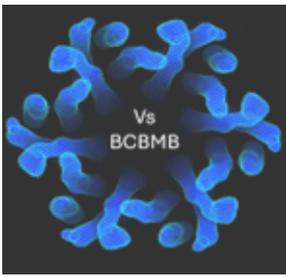




Biochemistry Fundamentals
CARBOHYDRATES



Goal Of this Unit



You will get the greatest gain from this short primer on carbohydrate biochemistry biochemistry if you looked over the following handouts (all free downloads):

- From Cell Biology to Social Media, the Internet and More (Page 17 most relevant)
- What Do You See?
- How Do Molecules See Part 1 & 2
- Biochemistry Fundamentals - LIPIDS

Building on what is covered in these handout, this handout will continue to look at the chemical inventory of living systems from an “engineering” point of view because that strategy will help you to understand **why** each class of biological macromolecules is uniquely suited for fulfilling certain roles.

Where we started:

From the first handout listed above, you learned that “life” depends on partitioning of matter across boundaries → the most logical first “pit stop” in exploring the chemical basis of “life” will be to explore “boundary formation“

To do that, we looked at “lipids” to start answering the following questions:

What types of molecules can form boundaries?

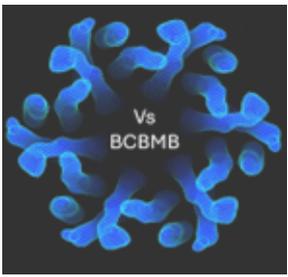
Are all boundaries alike?

(summary brief answer in “lipid handout”)

What causes these boundaries to form?

General tip about how to use these slide-decks for best results: you will notice that much of the narrative is driven by questions ... where indicated, think about the question and try to come up with your own answers first before flipping to the next slide. If you do this, you will find these handouts more engaging, and you will retain more of the content than simply scanning over the slides.

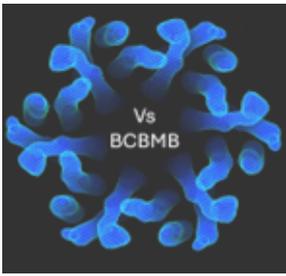
Recap: Boundaries Through Self-Assembly



The last slide-deck's narrative was centered on the consequences of placing hydrophobic/amphiphilic lipid molecules in water. If you did work through that "lipids" handout, then test your recall by trying to fill (some of) the bullet points yourself first before looking at the summary on the next slide:

- .
- .
- .
- .

Recap: Boundaries Through Self-Assembly



The last slide-deck's narrative was centered on the consequences of placing hydrophobic/amphiphilic lipid molecules in water. Here are the key takeaways from that handout:

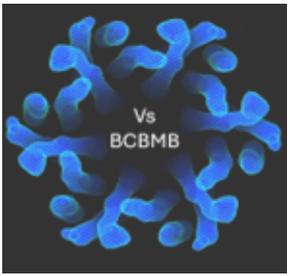


- **Key observation:** the **hydrophobic effect** drives a **spontaneous phase separation** when poorly water soluble (organic) compounds encounter an aqueous environment.
- Depending on the type of hydrophobic compound – **phase separation creates an emulsion**, (micelle – we didn't cover that), **or bilayer**, in which favorable **weak interactions** between molecules are maximized.
- Life **exploits both** – emulsions and bilayers – to **compartmentalize** space and function
- **Bilayers** are a particularly useful and **versatile structural template for implementing physical barriers** that surround cells and many of their intracellular compartments, thus allowing for the fundamental **asymmetry** that enables life processes to be maintained.

Like in previous handouts, you may notice words highlighted in "pink". Use of, and highlighting these words is **not** random/arbitrary. Rather, these "pink" terms represent fundamental **CONCEPTS** (= abstract, overarching ideas, that allow you to easily connect, to structure, and to understand the fundamental "Whys" of (molecular) biology.

If you are interested in how to make "concepts" work for you, then consider registering for the 50 min online workshop on that topic (offered from mid March).

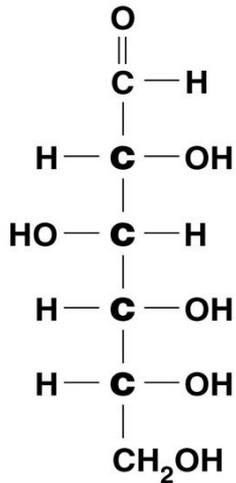
Recap: Boundaries Through Self-Assembly



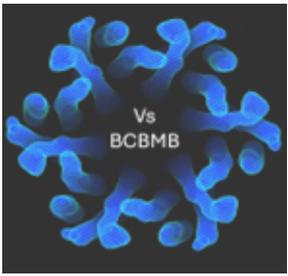
Moving on from Lipids, not all boundaries are made from lipids – in fact some types of boundaries are build from components that appear the least likely to create a physical barrier based on what we covered

What do you see right away?

*...try to find the answer ... it's not very difficult ...
and just needs you to count a few things*

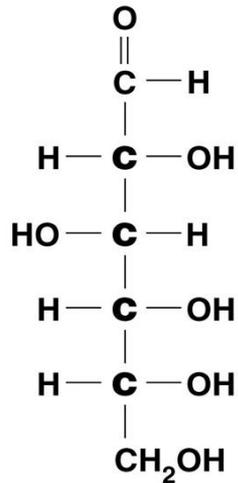


Recap: Boundaries Through Self-Assembly



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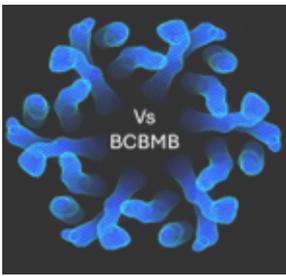


6C, 6O, 12H; 5 hydroxyl groups, 1 aldehyde group

Based on what we covered in the Lipids handout – why does it seem unlikely that this molecule could form a physical barrier?

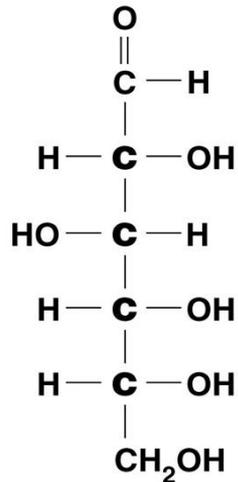
...try to answer

Recap: Boundaries Through Self-Assembly



Moving on from Lipids, not all boundaries are made from lipids – in fact some types of boundaries are build from components that appear the least likely to create a physical barrier based on what we covered

What do you see right away?



6C, 6O, 12H; 5 hydroxyl groups, 1 aldehyde group

Based on what we covered the last two days – why does it seem unlikely that this molecule could form a physical barrier?

Molecule is extremely hydrophilic/polar → it can readily form H-bonds with water → it should be very soluble in water

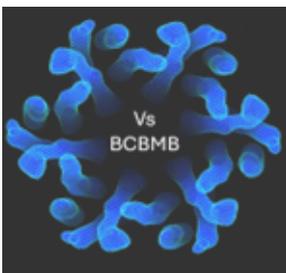
→ well.....it is!

→ **How then can this make a barrier?**

Answer: not obvious...need to explore further to understand it

→ **Lets continue looking at the molecule to see if we can discover more things about it.**

Molecular Asymmetry



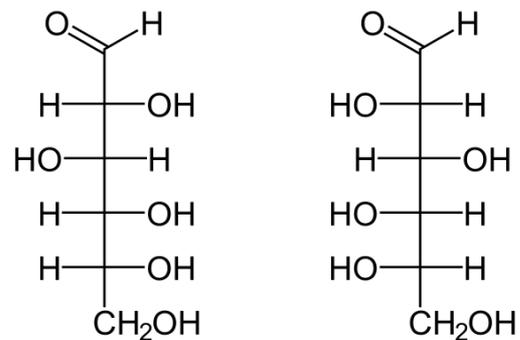
Closer look - compare the two molecules shown to the right, are they the same?

6C, 6O, 12H; 5 hydroxyl groups, 1 aldehyde group

→ so? Are they?

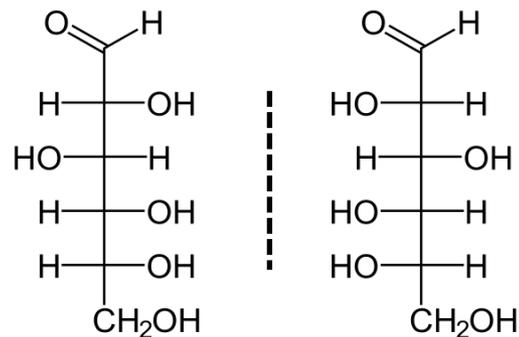
Answer: chemically – yes, but structurally they seem to be mirrors of each other. Does this matter?

...try to answer



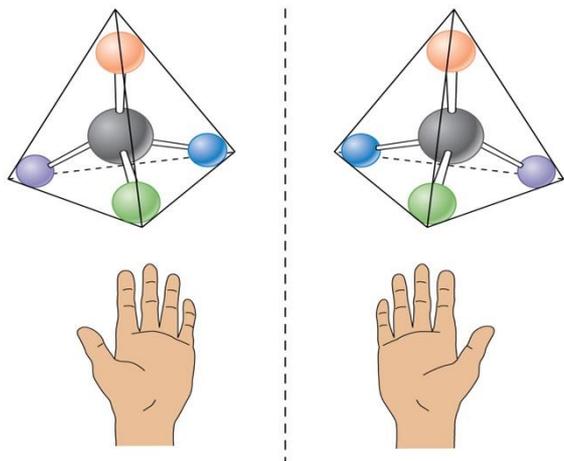
Molecular Asymmetry

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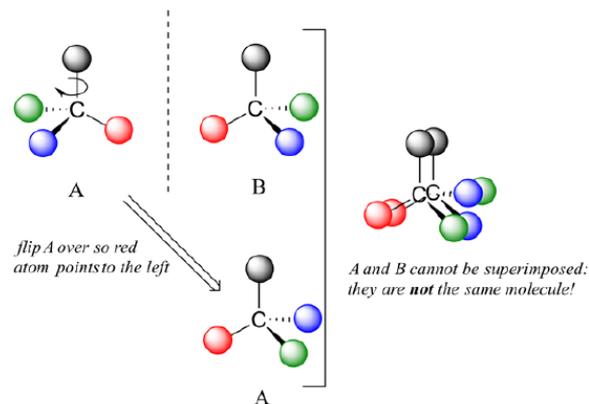


Answer: sure does – why?

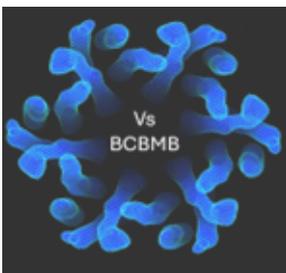
→ Matters because in these molecules, some carbons are sp³-hybridized and carry four different substituents. Such carbons are called **asymmetric** because the **compound** and its mirror image **cannot be superimposed through simple translations and rotations**.



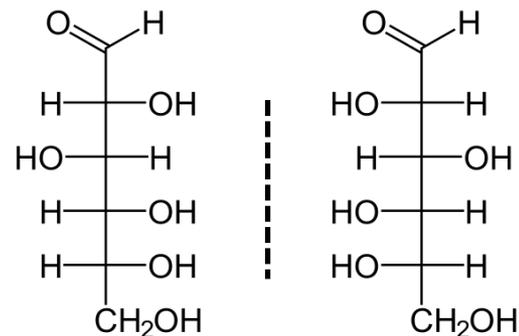
chiral from greek χείρ (*kheir*), = hand



Molecular Asymmetry

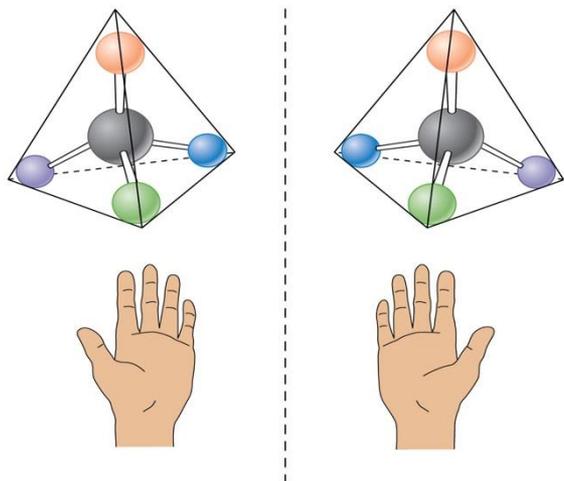


Answer: chemically – yes, but structurally they seem to be mirrors of each other. Does this matter?



Answer: sure does – why?

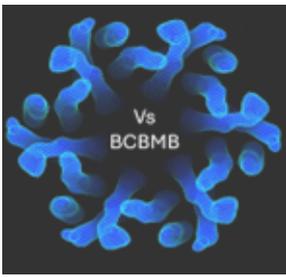
→ Matters because in these molecules, some carbons are sp^3 -hybridized and carry four different substituents. Such carbons are called **asymmetric** because the **compound** and its mirror image **cannot be superimposed through simple translations and rotations**.



Organic compounds that are **identical in composition and connectivity** but differ from each other by the orientation of atoms in space are called **stereoisomers**.

If the two molecules behave like **mirror images**, they are called **enantiomers** (eg as shown in the image above)

The presence of more than one asymmetric carbon causes 2^n stereoisomers; not all of which relate to each other like simple mirror images, and you will learn a great deal more about their nomenclature and the consequences of stereoisomerism in your orgo classes.



Molecular Asymmetry

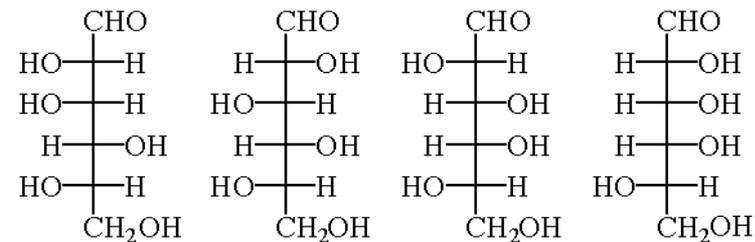
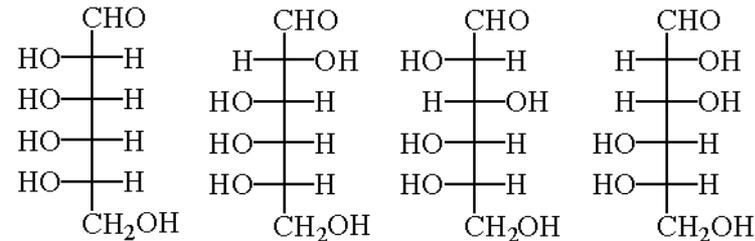
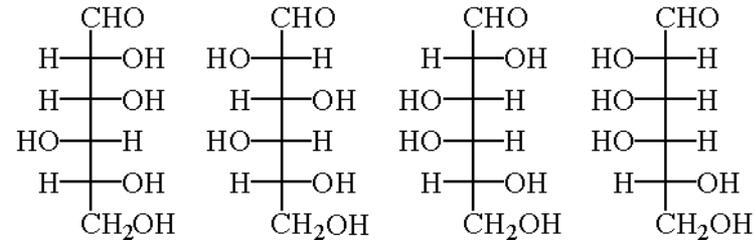
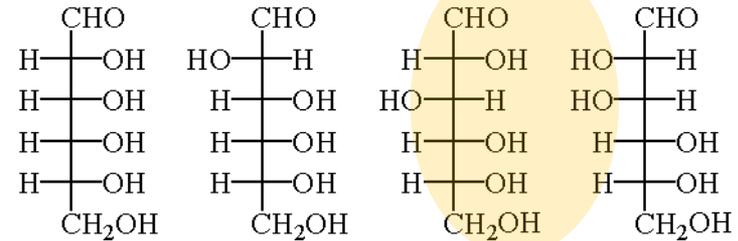


For instance: for a "hexose" that has 4 asymmetric C-atoms and an aldehyde group at C1 (the "top" of the molecule), this will look like this

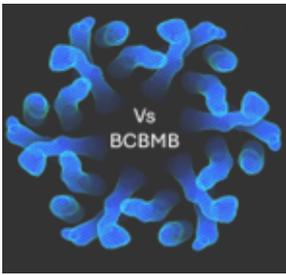
(don't worry about "nomenclature" here ... we'll cover some of it shortly)

The highlighted compound is glucose

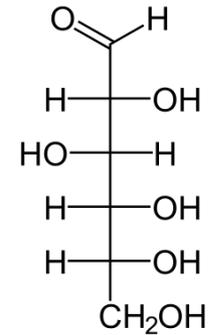
16 Aldohexoses



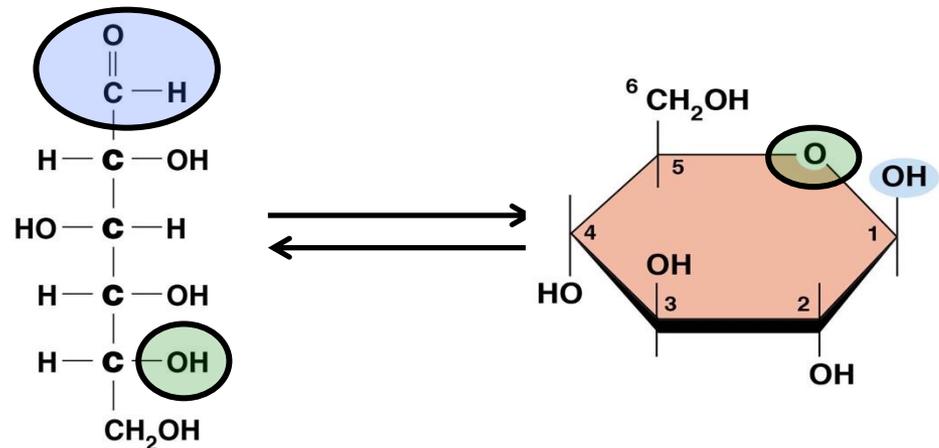
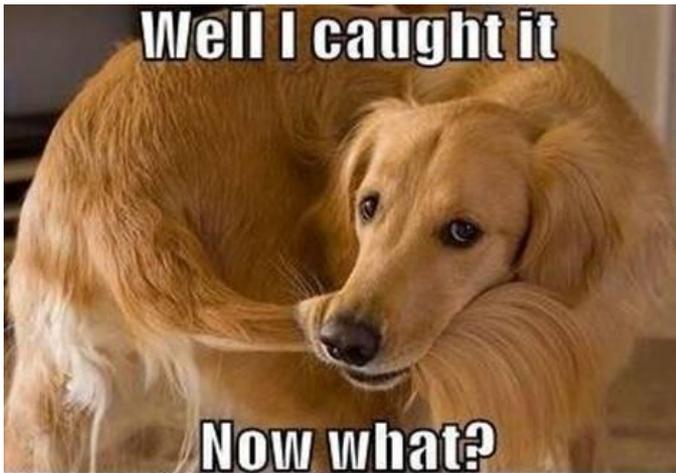
Carbohydrate Structure – Ring Formation



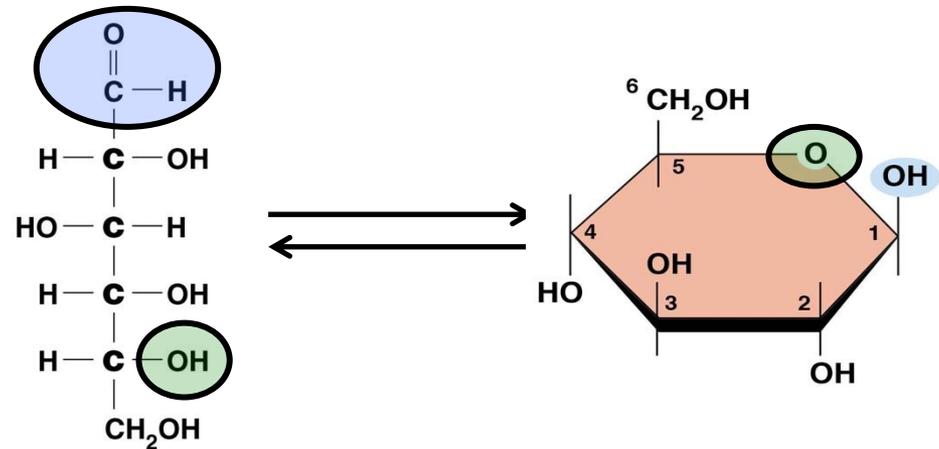
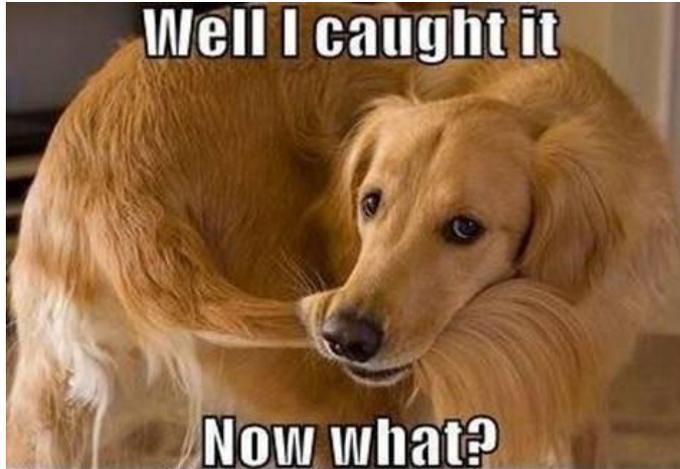
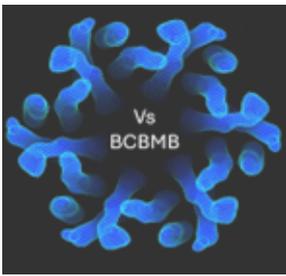
Chirality of the molecule, called glucose, is interesting – but **what, if anything, has that to do with the ability of glucose to form boundaries/barriers?**



Answer: A LOT ...but to understand it, we need to think more about structure of glucose (and molecules like it)...so I ask your patience as we work through the different levels of the answer.

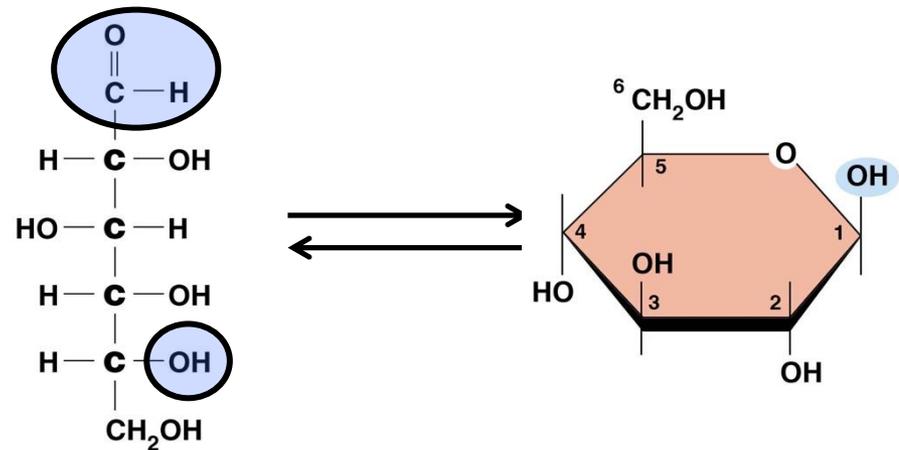
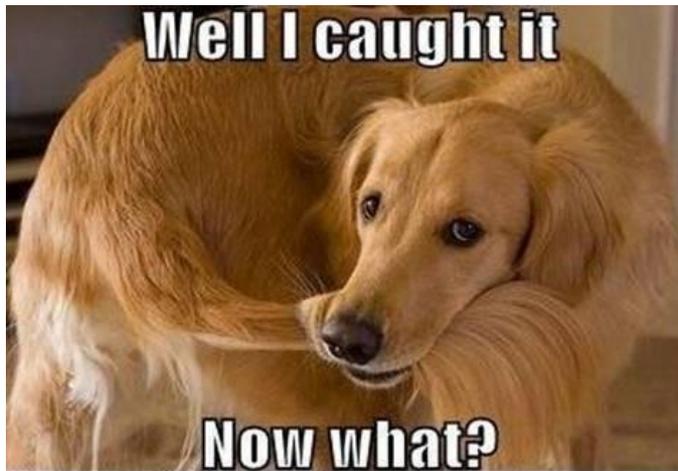
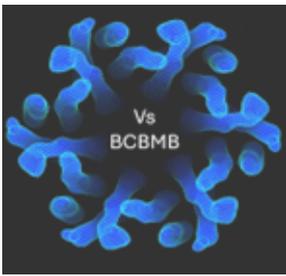


Carbohydrate Structure – Ring Formation



- The “**flexibility**” (free rotation around single bonds) of the **carbon backbone** in glucose and molecules like it – collectively called **carbohydrates** [= carbon + water = $(\text{CH}_2\text{O})_n$... $\text{C}_6\text{H}_{12}\text{O}_6$ for instance] **allows** an **intramolecular ring closure** reaction between one of the hydroxyl groups and the carbohydrate’s carbonyl function (which can be either an aldehyde in glucose (\rightarrow aldoses), or a ketone (\rightarrow ketoses) in other sugars).
- These rings typically have 5 or 6 atoms (including the ring oxygen) – which gives rise to their family name: pentose, hexose....(and you will learn more about it in the "Advanced Biochemistry" Handouts)but....here we just want to focus on the aspects that help understand how glucose can form barriers.....

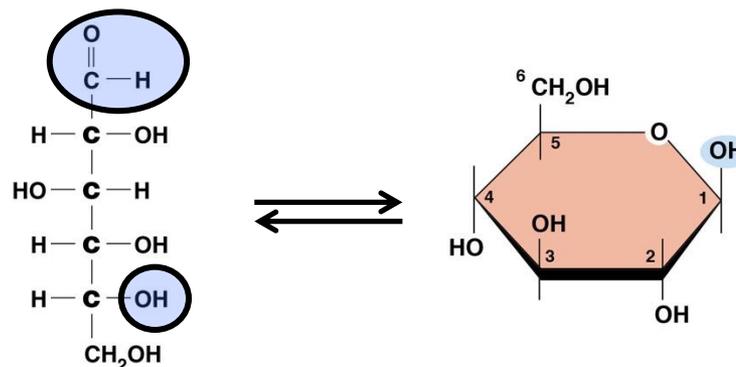
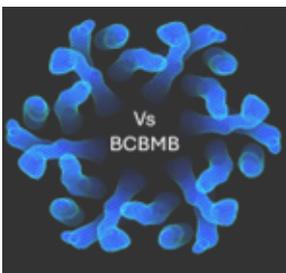
Carbohydrate Structure - Conformation



Writing the ring this way is convenient but also makes an **important omission**what could that be?

.....if you already took "Organic Chemistry" ... then you should be able to answer this try!

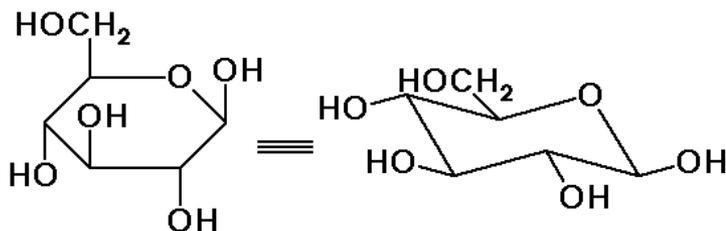
Carbohydrate Structure - Conformation



Writing the ring this way is convenient but also makes an **important omission**what could that be?

Answer: it ignores that the **carbons are sp^3 -hybridized** ... meaning **tetrahedral geometry**.

→ Accounting for that, the **overall shape of glucose is similar to cyclohexane** ... → we looked at that in the context of mechanisms of molecular recognition ("How Do Molecules See? Pt2, slide 6) . That is ...a representation closer to the "truth" would look like this:

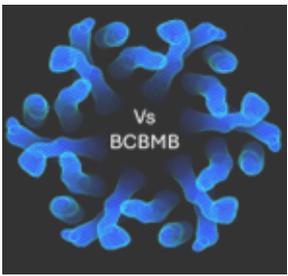


Which of the two ways of drawing it do you think people prefer?

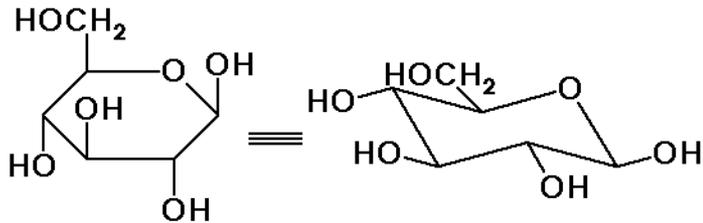
→ The one on the left

→ understandable but also makes it easy to forget about "spatial" realities.

Carbohydrates Beyond Monomers



Getting close to finish line now....but why? What does the “chair” conformation have to do with water solubility of glucose?

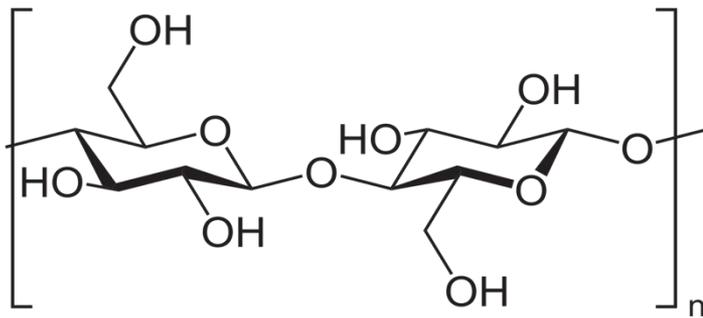


Answer: nothing if you deal with a single glucose molecule, **and everything** once you make a glucose polymer.

Important point we learn here: the chemical and physical properties of a polymer can but need not be reflective of the chemical and physical properties of the constituent monomers

→ In other words: polymer formation imparts **emergent properties...**!

Point in case: glucose polymers....lets begin with cellulose (...yep, there is >1 type of glucose polymer)

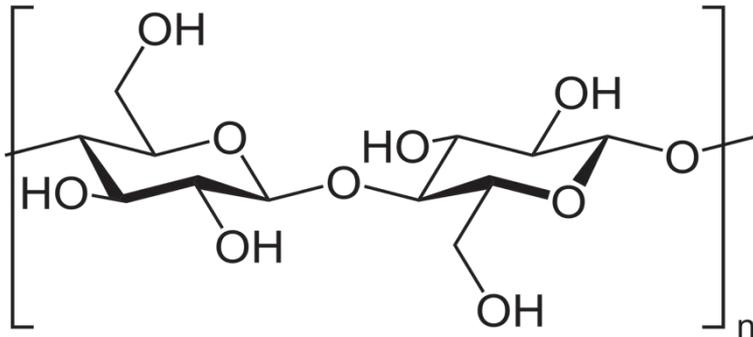
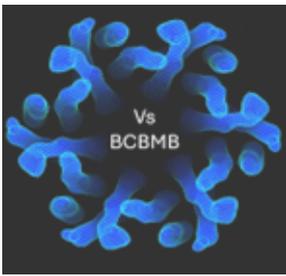


Cellulose, n = 10,000 – 15,000

→ First thing to notice: **structural “blueprint”** is fundamentally different from the polymer that is formed in the **aggregation of phospholipids? How?**

....try to answer before going on

Carbohydrates Beyond Monomers



Point in case: glucose polymers....lets begin with cellulose (...yep, there is >1 type of glucose polymer)

Cellulose, $n = 10,000 - 15,000$

→ First thing to notice: **structural “blueprint” is fundamentally different from** the polymer that is formed in the **aggregation of phospholipids? How?**

Answer: covalent bonds between monomers. In other words: cellulose is a first example for a **covalent polymer**. The polymerization reaction (elimination of water to make a bond between two glucose molecules in this case) is **not** spontaneous, fundamentally setting it apart from the spontaneous aggregation of phospholipids.

The lack of spontaneity in the reaction goes along with increased control "where" and "when" a boundary is formed,. but does not explain how cellulose can serve to form boundaries in the first place....

Cellulose



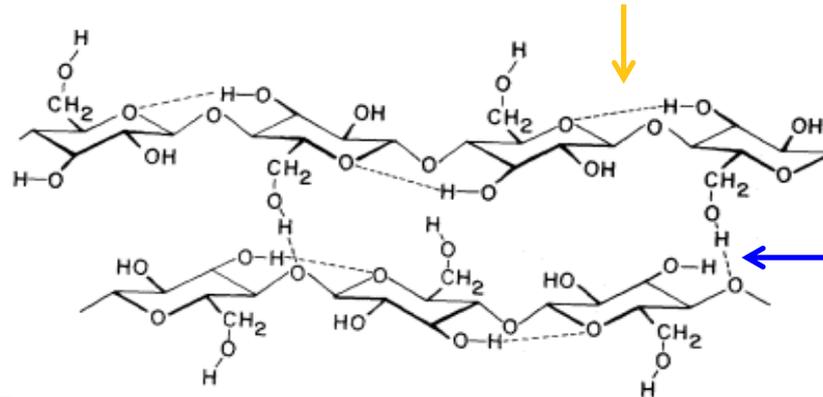
....**very rigid boundaries** in fact → found in the **cell walls of plants**.

Understanding of the **water insolubility and rigidity of cellulose based boundaries** comes from looking at the detailed structure:

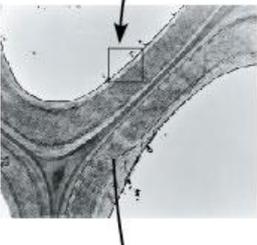
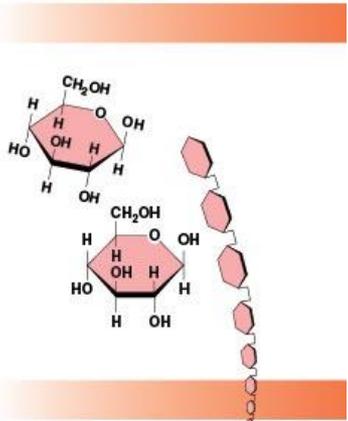
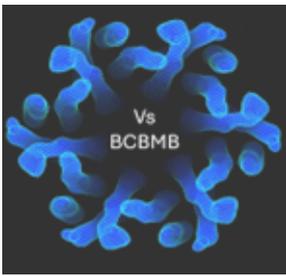


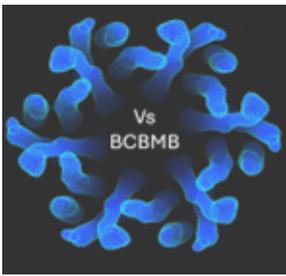
The **stereochemistry and chair conformation** of the glucose monomers allow this polymer to form long linear **H-bond stabilized strands** that **laterally aggregate through non-covalent (!) H-bonding between strands**. This results in “cables” that are so tightly packed that **water molecules cannot penetrate the assembled structure**.

→ If water cannot get there, then there is no “solvation” andyep: the polymer will be completely insoluble in water.



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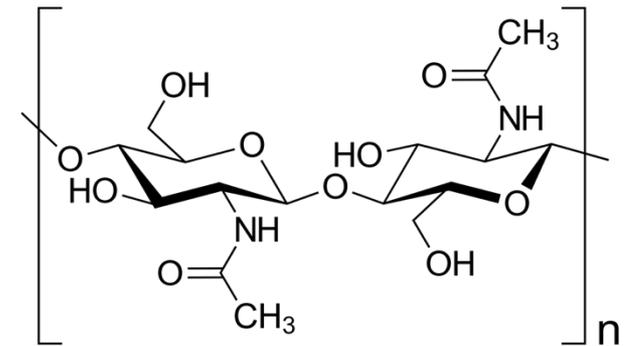
Chitin



Is cellulose the only polysaccharide that can form amazingly stable and resilient physical barriers?

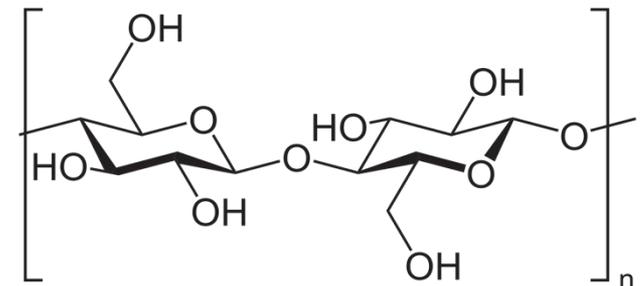
Answer: no – the hard exoskeletons of insects or crustaceans are another example.

The underlying polysaccharide, chitin, has this structural formula:

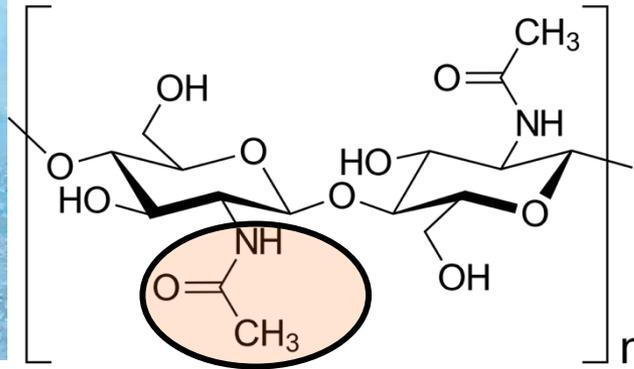
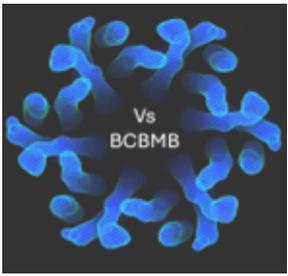


Do you notice what is different between cellulose (shown to the right) and chitin?

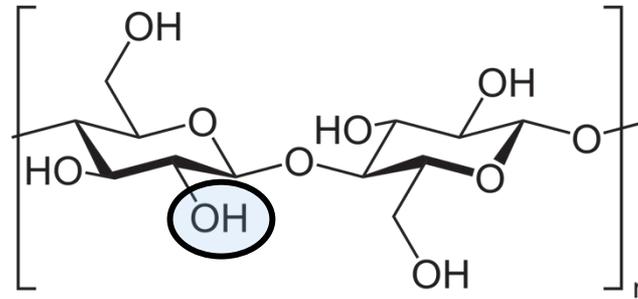
...try to describe in your own words.....



Chitin

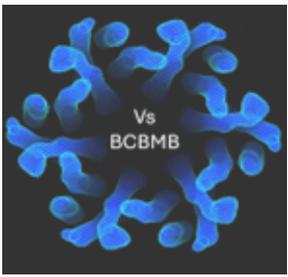


Do you notice what is different between cellulose and chitin?



Answer: Chitin is based on a chemically modified glucose molecule where one of the hydroxyl groups (blue underlay) was replaced by an acetylated amino group (N-acetyl).

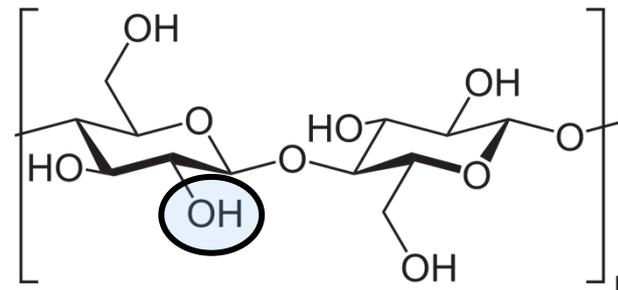
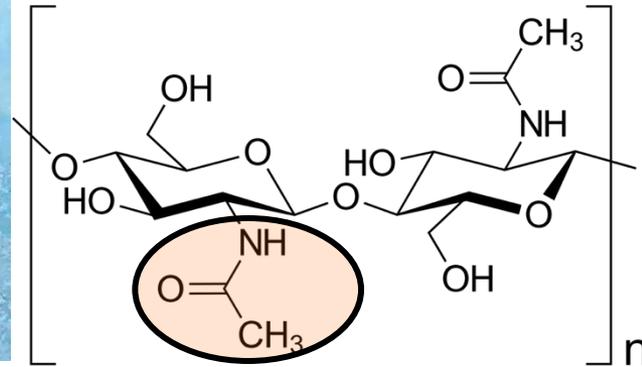
Although this modification causes the chemical formula of N-acetylglucosamine to deviate from the empirical $(\text{CH}_2\text{O})_n$ formula that globally defines carbohydrates, N-acetylglucosamine and other chemical variants are still categorized as carbohydrates because they share key chemical, structural and functional properties.

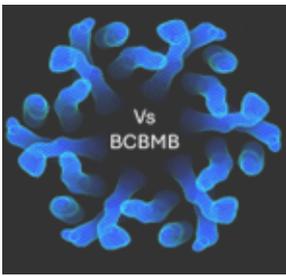


Chitin



Most importantly: the comparison between cellulose and chitin showcases another **important concept:** **redundancy** = the “tweaking” of a common template (glucose) to implement different biological solutions (cell wall, exoskeleton)

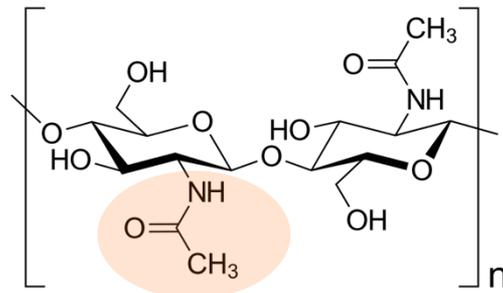
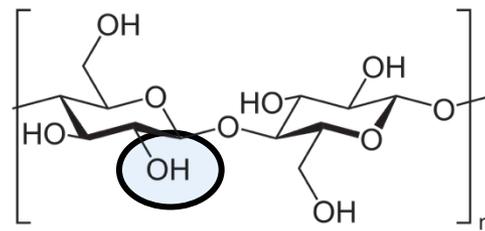
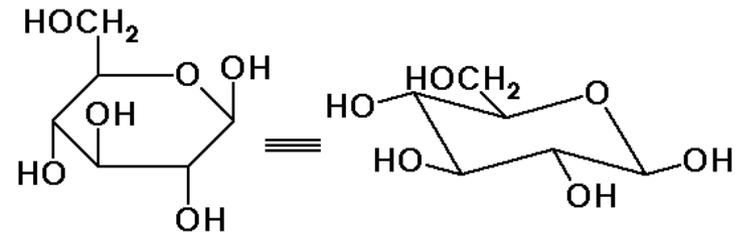
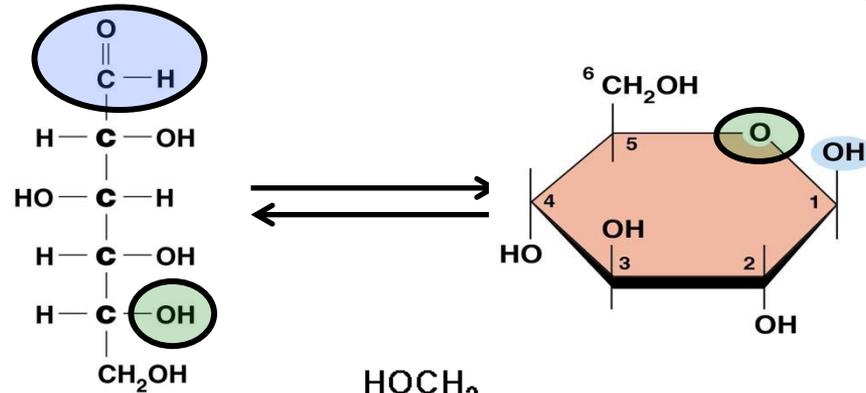




RECAP

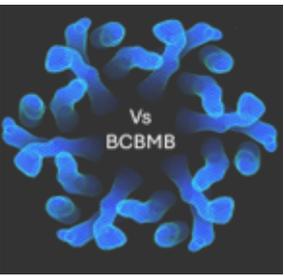


Carbohydrate: $(CH_2O)_n$
[some deviations are allowed]



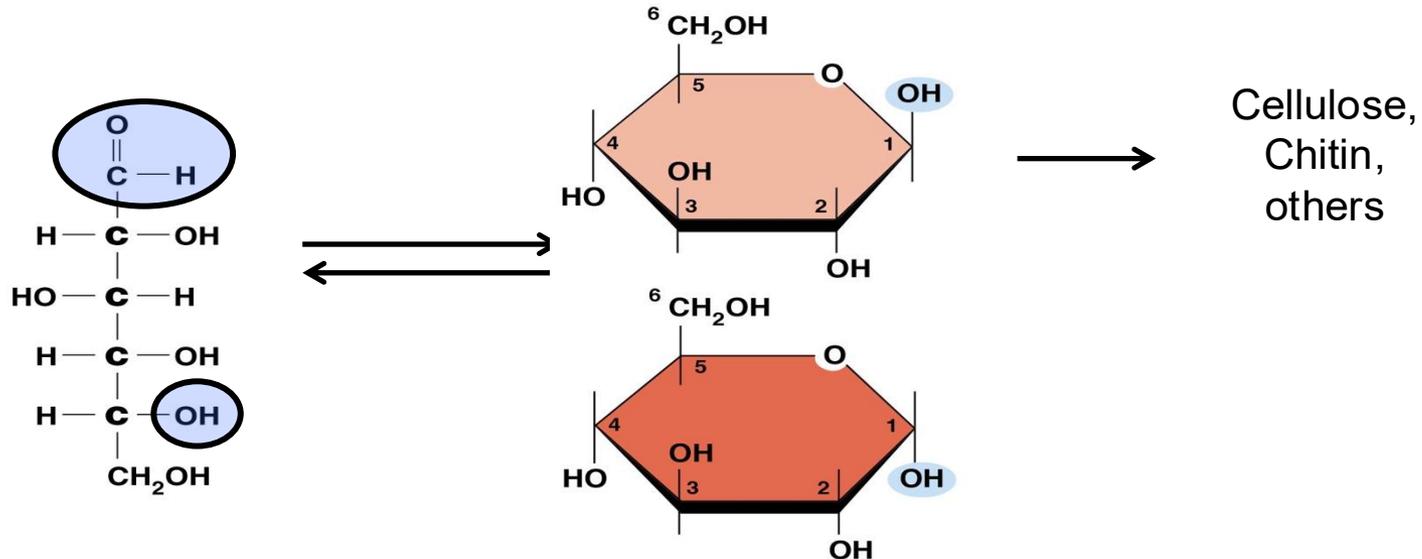
If you want to solidify your understanding before moving on, then use this "RECAP" slide as template to give a short verbal summary of how carbohydrates can form very stable boundaries, and why – at first sight – this is counterintuitive

Glucose Polymers – Devil in the Details



Now that we understand how glucose can be used to generate a physical barrier – the question becomes: **do ALL glucose polymers form rigid, cell-wall like boundaries?**

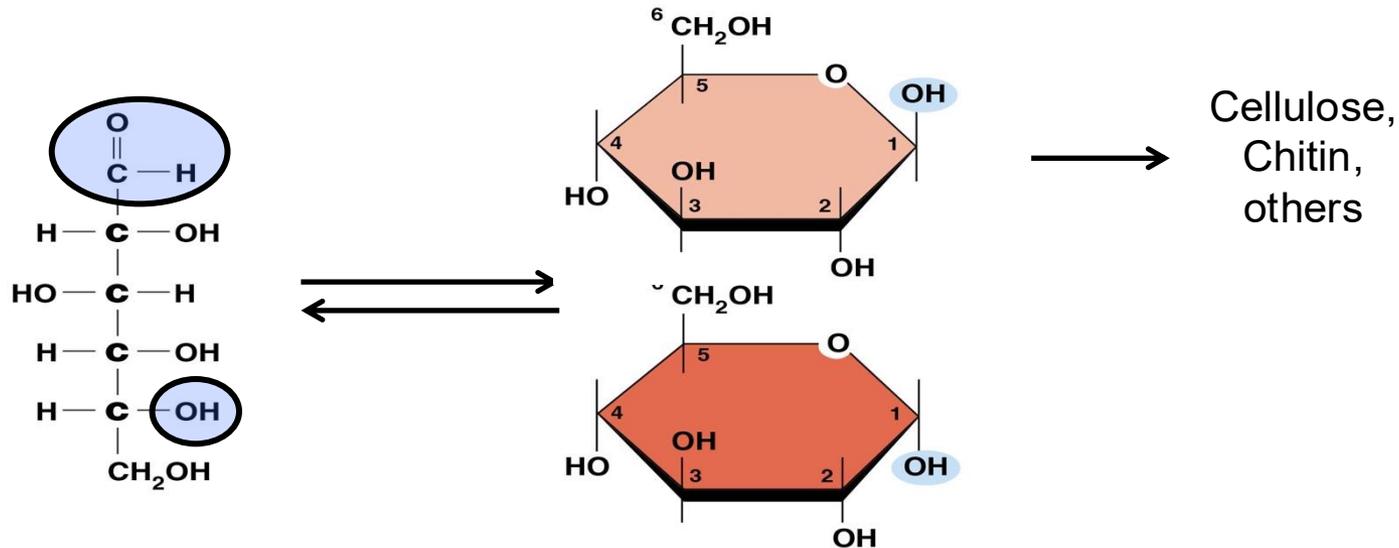
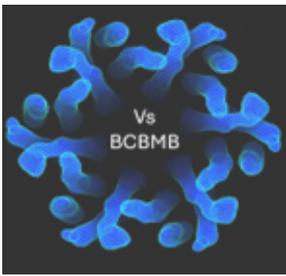
Answer: No – "of course" not. To make sense of this, we have to revisit the ring formation of glucose...because there is one important detail that was not brought up earlier:



The free rotation around C-C single bonds combined with the easy reversibility of the ring closure reaction (**equilibrium!**) means that the reaction can have two different outcomes. **What is the big deal about it = why would you want to care?**

...try to come up with a guess (or answer if you know it)

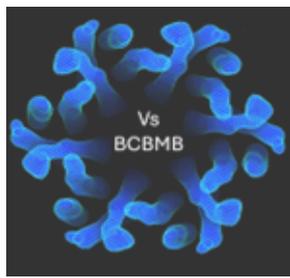
Glucose Polymers – Devil in the Details



The free rotation around C-C single bonds combined with the easy reversibility of the ring closure reaction (equilibrium!) means that the reaction can have two different outcomes. **What is the big deal about it = why would you want to care?**

Answer: If you apply what we learned so far, you realize that the ring closure creates **two stereoisomers**. In carbohydrate chemistry...this newly formed asymmetric carbon is “special” and is called anomeric carbon.

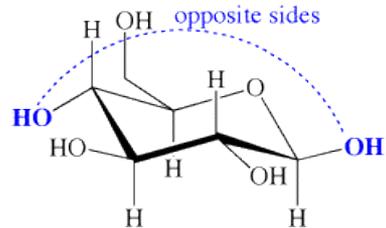
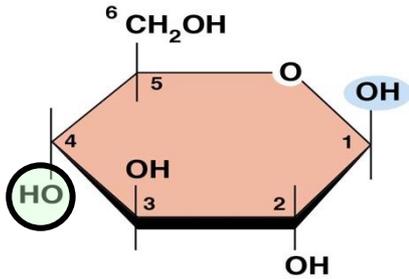
→ The existence of **anomers** has enormous significance in nature



Wall ...or no Wall ...It's All About "Up" or "Down"

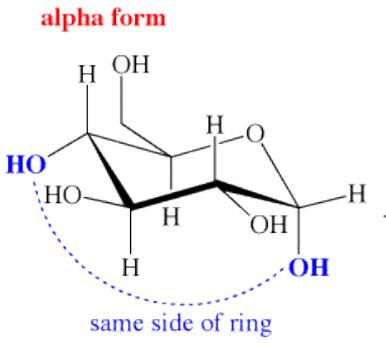
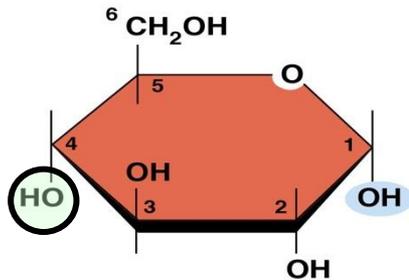
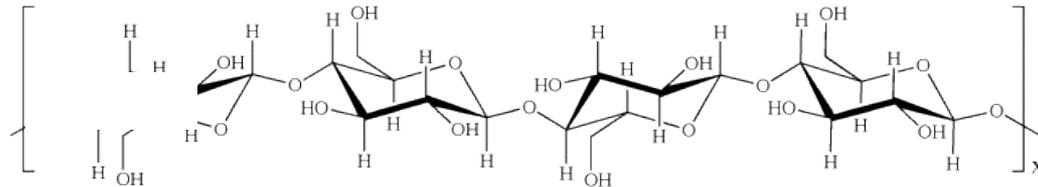


...for instance when it comes to what polymers of glucose look like, and are used for by biology.

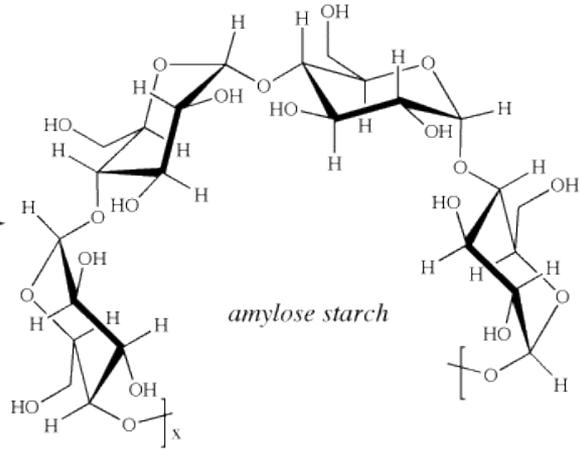


cellulose – cell walls

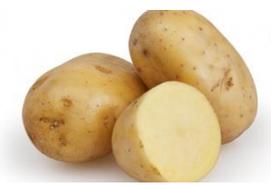
Linear polymer

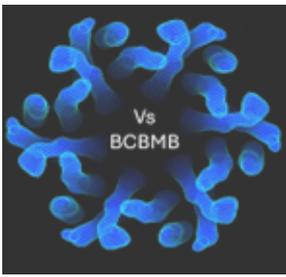


alpha form



Spiral shaped polymer





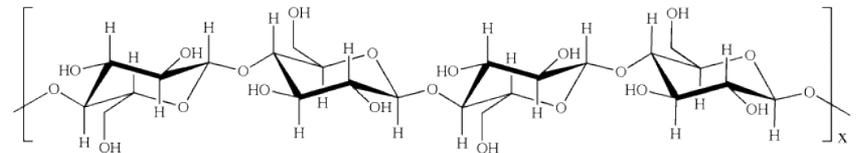
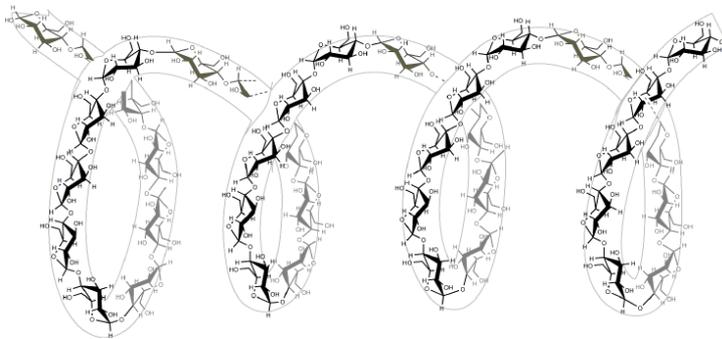
Structure Determines EVERYTHING....



Comparing just amylose and cellulose lets us derive an important general statement: **STRUCTURE DETERMINES FUNCTION**

→ this simple statement is a **fundamental paradigm in all of biology**. Based on what we covered in the handouts so far, you should be able to understand why this paradigm holds.... structure determines shape → shape determines what is presented to the environment → what is presented determines what it can see/recognize/interact with, and it also determines what chemistry can occur if the environment is suitable.

...the differences in the structures (and consequently function/role) of cellulose and amylose are entirely due to the fact that they are built from different anomers of glucose.

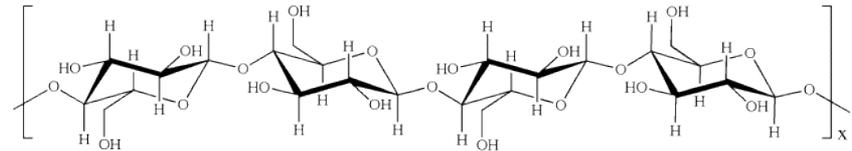
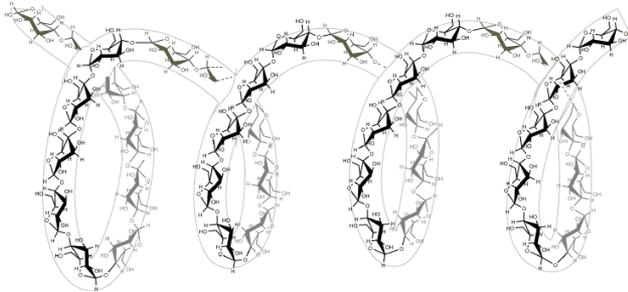
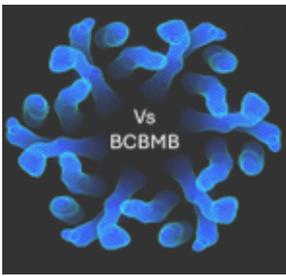


→ **Important insight: STEREOCHEMISTRY MATTERS IN BIOLOGY!**

→ true not only in the case of amylose vs cellulose, but in general because stereochemistry defines the patterning/presentation of functional groups → stereochemistry is key for molecular recognition (= way how molecules “see”) and the **specificity** that characterizes biological processes

....Though Physics is Important Too

One question that may linger on your mind considering that starch evidently is not cellulose - why isn't amylose used to form cell walls too?



Answer: here ... any physics/engineering background comes in handy. What has higher tensile strength.....cable or spring?

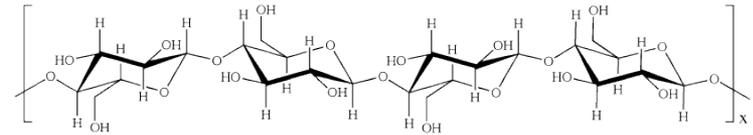
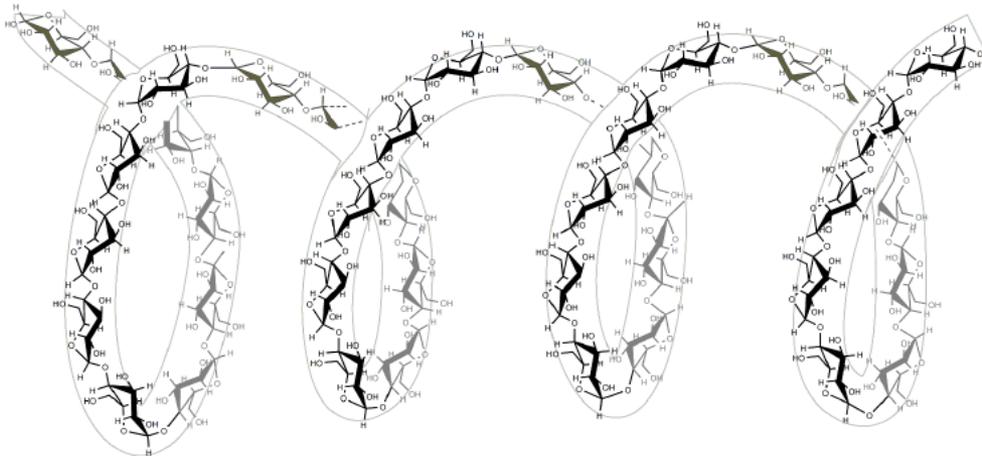
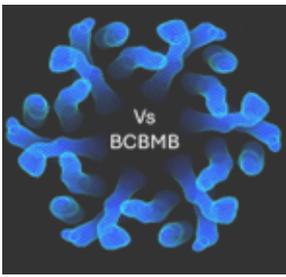
- **Cellulose;** $n=10,000-15,000$; polymer is maximally extended = can't stretch more without breaking covalent bonds; tensile strength further increased by parallel alignment of many polymer chains that are held together through weak interactions \rightarrow those add up causing a register that will not "slip" even under heavy load; layering cables at different angles on top of each other makes it even stronger (cellulose fibers can be used to generate fibrils that are stiffer and stronger than steel)
- **Amylose;** n averages $\sim 100-1000$; polymer is coiled; if at all - only few H-bonds form between turns, and lateral packing of independent spirals through direct H-bonds is far less favorable/prevalent than between cellulose strands.

\rightarrow amylose is fairly "flimsy" molecule and not able to resist big loads without deforming.

Yet: the one property it shares with cellulose isinsolubility in water ...why????

...make a guess based on what was said about cellulose earlier on

....Though Physics is Important Too



→ amylose (left) is fairly “flimsy” molecule and not able to resist big loads without deforming.

Yet: the one property it shares with cellulose isinsolubility in water ...why????

Answer: as open as the spirals may look ...if you think of them as a string wrapped around a “cylinder”, then all the –OH groups project parallel to the cylinder surface (no good for water to infiltrate) → the inside of the cylinder is quite hydrophobic + space is so tight that the van der Waals surfaces of the C, and H atoms fill it in.

Polysaccharides – Water Soluble at Last!!



Cellulose, Chitin, Amylose all water insoluble. This raises the question: **are all polymers of glucose water insoluble?**

Answer: no. Sticking with plant starchwhile amylose is water insoluble, a second glucose polymer in starch is actually water soluble. Its name: amylopectin.

What's happening here?

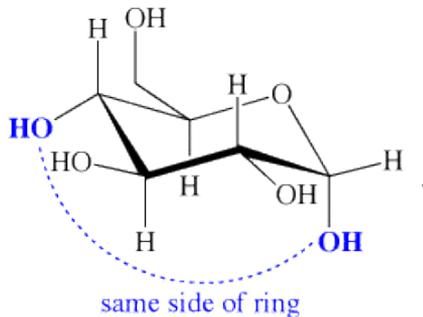
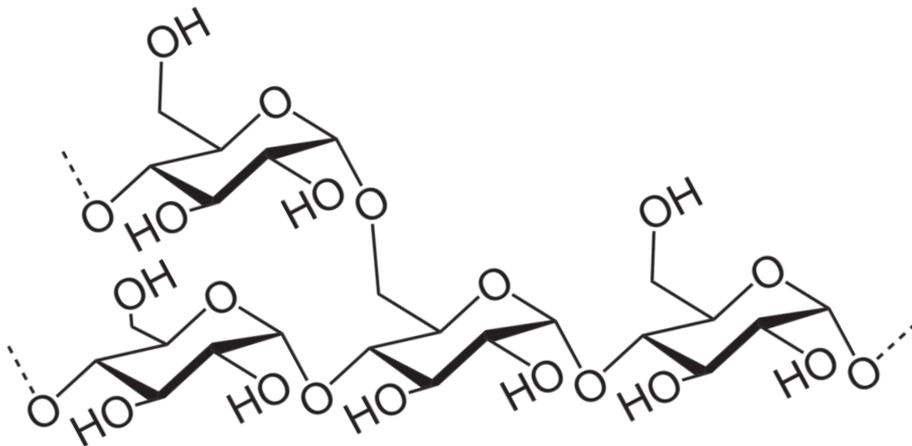
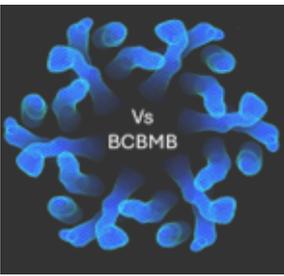
Answer: the chain is still made from the same glucose anomer than amylose – **BUT**, every 24-30 monomers along the chain this polymer branches! And each branch can spawn off additional branches.

→ The branching prevents coiling, and results in a much more open structure that water can access.

→ **water soluble** (...at last!)

Among covalent biological polymers ...branching of the polymer backbone is unique to carbohydrates

....it is, however, not the only way how you can make a polysaccharide water soluble



Polysaccharides – “Supercharging” Solubility

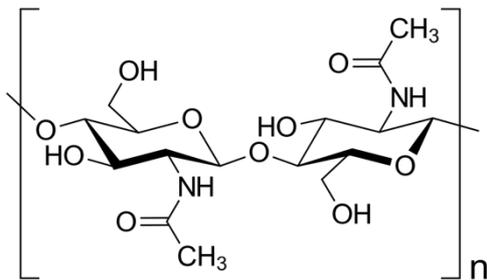


,,,if the key to water solubility is to minimize weak interaction within the polymer (and maximize H-bonding on surface) then besides steric hindrance, you should be able to exploit chemical properties too

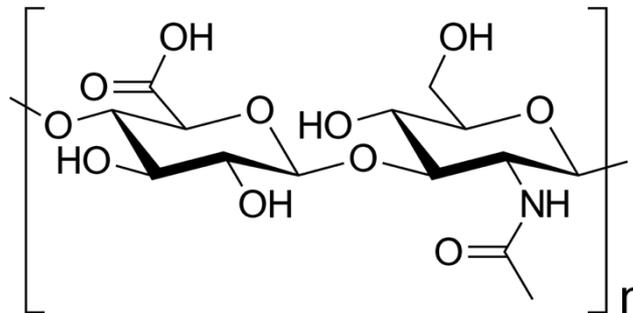
→ **Redundancy** = tweak a template to make it work in a different context (eg cellulose (all glucose) and chitin (all N-acetylglucosamine))

→ Here we encounter a different strategywhat is different?

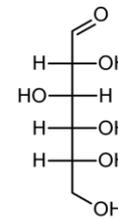
....look at the structures below and verbalize what you notice/observe/see



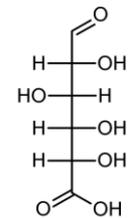
Chitin



Hyaluronic Acid; n ~20,000



Glucose

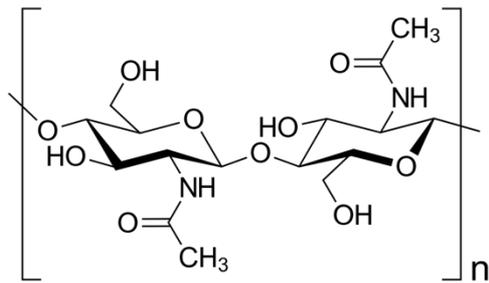
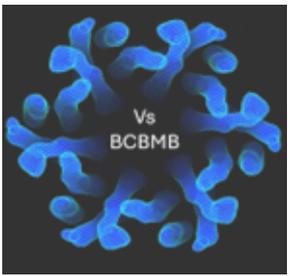


Glucuronic acid

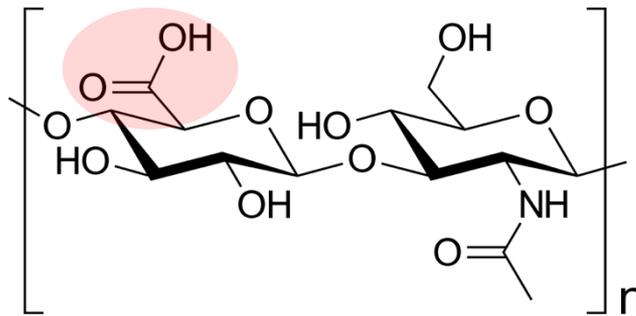
Polysaccharides – “Supercharging” Solubility



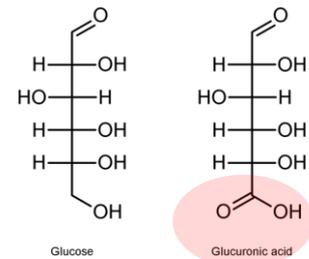
→ Here we encounter a different strategywhat is different?



Chitin



Hyaluronic Acid; n ~20,000

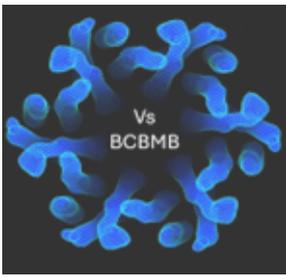


Answer: water insoluble **chitin** N-acetylglucosamine **homopolymer**; water soluble **hyaluronic acid** is a **heteropolymer** of **glucuronic acid:N-acetylglucosamine** (glucuronic acid: oxidized glucose with a -COOH instead of -CH₂OH). Hyaluronic acid is water soluble because the acidic carboxyl groups dissociate in water, leaving a negatively charged carboxylate anion (-COO⁻)



→ High negative charge density on hyaluronic acid prevents lateral association between polymer chains (electrostatic repulsion), but provides a very good hydrophilic surface to interact with water molecules.

Under physiological conditions: hyaluronic acid is a gel; used in connective tissue and as joint lubricant; the ability to bind and hold water molecule also makes hyaluronic acid a popular ingredient in skincare products (keeps skin hydrated and “plump”, smoothing out fine lines/wrinkles)



SUMMARY



- **Carbohydrates** are **globally defined** as molecules made from equimolar amounts of carbon and water = $(\text{CH}_2\text{O})_n$
- In their **monomeric** form, carbohydrates are **readily water soluble**
- Just as for other types of biological macromolecules, **chemical modifications** of the basic parent compounds are **common**. The resulting molecules are still thought of as carbohydrates, as long as their overall composition are within reason of the generic description $(\text{CH}_2\text{O})_n$
- With **very few exceptions** that are all limited to carbohydrates with 3 carbon atoms, carbohydrates are asymmetric molecules that **contain one or more chiral carbon atom**.
- Presence of one or more asymmetric carbon atoms gives rise to **complex stereochemistry**.
- A **characteristic structural property** of monomeric carbohydrates is the ability of their linear forms to spontaneously and reversibly **form closed 5- and/or 6-membered rings**.
- For any given sugar (= monomeric carbohydrate), **ring closure** of a sugar gives rise to a pair of stereoisomers – referred to as **anomers** - because the reaction creates an additional asymmetric carbon atom.
- In their monomeric state, anomers have very similar solubility in water. However, the **structural, physical, and chemical properties of carbohydrate polymers – called polysaccharides - vary tremendously depending on which anomer** of a sugar forms the basic unit of a polymer
- **Polysaccharides are covalent polymers**, which sets them apart from the non-covalent polymers that form when lipids are exposed to water

The emergent properties of polysaccharides are exploited for a broad spectrum of biological functions, ranging from cell wall formation in plants, to energy storage (eg starch), or lubrication of joints.

Adding two Mantras/Paradigms beyond “Everything is based on Equilibria”:
STEREOCHEMISTRY MATTERS and **STRUCTURE DETERMINES FUNCTION**