A Simple Paper Model Illustrates How to Cyclize Monosaccharides from Fischer Projections to Haworth

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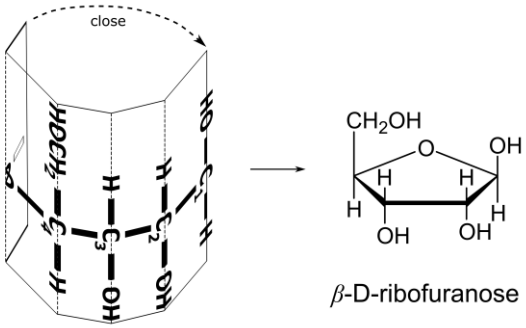
ABSTRACT

Turning a linear sugar into its cyclized form is an essential skill in biochemistry. A simple paper model is described that can be used by any student to transform a carbohydrate in its Fischer projection and correctly cyclize it into its Haworth form. The model can also be used to illustrate several key aspects of the Fischer projection of which many students are typically unaware.

GRAPHICAL ABSTRACT



KEYWORDS

Second-Year Undergraduate; Biochemistry; Hands-On Learning / Manipulatives; Carbohydrates

Understanding the structures of complex molecules is challenging. Students often have difficulty translating molecules from their 2-dimensional (2-D) representations to their actual 3-dimensional (3-D) shapes[1]. Because books and papers have to be printed in 2-D, chemists have developed very precise recipes to help correctly annotate the stereo geometries of different classes of compounds. While being able to interpret these 2-D representations seems second nature to most of those who teach chemistry, in my experience, it proves to be immensely difficult to the majority of first- or second-year undergraduates who are just learning biochemistry for the first time.

In biochemistry, a class of compounds that is particularly difficult to understand is carbohydrates[1] because there is not just one but multiple chiral carbons on each sugar. Mastering chirality is

therefore pivotal. While most students accept the reality that a tetrahedral carbon atom having four distinct substituents must exist in two different isomeric forms, the precise 3-D meaning of it is vague. Compounding this is the fact that many sequential chiral centers are positioned along every carbohydrate backbone. Further exacerbating this are the two rather different 2-D representation schemes, the Fischer projection and the Haworth projection, commonly used by chemists to represent sugar structures.

In this report, a simple paper model is described that can be used to illustrate how to cyclize a sugar properly from its linear form into its cyclic form. When teaching carbohydrates, many instructors encourage biochemistry students to build some sugar molecules using their molecular model sets at home and use them to learn to cyclize monosaccharides, but most students in my biochemistry classes either do not own a model set, or they own one but do not do it. The paper model described below (and in more detail in the Supporting Information) provides a hands-on in-class experience that any instructor can use to engage every student. The model has been used in a second-year undergraduate biochemistry course for two semesters by approximately 150 students.

FISCHER PROJECTIONS, CHIRAL CENTERS AND COMMON MISCONCEPTIONS

A typical sugar as drawn in most biochemistry textbooks is shown in Figure 1(a). D-Glyceraldehyde, the simplest chiral aldose, is a 3-carbon sugar with one chiral center (on the second carbon). Drawn in this Fischer representation, all D sugars have the same absolute geometry on the last chiral carbon farthest from the carbonyl group.

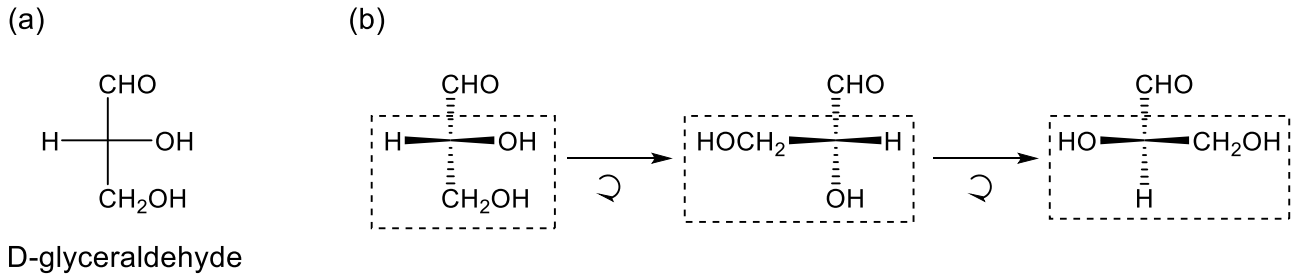


Figure 1. (a) Fischer projection of D-glyceraldehyde, a 3-carbon aldose. (b) The 3-D geometry of D-glyceraldehyde represented by wedge bonds. The three structures shown in (b) are equivalent. The second one is obtained from the first one by a clockwise rotation of the three substituent groups around the chiral carbon highlighted by the dashed box. The third structure is similarly obtained by a clockwise rotation of the three substituent groups on the second structure.

Mistaking the structure represented by Figure 1(a) for a simple stick drawing is the first common misconception of many students[1]. Coming from general chemistry where chirality is usually not extensively covered, students often misunderstand the drawing in Figure 1(a) to be just a representation of the chemical bonding. Missing altogether the 3-D implications of the Fischer projection is a serious deficiency.

The chirality of D-glyceraldehyde is displayed more explicitly in Figure 1(b) in a representation that most students would not miss. The two horizontal solid wedges indicate that the H and OH groups are coming out of the plane of the paper, while the dashes indicate that the CHO and CH_2OH groups are directed behind the plane of the paper. (In the Fischer projection, the structure appears to be coming towards you with arms open.) It is important to reiterate to students that the structure in Figure 1(a) must be interpreted as that particular 3-D geometry shown in Figure 1(b).

Thinking that there is only one unique way to draw a Fischer projection correctly is the second common misconception of many students[2-3]. Three different, but legitimate, representations for D-glyceraldehyde are shown in Figure 1(b). The three equivalent representations in Figure 1(b) indicate that rotation of all substituent groups around one particular bond at a chiral center preserves its absolute chirality.

A paper model (Figure 2) can help to illustrate some of these ideas. First, on a piece of paper or an index card, draw the Fischer projection of D-glyceraldehyde corresponding to the second structure from Figure 1(b). (In order to keep the structures in Figure 2 and in the drawings in the rest of this paper visually clear, the numbering of the carbon atoms are shown as subscripts[4].) Fold the card along the dashed line in Figure 2, which goes through the two horizontal bonds to CH_2OH and H in the drawing. This produces the object shown on the right side of Figure 2. This model suggests how the CHO and OH groups must be arranged in 3-D relative to the chiral center on C2. (For extra 3-D effects, students can make four additional cuts, indicated by the dotted lines on the right in Figure 2, to allow them to lift the $HOCH_2$ and H groups up away from the dashed line to produce an approximate tetrahedral geometry for the molecule, but without severing their bonds to the C2 atom.) Students may also try the same with the other two alternate projections from Figure 1(b). They may try

to do this on their own with L-glyceraldehyde, too, to examine how the D and L isomers are different in 3-D.

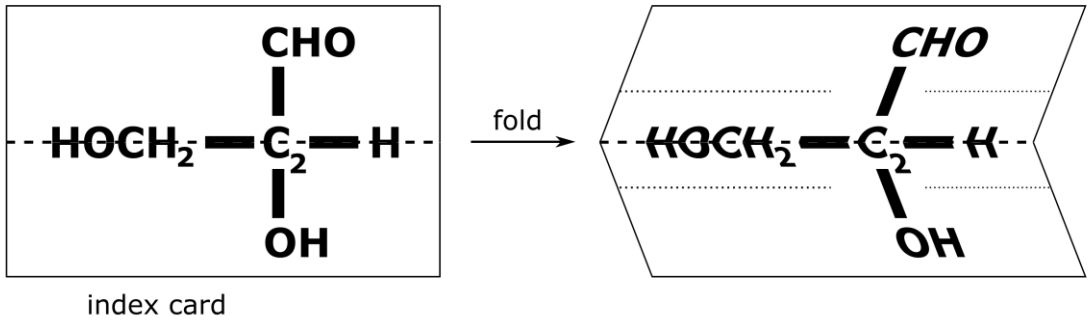


Figure 2. A paper model to illustrate the meaning of the Fischer projection on the chirality of the C2 carbon in D-glyceraldehyde. The structure on the left is taken from the second structure in Figure 1(b), drawn on an index card. Folding the card along the dashed line produces the 3-D shape indicated on the right.

CYCLIZING SIMPLE SUGARS USING PAPER MODELS

A common recipe for how to cyclize D-ribose into a furanose form (a 5-atom ring) is shown in Figure 3(a) and (b). Cyclization of the same D-ribose into a pyranose form (a 6-atom ring) is shown in Figures 3(c) and (d). While several schemes to help students learn how to cyclize sugars from their linear to their cyclic forms are available in the literature[5-11] as well as in many textbooks[12], a paper model similar to the one described below can more effectively illustrate this in actual 3-D. Unlike a molecular model set, a paper model is accessible to every student. It can also be incorporated as a hands-on demonstration during lecture.

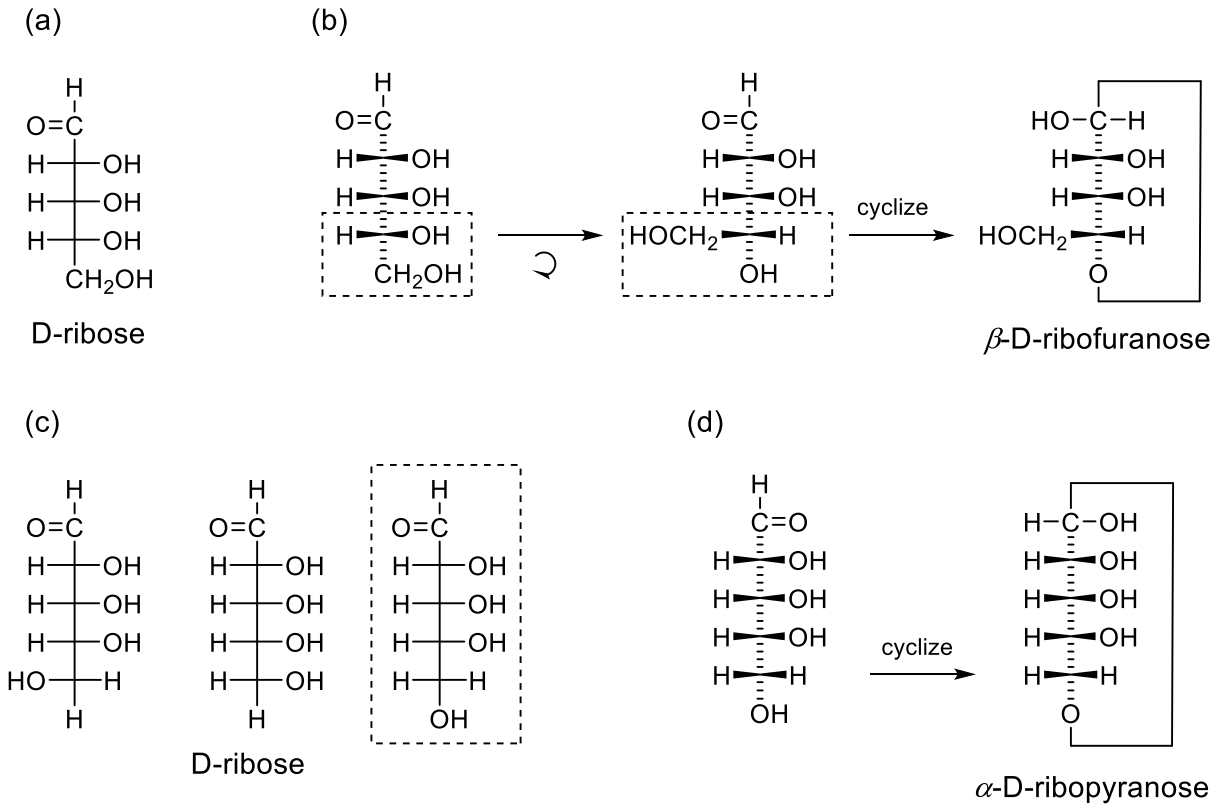


Figure 3. Cyclization of D-ribose from its linear structure into its cyclic furanose and pyranose forms. (a) D-ribose as a Fischer projection. (b) The process of cyclizing D-ribose into a furanose begins with a rotation of the three substituent groups on the C4 highlighted by the dashed box clockwise to arrive at the second structure with the OH group pointing down. (c) and (d) show the cyclization of D-ribose into a pyranose. Using the third structure (highlighted by the dashed box) in (c), the ring closing is visualized in the same way as in (b), but to arrive at the α anomeric form, the carbonyl oxygen is drawn in (d) pointing to the right. The three equivalent structures in (c) show the geometry of the last C5 carbon on the backbone. The one on the right with the dashed box around it positions the OH to point down to facilitate cyclization.

The Fischer projection of D-ribose is shown in Figure 3(a). The specific stereo geometries of all the chiral carbons are shown explicitly in Figure 3(b). The final cyclized structure of D-ribofuranose is shown on the far right of Figure 3(b). To form this ring, the O atom on C4 must make a new bond with C1 indicated by the solid line from the bottom of the structure looping back to the top. This structure is the starting point for ring cyclization. To construct the paper model, this structure is first reproduced onto an index card as shown in Figure 4. To prepare it for cyclization, two necessary modifications must be made, as indicated on the leftmost frame of Figure 4: (1) the H atom from the OH group on C_4 must be removed and transferred to the O on C1, and (2) a white bond has been added below the O on C_4 to indicate where the new O-C1 bond will be inserted when the cycle closes to make the hemiacetal. (Notice in Figure 4 that the new OH group on C1 has been put on the left, and when this structure is cyclized it will result in the β anomeric form. If the new OH group on C1 has

been put on the right, the cyclized structure will emerge in the α anomeric form. This will be discussed below.)

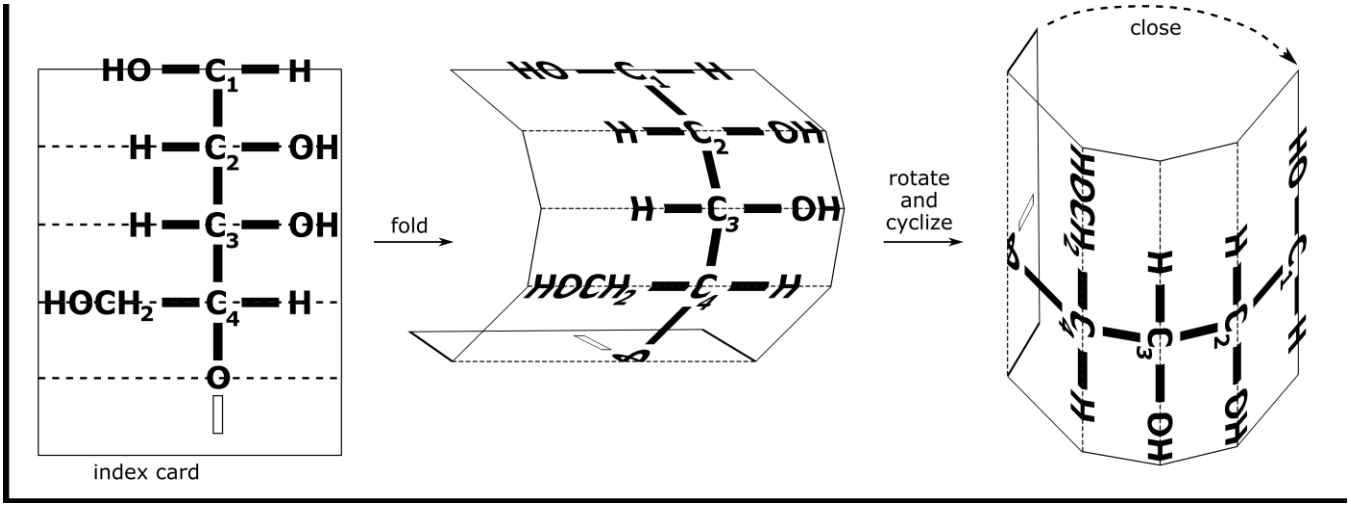


Figure 4. The paper model used to visualize the cyclization of D-ribose into β-D-ribofuranose. (See text for details.)

Folding the Fischer projection on the left in Figure 4 to produce a closed ring makes use of the central fact demonstrated by Figure 1(b) and Figure 2 that, in the Fischer projection, the top and bottom bonds emanating from each chiral carbon are already pointing into the back. As such, the Fischer projection implies a 3-D geometry for the chain that is already close to a cyclized form. The paper model illustrates this point more clearly. Folding the index card in Figure 4 along the indicated dashed lines then turns it into the object shown in the center of Figure 4. Rotating it as in the object on the far right of Figure 4 positions the carbohydrate backbone horizontally. When this structure is finally cyclized to synthesize the new (white) bond between O and C1, it will close into the structure shown by the Haworth projection in Figure 5(a). What is above the plane of the ring on the index card in Figure 4 (H on C2, H on C3, $HOCH_2$ on C4) will also appear above the plane in the Haworth projection, and what is below the plane of the ring on the index card in Figure 4 (OH on C2, OH on C3, H on C4) will also appear below the plane in the Haworth projection. If the rotation indicated in Figure 4 had been carried out in the other direction, the resulting absolute structure would have been identical, except turned upside down. In Figure 4, the ring has been closed into the β anomeric form, corresponding to the Haworth projection in Figure 5(a). If the H atom had been placed on C1 on the left side of the Fischer projection in Figure 4, it would have generated the alternate α anomeric form.

This paper model therefore very straightforwardly confirms which groups should end up above the ring in the Haworth projection and which groups should be below.

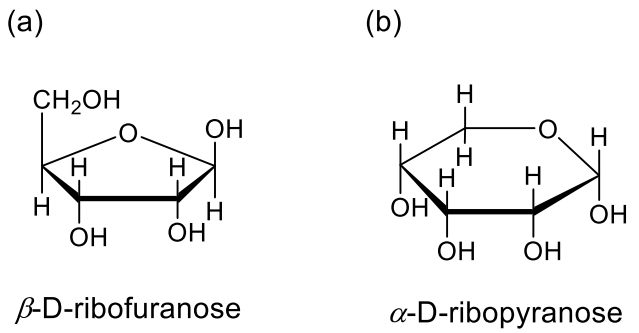


Figure 5. (a) Final Haworth projection of β-D-ribofuranose obtained by closing the ring using the paper model in Figure 4. (b) Haworth projection of α-D-ribopyranose.

Ribose can be cyclized into both a furanose and a pyranose. The ring-cyclized form of α-D-ribopyranose is shown in Figure 5(b). A paper model can also be easily used to illustrate its cyclization as well. Starting with the linear ribose in Figure 3(c), the linear structure is prepared for closure by the following process: (1) though the last carbon (C5) is achiral, it is drawn in its Fischer projection – the three structures in Figure 3(c) are all equivalent, (2) the structure on the far right of Figure 3(c), highlighted by the dashed box, is selected for cyclization, because it has the OH needed to close the ring pointing down, and (3) the ring is cyclized by forming an ether with the O on C5 now bonded also to C1; the new O-C1 bond is obvious in the right-hand structural formula in Figure 3(d). The corresponding paper model can easily be constructed following a procedure similar to that outlined for the furanose in Figure 4. The paper model will show clearly that the groups that are above the ring on the folded index card (H on C2, C3 and C4) should be above the ring in the Haworth projection, while those below the ring on the folded index card (OH on C2, C3 and C4) should be below the ring in the Haworth projection. The final cyclized structure for α-D-ribopyranose is shown in Figure 5(b).

One final point is that in the α-D-ribopyranose form (Figure 5(b)), the anomeric OH group is below the plane of the ring. There is often confusion about which one is the α anomeric form and which one is the β anomer. If the exocyclic CH_2OH group is used as the reference, the anomeric form in Figure 5(a), for example, can be rationalized as being the β form because the anomeric -OH on C1 is on the *same* side as the CH_2OH group on C4. However, this is not always the case, as in the example of α-D-

ribopyranose in Figure 5(b), which, having *no* exocyclic -CH_2OH group, is designated the α anomeric form.

OUTCOMES

Outcomes have been measured in two ways. First, the majority of students reported that, by using the paper model described in the paper, they were able to cyclize sugars easily, in contrast, before the model was implemented in this biochemistry course, many students reported having trouble with this subject even up to the very end of the semester. Questions students asked about ring cyclization of sugars during office hours were also far fewer than before this activity was introduced. Secondly, performance on test questions related to this subject was monitored before and after the implementation of this activity in the course. Prior to implementation, students scored approximately 50% on these questions. After implementation, students scored higher than 90% on similar questions. Improvement in outcomes in this content area was quite clear and far above what statistical variations alone could account for. (For this assessment, two semesters of data were available with a total sample size of approximately 150 students prior to implementation, and two semesters of data were also available with a similar sample size after implementation.)

ASSOCIATED CONTENT

Supporting Information

Details of implementation-and additional notes for instructors are provided in Supporting Information.

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ACKNOWLEDGMENTS

This material is based in part upon work supported by the National Science Foundation under Grant Number CHE-1664801.

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