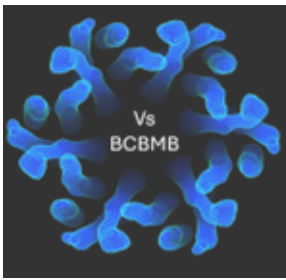


Advanced Biochemistry

CARBOHYDRATES



This is a Tutorial/Silent Lecture



What is a Tutorial/Silent Lecture?

a sequence of "slides" formatted to guide you through the exploration/study of the topic

you are the main actor in this active learning experience

think of it as working with a tutor without having to pay for it

as the slide sequence unfolds, you will get opportunities to engage with the material

➤ **by thinking about/answering questions,**

(my answer is always provided on the next slide).

➤ **by completing a "short assignment"**

(it never will take more than a few minutes, if at all that long),

➤ **by watching a short video/clip**

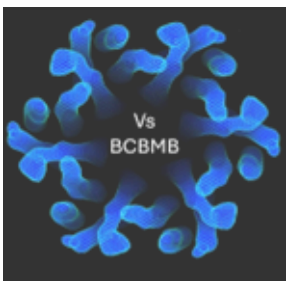
(the embedded links will take you to my YouTube@VsBCBMB channel or other creators;
key moments are shown in the slide-deck as still images, in case you don't want to watch the videos)

of course, you can skip the active learning aspect and look at the answers right away.

Why Give This a Go?

- **benefits: you set the pace** taking as much or as little time as you need.
- you **can turn tutorials/silent lectures into fully immersive experiences** (eg playing your favourite music while working through the content),
- **or invite friends to over the Q&A structured/guided materials together**, discussing the questions before looking at answers.

each of these features help you to hold on to the material.



Advanced Biochemistry



this collection of handouts builds on the "Biochemistry Fundamentals" collection

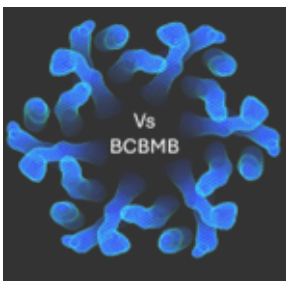
= the chapters assume that you know the basics covered in the "Fundamentals" handouts (free downloads), and have some basic knowledge of molecular/cell biology

this tutorial can be used stand alone
but does reference other tutorials

therefore, you will get the largest benefits if you

- work through other chapters in the order that they are posted in the "download gallery"
- **review the associated "Biochemistry Fundamentals" chapter** to refresh your memory
- spend 5-10 minutes to **summarize for yourself what you already know/remember** about the topics of the handout you are about to look at.
 - **take advantage of the "interactive" elements**

I welcome your thoughts and ideas for further improvements of the chapters. You can submit your comments by contacting me at pdf-comments@vsbcbmbstudy.com



Setting The Stage



following a narrative that builds **life from scratch**

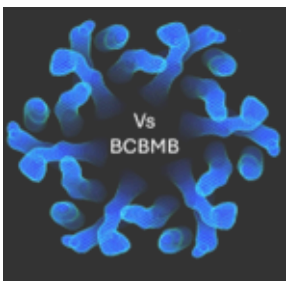
- we started off by **retracing the origins of simple biological macromolecules** and the emergence of polymers and cells
(chapter: Chemical Evolution)
- took reasonably detailed **look at how Nature succeeded in compartmentalizing space** by exploiting chemical properties of amphiphiles to build flexible membranes
(chapter Lipids and Membranes)
- caught up on and **extended what you know about proteins**, this time including membrane proteins that are needed to make membranes semi-permeable
(chapter: Proteins)
- and built a reasonably **detailed core knowledge of membrane associated transport processes**
(chapter: Membrane Transport)

continuing the narrative, with solutions for mass-transfer between compartments in hand, we now

- **need a way to store information** about “cell identity, content and dynamics”
- **need a way to communicate with other units** and to interpret environment
 - **need a way to power the unit** and to manufacture the components

having been in that place before ([Biochemistry Fundamentals Collection of Tutorials](#)), we **derived how and why "information storage and processing" is built around** the chemistry of two classes of macromolecular building blocks: **carbohydrates and heterocyclic aromatic compounds** (nucleobases).

back then, however, we only covered essential basic facts that helped us to follow the narrative, skipping over some details and advanced aspects of the material.

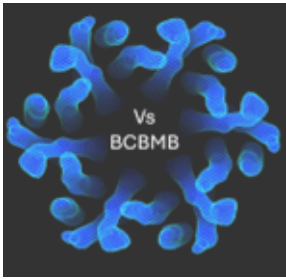


Goals of This Tutorial/Silent Lecture



by the end of this tutorial

- ✓ you will have a **more complete understanding of carbohydrate structure**
- ✓ you will have learned about **important chemical modifications** to basic carbohydrate structure
- ✓ you will better understand the **principles of polysaccharide design**
- ✓ you will have a more complete knowledge and understanding of **carbohydrate function in biology**



"Carbs" Seen From the Perspective of the Biochemistry Fundamentals Collection



Boundaries/Structural Support

- ✓ cellulose
- ✓ chitin

Energy Storage/Generation

- ✓ amylose
- ✓ amylopektin
- ✓ Monosaccharides (eg glucose)

CARBOHYDRATES

Information Storage

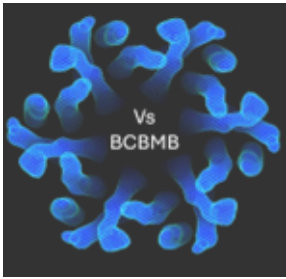
- ✓ nucleic acid backbone

Lubrication

- ✓ hyaluronic acid

what else could Carbs do in biology?

...list what you know already...



"Carbs" Seen From the Perspective of the Biochemistry Fundamentals Collection



Boundaries/Structural Support

- ✓ cellulose
- ✓ chitin

Energy Storage/Generation

- ✓ amylose
- ✓ amylopektin
- ✓ Monosaccharides (eg glucose)

CARBOHYDRATES

Information Storage

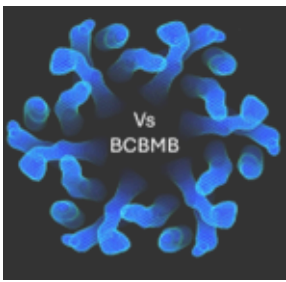
- ✓ nucleic acid backbone

Lubrication

- ✓ hyaluronic acid

what else could Carbs do in biology?
additional functions you will learn about

- ✓ signaling
- ✓ protein sorting
- ✓ protein membrane anchors
- ✓ blood clotting
- ✓ tissue profiling



Chemical Structure of Monosaccharides

Filling Gaps in Nomenclature



- chemically carbohydrates are
- polyhydroxy-aldehydes (**Aldoses**) or
 - polyhydroxy-ketones (**Ketoses**)

typically have 3-7 carbon atoms
(triose, tetroses, pentoses, hexoses, heptoses)

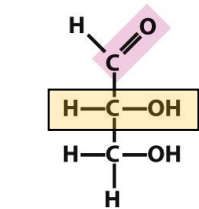
except for dihydroxyacetone, monosaccharides have at least one **asymmetric** carbon atom
(examples shown with orange underlay)

n chiral carbon atoms give rise to 2^n stereoisomers

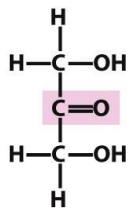
(eg: hexoses – 4 asymmetric C-atoms → 16 stereoisomers)

based on the configuration at the **chiral carbon center** that is the **farthest away from the aldehyde/ketone group**, monosaccharides are either D (from "*dexter*" = right) or L (from "*laevus*" = left).
in this system D-Glyceraldehyde serves as reference compound

most hexoses in living organisms are D isomers;
hexoses also are the most abundant

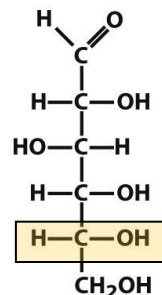


D-Glyceraldehyde,
an aldotriose

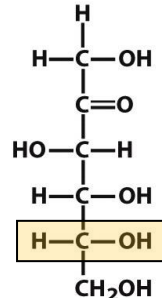


Dihydroxyacetone,
a ketotriose

(a)

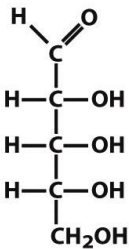


D-Glucose,
an aldohexose

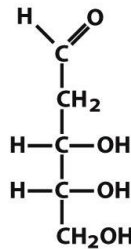


D-Fructose,
a ketohexose

(b)

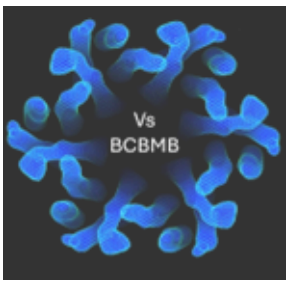


D-Ribose,
an aldopentose



2-Deoxy-D-ribose,
an aldopentose

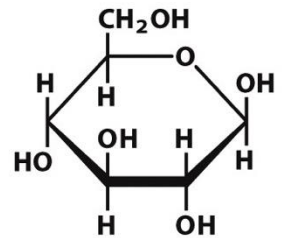
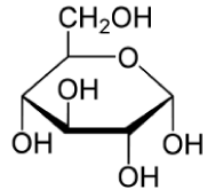
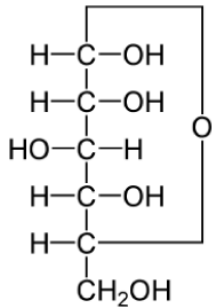
knowing/memorizing these structures will help you with holding on to a lot of biochemical knowledge



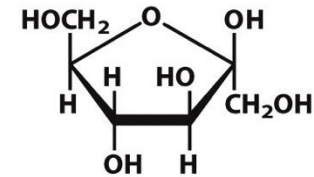
Structure of Monosaccharides Nomenclature continued



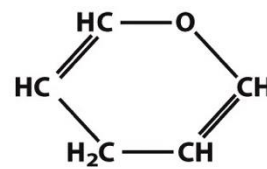
because of the remote similarity of the cyclic hemiacetals/hemiketals with pyran and furan, cyclic forms of the monosaccharides are identified with the suffix “*pyranose*” and “*furanose*”



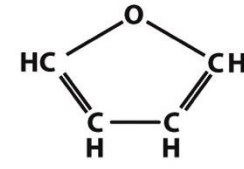
D-Glucopyranose



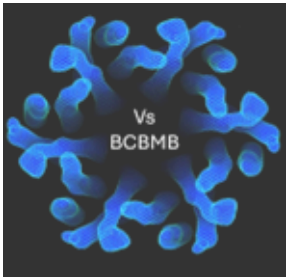
D-Fructofuranose



Pyran



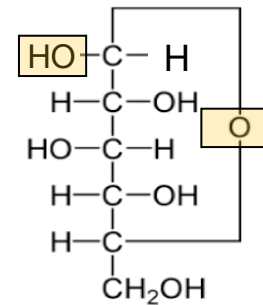
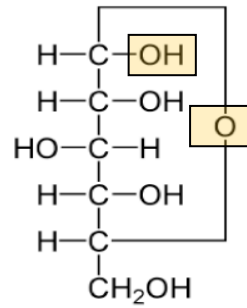
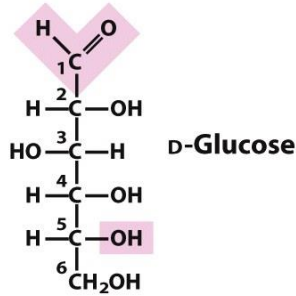
Furan



Carbohydrate Structure – Reminder...C1 (C2) is special....



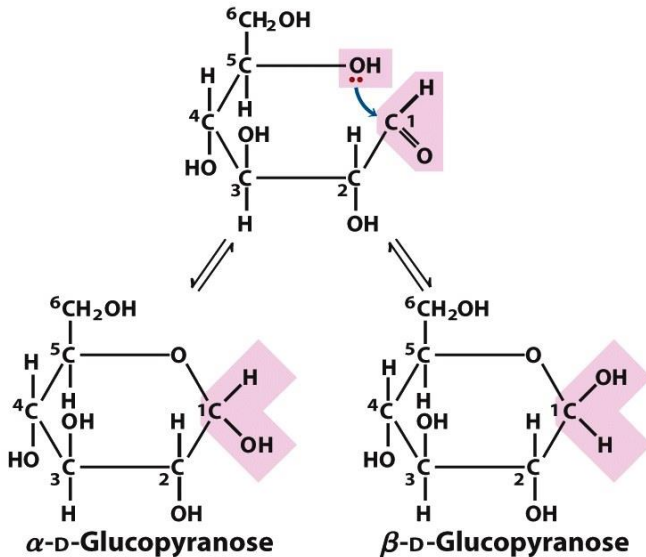
ring closure at **C1 (aldoses) or C2 (ketoses)** creates an **additional asymmetric carbon atom** this carbon is called “**anomeric**”, and gives rise to two **anomers**, referred to as α and β forms of the sugar
(Biochemistry Fundamentals – CARBOHYDRATES slide 30)

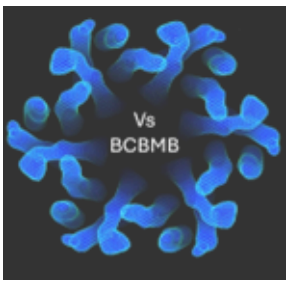


in the α -form, the -OH groups at the anomeric carbon and the most distant chiral carbon are on the same side in the Fischer projection, for the β -form they are on opposite sides.

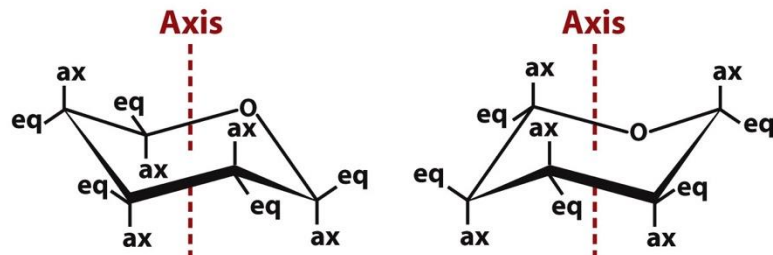
cyclic forms are always in **equilibrium** with the open forms, **unless** the -OH group on the anomeric carbon has reacted to form a glycosidic bond.

(loss of the -H from the -OH prevents ring opening because the aldehyde or ketone cannot be restored to reach the linear intermediate)

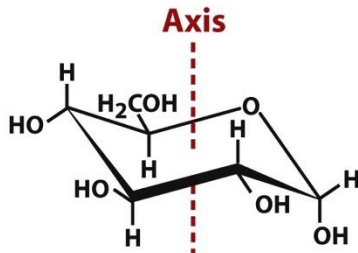




Carbohydrate Structure More Nomenclature



Two possible chair forms



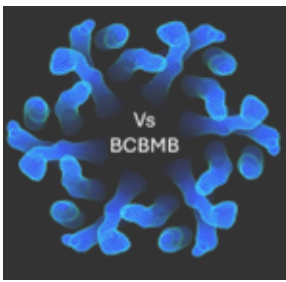
α -D-Glucopyranose

- the pyranose is **not flat**, it usually adopts one of two “**chair**” conformations.
- in these conformations, **groups bound to the ring carbon atoms can have two spatial orientations** because of the tetrahedral geometry of the carbon atoms:
equatorial (“eq”) and axial (“ax”); equatorial groups are less sterically hindered than axial groups
- the α and β anomer differ in the **position of the -OH group - eq or ax - on the anomeric carbon**

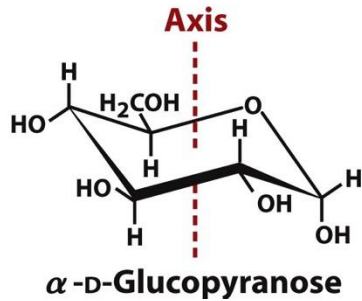
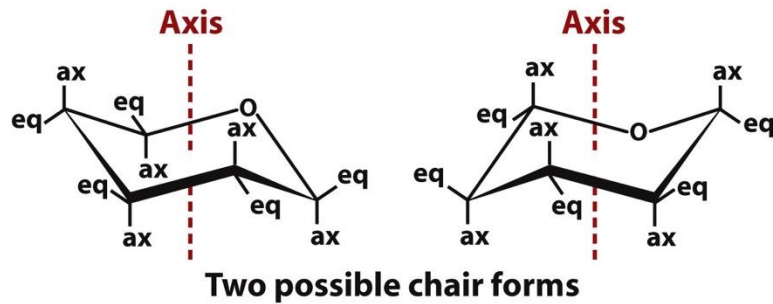
for each conformation, both **anomers** are possible (though typically one of them is more stable), and **interconvert freely**

(because cyclic and linear form are in equilibrium = rotational conformation about C1-C2 single bond at the moment of ring closure decides which anomer is formed)

- note: while **anomers interconvert freely** and spontaneously – **chair conformations DO NOT** even though they are **separated by only ~10kcal/mol** – this is odd, why?



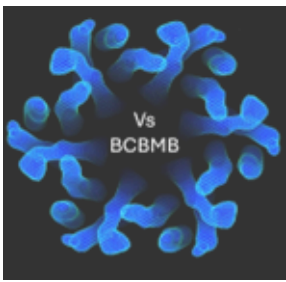
Carbohydrate Structure More Nomenclature



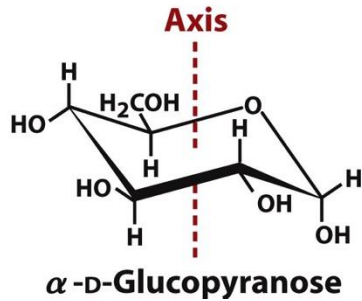
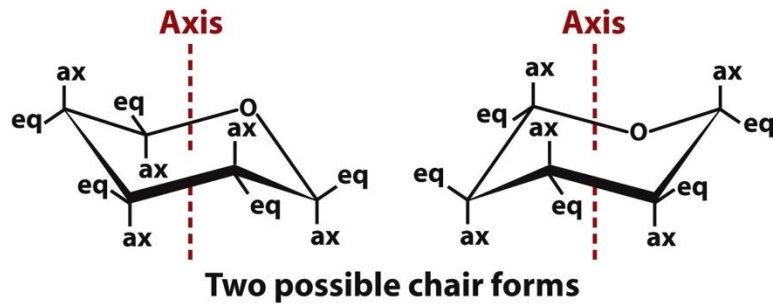
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equatorial groups are less sterically hindered than axial groups
- **note: while anomers interconvert freely and spontaneously – chair conformations DO NOT.** Separated by only $\sim 10\text{kcal/mol}$ – this is odd, why?

how does that compare to protein stabilization?

...what do you remember...?



Carbohydrate Structure More Nomenclature



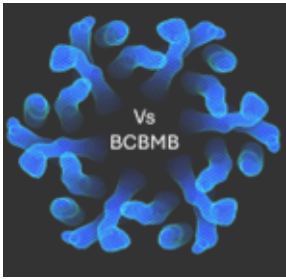
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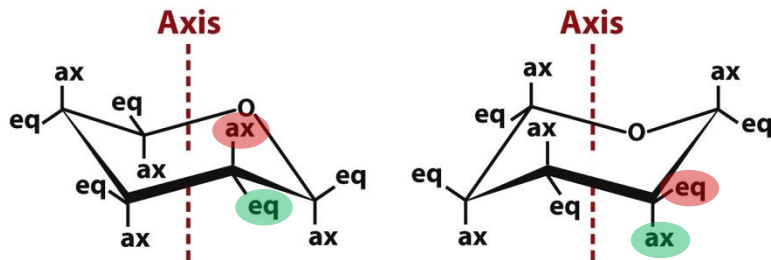
how does that compare to protein stabilization?

~ 10 kcal/mol, which meant a marginal stabilization of the native fold

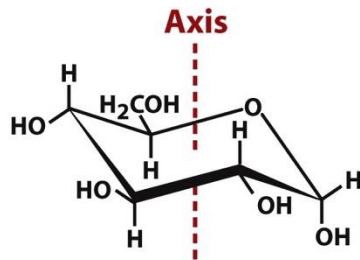
why then can chair conformations not convert spontaneously in carbohydrates?



Carbohydrate Structure More Nomenclature



Two possible chair forms



α -D-Glucopyranose

- in these conformations, **groups bound to the ring carbon atoms can have two spatial orientations** because of the tetrahedral geometry of the carbon atoms:
equatorial (“eq”) and axial (“ax”);
 equatorial groups are less sterically hindered than axial groups

- **note: while anomers interconvert freely and spontaneously – chair conformations DO NOT.** Separated by only ~10kcal/mol – this is odd, why?

how does that compare to protein stabilization?

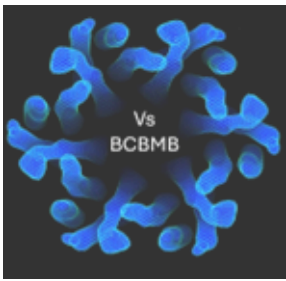
~10 kcal/mol, which meant a marginal stabilization of the native fold

not hindered by energy - but **simultaneous inversion** of all carbon atoms **is kinetically hindered because it simultaneously changes**

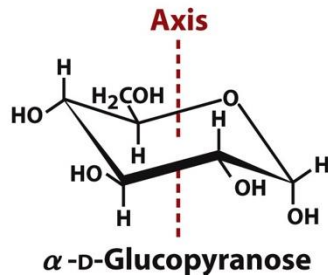
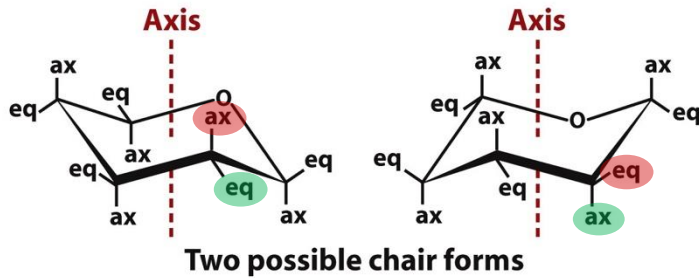
all eq \rightarrow ax + all ax \rightarrow eq

in contrast: conformational changes in linear proteins (or sugars) involve simple bond rotations.

why then can chair conformations not convert spontaneously in carbohydrates?



Carbohydrate Structure More Nomenclature



why then can chair conformations
not convert spontaneously in
carbohydrates?

➤ note: while anomers interconvert freely and spontaneously – chair conformations DO NOT. Separated by only ~10kcal/mol – this is odd, why?

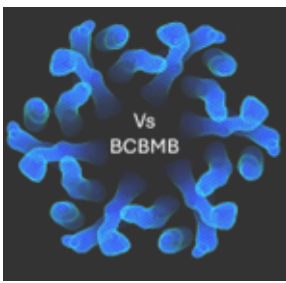
how does that compare to protein stabilization?

~10 kcal/mol, which meant a marginal stabilization of the native fold

not hindered by energy, but it would involve inversion of all the carbon atoms = all eq \rightarrow ax + all ax \rightarrow eq; conformational changes in linear proteins (or sugars) involve simple bond rotations.

caution: there is **NO** correlation between α/β and eq/ax. The α/β nomenclature is based only on the stereochemical configuration at the anomeric and reference carbon atoms!

yes – carbohydrate stereochemistry and nomenclature are an "acquired taste" = they are difficult to absorb because there are so many layers of complexity (D,L enantiomers, diastereomers; anomers and then eq/ax if you draw it in chair conformation) = give it time and be patient



with the expansion of knowledge about carbohydrate structure and nomenclature out of the way

we next **want to move on to the functional aspects**

recalling what you learned in the associated Fundamentals Chapter

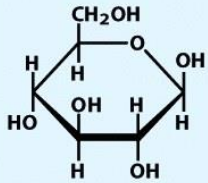
....**differences in the biological roles of polysaccharides** not only related to differences in stereochemistry of the polymer's units but also **involved significant differences in the chemical modification patterns of the carbohydrate building blocks.**

consequently – exploring the spread of functional roles of carbohydrates requires taking another look at common chemical modifications of carbohydrates....

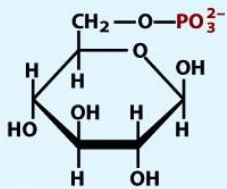
Common Monosaccharide Derivatives

A Closer, More Systematic and Complete Look Than in the Fundamentals

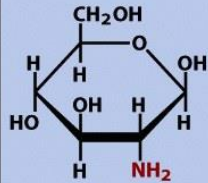
Glucose family



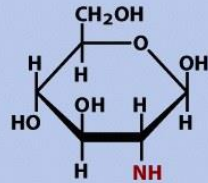
β-D-Glucose



β-D-Glucose 6-phosphate



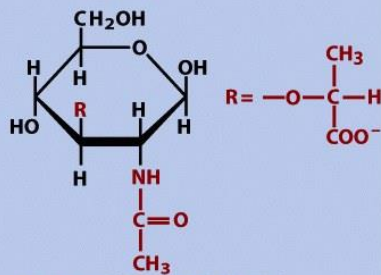
β-D-Glucosamine



N-Acetyl-*β*-D-glucosamine

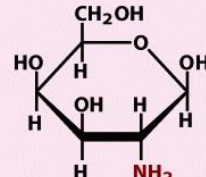


Muramic acid



N-Acetylmuramic acid

Amino sugars

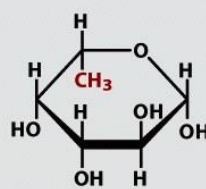


β-D-Galactosamine

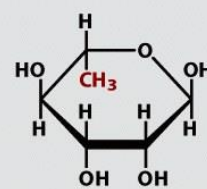


β-D-Mannosamine

Deoxy sugars



β-L-Fucose

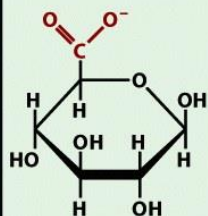


α-L-Rhamnose

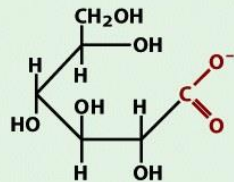
chemical modifications are very common in carbohydrates

missing from this figure are carbohydrates that have been modified by the addition of a -SO₃ group.

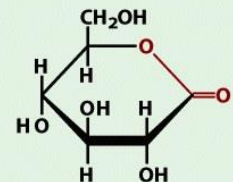
Sulfated carbohydrate derivatives play important roles in the extracellular matrix and in providing lubricants in joints



β-D-Glucuronate

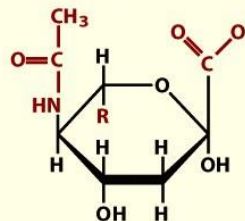


D-Gluconate

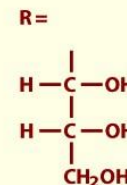


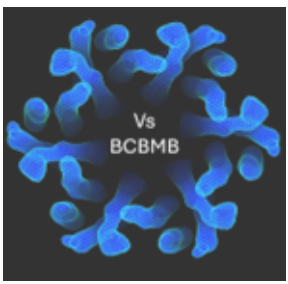
D-Glucono- δ -lactone

Acidic sugars



N-Acetylneuraminic acid (a sialic acid)





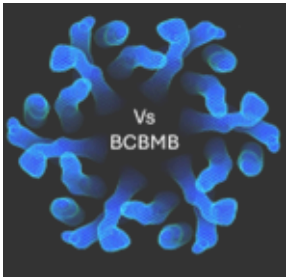
with a more complete repertoire of chemical modifications at hand

we are almost ready to explore new functional aspects of carbohydrates

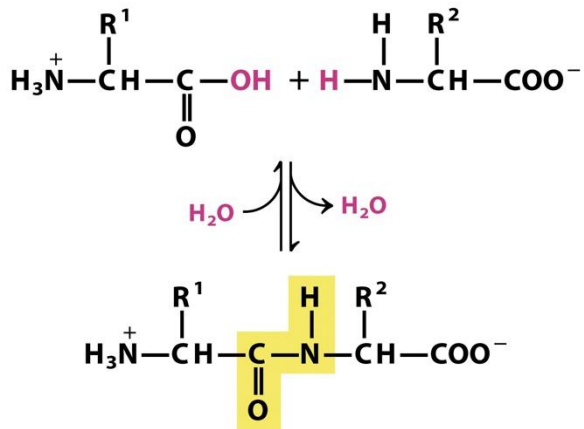
just two loose ends to "tidy up"

- chemical linkage between carbohydrate units
- alignment of structural organization characteristics with "primary, secondary, tertiary" structure nomenclature

....starting with

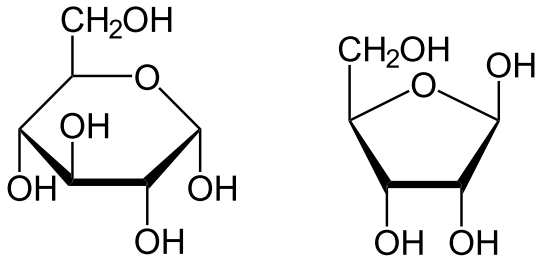


The Sugar Connection



exploring the structure of proteins, you learned that amino acids are joined through the $-\text{NH}_2$ and $-\text{COOH}$ groups of the invariant scaffolding unit (C_α -carbon)

using a condensation to form a peptide bond seemed intuitive because it involved two chemically very different functional groups

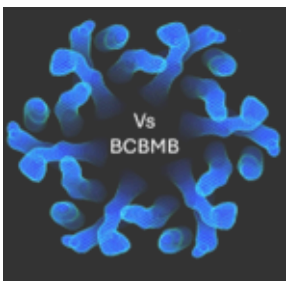


looking at the structure of monomeric carbohydrates like glucose or ribose (shown)

you immediately notice that carbohydrates are different because there are two fundamentally different ways to join monomeric sugars to form a disaccharide

By NEUROtiker - Own work, Public Domain, <https://commons.wikimedia.org/w/index.php?curid=1787650>

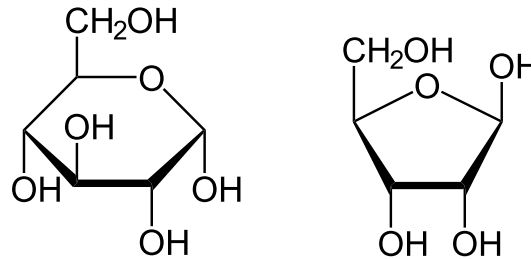
....collect your thoughts on thiswhat are the options?...



The Sugar Connection



....collect your thoughts on thiswhat are the options?...



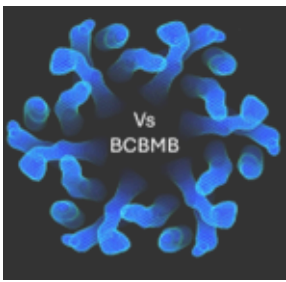
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Answers

if you are unbiased, you realize that – in principle – **any of the –OH groups on one monomer could undergo a condensation reaction with any of the –OH groups on the other monomer**

you, furthermore, realize that each monomer **could react more than once** if the first reaction still leaves free –OH groups

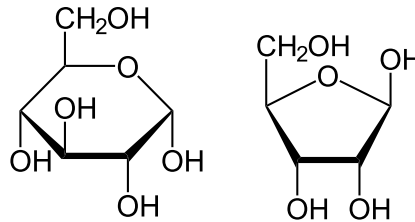
both these characteristics set carbohydrates apart from amino acids and nucleobases



The Sugar Connection



....collect your thoughts on thiswhat are the options?...



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equally important

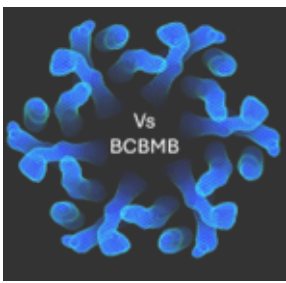
the type of **bond formed** in a condensation between two carbohydrates depends on exactly which $-OH$ groups react with each other

- any bond **involving one or both anomeric carbons** is called a "**glycosidic bond**"
- a bond formed by **joining two non-anomeric carbons** will be an **ether (R_1-O-R_2) bond, or an ester** (if an acid was the reaction partner)

glycosidic bonds are very common

ether bonds are rare and are not used to connect two sugars, their occurrence is limited to serving as chemical modification (methylation) and linkage to other non-carbohydrate macromolecules

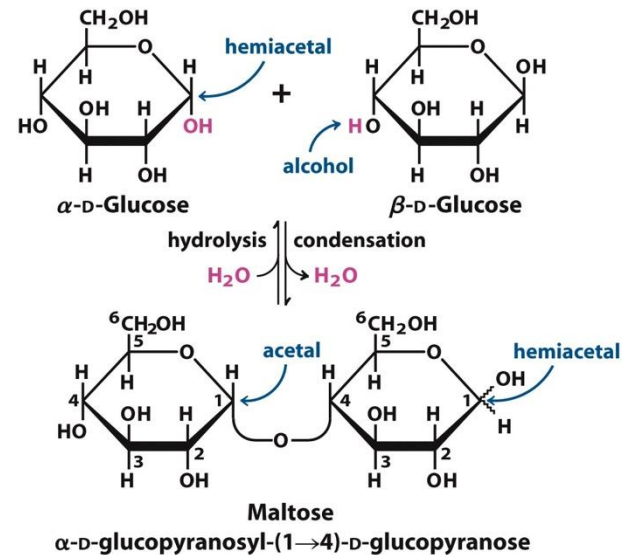
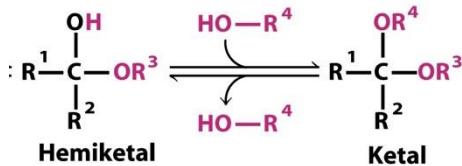
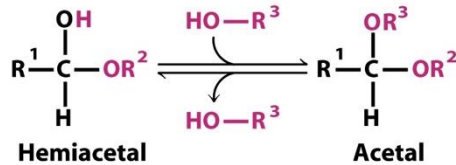
ester bonds – do not occur directly between two sugars but in nucleic acids phosphodiester linkages are used on two of the (deoxy)ribose $-OH$ groups to connect nucleobases



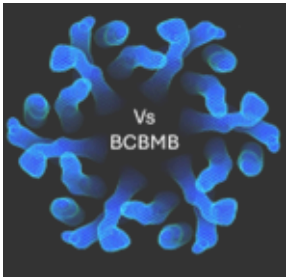
The Glycosidic Bond



- the glycosidic bond is formed by a condensation reaction, that involves the anomeric carbon in one of both reaction partners.
 - the reaction results in an acetal or ketal, depending on whether an aldose or ketose serves as starting point.
- the link can occur between the anomeric –OH group and any –OH group on another mono-/oligo-/polysaccharide.
- if linkages between sugars leave at least one (can be more if branched) **anomeric carbon of an aldose unreacted**, then the resulting oligo/polysaccharide is said to be "reducing" since terminal anomeric –OH can be oxidized (due to equilibrium with open aldehyde form)
 - confers "strand polarity" on the oligo/polymer



Short: **Glc(α1-->4)Glc**



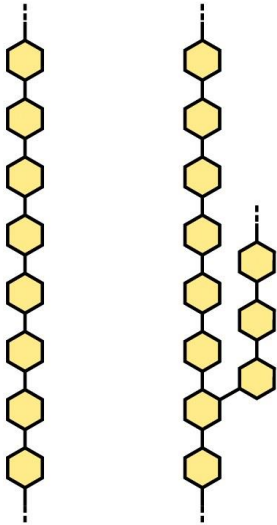
Polysaccharides – 1°, 2°, 3° Structure



condensation of multiple monosaccharides gives rise to oligo- and polysaccharides

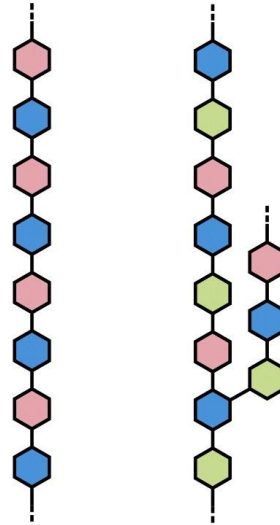
Homopolysaccharides

Unbranched Branched



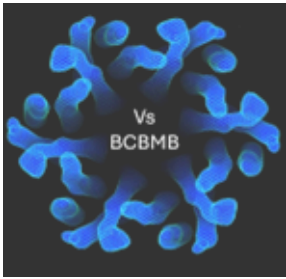
Heteropolysaccharides

Two monomer types, unbranched Multiple monomer types, branched



- in contrast to polypeptides, **branching is very common in oligosaccharides and polysaccharides**
- also contrasting with most proteins, molecular masses of polysaccharides can reach millions of daltons.

can you think of a reason for this?



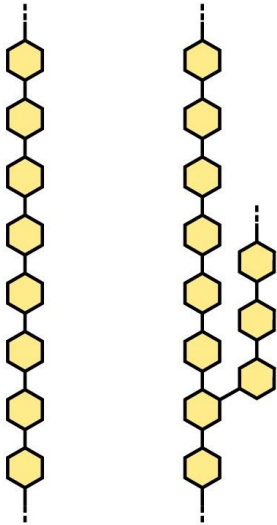
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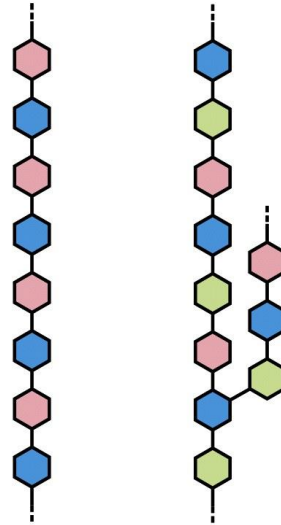
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Heteropolysaccharides

Two monomer types, unbranched Multiple monomer types, branched



➤ in contrast to polypeptides, **branching is very common** in oligosaccharide and polysaccharides

➤ also contrasting with most proteins, molecular masses of polysaccharides can reach millions of daltons.

Can you think of a reason for this?

Answer:

biosynthesis is not template driven
(as long as monomers are available, the polymerization will carry on)

do polysaccharides have 2° and 3° structures?

...what do you think?



Polysaccharides – 1°, 2°, 3° Structure

do polysaccharides have 2° and 3° structures?

going over aspects of protein structure you learned that

2° structure is defined as the local conformation of the backbone atoms of the polymer

(Fundamentals – PROTEINS, slide 42; Advanced – PROTEINS, slide 21)

if you want to answer the question of whether or not polysaccharides have 2° structure, you will need to define what a polysaccharide's "backbone" is.

in proteins – **the backbone is formed by the invariant scaffolding group** that is present in each amino acid.

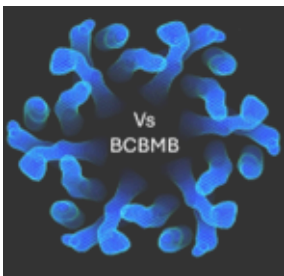
→ **what is the "invariant element" in each of the carbohydrate monomers that make up the polymer chain?**

marked in orange, **the "backbone" of the polysaccharide is formed by the entire cyclic monomer (carbons, ring-oxygen, and glycosidic bond(s))**

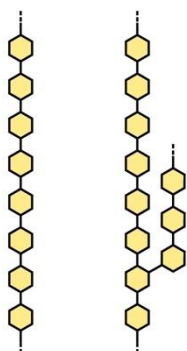
→ **yes, polysaccharides have 2° structure because the local conformation of the backbone can be linear or branched, extended or spiral**

(as you learned in in the Fundamentals - CARBOHYDRATES; slide 31)

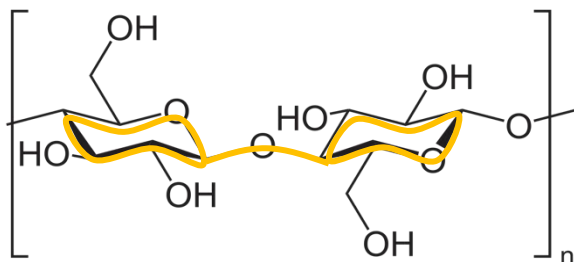
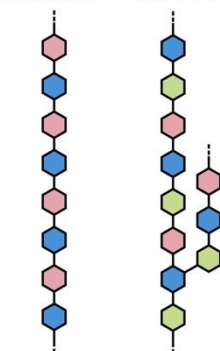
however, the very similar chemistries of the building blocks, and often limited repertoire of monosaccharides used in each polysaccharide result in **much less diversity in the "folds"/2° structure compared to proteins**



Homopolysaccharides
Un Homopolysaccharides
Unbranched Branched



Heteropolysaccharides
Heteropolysaccharides
Two monomer types, unbranched Multiple monomer types, branched





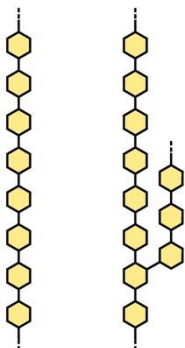
Polysaccharides – 1°, 2°, 3° Structure

What about 3° structure?

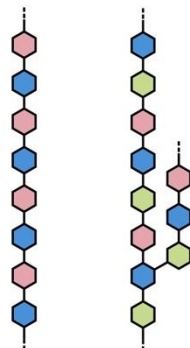
going over aspects of protein structure, you learned that **3° structure is defined as the overall structure that forms through long-range interactions between different regions of the polypeptide** (Fundamentals – PROTEINS, slide 43, Advanced – PROTEINS, slide 22)

this question about 3° structure is more interesting in the case of polysaccharides because it does not have a single answer.

Homopolysaccharides
Unbranched Branched



Heteropolysaccharides
Two monomer types, unbranched Multiple monomer types, branched

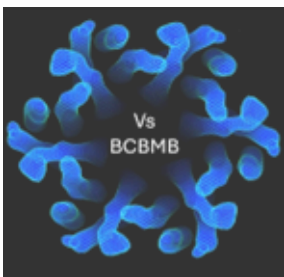


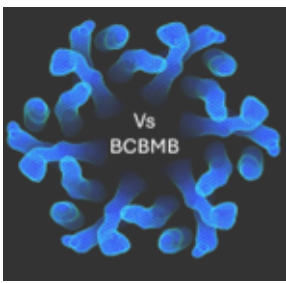
- unbranched oligo-/polysaccharides do not have 3° structure because the extended or spiral chains are quite rigid and do not fold back on themselves to allow for long-range interactions
- however, in branched polysaccharides different branches can engage in interactions and hence do have the potential to form 3° structures.

in fact, the complex overall structure of small branched oligosaccharides are used as molecular markers for protein targeting though overall, the 3° structure repertoire of oligo-/polysaccharides is not even close to that of proteins

What about 4° structure?

exists but is limited to a few specific examples like cellulose (colinear strings of cellulose fibers, Fundamentals Chapter slide 23), bacterial biofilm matrices and some gels like agar agar





Functional Roles of Polysaccharides



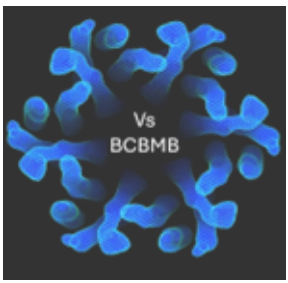
Key functions you already know:
storage and mechanical support

a question we did not consider at the time

why are **polymers** used as storage form

wouldn't storing the monomeric form not be easier, less convoluted and with less machinery needed for making & breaking the polymer?

...your thoughts?



Functional Roles of Polysaccharides



key functions you already know:
storage and mechanical support

a question we did not consider at the time

why are **polymers** used as **storage** form

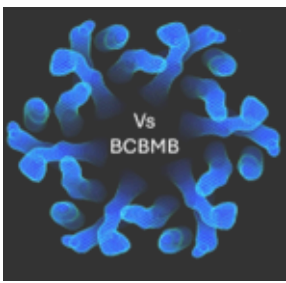
wouldn't storing the monomeric form not be easier, less convoluted and needing less machinery for making & breaking the polymer?

if you were thinking about the molecular overhead for synthesizing and breaking down the polymer, then that is a great sign because it shows that you are starting to think in terms of how to get everything done with the smallest number of movable parts

that said:

there are two reasons why a polymer is necessary

- **storing the same amount as monomer would lead to unacceptable osmotic pressure**
(because osmotic pressure is a colligative property = depends on the concentration of a molecule, but not its size= a polysaccharide made from 100 glucose molecule contributes the same to the osmotic pressure as a single glucose molecule)
- **transport of monomers into cells would be very costly because it would have to occur against a large concentration gradient**



Exploring Additional/New Functions for Carbohydrates



Glycoconjugates

remembering what you learned in the **Chemical Evolution** Chapter
(slide 23)

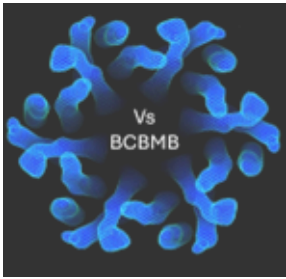
vertical exploration of chemical space led to composite molecules in which different compound families were combined within one more complex macromolecule

following this "logic" you would expect to find combinations of carbohydrates with other molecule types

that expectation would be fully justified as you will find

three classes of biologically active conjugates:

- **proteoglycans and glycoproteins if conjugated to proteins,**
 - **glycolipids if conjugated to lipids**



Exploring Additional/New Functions for Carbohydrates



Glycoconjugates

Glycolipids

- **glycosylphosphatidylinositol-anchor (GPI)** for extracellular cell surface proteins that serve a broad spectrum of biological functions
examples: signaling, or cell adhesion

- **sphingolipids**

(oligosaccharides, some sulfated)

examples: blood group determinant, central nervous system (LIPIDS and MEMBRANES Chapter, slides 55-57)

the carbohydrate moiety on sphingolipids plays roles in signaling & cell surface recognition

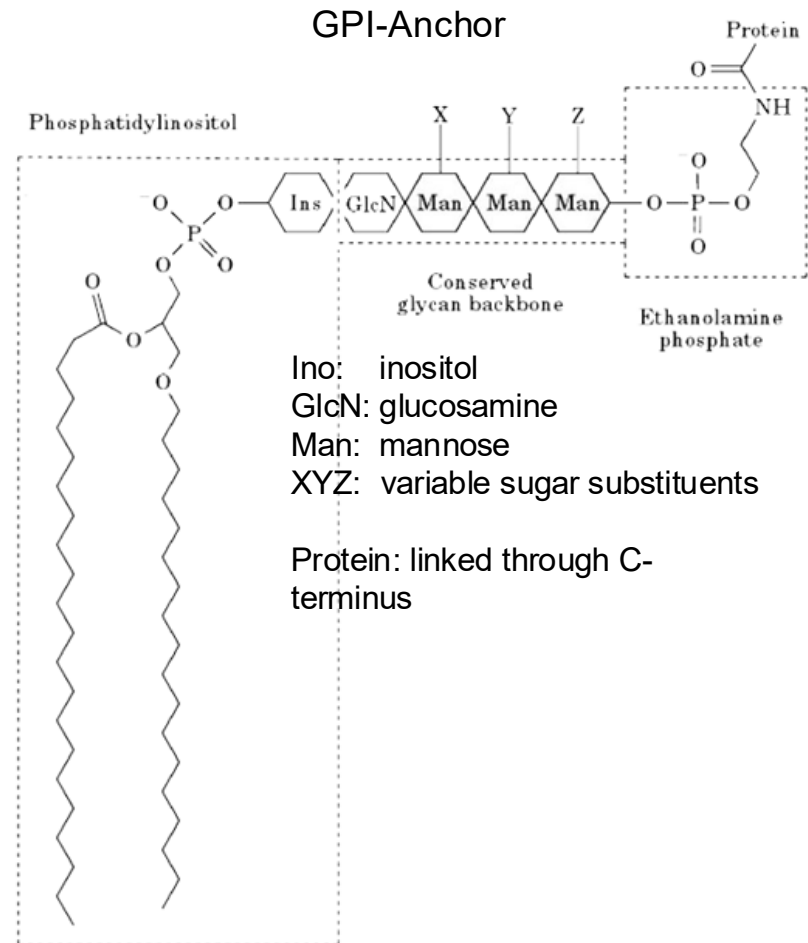
and requires proteins known as **lectins** (a protein family that “reads” the “sugar code”).

on the cell surface:

lectins guide decisions about cell clearance, cell invasion, cell adhesion, or clearance of glycoproteins from the plasma.

inside cells

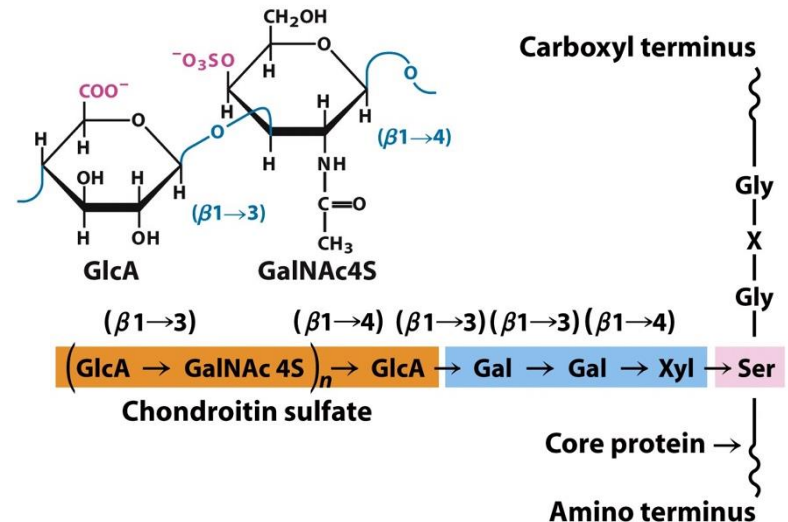
lectins are involved in protein sorting to different compartments



Glycoconjugates – Continued

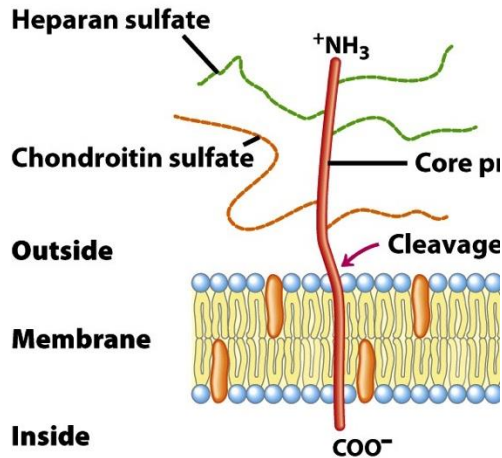
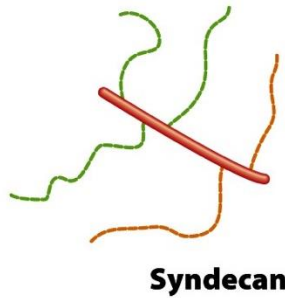
Proteoglycans

- (mostly) at **cell surface and in extracellular matrix**
- contain **many charged building blocks** (carboxylic acids, sulfated monosaccharides)
- the polysaccharide component is **linked to the protein via serine residues**
- **protein component small compared to the carbohydrate component**
- their structural organization is very complex

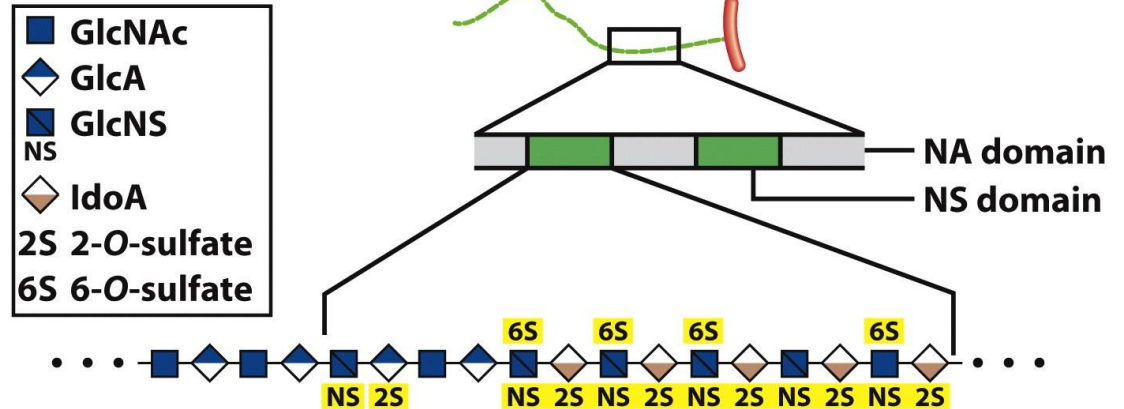


proteoglycan design - an example;
the type of carbohydrate moiety is called
glycosaminoglycan

Proteoglycans - Continued:



Heparan sulfate



the exact pattern of sulfation is specific for each type of proteoglycan

notably: the same core protein can have different types of heparan sulfate chains in different cell types/tissues (=redundancy)

(note how this is similar to the differences in membrane lipid acyl chain composition in different tissues!)

➤ ~ 40 types of proteoglycans in mammals

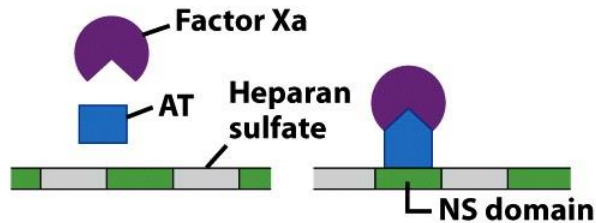
act as tissue organizers & influence activities such as growth factor activation and adhesion

➤ many proteoglycans are secreted,

but some - like syndecans - are tethered to the bilayer through an alpha helix or a GPI lipid anchor

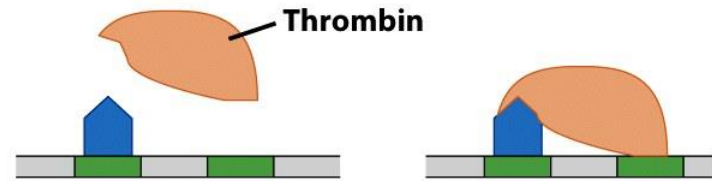
Functions of Proteoglycans

(a) Conformational activation



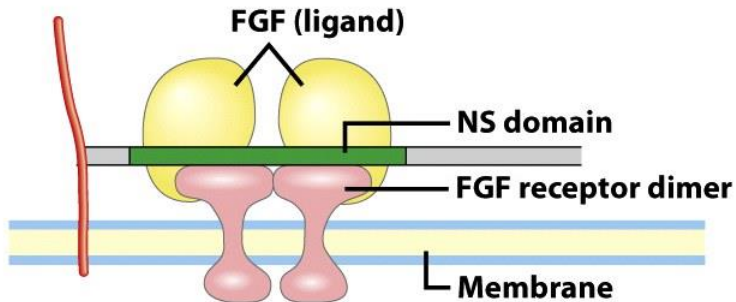
A conformational change induced in the protein antithrombin (AT) on binding a specific pentasaccharide NS domain allows its interaction with blood clotting factor Xa, preventing clotting.

(b) Enhanced protein-protein interaction



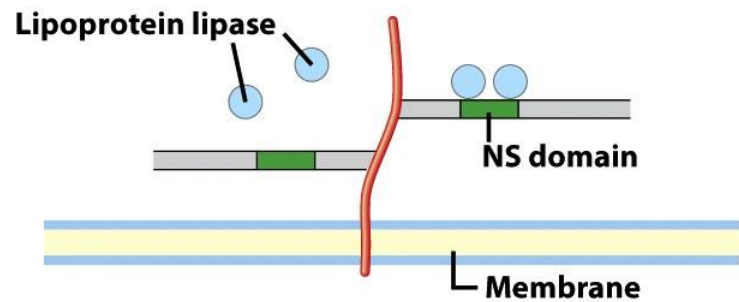
Binding of AT and thrombin to two adjacent NS domains brings the two proteins into close proximity, favoring their interaction, which inhibits blood clotting.

(c) Coreceptor for extracellular ligands



NS domains interact with both the fibroblast growth factor (FGF) and its receptor, bringing the oligomeric complex together and increasing the effectiveness of a low concentration of FGF.

(d) Cell surface localization/concentration



The high density of negative charges in heparan sulfate attracts positively charged lipoprotein lipase molecules and holds them by electrostatic and sequence-specific interactions with NS domains.

put into perspective

failure to produce the correct patterns of sulfated heparans can have devastating consequences.

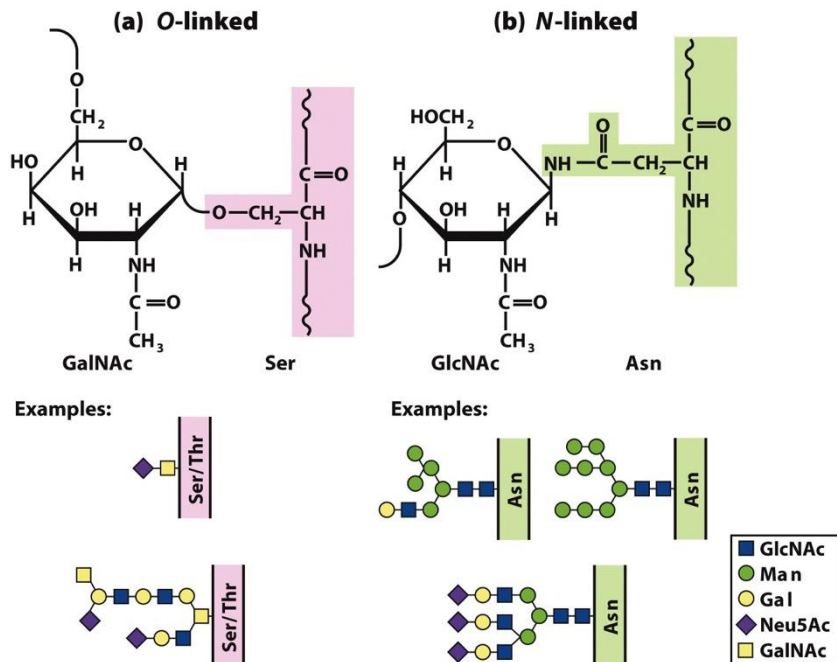
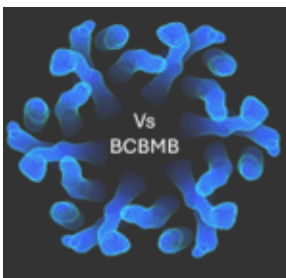
example: knockout mice lacking one of the sulfate adding enzymes are born without kidneys and have abnormalities of skeleton and eyes.



Glycoconjugates - Continued Glycoproteins

mostly extracellular

if intracellular - then found in organelles such as lysosomes or the Golgi



➤ two types

- ✓ **O-linked** (on S and T; **no clear consensus sequence**, very context dependent)
- ✓ **N-linked** (consensus motif NxS/T, x all except P)

➤ **N-glycosylation is initiated in the (rough) ER** by grafting a high-mannose core onto the acceptor site. This core is further processed in the Golgi compartments

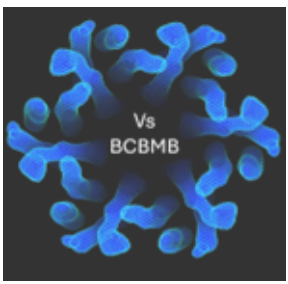
➤ **size of carbohydrate group varies: 1 to ~15**
 ➤ (= the carbohydrate moiety is **small** compared to the protein)

➤ **~50% of all proteins are glycosylated**

➤ **~1% of all genes encode enzymes that are involved in processing of oligosaccharide chains**

notes:

- ❖ N-linked = linkage through an N-glycosidic bond
- ❖ **Glycoprotein vs Proteoglycan**
 (nomenclature acknowledges the component that contributes less mass as a modification)
 glyco protein = a protein modified by a few sugars
 proteo glycan = a complex carbohydrate modified by a protein

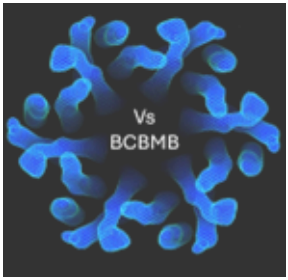


Glycoproteins - continued Gedankenexperiment:

using the 20 common amino acids - how many
different hexapeptides can you make?

...give it a try !





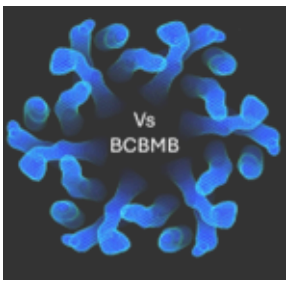
Glycoproteins - continued Gedankenexperiment:



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✓ Answer: 6.4×10^7 ($= 20^6$)

➤ using the four nucleotides of DNA - how many hexanucleotides can you make?



Glycoproteins - continued Gedankenexperiment:



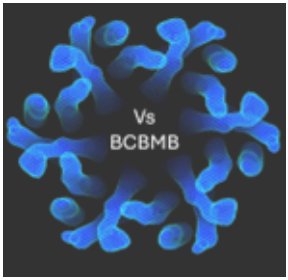
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➤ using the four nucleotides of DNA - how many hexanucleotides can you make?

✓ Answer: 4,096 ($= 4^6$)

➤ assuming there are 20 different monosaccharides to choose from - how many hexasaccharides can you make?



Glycoproteins - continued Gedankenexperiment:



using the 20 common amino acids - how many different hexapeptides can you make?

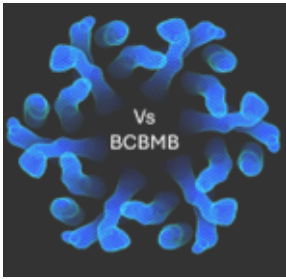
✓ Answer: 6.4×10^7 ($= 20^6$)

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✓ Answer: 4,096 ($= 4^6$)

➤ assuming there are 20 different monosaccharides to choose from - how many hexasaccharides can you make?

✓ Answer: **over a trillion**. Why is this different from the hexapeptide?



Glycoproteins - continued Gedankenexperiment:



using the 20 common amino acids - how many different hexapeptides can you make?

✓ Answer: 6.4×10^7 (= 20^6)

➤ using the four nucleotides of DNA - how many hexanucleotides can you make?

✓ Answer: 4,096 (= 4^6)

➤ assuming there are 20 different monosaccharides to choose from - how many hexasaccharides can you make?

✓ Answer: **over a trillion. Why is this different from the hexapeptide?**

✓ Answer: **can have different linkages** - α/β , branching, multiple options for which C-atoms are linked
→ this flexibility makes the number of combinatorial permutations "explode"

that is: oligosaccharides allow for large numbers of **complex shapes** that are **extremely rich in information** - far surpassing proteins and making DNA look like a "toddler".

this complexity is **exploited in**

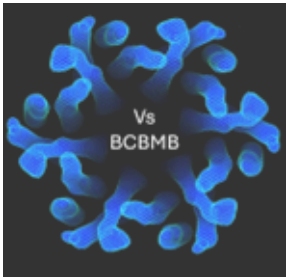
➤ **signaling,**

➤ **to "sort" proteins for distribution** to their appropriate compartments, and

➤ **to "flag" misfolded proteins** for degradation.

if even **oligo**saccharides are rich in information and can create different shapes

why have they (or polysaccharides) not evolved to take care of catalysis and information storage?



Glycoproteins - continued Gedankenexperiment:

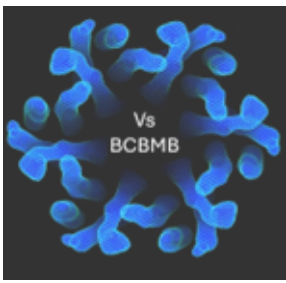


if even oligosaccharides are rich in information and can create different shapes - **why have they (or polysaccharides) not evolved to take care of catalysis and information storage?**

✓ **Answer:**

- very limited chemistry, very limited repertoire of “folds”, and rigidity
 - ➔ not good for catalysis
- using polysaccharides to code large amounts of information would need to excessively rely on 3D shape to keep size of molecules as small as possible = this would require complex branching
 - ➔ impossible to encode + would require large number of different molecular machines to implement on a large scale.
 - lastly, branched and/or linear polymers are not very complementary to each other
 - ➔ would be as difficult to recognize (= read out) as it would be to make it (=replicate)
(alas: for largescale coding, information **must not** depend on 3D shape information
see Fundamentals – NUCLEIC ACID chapter)

circling back to the use of small branched oligosaccharides in signaling, protein sorting
now you may understand better why 1% of the genome is dedicated to make these modifications
and
why recognizing these modifications requires very specific "receptor" molecules specifically
designed for these purposes only

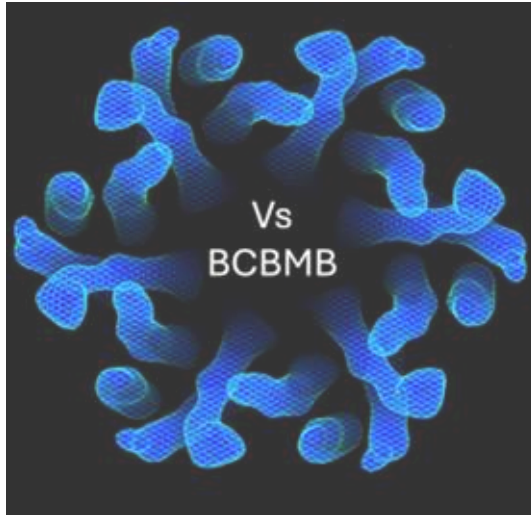


Carbohydrates – SUMMARY of The Most Basic Facts

(both Fundamentals and Advanced Chapter)



- as the names suggests, pure carbohydrates are **made from “carbon and water”** in roughly equimolar amounts. Many, but not all, have an **empirical formula $(\text{CH}_2\text{O})_n$** and fall into two classes: polyhydroxy-aldehydes or polyhydroxy ketones.
- **sometimes**, carbohydrates are **chemically modified** (deoxy or addition of amino groups, acetyl groups, sulfate groups, phosphate, $-\text{COOH}$ groups). These modifications are functionally significant.
- most abundant biomolecules (100 billion metric tons of $\text{CO}_2 + \text{H}_2\text{O}$ are converted into carbohydrates by photosynthesis)
- most **important energy source in non-photosynthetic organisms**
- the monomeric form of carbohydrates is called: monosaccharide (or sugar)
- monosaccharides can form very stable oligomers (=oligosaccharides; <20 units) and polymers (polysaccharides, >20 up to thousands of units) [saccharide from greek sakcharon = sugar]
- **polysaccharides serve as storage form** (eg starch, glycogen) **or to provide mechanical support (cellulose)**. They can be **linear and branched**.
- **additional functions** of polysaccharides are to provide **“lubrication” in joints and support cell adhesion** (extracellular matrix) **and tissue identity**. Some oligosaccharides are involved in **signaling and protein sorting**.
- oligo-/polysaccharides can be conjugated to proteins (=proteoglycans, glycoproteins) and lipids (glycolipids)
- **oligosaccharides** can form an almost unlimited number of unique structural signatures (“sugar code”) that – at this “small scale” level - are perfect for coordinating biological processes.



Thank You for Working Through This

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