Lecture 30 (12/6/21)

TODAY

•Reading: Ch7; 236-241, 251-254, 258-260
Ch7; 241-250

•Problems: Ch7; 4,6,7,8,13,14,15,18
Ch7; 16,17,25,27

NEXT

•Reading: Ch4; 188-199
Ch6; 178
Ch8; 295
Ch10; 356-359
Ch14; 530-531,534-535
Ch16; 576, 590
Ch17; 613-615
Ch18; 629, 641-643

Carbohydrates

A. Definition
B. Roles
C. Monosaccharides-Chemistry
   1. Chirality
      a. One or more asymmetric carbons
      b. Linear and ring forms
   2. Derivatives: the chemistry of carbohydrates
      a. Oxidation
         i. C1
         ii. C6
      b. Reduction
         i. C1/C2
         ii. Other carbons
      c. Ester formation
      d. Amino sugars
   3. Polymerization
      a. The Glycosidic Bond
      b. Non-covalent bonds in macro-molecular structure
D. Oligosaccharides
   1. Glycoproteins & glycolipids
   2. O-linked
   3. N-linked
   4. Sequence determination-ABO
E. Polysaccharides
   1. Polymers of glucose
   2. Polymers of disaccharides

Carbohydrates

Monosaccharides: Chemistry

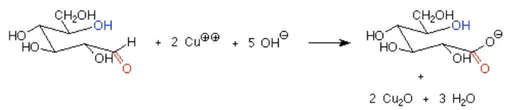
- **Chemical Features:**
  - Chirality
    - One or more asymmetric carbons
    - Linear and ring forms
  - Derivatives: the chemistry of carbohydrates
    - ① Oxidation
      - C1
      - C6
    - ② Reduction
      - C1/C2
      - Other carbons
    - ③ Ester formation
    - ④ Amino sugars
  - Polymerization
    - The Glycosidic Bond
    - Non-covalent bonds in macro-molecular structure

Carbohydrates ①

Monosaccharides: Derivatives

Oxidation: These make "sugar acids" or "acid sugars"

- Oxidation of aldehyde/ketone to acid (2e⁻ loss); reaction from the C1 of aldoses
  - named as "onic" acids ("onate" for conjugate base)
  - these sugars can reduce Cu^{2+} to Cu^{+} (Fehling's/Benedict's test) or Ag^{+} to Ag^{0} (Tollens' test)
  - Example: gluconic acid



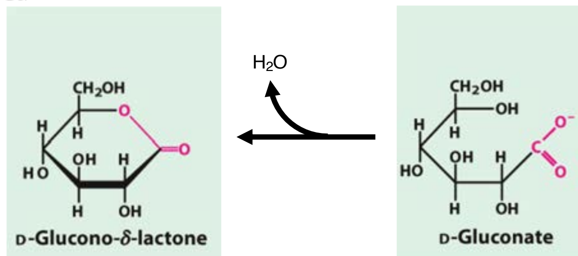
$CuSO_4 \rightarrow Cu^{2+} + SO_4^{2-}$
Blue

Cu^{2+} + Reducing sugar $\rightarrow Cu^{+}$

$Cu^{+} \rightarrow Cu_2O$
Red (ppt)

This reaction is called Benedict's test

The copper is reduced and the sugar is oxidized. So, the sugar is called a **Reducing Sugar**. Reducing sugars have a free anomeric carbon.

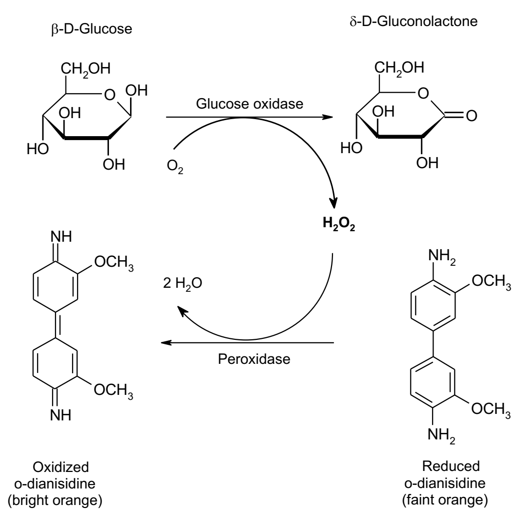


Carbohydrates ①

Monosaccharides: Derivatives

Oxidation: These make "sugar acids" or "acid sugars"

Colorimetric Glucose Analysis



- Enzymatic methods are used to quantify reducing sugars such as glucose.
  - The enzyme glucose oxidase catalyzes the conversion of glucose to glucono-δ-lactone and hydrogen peroxide.
  - Hydrogen peroxide oxidizes organic molecules into highly colored compounds.
  - Concentrations of such compounds is measured colorimetrically.
- Electrochemical detection is used in portable glucose sensors.

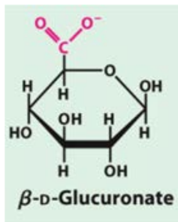
Carbohydrates ①

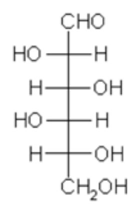
Monosaccharides: Derivatives

Oxidation: These make "sugar acids" or "acid sugars"

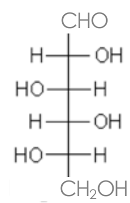
Oxidation of alcohol to acid ($4e^-$ loss)

- Reaction for C6 groups; like C1 oxidation, normally on aldoses
- Named as **ur**onic acids ("uronate" for conjugate base)
- Many L-sugars are Uronic acids
- Examples: D-glucuronic acid, L-iduronic acid

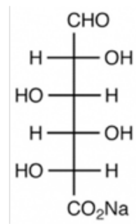




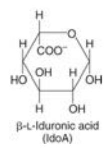
D-Idose



L-Idose



L-Iduronic acid



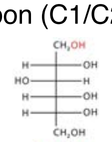
Carbohydrates ②

Monosaccharides: Derivatives

Reduction: These make "sugar alcohols" or "deoxysugars"

Reduction of aldehyde/ketone to alcohol ($2e^-$ gain)

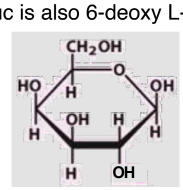
- Only carbon not already an alcohol is the anomeric carbon (C1/C2)
- Named as sugar **"ol"** or "itol"
- Examples: glycerol, mannitol, glucitol (sorbitol)



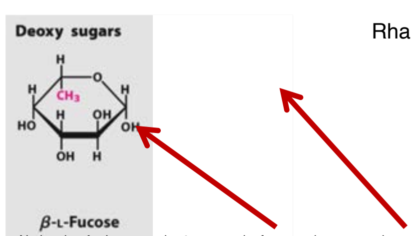
Reduction of alcohol carbon to methyl/methylene ($2e^-$ gain)

- Can react at any except the anomeric carbon
- Named as "x-deoxy" sugar with x being the reduced carbon
- Many are L-sugars, and have specific trivial names
- Examples: 2-deoxyribose, L-Fucose (Fuc) and L-Rhamnose (Rha)

Fuc is also 6-deoxy L-Gal

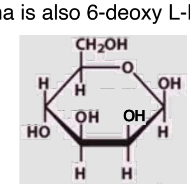


β-D-Gal



Notice that for L-sugars the β-anomer is **down** and α-anomer is **up**

Rha is also 6-deoxy L-Man



β-D-Man

Carbohydrates ②

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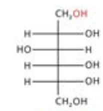
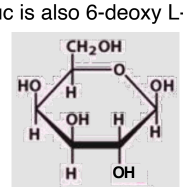


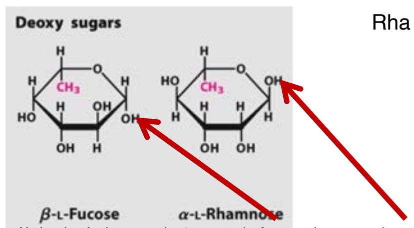
Sorbitol

Reduction of alcohol carbon to methyl/methylene (2e⁻ gain)
- Can react at any except the anomeric carbon
- Named as “x-deoxy” sugar with x being the reduced carbon
- Many are L-sugars, and have specific trivial names
- Examples: 2-deoxyribose, L-Fucose (Fuc) and L-Rhamnose (Rha)

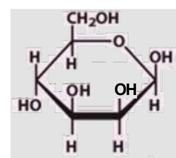
Fuc is also 6-deoxy L-Gal



β-D-Gal



Rha is also 6-deoxy L-Man



β-D-Man

Notice that for L-sugars the β-anomer is **down** and α-anomer is **up**

Carbohydrates

Monosaccharides: Chemistry

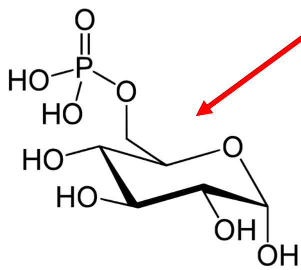
- **Chemical Features:**
  - Chirality
    - One or more asymmetric carbons
    - Linear and ring forms
  - Derivatives: the chemistry of carbohydrates
    - ① Oxidation
      - C1 -onic
      - C6 -uronic
    - ② Reduction
      - C1/C2 -tol
      - Other carbons deoxy-
    - ③ Ester formation
    - ④ Amino sugars
  - Polymerization
    - The Glycosidic Bond
    - Non-covalent bonds in macro-molecular structure

Carbohydrates ③

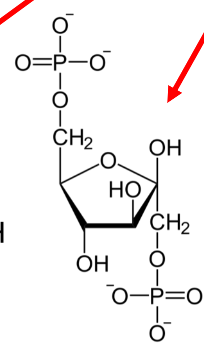
Monosaccharides: Derivatives

Esters: condensation of alcohol (sugar) and an acid

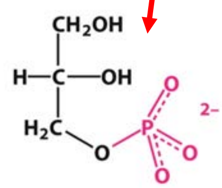
- Most important sugar esters use a phosphoric acid
  - These are called phospho-sugars or sugar phosphates
  - Examples: nucleotides, Glc 6-P, Fru 1,6-P_2, glycerol 3-phosphate



α–D–Glucose 6–phosphate



β–D–Fructose 1,6–bisphosphate



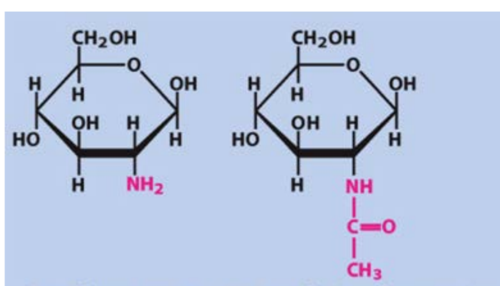
D-Glycerol 3-phosphate

Carbohydrates ④

Monosaccharides: Derivatives

Amines: condensation of alcohol (sugar) and ammonia

- These are called amino-sugars
- In biology, its ALWAYS at C2
- Often, the amino group will be further modified by an acetyl group (CH_3CO–) making an amide
- Named as sugar"amine" and when acetylated, the "N-acetyl" comes first. When abbreviation used "NAc" it comes after.
- Examples: glucosamine, N-acetyl-glucosamine (GlcNAc)

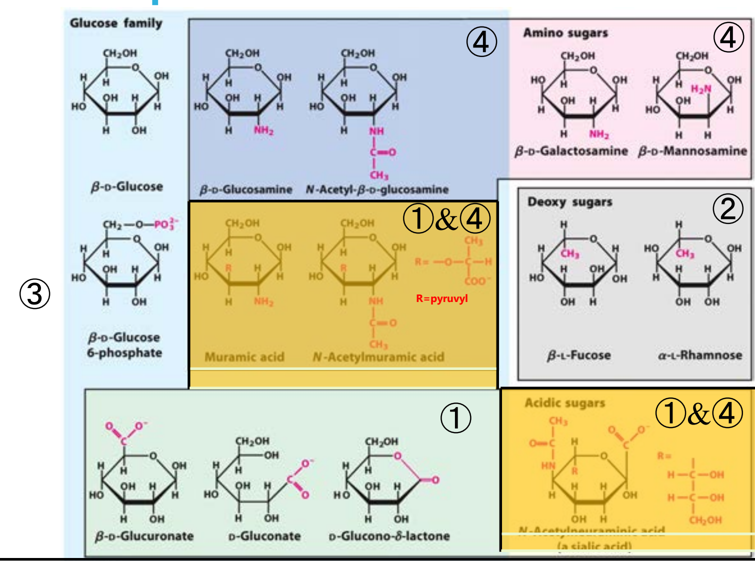


β-D-Glucosamine *N*-Acetyl-*β*-D-glucosamine (GlcNAc)

Carbohydrates

Monosaccharides: Derivatives

Important Hexose Derivatives



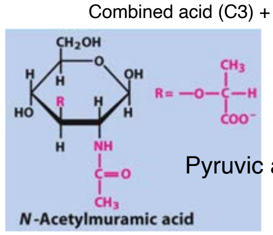
Carbohydrates

①&④

Monosaccharides: Derivatives

Muramic acid

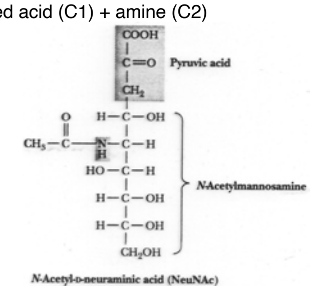
Combined acid (C3) + amine (C2)

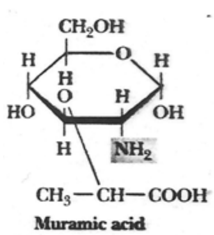


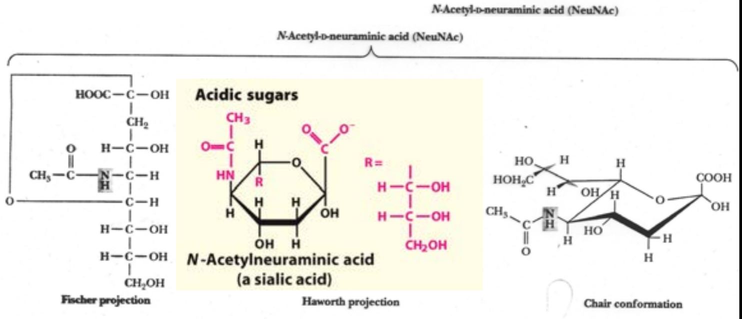
Pyruvic acid = $H_3C\text{-}\overset{O}{\overset{\|}{C}}\text{-}COO^-$

Sialic Acid (Sia) (aka NeuNAc)

Combined acid (C1) + amine (C2)







Carbohydrates

Monosaccharides: Chemistry

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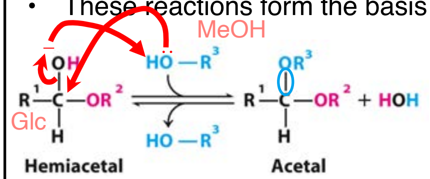
Carbohydrates

The Glycosidic Bond

Carbohydrates

Hemiacetals and Hemiketals are reactive to alcohols in condensation reactions

- Hemiacetals condense with alcohols to form Acetals.
- Hemiketals condense with alcohols to form Ketals.
- These reactions form the basis of the GLYCOSIDIC BOND.

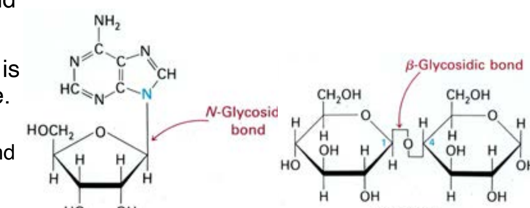


α-D-Methylglucoside

β-D-Methylglucoside

- Two sugar molecules can be joined via a glycosidic bond between an anomeric carbon (the hemiacetal/hemiketal) and a hydroxyl carbon (the other sugar).
- The glycosidic bond between sugars is stable and does not readily hydrolyze.
  - The anomeric carbon involved in the glycosidic linkage is fixed in its chirality and is therefore nonreducing.
  - The second monomer, with its unreacted hemiacetal, is still reducing.

The Glycosidic Bond



Adenosine
(β-D-adenine riboside)

Cellobiose
(Glucose-β(1→4)-glucose)

Carbohydrates

Hemiacetals and Hemiketals are reactive to alcohols in CONDENSATION reactions

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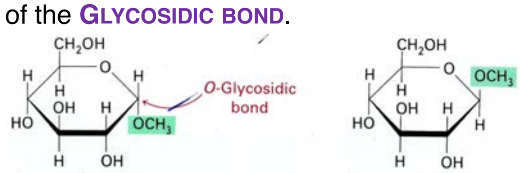

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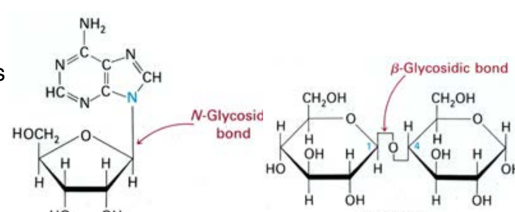


Adenosine
(β-D-adenineriboside)

Cellobiose
(Glucose-β(1→4)-glucose)

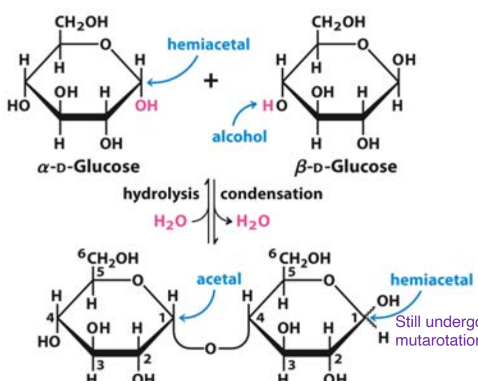
Carbohydrates

Disaccharides

Carbohydrates

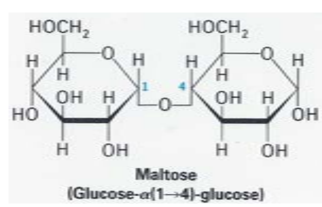
Disaccharides:

- Disaccharides can be named by the organization and linkage or a common name.
  - The disaccharide formed upon condensation of two glucose molecules via a 1 → 4 bond is described as α-D-glucopyranosyl-(1→4)-D-glucopyranose.
  - The common name for this disaccharide is maltose.



Still undergoing mutarotation

Maltose
α-D-glucopyranosyl-(1→4)-D-glucopyranose



If you only know the sugar and the linkage

Non-reducing → reducing

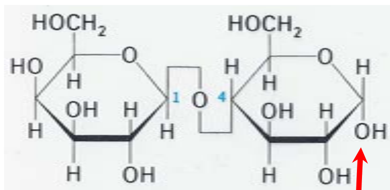
If you know the exact structure of the sugar

As we make sugar-polymers, the convention is to have the non-reducing sugar to the LEFT and the reducing end at the RIGHT.

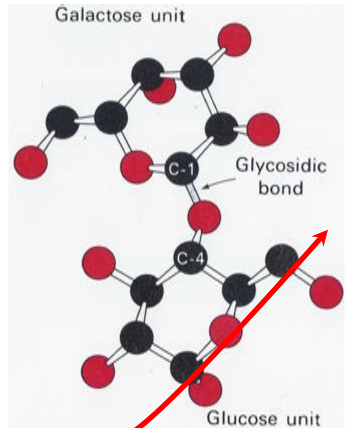
Carbohydrates

Disaccharides:

Here is likely the first disaccharide you encountered in your life:
Lactose.



Lactose
(Galactose-β(1→4)-glucose)



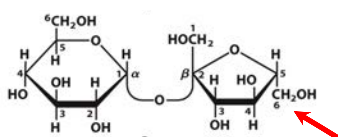
Non-reducing → reducing

Still undergoing mutarotation

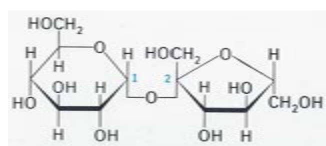
Carbohydrates

Disaccharides:

Here is likely the disaccharide you ingest the most:
Sucrose.



Sucrose
β-D-fructofuranosyl α-D-glucopyranoside
Fru(2β↔α1)Glc ≡ Glc(α1↔2β)Fru



Sucrose
(Glucose-α(1→2)βfructose)

Notice that these are drawn upside down

Trehalose

Nonreducing Disaccharides

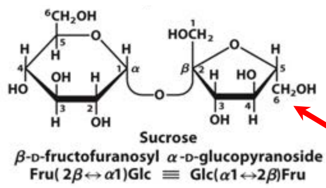
- Two sugar molecules can be also joined in a glycosidic bond between two anomeric carbons.
- The product has two acetal groups and no hemiacetals or hemiketals.
- There are no reducing ends; this is a nonreducing sugar.

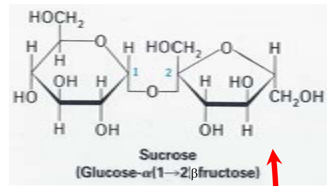
Carbohydrates

Disaccharides:

Here is likely the disaccharide you ingest the most:

Sucrose.





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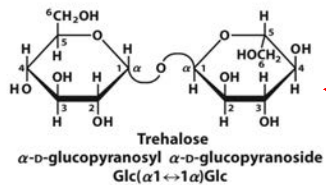
Trehalose



Nonreducing Disaccharides

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Carbohydrates

Oligosaccharides

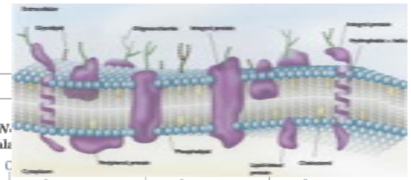
Carbohydrates

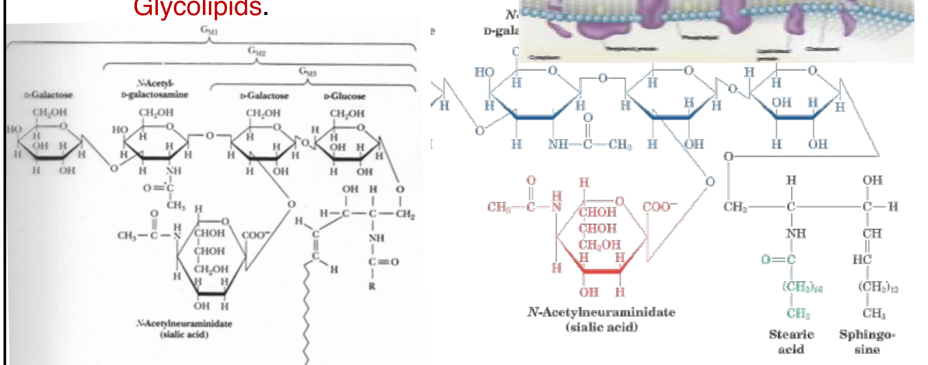
Oligosaccharides:

Here is an oligosaccharide that we encountered with sphingoglycolipids, or for short:

Glycolipids.

Glycoconjugates: Glycolipids



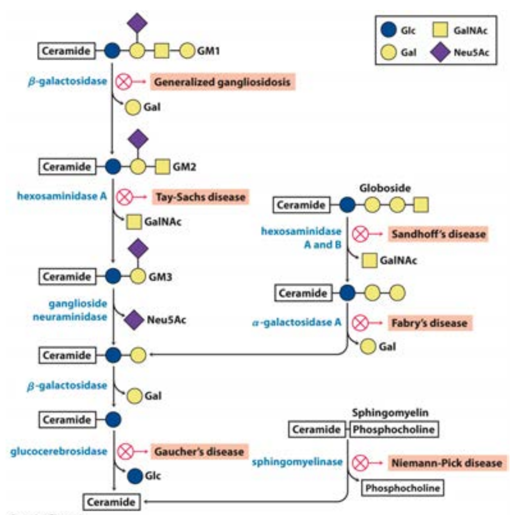


Gangliosides G_{M1}, G_{M2}, and G_{M3}

G_{M1}: structural formula with its sphingosine residue in Fischer projection (contain sialic acid)

GM1 = Gal-β(1→3)GalNAc-β(1→4)Gal-β(1→4)Glc-β(1→Ceramide)
Sia-β(2→3)

Dysfunction in Ganglioside Recycling Leads to a Variety of Medical Disorders



Box 10-1 Figure 1
Lehninger Principles of Biochemistry, Seventh Edition
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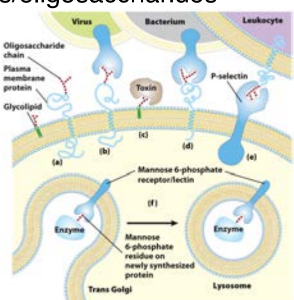
Carbohydrates

Oligosaccharides: Glycoconjugates: Glycoprotein

When you attach an oligosaccharide to a protein: Glycoproteins.

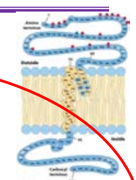
- A protein with small oligosaccharides attached:
  - Carbohydrate is attached via its anomeric carbon to amino acids on the protein.
    - Common connections occur at Ser, Thr, and Asn.
  - About half of mammalian proteins are glycoproteins.
  - Generally, bacteria do not glycosylate their proteins.
  - Carbohydrates play role in protein-protein recognition.
  - Viral proteins are heavily glycosylated; this helps evade the immune system.
- Proteins whose role is to bind specific carbohydrates/oligosaccharides = Lectins (or selectins)
  - Lectins important for many biological functions
    - Recruitment of leukocytes to sites of inflammation
    - Sperm-egg recognition
    - Virus-target cell interaction
    - Attachment of flora (microbiome) in gut
    - Nervous system development
    - Serum-protein turnover (sialic acid)
    - Targeting proteins to lysosomes for degradation (Man)



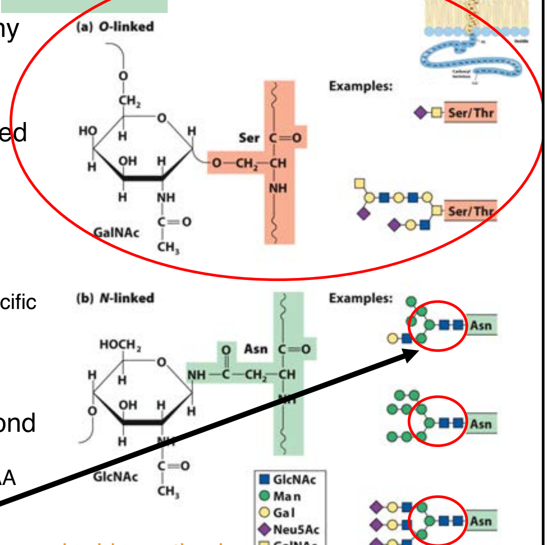
How are these sugars attached?

Carbohydrates

Oligosaccharides: TWO classes attached to proteins, O-linked and N-linked



- First, these polymers, unlike any others we have studies, are BRANCHED
- Second, like glycolipids, O-linked sugars are attached via an O-glycosidic bond
  - Use a Ser or Thr in the sequence (recall glycophorin)
  - Usually smaller than N-linked
  - Synthesized one at a time by specific glycosyltransferases (specific for sugar, linkage, and chirality)
- Third, N-linked sugars are attached via an N-glycosidic bond
  - Use an Asn
  - The Asn residues are within a 3 AA sequence context: $NX^{S}/_{T}$
  - All the same at the core



Let's look more closely at O-linked oligosaccharide synthesis

Lecture 30 (12/6/21)

TODAY

•Reading: Ch7; 236-241, 251-254, 258-260
Ch7; 241-250

•Problems: Ch7; 4,6,7,8,13,14,15,18
Ch7; 16,17,25,27

NEXT

•Reading: Ch4; 188-199
Ch6; 178
Ch8; 295
Ch10; 356-359
Ch14; 530-531,534-535
Ch16; 576, 590
Ch17; 613-615
Ch18; 629, 641-643

Carbohydrates

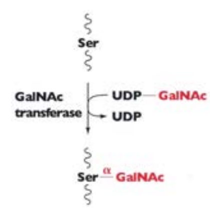
A. Definition
B. Roles
C. Monosaccharides-Chemistry
   1. Chirality
      a. One or more asymmetric carbons
      b. Linear and ring forms
   2. Derivatives: the chemistry of carbohydrates
      a. Oxidation
         i. C1
         ii. C6
      b. Reduction
         i. C1/C2
         ii. Other carbons
      c. Ester formation
      d. Amino sugars
   3. Polymerization
      a. The Glycosidic Bond
      b. Non-covalent bonds in macro-molecular structure
D. Oligosaccharides
   1. Glycoproteins & glycolipids
   2. O-linked
   3. N-linked
   4. Sequence determination-ABO
E. Polysaccharides
   1. Polymers of glucose
   2. Polymers of disaccharides

Carbohydrates

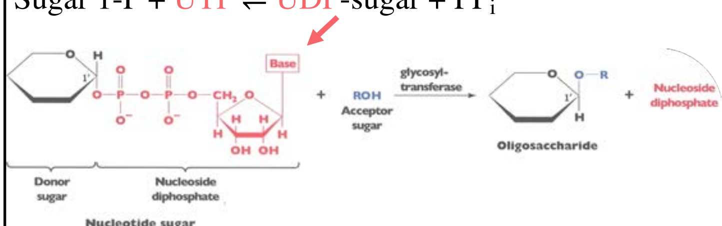
Oligosaccharides: O-linked

- Specific glycosyltransferases use “activated” sugars
- Activated by attaching to nucleotides: UDP, CDP, etc.

EXAMPLE:



Sugar 1-P + UTP ⇌ UDP-sugar + PP_i



Carbohydrates

Oligosaccharides: O-linked

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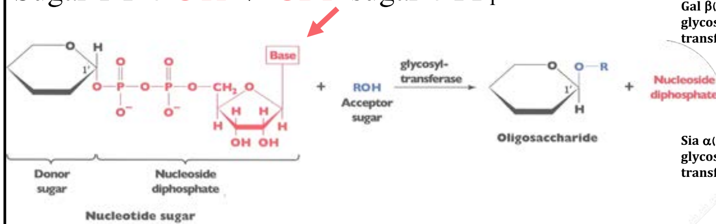
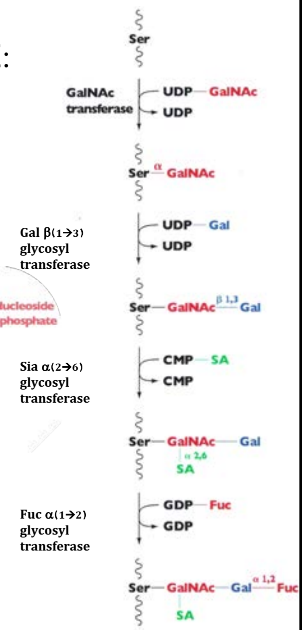
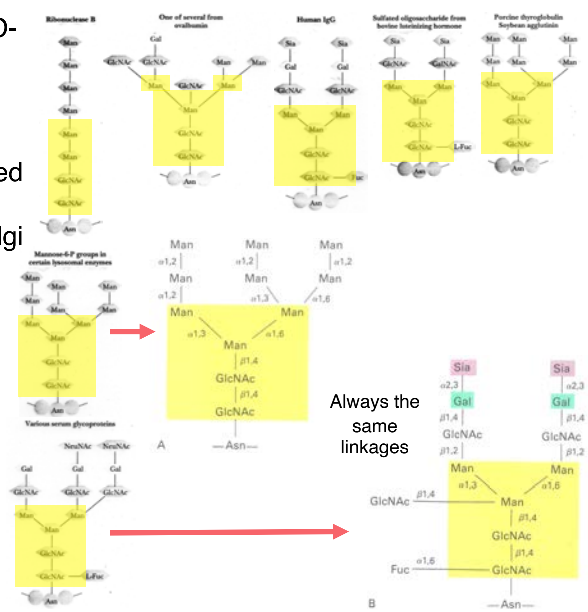




Carbohydrates

Oligosaccharides: N-linked

- Larger, more complex than O-linked
- All have a "Core" containing GlcNAc & Man
- Added as a unit, then modified before adding to Asn groups on proteins; all in the ER/Golgi
- Use an isoprene, called Dolichol, to build core
- Examples:

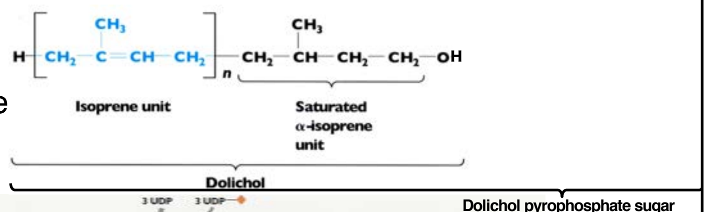


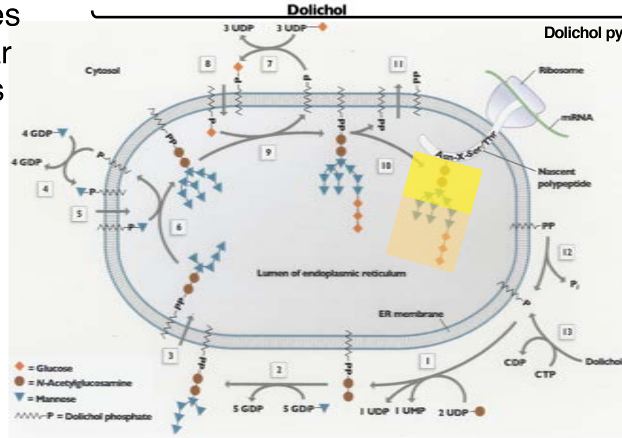
Let's look at this Dolichol & its use in biosynthesis more closely….

Carbohydrates

Oligosaccharides: N-linked

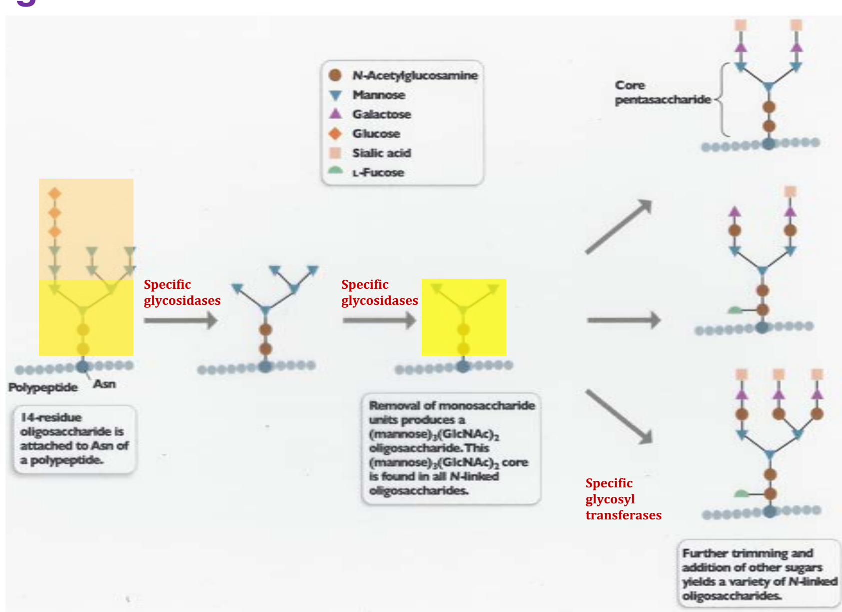
- Activated by attaching two phosphates, one using CTP (step 13)
- Again, uses NDP-sugar precursors





Carbohydrates

Oligosaccharides: N-linked



Carbohydrates

Oligosaccharides: Determination of Sequence

- Whole different problem compared to proteins and nucleic acids…. Its branched!!
- Moreover, a given residue can have several (and stereo-specific) ways of attaching to a neighboring residue.
- Need to use a combination of methods:
  - Chemical
    - Hydrolysis & chromatography to identify sugars
    - Exhaustive methylation & hydrolysis, then chromatography to identify what positions were not methylated
  - Biochemical
    - Use of enzymes that stereo-specifically hydrolyze glyosidic bonds (from the non-reducing end)

EXAMPLE: First, just like protein sequencing, you need to purify glyco-protein or lipid. Lets say we isolate the glycolipid from a person's RBC's who is O-positive. Treat it with a ceramidase to hydrolyze the lipid from the sugar.

Second, take an aliquot and just hydrolyze (like what was done for amino acid analysis). This gets the composition and stoichiometry.

Carbohydrates

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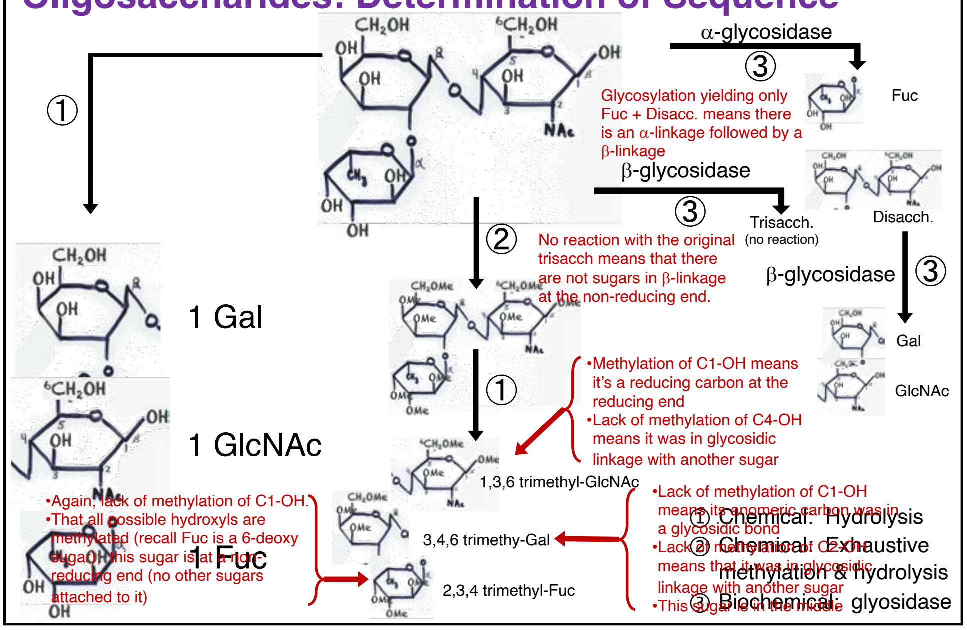
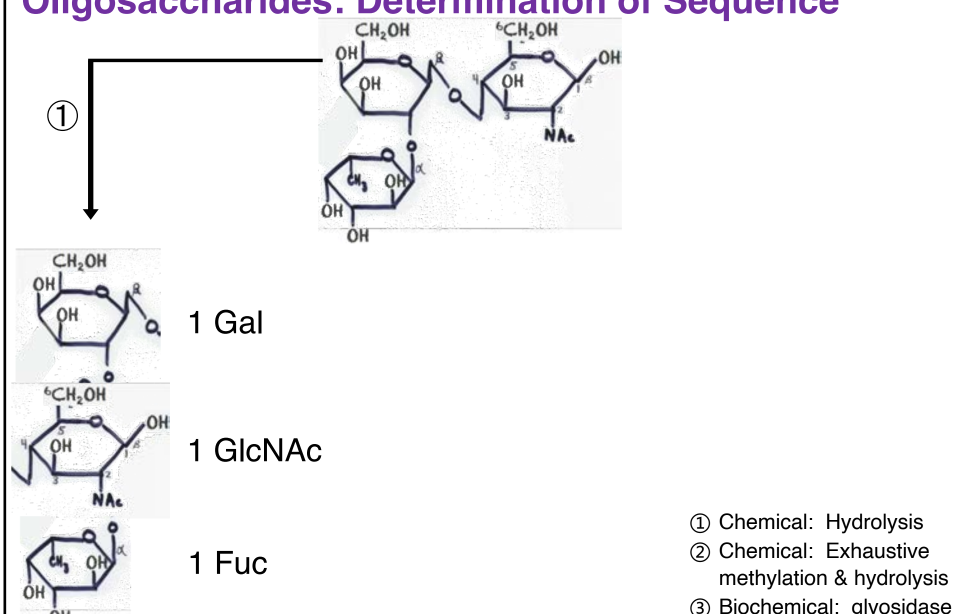
Carbohydrates

Oligosaccharides: Determination of Sequence



Carbohydrates

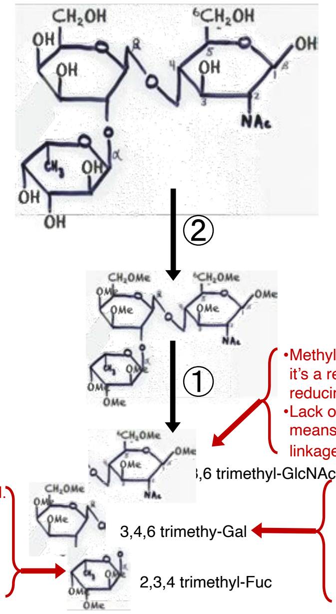
Oligosaccharides: Determination of Sequence



Carbohydrates

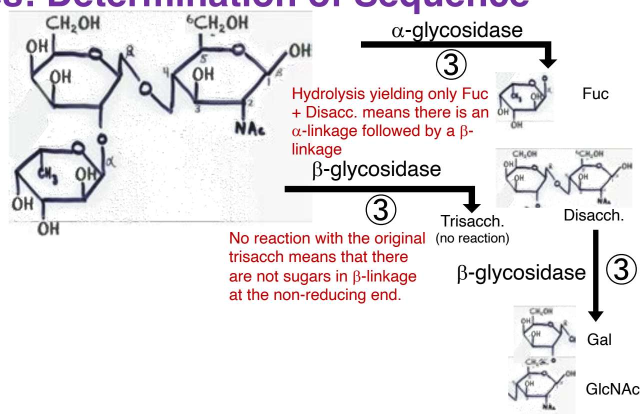
Oligosaccharides: Determination of Sequence

① Chemical: Hydrolysis
② Chemical: Exhaustive methylation & hydrolysis
③ Biochemical: glyosidase



Carbohydrates

Oligosaccharides: Determination of Sequence

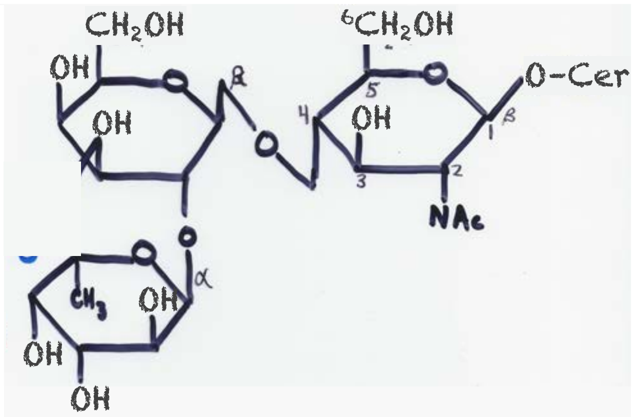


① Chemical: Hydrolysis
② Chemical: Exhaustive methylation & hydrolysis
③ Biochemical: glyosidase

Carbohydrates

Oligosaccharides: Determination of Sequence

– In vertebrates, ganglioside carbohydrate composition determines blood groups.



L-Fuc α(1→2)-D-Gal β(1→4) D-GlcNAc β-Ceramide — O blood group

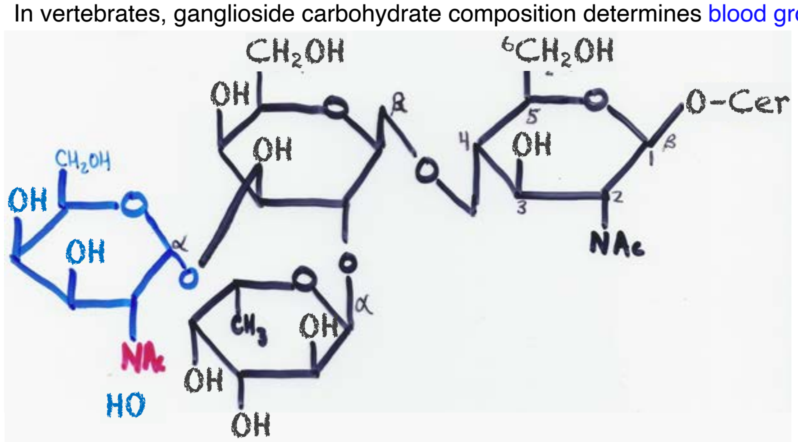
D-Gal α(1→3) — B blood group

D-GalNAc α(1→3) — A blood group

Carbohydrates

Oligosaccharides: Determination of Sequence

– In vertebrates, ganglioside carbohydrate composition determines blood groups.



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D-GalNAc α(1→3) — A blood group

Glycoconjugates: Analysis

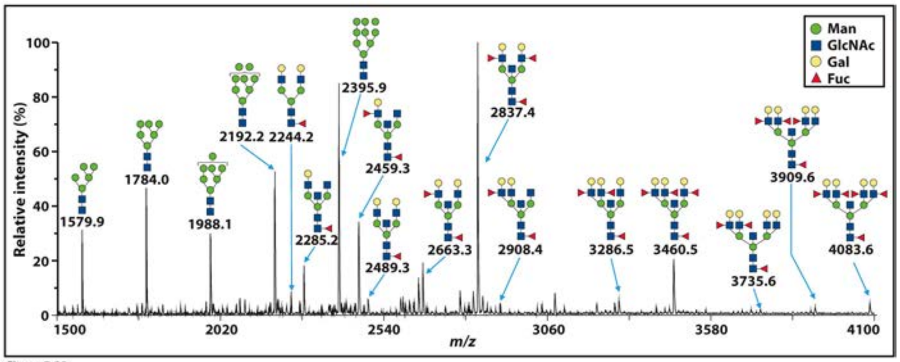

Figure 7-39
Lehninger Principles of Biochemistry, Seventh Edition
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Carbohydrates

Polysaccharides

Carbohydrates

Polysaccharides

- The majority of natural carbohydrates are usually found as large polymers.
- These polysaccharides can be:
  - homopolysaccharides (one monomer unit)
  - heteropolysaccharides (multiple monomer units)
  - linear (one type of glycosidic bond)
  - branched (multiple types of glycosidic bonds)
- Polysaccharides do not have a defined molecular weight.
  - This is in contrast to proteins because, unlike proteins, no template is used to make polysaccharides.
  - Polysaccharides are often in a state of flux; monomer units are added and removed as needed by the organism.

Carbohydrates

Polysaccharides: Polymers of Glucose

Homopolymers of Glucose:

- Starch
- Glycogen
- Cellulose
- Chitin

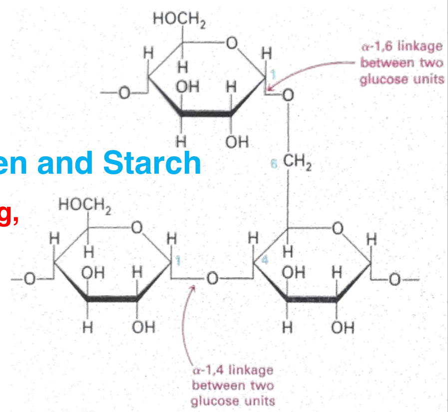
- Glycogen and Starch are the main storage polysaccharides for energy.
  - Glycogen and starch are insoluble due to their high molecular weight and often form granules in cells.
  - Molecular weight reaches several millions (~200×10^6)(can see in microscope).
- Glycogen is a branched homopolysaccharide of glucose.
  - Glucose monomers form $\alpha(1 \rightarrow 4)$ linked chains.
  - There are branch points with $\alpha(1 \rightarrow 6)$ linkers every 8–12 residues.
- Starch is a mixture of two homopolysaccharides of glucose.
  - Amylopectin is like glycogen, but the branch points ($\alpha(1 \rightarrow 6)$ linkages) occur every 24–30 residues.
  - Amylose is an unbranched polymer of $\alpha(1 \rightarrow 4)$ linked residues.

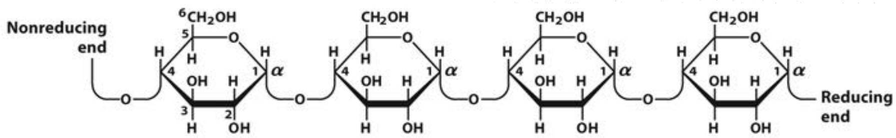
Carbohydrates

Polysaccharides: Glycogen & Starch

Glycosidic Linkages in Glycogen and Starch

(Glc-α(1→4)Glc)$_n$ with α(1→6) branching, where n≈10^6





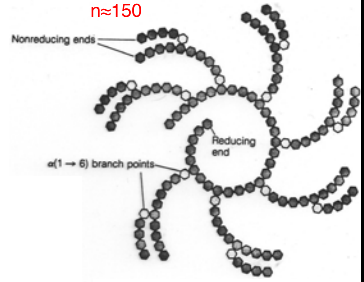
Non-reducing → reducing

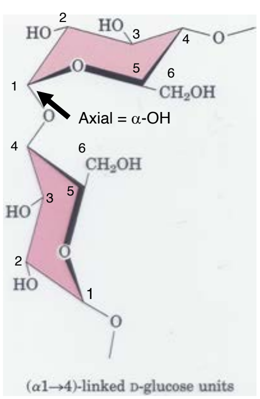
Haworth projections are not good to show the actual shape, which is helical!

Carbohydrates

Polysaccharides: Glycogen & Starch

I_2



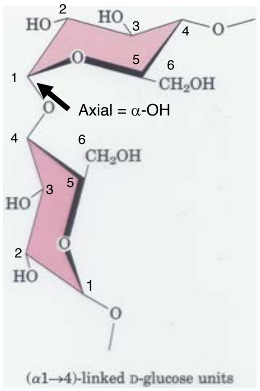


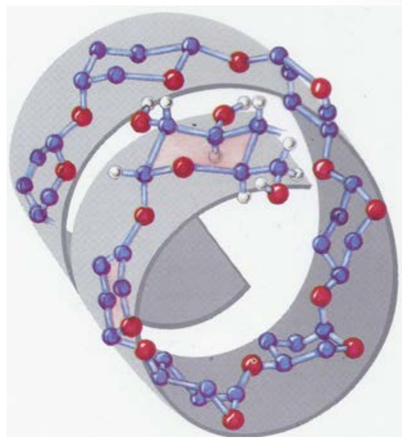
- Granules contain enzymes that synthesize and degrade these polymers.
- Glycogen and amylopectin have one reducing end but many nonreducing ends.
- Enzymatic processing occurs simultaneously in many nonreducing ends.

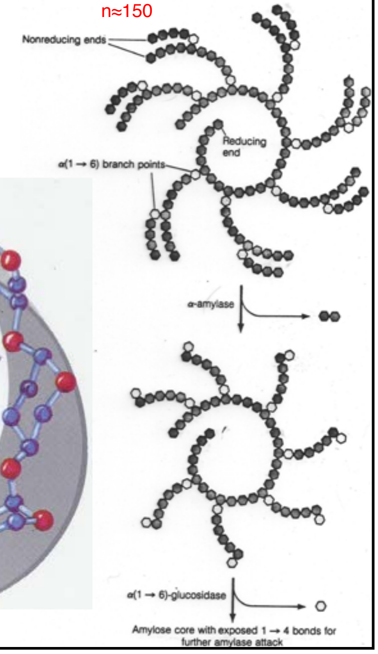
Carbohydrates

Polysaccharides: Glycogen & Starch

I_2

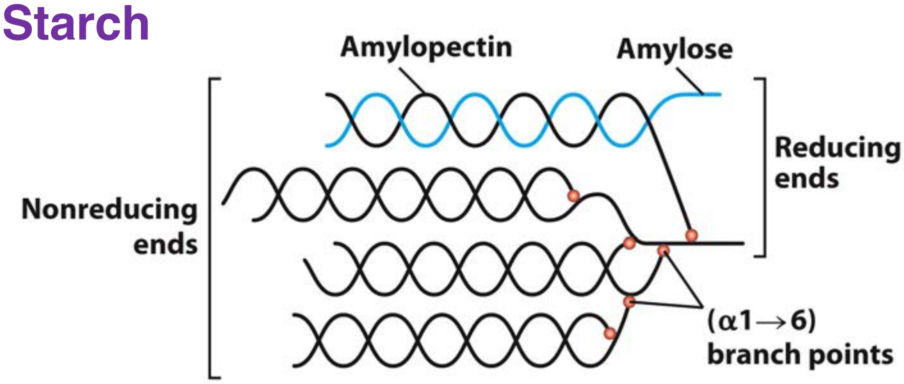






Carbohydrates

Polysaccharides: Glycogen & Starch



Mixture of Amylose and Amylopectin in Starch

Carbohydrates

Polysaccharides:

Homopolymers of Glucose:

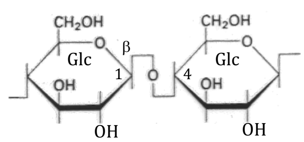
- Starch
- Glycogen
- Cellulose
- Chitin

- Cellulose is a linear homopolysaccharide of glucose.
  - Glucose monomers form $\beta(1 \rightarrow 4)$ linked chains.
  - Hydrogen bonds form between adjacent monomers.
  - There are additional H-bonds between chains.
  - Structure is now tough and water insoluble.
  - It makes up almost 50% of plant mass; in cell walls.
  - Cotton is nearly pure fibrous cellulose.
- Chitin is a linear homopolysaccharide of *N*-acetylglucosamine (GlcNAc).
  - *N*-acetylglucosamine monomers form $\beta(1 \rightarrow 4)$-linked chains.
  - forms extended fibers that are similar to those of cellulose
  - hard, insoluble, cannot be digested by vertebrates
  - structure is tough but flexible, and water insoluble
  - found in cell walls in mushrooms and in exoskeletons of insects, spiders, crabs, and other arthropods

Carbohydrates

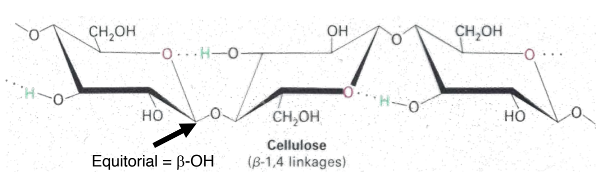
Polysaccharides:

Cellulose & Chitin

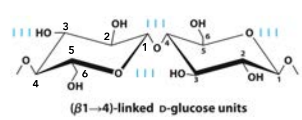


Glycosidic Linkages in Cellulose & Chitin

$(Glc\text{-}\beta(1\rightarrow4)Glc)_n$ with NO branching,
$n \approx 10^4$



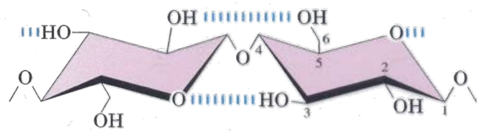
Notice that each chair is alternatively flipped



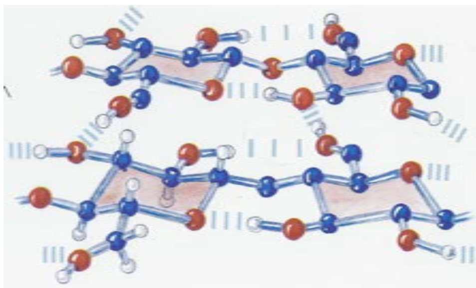
THE most abundant biological molecule in the world: ~300 trillion kg

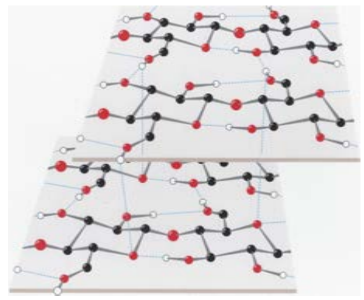
Carbohydrates

Polysaccharides: Cellulose & Chitin

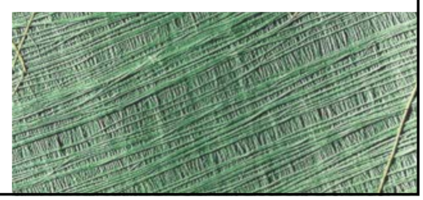


(β1→4)-linked D-glucose units





- The fibrous structure and water insolubility make cellulose a difficult substrate to act upon.
- Most animals cannot use cellulose as a fuel source because they lack the enzyme to hydrolyze $\beta(1\rightarrow4)$ linkages (β-Amylase or cellulase).
- Fungi, bacteria, and protozoa secrete cellulase, which allows them to use wood as source of glucose.
- Ruminants and termites live symbiotically with microorganisms that produce cellulase and are able to absorb the freed glucose into their bloodstreams.
- Cellulases hold promise in the fermentation of biomass into biofuels.

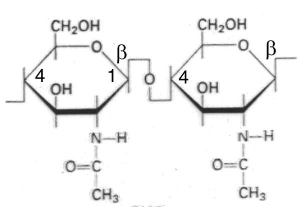


Carbohydrates

Polysaccharides: Cellulose & Chitin

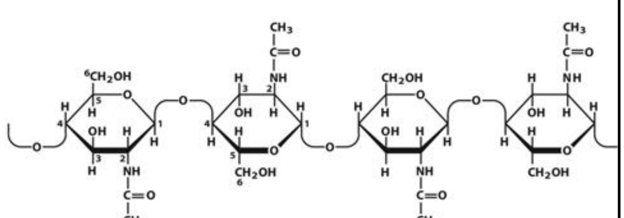
A Sally lightfoot crab. The exoskeleton of this arthropod is rich in chitin, one of the most abundant biopolymers on earth.

Paul Whitten/Science Source



Chitin

$(GlcNAc\text{-}\beta(1\rightarrow4)\text{-}GlcNAc)_n$

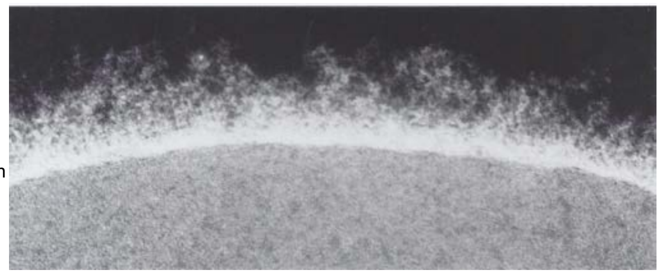


Carbohydrates

Polysaccharides: Polymers of Disaccharides

First, need to describe the Extracellular Matrix (ECM)

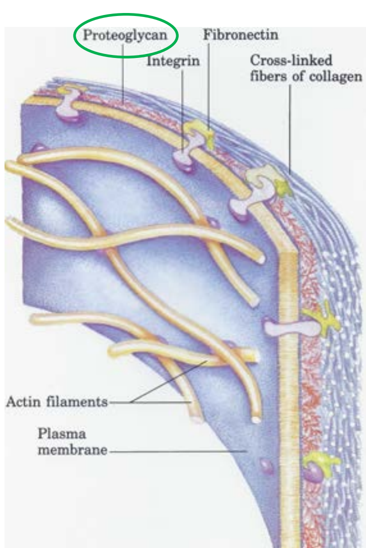
- Material outside the cell
- Strength, elasticity, and physical barrier in tissues (varies tremendously)
- Main components
  - proteoglycans
  - collagen & elastin fibers
- Proteoglycans
  - Different glycosaminoglycans are O-linked to the "core protein."
  - Linkage from anomeric carbon of xylose to serine hydroxyl
  - Our tissues have many different core proteins; aggrecan is the best studied.

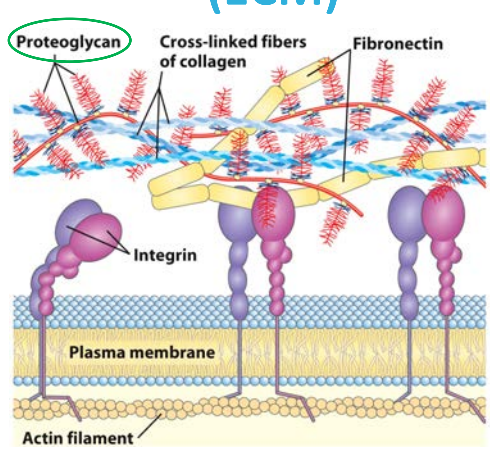


Carbohydrates

Polysaccharides: Polymers of Disaccharides

Extracellular Matrix (ECM)





Carbohydrates

Polysaccharides: Polymers of Disaccharides
Glycosaminoglycans

(the carbohydrate part of proteoglycans)

- Linear polymers of repeating disaccharide units $(\text{sugarX-sugarY})_n$
- One monomer (sugarX) is either sugar acid or Gal
  - uronic acids (C6 oxidation)
  - Most have sulfate esters
- One monomer (sugarY) is either:
  - *N*-acetyl-glucosamine (GlcNAc) or *N*-acetyl-galactosamine (GalNAc)
  - Also sulfate esters
- Extended hydrated molecule
  - Negatively charged
  - minimizes charge repulsion
- Forms meshwork with fibrous proteins to form extracellular matrix
  - connective tissue
  - lubrication of joints
- Form huge ($M_r > 2 \cdot 10^8$) noncovalent aggregates (Hyaluronan and Aggrecan).
  - They hold a lot of water (1000× its weight) and provide lubrication.
  - Very low friction material
  - Covers joint surfaces: articular cartilage
    - reduced friction & load balancing