

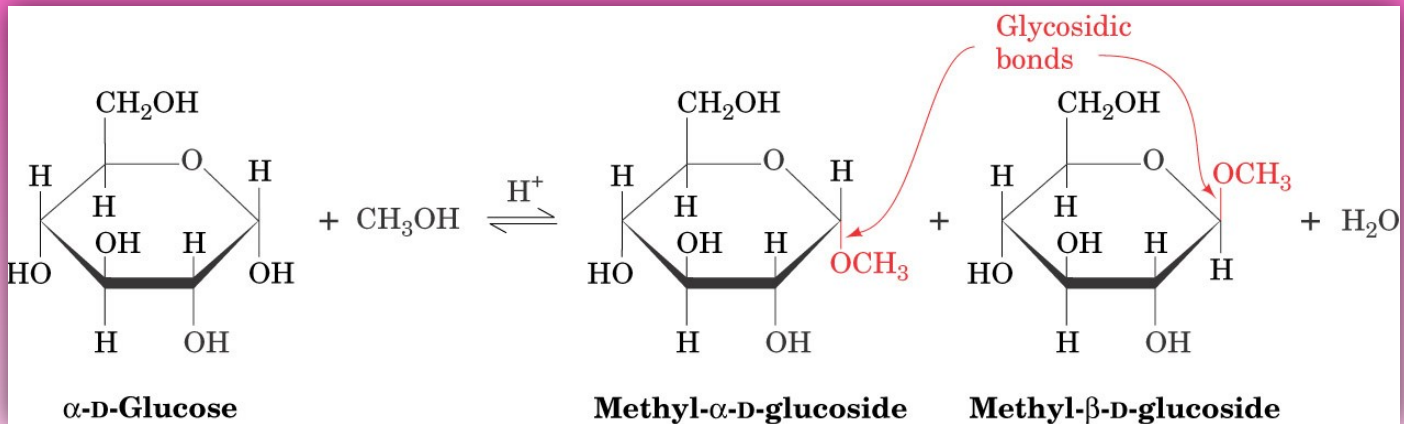
**CHEM 537**  
**Carbohydrate Biochemistry and Glycobiology**  
Part II: Oligosaccharides & Polysaccharides

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**Slide Set 2a**

Chapters 11 & 23: *Biochemistry*, Voet/Voet, 4rd edition, 2011  
*Introduction to Glycobiology*, Taylor/Drickhamer, 3rd edition, 2011

# Chemical glycosylation

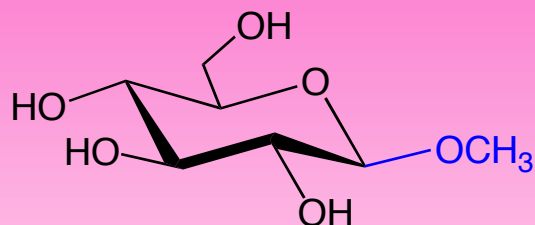


The acid-catalyzed condensation of  $\alpha$ -D-glucopyranose in methanol solvent to form an anomeric pair of methyl D-glucopyranosides (Fischer glycosidation).

Furanosides also form under these conditions (kinetically favored). The anomeric (C1) carbon of the two pyranosides (methyl  $\alpha$ - and  $\beta$ -D-glucopyranosides) is an **acetal** carbon, whereas the anomeric (C1) carbon of D-glucose is a **hemiacetal** carbon. Glycosides are not reducing sugars, and they do not undergo anomerization in solution under neutral and basic conditions.

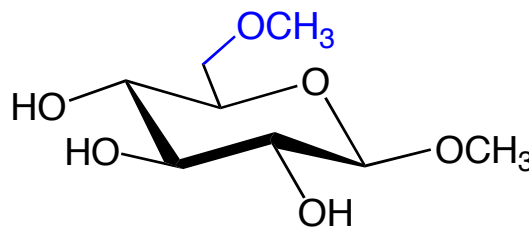
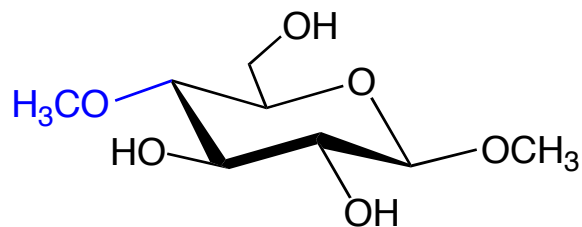
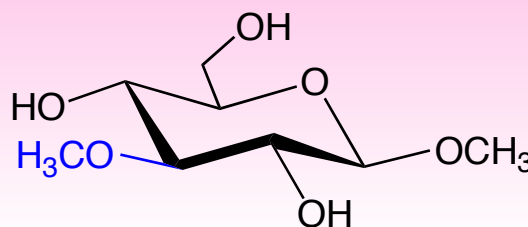
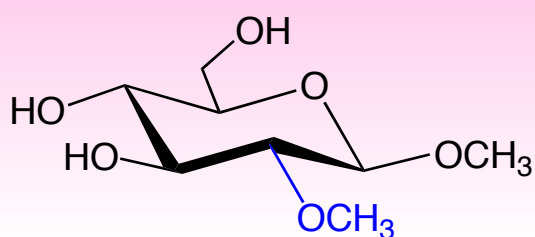
**Glycosides are always formed under acidic conditions, and are always hydrolyzed under acidic conditions. Glycosides are stable in neutral and basic solution.**

# The distinction between methyl glycosides and methyl ethers



a methyl glycoside  
(methyl  $\beta$ -D-glucopyranoside)

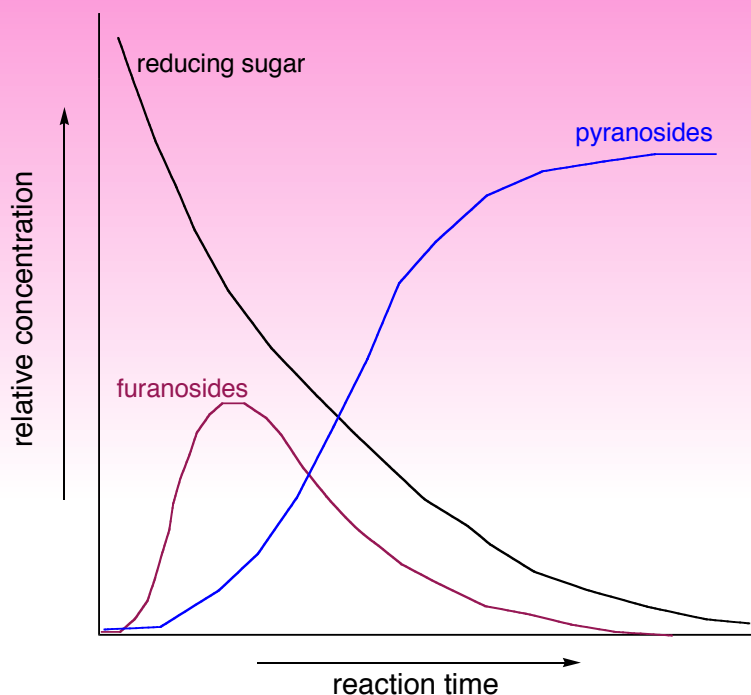
acid-labile;  
base stable



methyl ethers

acid and  
base stable

The kinetically-favored and thermodynamically-favored products of Fischer glycosidation of D-glucose in acidic methanol differ.

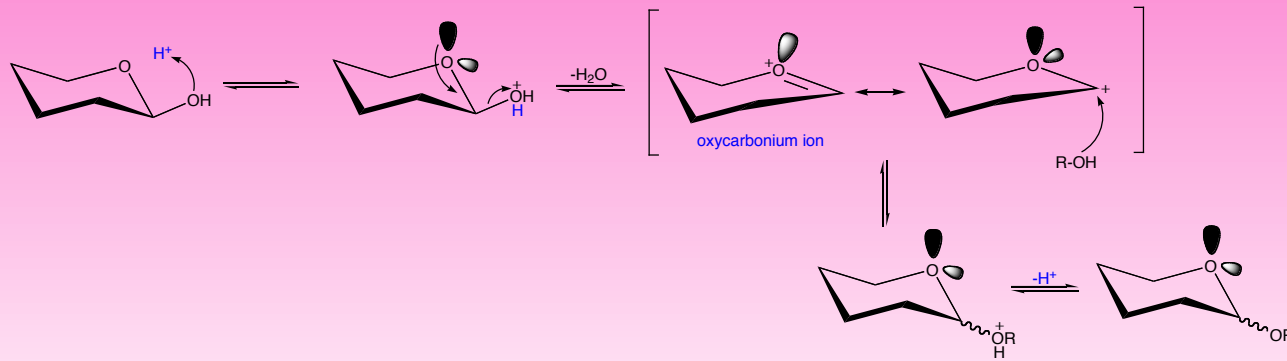


Glucofuranosides form initially (kinetically favored), followed by glucopyranosides. At equilibrium, pyranosides (thermodynamically favored) are more abundant than furanosides. The relative proportions of pyranosides and furanosides at equilibrium depend on aldohexose structure.

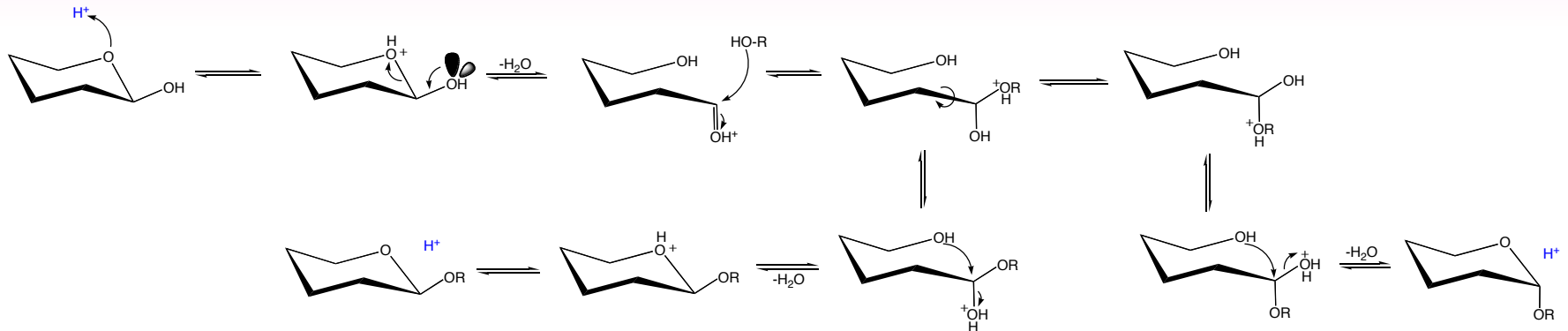
The final **anomeric** distribution of pyranosides and furanosides also depends on aldohexose structure.

# Mechanisms of acid-catalyzed glycoside bond formation

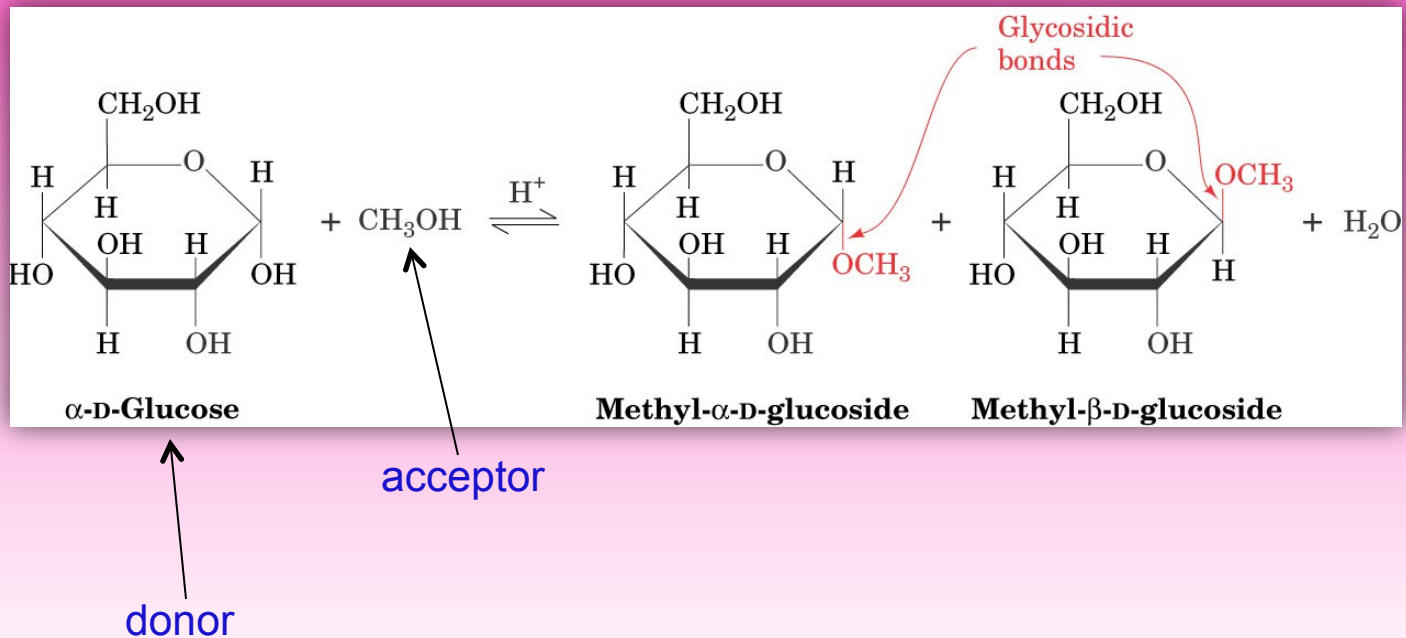
## Exocyclic mechanism: oxycarbonium ion intermediate



## Endocyclic mechanism: acyclic hemiacetal intermediate

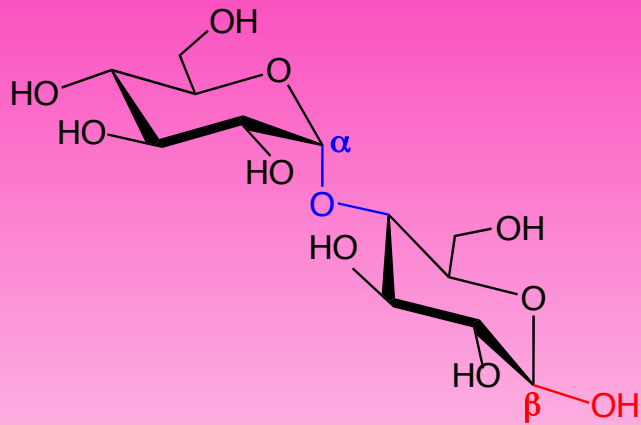


## Disaccharide formation



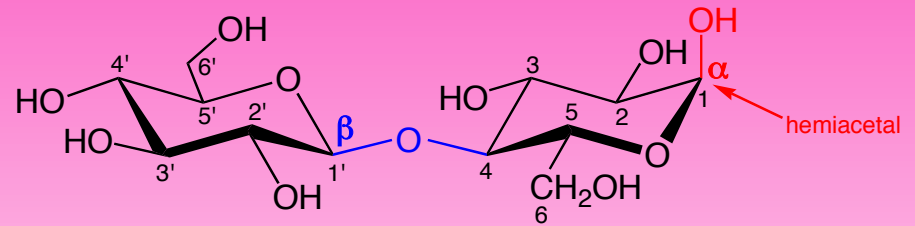
When the alcohol functional group is supplied by another monosaccharide like D-glucose instead of methanol, a **disaccharide** forms. Ten different Glc-Glc disaccharides are possible since five different hydroxyl groups are present in the Glc acceptor, and the Glc donor can have the  $\alpha$  or  $\beta$  anomeric configuration.

Disaccharides *in vivo* play important roles as independent sugars (e.g., lactose) or occur as repeating subunits in the construction of oligo- and polysaccharides.



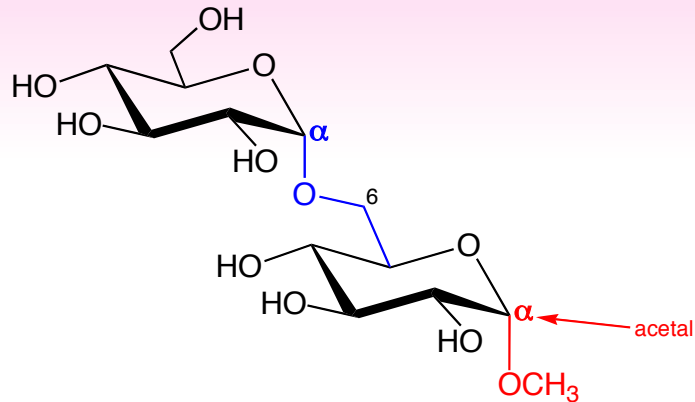
$\beta$ -maltose  
 $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranose  
 (reducing disaccharide; anomerizes in solution)

$\alpha$ -(1  $\rightarrow$  4)linkage



$\alpha$ -cellobiose  
 $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)- $\alpha$ -D-glucopyranose  
 (reducing disaccharide; anomerizes in solution)

$\beta$ -(1  $\rightarrow$  4)linkage

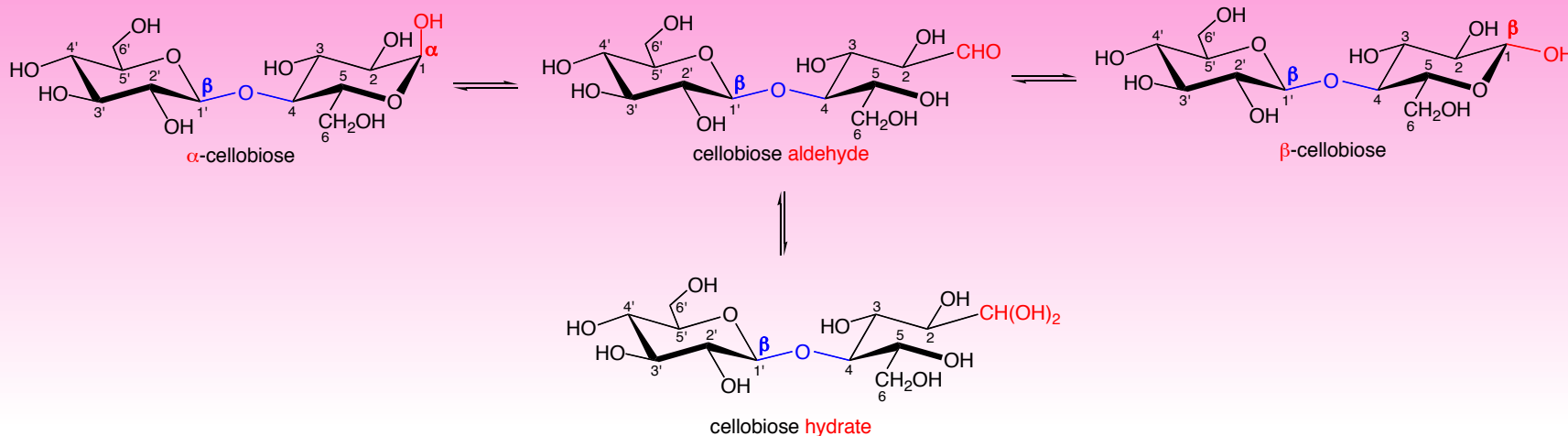


methyl  $\alpha$ -isomaltoside  
methyl  $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 6)- $\alpha$ -D-glucopyranoside  
 (non-reducing disaccharide; does not anomerize in solution)

$\alpha$ -(1  $\rightarrow$  6)linkage

**Some Glc-Glc disaccharides showing different regiochemistries and stereochemistries. Only two of the three structures are **reducing disaccharides**.**

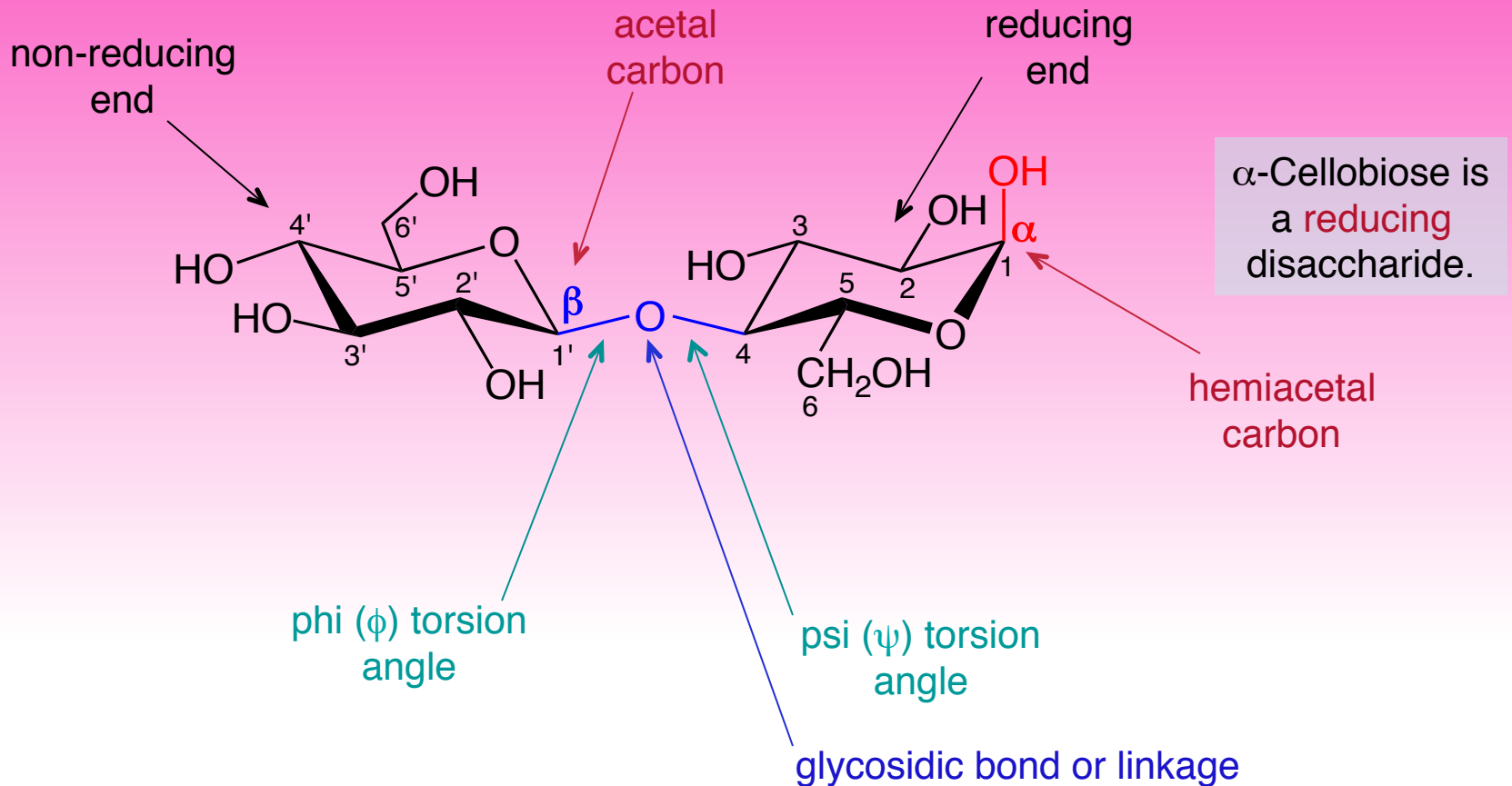
## Anomerization of $\alpha$ -cellobiose in aqueous solution (occurs spontaneously upon dissolving $\alpha$ -cellobiose in water)



Cyclization to form  $\alpha$ - and  $\beta$ -furanoses cannot occur in cellobiose because the C4 hydroxyl group is protected (it participates in the glycosidic linkage). Furanoses are possible in the anomerization of isomaltose.

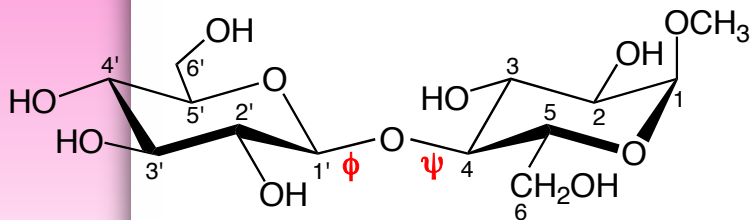


# Some nomenclature, symbolisms and conventions

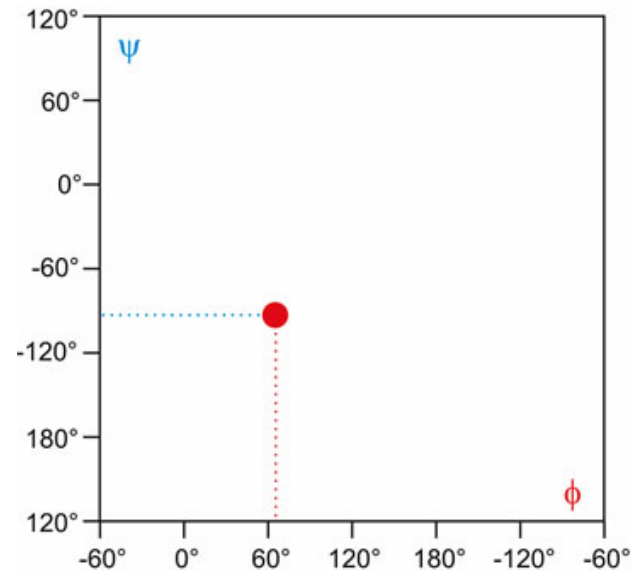


**Proper name:**  
 **$\beta$ -D-glucopyranosyl-(1  $\rightarrow$  4)- $\alpha$ -D-glucopyranose**

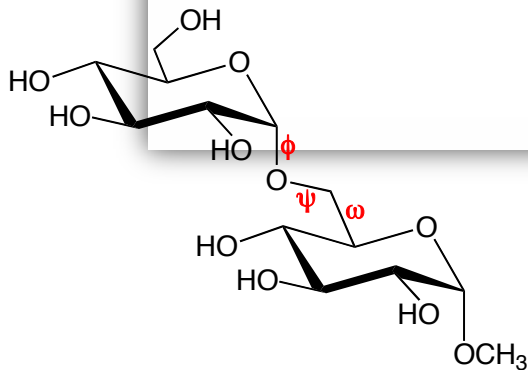
## An idealized $\phi/\psi$ plot for a glycosidic linkage (analogous to a Ramachandran plot for a peptide/protein)



phi ( $\phi$ ): defined as the H1'-C1'-O4-C4 torsion angle  
psi ( $\psi$ ): defined as the C1'-O4-C4-H4 torsion angle



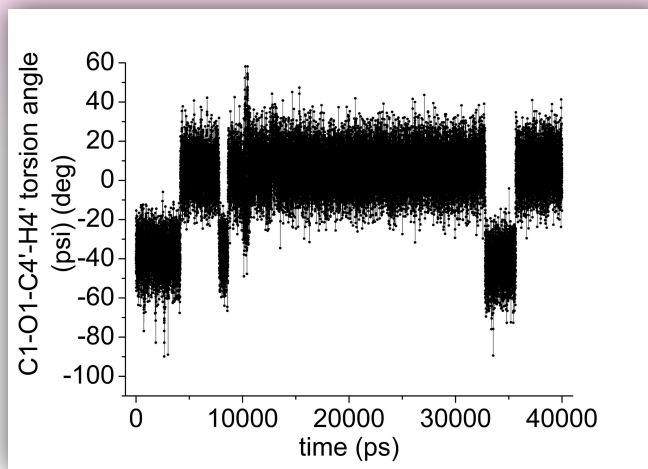
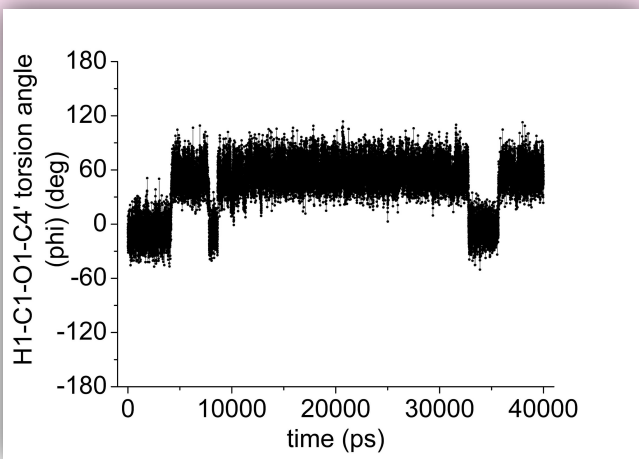
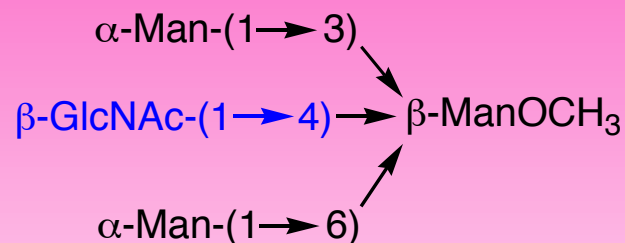
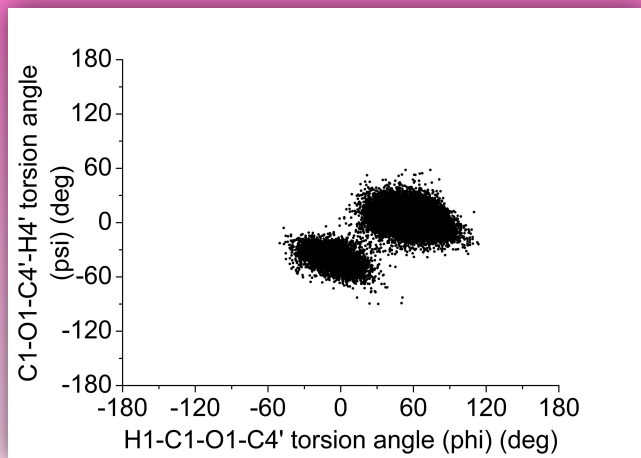
Taylor and Drickamer  
Introduction to Glycobiology



For 1,6 linkages, an additional torsion angle,  $\omega$  (omega), affects linkage conformation. These linkages have the potential for greater flexibility compared to those characterized by only two C-O bond torsions.

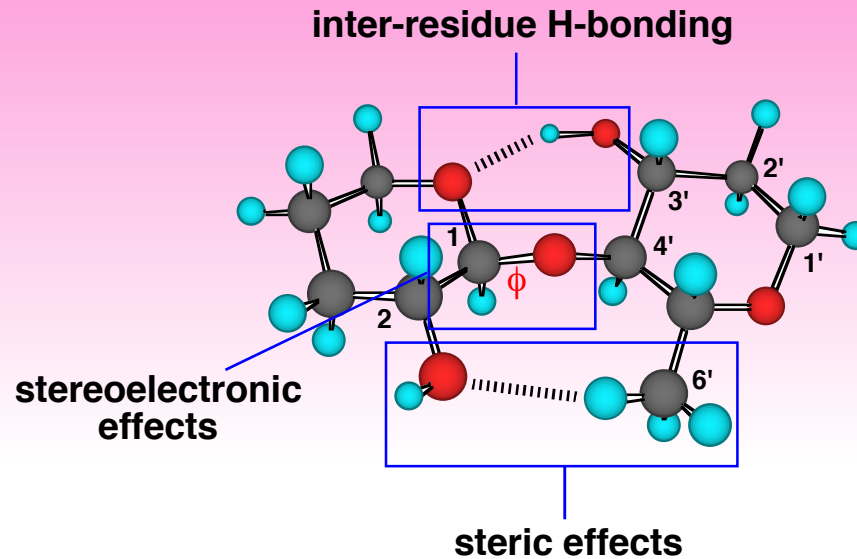
# An “real” $\phi/\psi$ plot for a glycosidic linkage

Hydrated molecular dynamics simulation (40 ns) of a tetrasaccharide

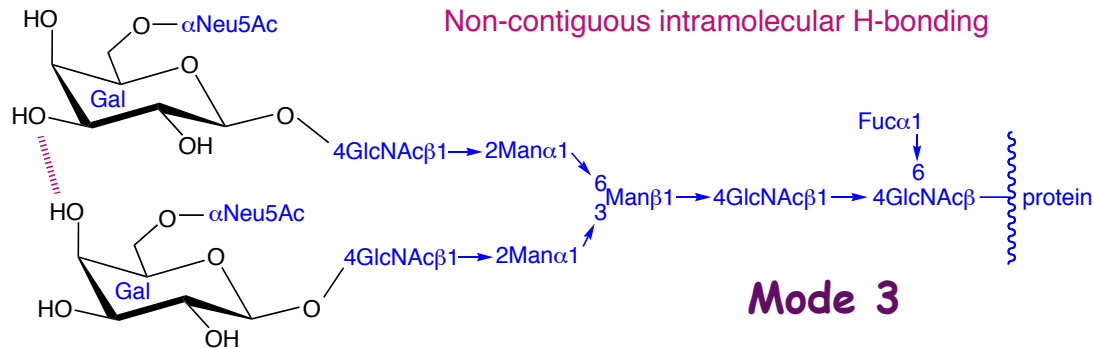
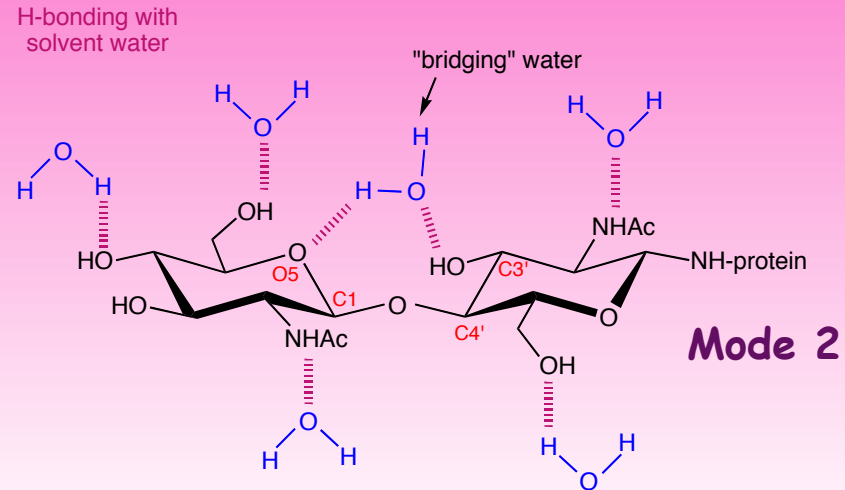
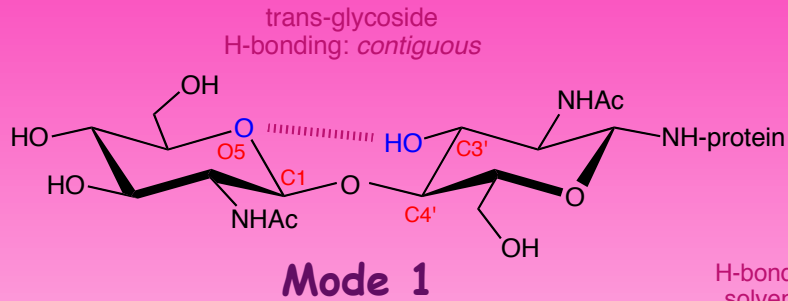


Results suggest **correlated** behavior between  $\phi$  and  $\psi$  for the 1,4-linkage in this branched tetrasaccharide

## Structural factors influencing O-glycoside linkage conformation in oligosaccharides

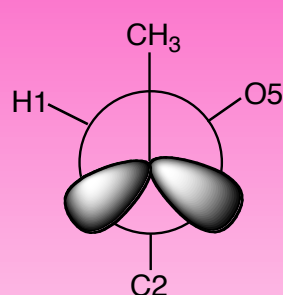


# Different potential modes of intramolecular and intermolecular H-bonding in saccharides



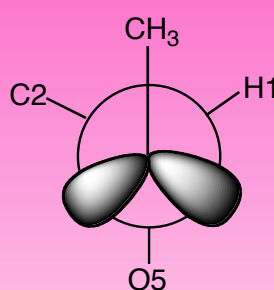
# The *exo*-anomeric effect: conformational control of $\phi$ in *O*-glycosidic linkages

## $\beta$ -D-glucopyranose



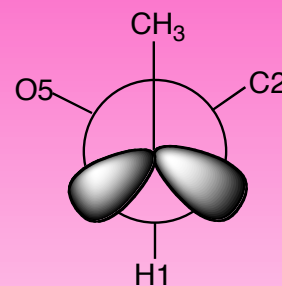
$n_{O1} \rightarrow \sigma^*_{C1-O5}$   
 1,3 Me-lp  
 1,3 lp-lp  
 1,3 lp-O  
 1,3 lp-H

most preferred



1,3 lp-lp  
 1,3 lp-lp  
 1,3 lp-H  
 1,3 Me-O

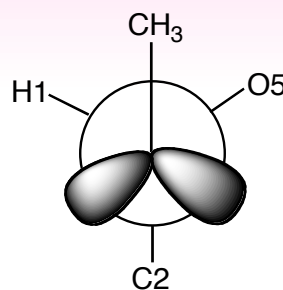
least preferred



$n_{O1} \rightarrow \sigma^*_{C1-O5}$   
 1,3 Me-H  
 1,3 Me-lp  
 1,3 lp-lp  
 1,3 lp-O

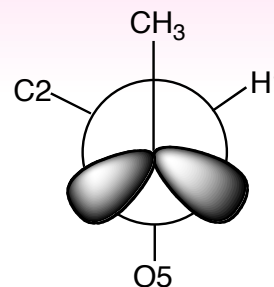
no competing  
 endo-anomeric  
 effect in  
 any of the three  
 rotamers

## $\alpha$ -D-glucopyranose

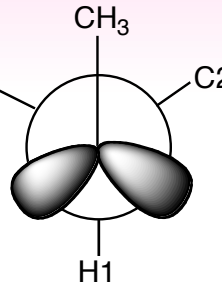


$n_{O1} \rightarrow \sigma^*_{C1-O5}$   
 1,3 Me-lp  
 1,3 lp-ring  
 1,3 lp-O

most preferred



1,3 lp-lp  
 1,3 lp-ring  
 1,3 Me-O

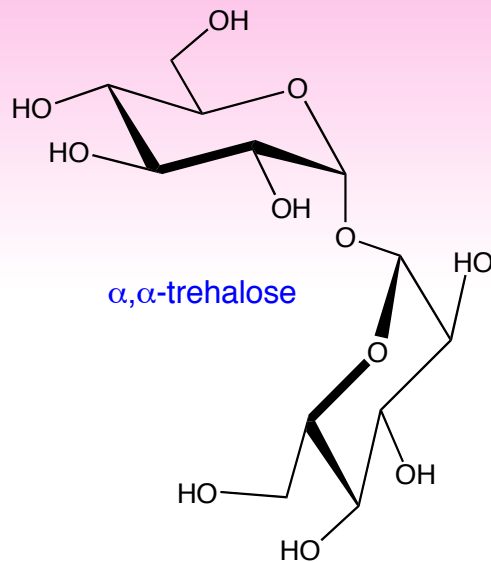
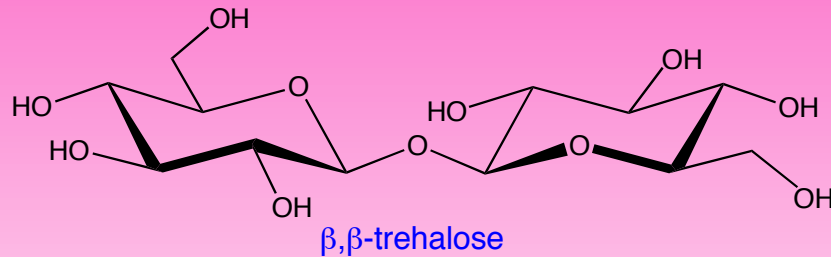


$n_{O1} \rightarrow \sigma^*_{C1-O5}$   
 1,3 Me-ring  
 1,3 lp-lp  
 1,3 lp-O

least preferred

competing endo-  
 anomeric effect in  
 all three rotamers

**A non-reducing Glc-Glc disaccharide:**  
 $\alpha,\alpha$ -trehalose,  $\beta,\beta$ -trehalose,  $\alpha,\beta$ -trehalose  
(D-glucopyranosyl-(1 $\rightarrow$ 1')-D-glucopyranoside)



transport form  
of glucose in insect  
hemolymph

The anomeric hydroxyl groups on the donor and acceptor Glc units are involved in the glycosidic linkage.