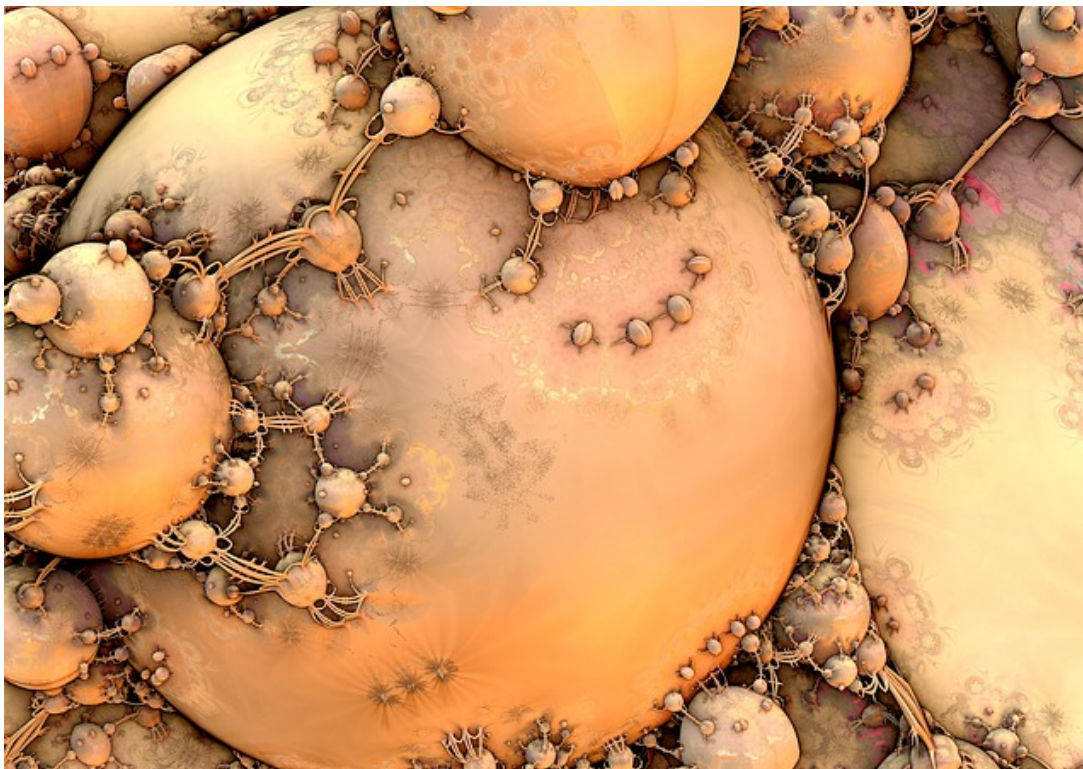


Biochemistry for Physicians: The Chemistry of Carbohydrates

[See online here](#)

Everywhere in biochemistry, there is mention of carbohydrates and sugars; they are a fundamental part of almost all essential biochemical processes and, what's more, they form an extremely important part of medical exams, but what is it that makes carbohydrates so essential for biochemistry?



Structure and Function of Carbohydrates

Carbohydrates are the aldehydes or ketones of polyalcohols (alcohols with several carboxyl groups) with a carbon/water ratio of 1:1 which results in the chemical molecular formula of $C_n(H_2O)_n$. In case of a hexose with six C-atoms, the molecular formula would, therefore, be $C_6(H_2O)_6$.

The number of relevant carbohydrates that you have to know as a medical student, however, is very limited and, with a few tricks, they can be studied and understood very quickly.

Note: The terms sugar, saccharides, and carbohydrates are used as synonyms or interchangeably.

Monosaccharides (or simple sugars) can be further classified by counting their carbon

atoms. The most relevant monosaccharides for the metabolism (as well as for medical exams) are **hexoses** (6 C atoms) and **pentoses** (5 C atoms).

Carbohydrates with more or fewer C atoms also play a role, but to a smaller extent, i.e., glycerin aldehyde (3 C atoms), erythrose (4 C atoms) or sedoheptulose (7 C atoms), of which the last two represent an intermediate product in the hexose monophosphate pathway of glucose metabolism (see below). Aside from sedoheptulose, however, tetroses, trioses or heptoses are not as relevant for students of medicine which is why they are not mentioned here further.

Chirality and Isomerism of Monosaccharides

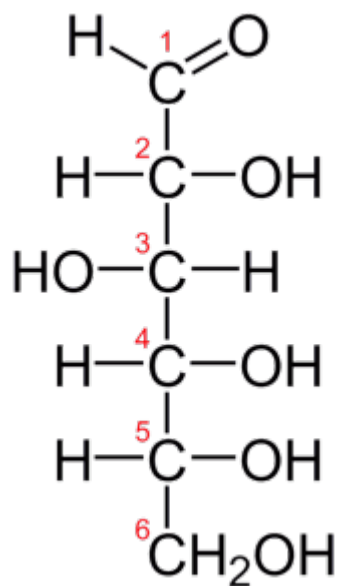


Image: "D-Glucose" by Ben; Yikrazuul.
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Essential for the detection of isomerism is the ability to identify **chiral centers** in a molecule. An atom is always chiral if it has four different binding partners. Therefore, if this is applied to an aldohexose, i.e., D-glucose, one realizes that it possesses four chiral centers (C2-C5). As pentoses are one carbon atom smaller than hexoses, they only possess three chiral centers (C2-C4).

The D- and L-nomenclature of sugars always refer to the position of the OH group at the C5 atom in the Fischer projection (i.e., the second carbon atom from the bottom). If the OH group is to the left, it is an L-sugar; if it is to the right, it is a D-sugar ('D' from lat. dexter = right). **All sugars occurring in the human body are D-sugars.**

Three of the four most important hexoses for the body are **isomers** and they are therefore very similar to each other which, on one hand, make them easy to learn. On the other hand, however, special caution is warranted as to not mistake one for the other.

Excursus: Stereochemistry and Isomerism

Relationships of the Most Important Carbohydrates

With this flow chart, all isomerisms - not only those of carbohydrates - in organic chemistry can be identified.

Definition:

- **Constitutional isomers = structural isomers** (same molecular formula, different bonding pattern)
- **Stereoisomers** (same molecular formula, same bonding pattern, different spatial arrangement)
- **Conformers** (they can be converted into each other via rotation of the substituents to C-C mono binding (tub shape/chair shape))
- **Configurational isomers** (same bonding pattern, different arrangement of the substituents around a center)
- **Cis/trans isomers** (they cannot be converted into each other via rotation of the substituents but rather face each other (trans) or are on the same side (cis) - often the case in double bonds)
- **Chirality** (C atom is asymmetrically substituted - from the Greek word for hand "cheir") is the geometric property displayed by any object which is non-superimposable on its mirror image
- **Enantiomers** (non-superimposable mirror-image molecules)
- **Diastereomers** (not (entirely) mirror-image molecules)

When trying to memorize the structural formula of the most important hexose, **glucose**, from which all other hexoses can be synthesized and through whose breakdown (glycolysis) 50 % of the daily energy needs of a human being is covered, you can use the sound of a German fire engine as a mnemonic. "**Ta Tü Ta Ta**" is the code for the glucose molecules that satisfy ravenous hunger if one remembers that starting at the first chiral C atom, "tü" stands for an OH group to the left and "ta" for an OH group to the right.

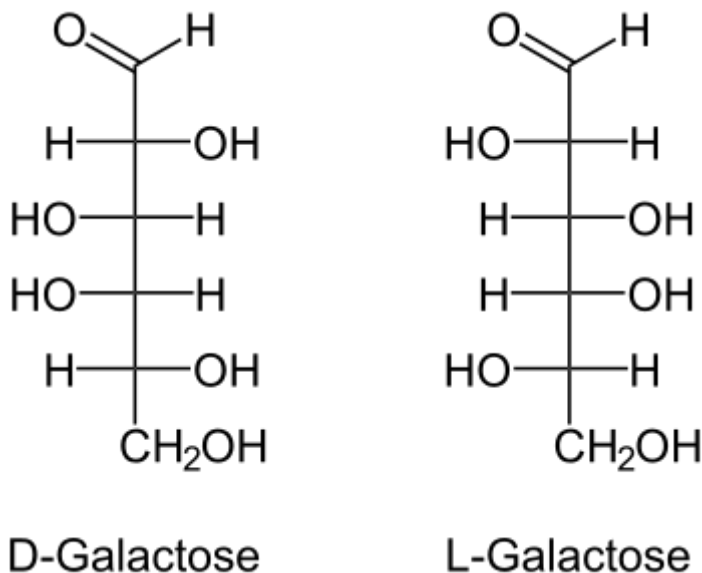


Image: "Structure of galactose" by NEUROtiker. License: [Public Domain](#)

Galactose is an epimer of glucose and only differs from it in one chiral center (C₄). If the OH groups are connected, the result is a "galactic fighter plane", a type of spacecraft.

Mannose is an epimer of glucose as well, and only differs in the second C atom. Here, one can remember "**The second man is epimer**", meaning that mannose is a C-2 epimer of glucose.

The last most important sugar for the body is the **fructose**, which differs from glucose remove, as its carbonyl group is attached to the second carbon atom, making it

a **ketose**. As a ring form, fructose forms a furanose – in contrast to the other three hexoses which form a pyranose.

Caution: The ring formation creating a pyranose/furanose, generates a new chiral center!

The ring formation creating a **pyranose** in aldoses is generated through a reaction between the functioning aldehyde group at C₁ and the OH group at C₅. The molecule thus formed is also called **hemiacetal**. The hereby newly created carboxyl group in the new chiral center is highly reactive; as it lends the sugar its reducing capabilities; it even has its own name: glycosidic OH group.

A **hemiketal** (i.e., fructose) is created when the keto group at C₂ of a ketose reacts with the hydroxyl group at C₅ thereby forming a pyranose instead of a **furanose**.

Pyranoses or furanoses are mostly written using the **Haworth formula**, meaning another nomenclature rule is added which is, however, just as simple as the D-/L- nomenclature.

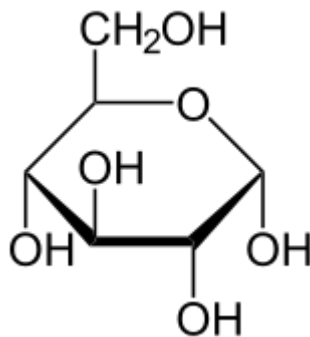


Image: "Structure of alpha-D-glucopyranose" by NEUROtiker.
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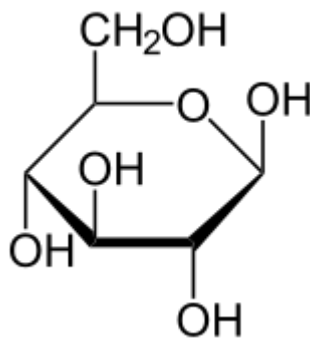


Image: "Structure of beta-D-glucopyranose" by NEUROtiker.
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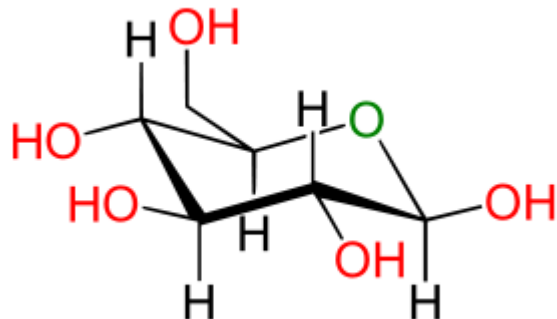
When the OH group is the first C atom from the bottom, it is a α -molecule; if it is at the top, it is a β -molecule.

For the process of converting the sugar from the Fischer projection to the Haworth formula and vice versa, the "FLOH"-rule is helpful which states: **"What's left at Fischer's is at the top at Haworth's."**

α - and β -glucoses are **anomers** and can be converted into each other via the open-chain form. As, however, the OH groups in α -glucose at the C1 and C2- atom are closer together than in β -glucose and nature ensures that conditions are as low energy as

possible, the balance shifts to the side of β -glucose.

In the **chair conformation**, the cis/trans isomerisms, as well as the spatial structure of molecules, are best recognized.



" β -glucoses" by Lecturio.

Thereby, the question is frequently asked which OH groups are in axial, and which are in equatorial position. Here, the hydroxy groups are positioned equatorially. An axial position can always be recognized by the vertical binding line (in this case hydrogen atoms).

Caution: In α -D-glucose in chair form, the carboxyl group is positioned axially on C1. The same OH group (C1) is positioned downward in the Haworth formula!

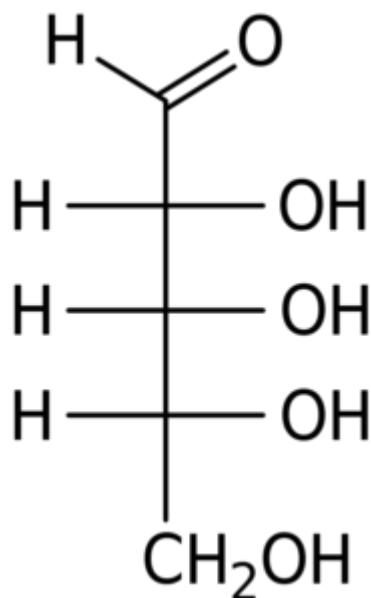


Image: "Fischer projection of the aldopentose monosaccharide, D-ribose." by Christopher King. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

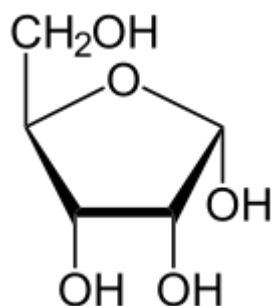


Image: "Structure of alpha-D-ribofuranose" by NEUROtiker.
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The most important pentose overall is the D-ribose on whose exact origin the pentose phosphate pathway provides more detailed information. Pentoses are essential components of ribonucleic acids.

Bond Structures of Sugars

Sugars can form a **glycosidic bond** with each other, as well as with other molecules, whereby one differentiates between an O-glycosidic bond and an N-glycosidic bond. An **O-glycosidic** bond exists when the anomeric C atoms of two molecules react. The nomenclature of these bonds again consists of the α - or β -conformation, as well as the indication of the numbers of the particular anomeric centers.

The α - β -conformation refers to the position "top" (β) or "bottom" (α) just like with the monosaccharides.

The **N-glycosidic** bond describes the binding of a sugar – not with another OH group – but rather with an NH group of another molecule. The most frequent occurrence of this type of bond is with asparagine, but the binding of a DNA-ribose, with bases such as adenine, should be remembered under the term "n-glycosidic bindings" as well.

Classification of Carbohydrates

Disaccharides

Even though there is an incredibly large amount of disaccharides, only three of them are applicable knowledge for a medical student, including their structural formula, as well as all their characteristics such as splitting and bond structure.

1. Sucrose (fructose + glucose)
2. Lactose (galactose + glucose)
3. Maltose (glucose + glucose)

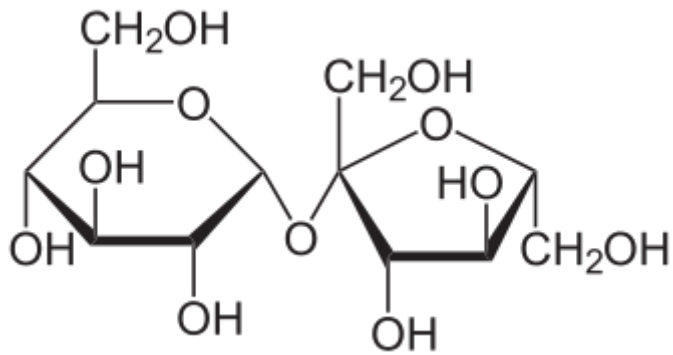


Image: "Structure of sucrose (saccharose)" by NEUROtiker. License: [Public domain](#)

Sucrose

With regard to sucrose, it is important to note that it is **not a reducing sugar** because all anomeric carboxyl groups are involved in the bond.

Lactose, the Milk Sugar

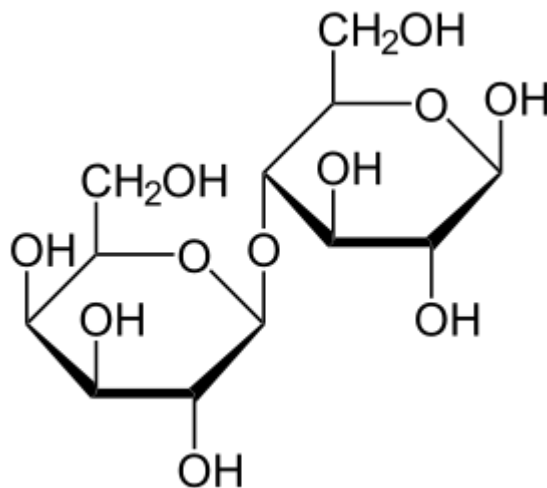


Image: "Struktur von Lactose" by NEUROtiker. License: [Public domain](#)

The splitting of the clinically, rather significant lactose, is an exception for the human body. The **β -glycosidic** bond of lactose is the only β -glycosidic bond that can be split by a human being.

In cases of the metabolic defect **lactose intolerance**, this splitting of the β -glycosidic bond is no longer possible. The typical symptoms, such as diarrhea and pain in the abdomen, occur because lactose remains in the intestinal lumen and causes osmotic absorption of water and osmotic diarrhea.

Maltose, the Sugar in Beer

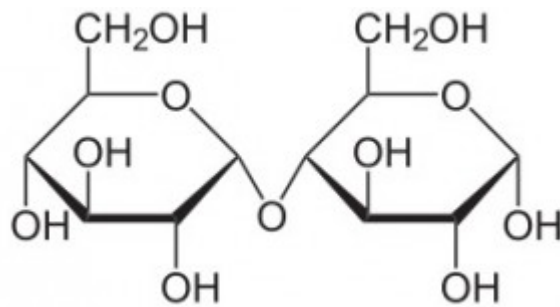


Image: "Gleichgewicht zwischen zyklischer und offener Form von Maltose" by NEUROtiker. License: [Public domain](#)

Maltose (as well as isomaltose $\text{Glc } \alpha 1 \rightarrow 6 \text{ Glc}$) is created, among others, by splitting starch with α -amylase. Maltose is a reducing sugar.

Reducing and non-reducing sugars can easily be distinguished by the fact that non-reducing disaccharides have **two Greek letters** in their names (sucrose: α -D-glucose(1.2)- β -fructose) and reducing ones only have one (maltose: α -glucose (1.4)-glucose)

Oligosaccharide

Oligosaccharides are combinations consisting of between three and 20 sugars and mostly play a role in metabolism as a glycoprotein.

Polysaccharides

Polysaccharides are the carbohydrates one probably thinks of first due to diets, bodybuilding, and alternative lifestyles which are broadcast by the media. **Starch**, enemy number one in the "low carbohydrate diet", is a polysaccharide, for instance.

With regard to the general structure of polysaccharides, one should know that there is hetero- and homo-polysaccharides. **Hetero-polysaccharides** consist of several different monosaccharides, while **homo-polysaccharides** are a sequence of several of the same monosaccharides.

The most important homo-polysaccharides are cellulose, glycogen and starch. All of them consist of several glucose molecules.

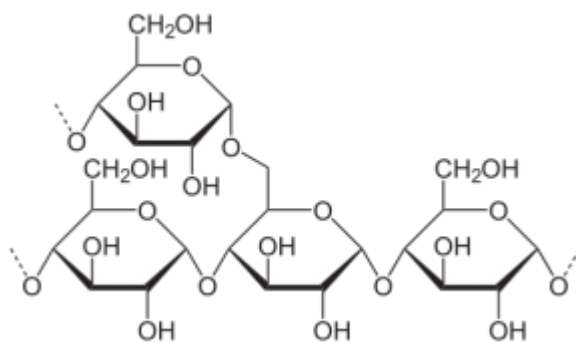


Image: "Ausschnitt aus einem Amylopektinpolymer" by NEUROtiker. License: [Public domain](#)

Starch is the carbohydrate stored in plants, as opposed to **glycogen** with which animals (as well as humans) store carbohydrates.

Starch consists of amylose (α -(1.4) Glc) as well as amylopectin (α -(1.4) Glc and sometimes α -(1.6) Glc) branched out due its bonds α (1.6). Glycogen consists of α -(1.4) Glc and α -(1.6) Glc as well (glycosidic bonds between glucose molecules). It does, however, have more α -(1.6)-bonds which are why it is more branched out than amylopectin.

Cellulose does not play a role with regard to the human metabolism, but it is an important **fiber** and promotes the proper functioning of the intestines.

Hetero-Polysaccharides: Complex Structure, Easy to Understand

Heteropolysaccharides are polysaccharides consisting of at least two different monosaccharides.

They are further categorized as follows:

1. Mucopolysaccharides
2. Proteoglycans
3. Glycoprotein

Mucopolysaccharides (Glycosaminoglycans)

These polysaccharides occur mainly in the extracellular matrix and support it through their extraordinary water binding capacity. The **hyaluronic acid**, used by the cosmetics industry, is such a mucopolysaccharide and is supposed to fill in wrinkles with its water binding characteristics and thereby smooth the skin.

Proteoglycans

Proteoglycans are basically glycosaminoglycans that are covalently bound to a protein (**core protein**), thereby organizing the saccharide chains and preventing them from scattering about without any structure in the extracellular matrix. The proportion of saccharides is higher in relation to the proteins.

Glycoproteins

Glycoproteins are saccharides bound to proteins. Their proportion is smaller in relation to the proteins. The attachment of the oligosaccharides to a protein is called glycosylation, which is a posttranslational modification mainly taking place in the Golgi apparatus. Almost all blood cells are glycosylated, except for albumin. Therefore, glycoproteins have different tasks such as immune defense in the form of immunoglobulins.

Glycolipids

In addition to bonds between individual carbohydrates, carbohydrates can also form bonds to other biomolecules. Glycolipid means a sugar that has been attached to a lipid; this lipid is designated beneath the sugar. For example a molecule like in the figure on the right; on the top, there is glucose, drawn in the axial equatorial form and that glucose is linked in the alpha position to a molecule that is a diacylglycerol.

Diacylglycerol is related to fat. Normally, if this were fat, this would have a glycerol backbone which would be the three carbons and each carbon would be attached to a

fatty acid. Such a molecule could exist, for example, in the membrane of a cell. Glycoglycerol lipids exist, but they are not very common. A much more common glycolipid is that of the sphingolipid.

Sphingolipid

Sphingolipids are related in structure to glycolipids, but they are not the same, the glycolipid had a glycerol backbone which consisted of three carbons. The sphingolipid have a backbone that's a little bit different; on the right side of the molecule, part of this backbone, that includes the N. the carbon that's bonded above it and then the CH₂ which is bonded to the glucose at the very top.

This backbone is common to sphingolipids. In contrast to the glycolipid, the diacylglycerol, these sphingolipids have only one fatty acid and they have another molecule attached to that, that looks like a fatty acid known as sphingosine.

In the third position at the very top is glucose, a combination of glucose and sphingolipid, creating cerebroside. Cerebrosides are very common components of the nerve tissue, they were discovered for example in the brain. Whenever a simple sugar like glucose in this case, is attached, a cerebroside is formed.

However, if a more complex sugar is attached at the very top, you get ganglioside.

Peptidoglycans

Another interesting group of modified saccharides are the peptidoglycans. Now peptidoglycans, as its name suggests, are long polymers of carbohydrate residues and they're modified sugars and they're presented with a repeating disaccharide. These components are linked to short peptides, in the case of the bacterial cell wall. The peptides are linked to only contain four amino acids.

The other repeating disaccharide is N-acetylglucosamine. When laying it out, the linkage makes a mesh or a network. There's long polymers running diagonally from the upper left to the lower right, those polymers and those diagonals contain the repeating glycan structure of N-acetylglucosamine and N-acetylmuramic acid. Perpendicular to those are the tetrapeptides that are interacting with each other.

Now those tetrapeptides are really interesting for two reasons; one is that the tetrapeptides contain within them at least one amino acid in the D configuration, this almost never happens in nature and this almost never happens for accidental purposes. And the other reason is, this is an example of where bacteria have used chemistry to their advantage.

Proteases means enzymes that break down proteins, enzymes that would break down peptides will not work on D amino acids; they are designed to work on L. So this is a defense mechanism bacteria, evolved over the years to protect their cell walls from being degraded.

Bacteria don't get the last word in this overall scheme though, and the reason that's the case is the antibiotic penicillin. Penicillin is killing bacteria for a very important reason, it stops the bacterial cell wall from being assembled. Bacteria that can't make a cell wall divide, and bacteria that can't divide are doomed to die.

Easy Distinction in Exams:

Proteoglycans: more carbohydrates than proteins, no branched out chain.

Glycoproteins: fewer carbohydrates than proteins, branched out the chain.

This basic information establishes the foundation to capture all metabolisms of carbohydrates.

Review Questions

The correct answers can be found below the references.

1. In the 4 C1 conformations, all substituents of the β -D-glucopyranose take an equatorial position.

- A. True
- B. False

2. Galactose and glucose are C4-epimers.

- A. True
- B. False

3. Sucrose has a free hemiacetal OH group.

- A. True
- B. False

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Correct answers: 1A, 2A, 3B

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