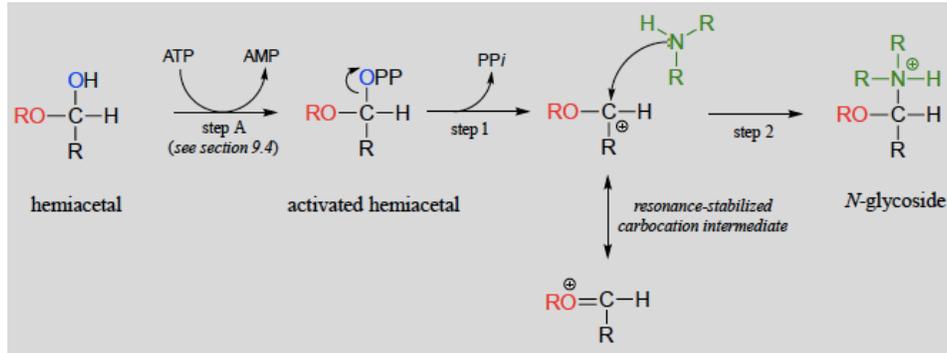
N-glycosidic bonds: mechanism



Step (A): activation of the hemiacetal by phosphorylation of the OH group

Step (1): loss of the OPP good LG to form a resonance-stabilized carbocation

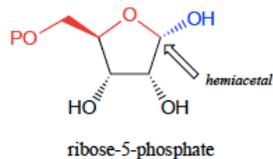
Step (2): secondary amine Nu: attacks the carbocation and is added



So this is an **SN1** reaction.

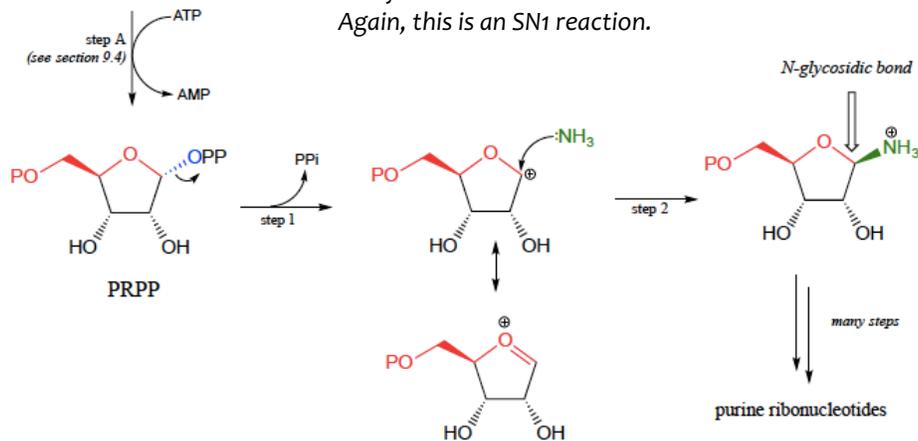
49

N-glycosidic bond to start purine n'tide



Here a similar mechanism is used to add ammonia to the sugar ribose-5-phosphate via an **N-glycosidic bond** as the first step of purine (A, G) biosynthesis.

Again, this is an **SN1** reaction.

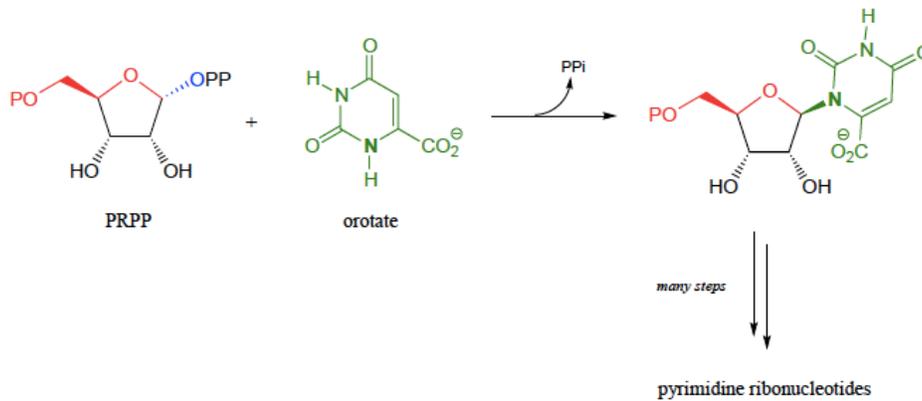


50

N-glycosidic bond for pyrimidine n'tide



Here a similar mechanism is used to add orotate (a pyrimidine precursor molecule) to the sugar ribose-5-phosphate via an **N-glycosidic bond** as the first step of pyrimidine (T, U, C) biosynthesis. Again, this is an S_N1 reaction.

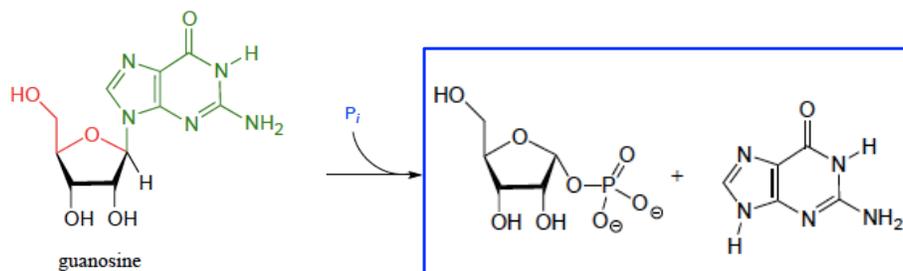


51

Try this



In the catabolic (degradative) direction, an N-glycosidic bond must be broken, in a process which is analogous to the hydrolysis of a glycosidic bond (illustrated earlier). In the catabolism of guanosine nucleoside, the N-glycosidic bond is broken by inorganic phosphate (not water!) apparently in a concerted (S_N2 -like) displacement reaction (Biochemistry 2011, 50, 9158). Predict the products of this reaction and draw a likely mechanism.



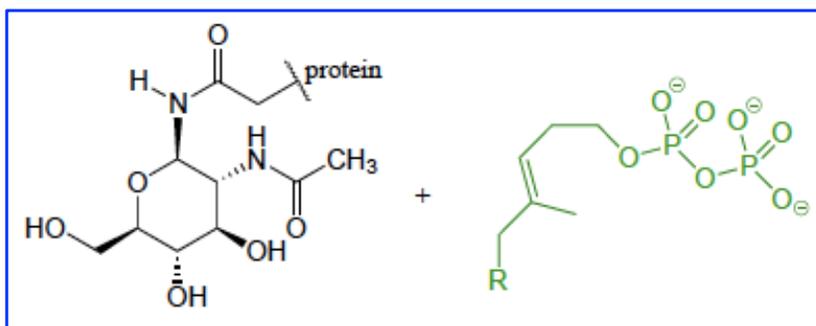
52

Try this



Glycoproteins are proteins that are linked, by glycosidic or N-glycosidic bonds, to sugars or carbohydrates through an asparagine, serine, or threonine side chain on the protein. As in other glycosylation and N-glycosylation reactions, the hemiacetal of the sugar must be activated prior to glycosidic bond formation. Below is the structure of the activated sugar hemiacetal substrate in an asparagine glycosylation reaction.

Draw the product of the asparagine glycosylation reaction, assuming inversion of configuration of the anomeric carbon.



53

Can you?



- (1) Define an *N*-glycosidic bond and draw a molecule containing one.
- (2) Identify and draw the mechanism that converts a hemiacetal to a *N*-glycoside.
- (3) Identify the *N*-glycosidic bond in nucleotides.

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7. Nucleophilic addition to carbonyls



7.5: Imines and iminium ions

Resources for students:

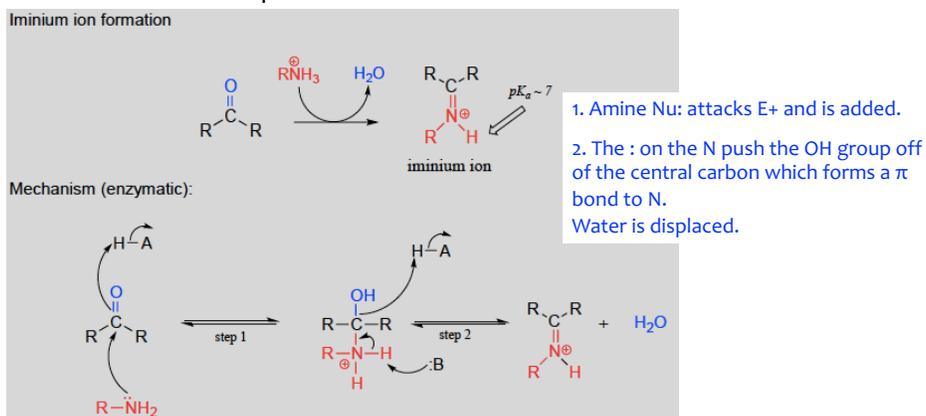
55

Imines are formed when Nu: = amine



When the carbonyl carbon E^+ of aldehydes and ketones is attacked by an **amine Nu:** rather than an alcohol Nu:, the substrate's carbonyl group is replaced by an **imine C = N** group.

- Note that imine groups are also called Schiff's bases.
- **The pK_a of imine groups is ~ 7** , so at physiological pH these groups can be neutral imines or protonated iminium ions.



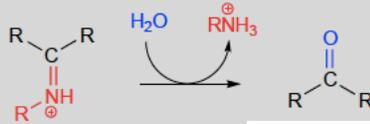
56

Reversal is hydrolysis

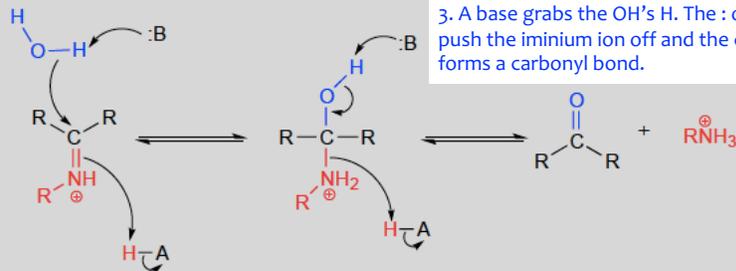


You've seen this pattern of reversal before.

Hydrolysis of an iminium ion:



Mechanism (enzymatic):



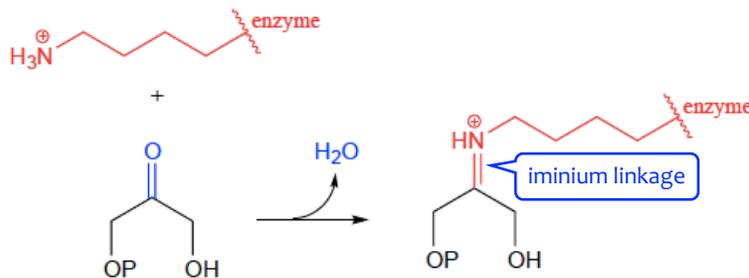
1. H₂O Nu: attacks the imine C E⁺ and is added.
2. The imine π bond acts as Nu: and grabs H from a weak acid.
3. A base grabs the OH's H. The : on O then push the iminium ion off and the central C forms a carbonyl bond.

57

Aldolases use iminium in photosynthesis



Aldolase enzymes in photosynthesis Calvin cycle (converting CO₂ to glucose) use **iminium linkages** as the enzyme's lysine side-chain grabs a three-carbon ketone substrate.



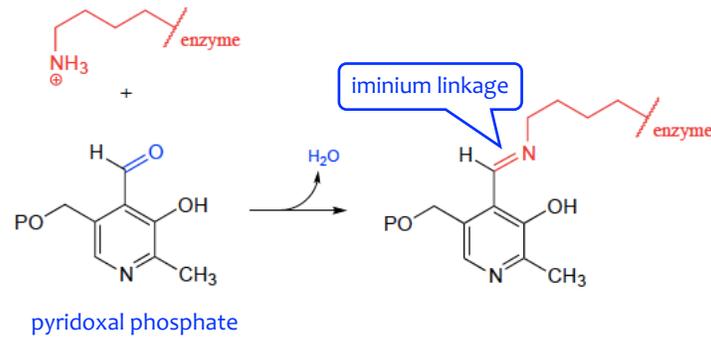
Once other amino acids in the enzyme's active site do some additional chemistry on the substrate and convert it to product, hydrolysis is used to break the iminium linkage, release the product and return the lysine to its original state.

58

PLP's coenzyme vitamin B6 uses iminium



The **coenzyme pyridoxal phosphate (aka vitamin B6)** is held in the active site of then enzyme it helps by **iminium linkage** via a lysine side-chain in the enzyme's active site.

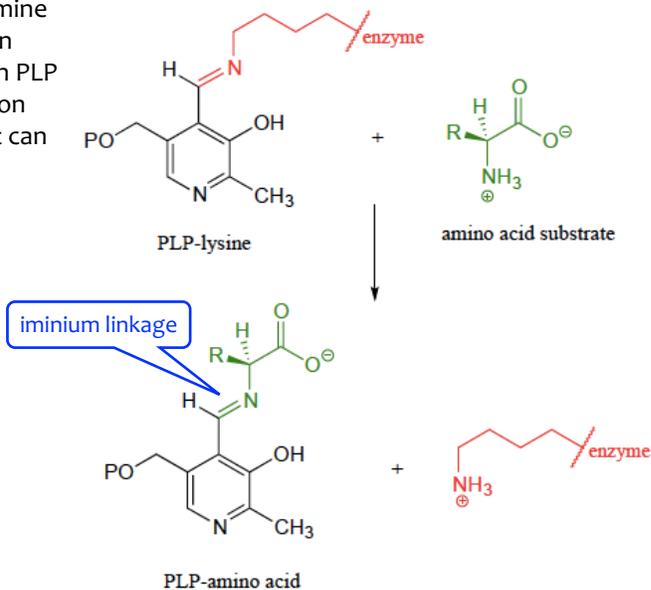


59

Transimination moves the vitamin B6



Then, the PLP-lysine imine linkage is traded for an imine linkage between PLP and the amino group on the substrate, in what can be referred to as a **transimination**.



60

Transimination mechanism

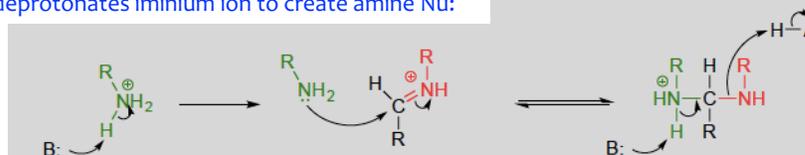


Transimination reaction:



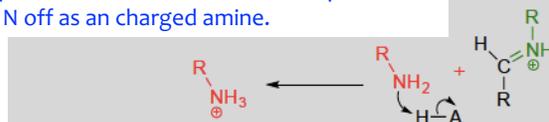
Mechanism:

1. A base deprotonates iminium ion to create amine Nu:



2. Amine Nu: attacks imine carbon E+ and adds...
... causing π bond to swing up and resolve the charge of the imine N.

3. Base deprotonates the added N and its : push the first imine N off as a charged amine.

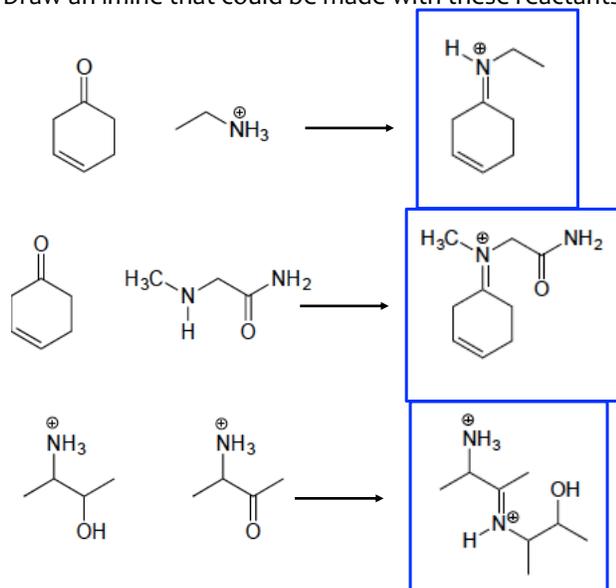


61

Try this



Draw an imine that could be made with these reactants.

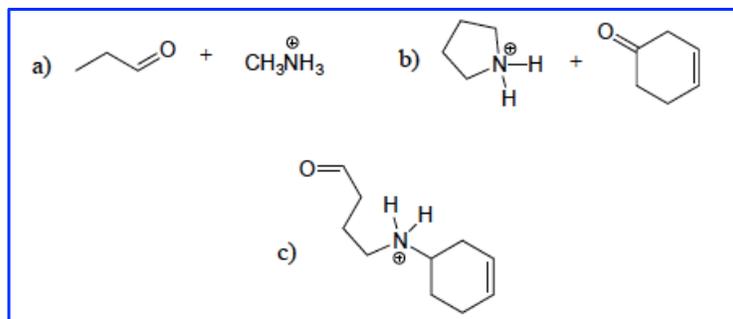
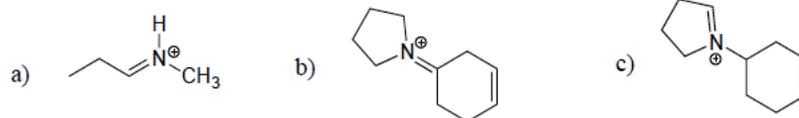


62

Try this



Draw the iminium hydrolysis product for each reactant.

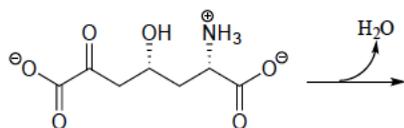


63

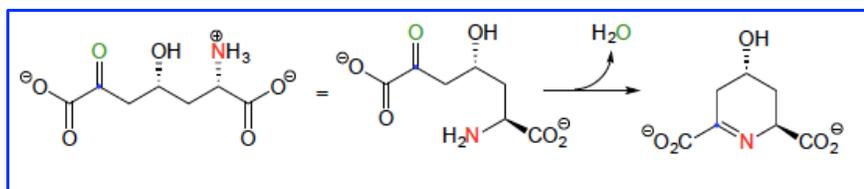
Try this



The metabolic intermediate shown below undergoes an intramolecular imine formation as a step in the biosynthesis of lysine. Draw the product of this intramolecular imine formation step.



First, identify the nucleophilic amine nitrogen (in red below), the electrophilic ketone carbon (blue dot), and the ketone oxygen that leaves as water (green).

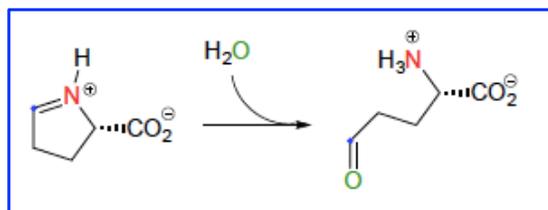
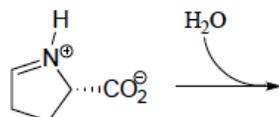


64

Try this



Predict the product of this iminium hydrolysis step from the proline degradation pathway.



65

Can you?



- (1) Draw and describe imine and iminium groups?
- (2) Compare carbonyl and imine groups and their ability to serve as E+?
- (3) Remember the pKa of imine groups and describe how that pKa value allows this functional group to change at physiological pH?
- (4) Draw the mechanism for formation of iminium linkages to lysine?
- (5) Describe the phenomenon of transamination?
- (6) Draw the mechanism of transamination?
- (7) Given reactants, predict the imine product they would produce.
OR given an imine or iminium substrate and water, predict hydrolysis products.

66

7. Nucleophilic addition to carbonyls

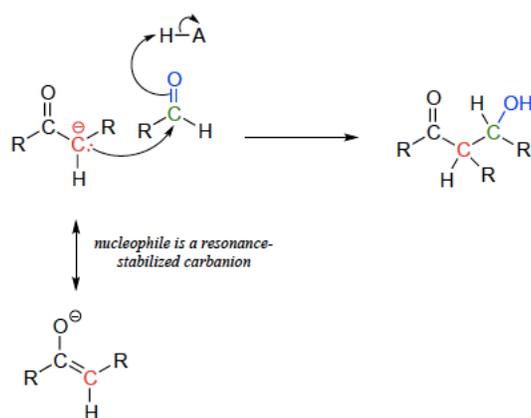


7.6: A look ahead: addition of carbon and hydride nucleophiles to carbonyls

Resources for students:

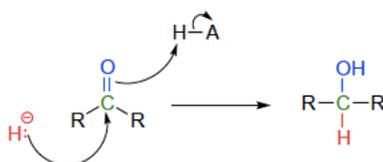
67

Carbanion Nu:-



68

Hydride ion Nu:-



69

Can you?



(1) Imagine how other nucleophiles can attack the carbonyl carbon?

70