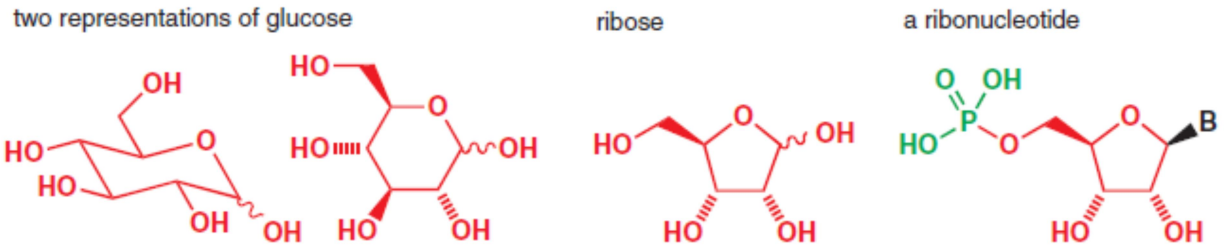
Sugars—just energy sources?

Sugars are the building blocks of carbohydrates. They used to be thought of as essential but rather dull molecules whose function was principally the (admittedly useful) storage of energy. In fact they have much more interesting and varied roles than that. We have already noted that ribose plays an intimate role in DNA and RNA structure and function. Sugars are also often found in intimate association with proteins and are involved in recognition and adhesion processes. Here are two examples. How does a sperm recognize the egg and penetrate its wall? Recognition of a carbohydrate attached to the membrane of the egg was the fi rst event in all of our lives. And how does a virus get inside a cell? Here again, the recognition process involves specifi c carbohydrates. One of the ways in which AIDS is being tackled with some success is by a combination of the antiviral drugs we met earlier in this chapter with HIV protease inhibitor drugs, which aim to prevent recognition and penetration of cells by HIV.

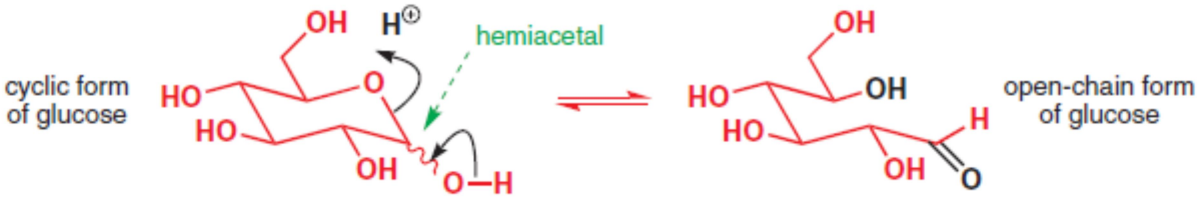
Sugars normally exist in cyclic forms with much stereochemistry

The most important sugar is glucose. It has a saturated six-membered ring containing oxygen and it is best drawn in a chair conformation with nearly all the substituents equatorial. It can also be drawn as a flat configurational diagram. We have already met one sugar in this paper, ribose, because it was part of the structure of nucleic acids. This sugar is a five-membered saturated oxygen heterocycle with many OH groups. Indeed, you can define a sugar as an oxygen heterocycle with every carbon atom bearing an oxygen-based functional group—usually OH, but alternatively C=O.

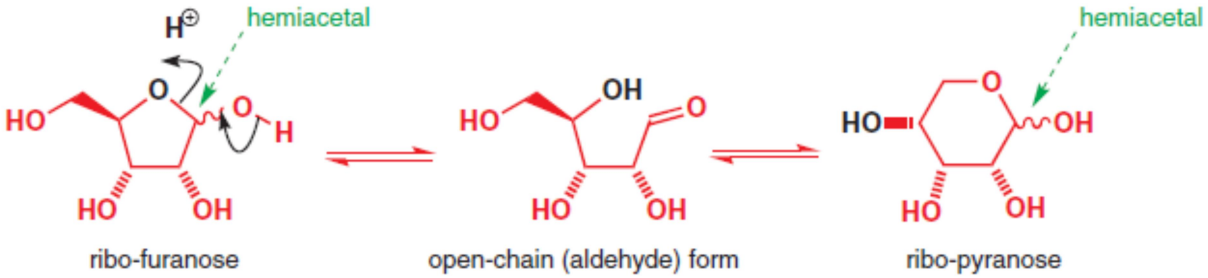


The drawings of glucose and ribose show a number of stereogenic centres, with one centre undefined—an OH group shown with a wavy bond. This is because one centre in both sugars is

a hemiacetal and therefore the molecule is in equilibrium with an open-chain hydroxyaldehyde. For glucose, the open-chain form is this.



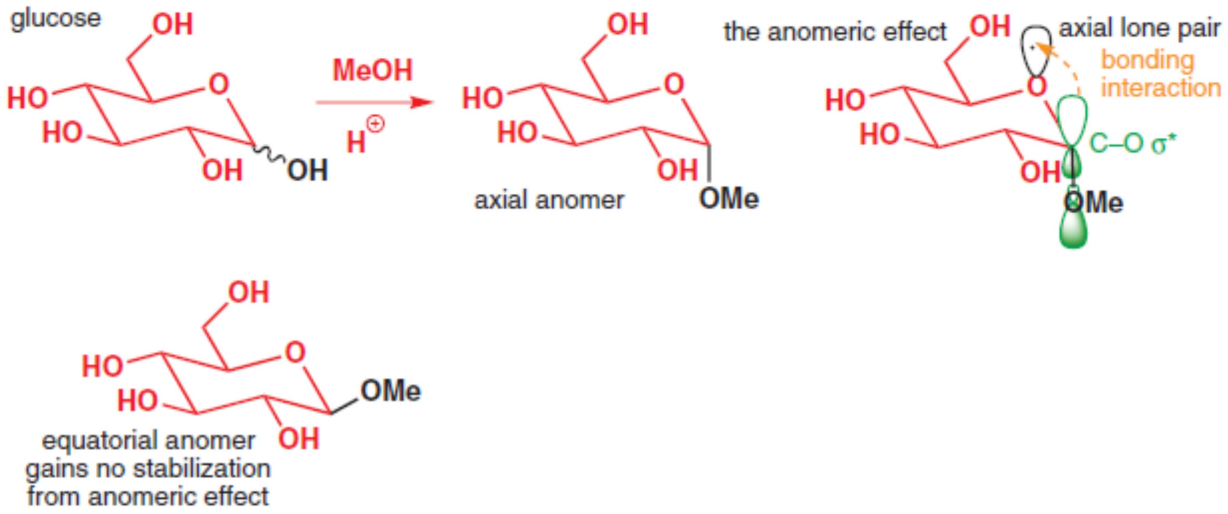
When the ring closes again, any of the OH groups could cyclize on to the aldehyde but there is no real competition—the six-membered ring is more stable than any of the alternatives (which could have three-, four-, five-, or seven-membered rings — check for yourself). However, with ribose there is a reasonable alternative.



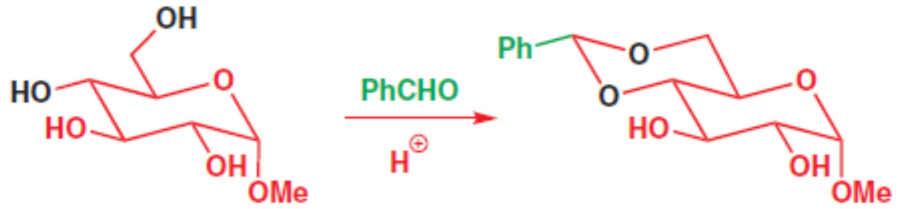
The most important sugars may exist in an open-chain form, as a fi ve-membered oxygen heterocycle (called a *furanose*, after the fi ve-membered aromatic compound furan) or a sixmembered oxygen heterocycle (called a *pyranose*, after the six-membered pyran). Glucose prefers the pyranose structure; ribose prefers the furanose structure.

Sugars can be fixed in one shape by acetal formation

The simplest way to fi x glucose in the pyranose form is to trap it as an acetal. Acid-catalysed condensation with an alcohol, methanol, for example, gives an acetal and, remarkably, the acetal has an *axial* OR group. Acetal formation is under thermodynamic control so the axial compound must be the more stable. This is because of the anomeric effect—so called because this C atom is called the anomeric position and the acetal diastereoisomers are called anomers. The effect is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the σ* orbital of the OMe group.

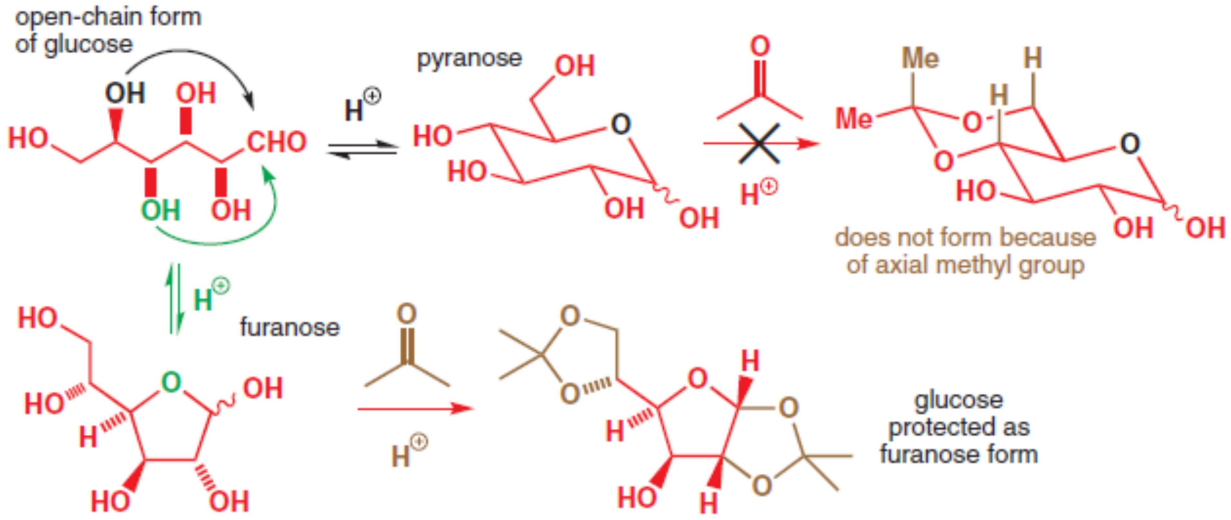


The formation of acetals allows a remarkable degree of control over the chemistry of sugars. Apart from the simple glucoside acetal we have just seen, there are three important acetals worth understanding because of the way in which they illustrate stereoelectronic effects—the interplay of stereochemistry and mechanism. If we make an acetal from methyl glucoside and benzaldehyde, we get a single compound as a single stereoisomer.



The new acetal could have been formed between any of the adjacent OH groups in the starting material but it chose the only pair (the black OH groups) which give a six-membered ring. The stereochemistry of glucose is such that the new six-membered ring is *trans*-fused to the old so that a beautifully stable all-chair bicyclic structure results, with the phenyl group in an equatorial position in the new chair acetal ring. Acetal formation is under thermodynamic control and this product is the most stable possible acetal. Acetal formation from sugars and acetone shows quite different selectivity. For a start, cyclic acetals of acetone prefer to be five- rather than six membered rings. In a six-membered ring, one of the acetone's methyl groups would have to be axial, so the five-membered ring is preferred. A 5,5 or 5,6 ring fusion is more stable if it is *cis*, and so acetone acetals (acetonides) form preferentially from *cis* 1,2-diols.

Glucose has no neighbouring *cis* hydroxyls in the pyranose form, but in the furanose form it can have two pairs. Formation of an acetal with acetone fixes glucose in the furanose form. This is all summarized in the scheme below.



The open-chain form of glucose is in equilibrium with both the pyranose and the furanose forms through reversible hemiacetal formation using the black and green OH groups, respectively. Normally, the pyranose form is preferred, but the furanose form can form a double

acetal with acetone, one acetal having two *cis*-fused fi ve-membered rings and the other being on the side chain. This double acetal is the product isolated from the reaction. If we want to fi x glucose in the open-chain form, we must make an 'acetal' of quite a different kind using a thiol (RSH) instead of an alcohol, an aldehyde, or a ketone. The thiol combines with the aldehyde group of the open-chain form to give a stable dithioacetal. The dithioacetal is evidently more stable than the alternative hemiacetals or monothioacetals that could be formed from the pyranose or furanose forms.