7 Steroids and sugars

Purpose

In this chapter you widen your scope on stereochemistry from that of relatively simple compounds to that of more complex and naturally occurring compounds. One stereochemically intriguing system is the conformational analysis of compounds with fused cyclohexane rings. You have already learned decalin as an example. Your final goal along this line will be steroids.

Another interesting system is the ring system, glucopyranose, formed by the ring closure of glucose. You will learn that there are two configurational isomers for glucopyranose, and that the structure and properties of disaccharides and polysaccharides are determined by the configuration of the monomer glucopyranose.

New terms and concepts

exo isomer
endo isomer
α and β bonds of steroids
α and β bonds of sugars
anomer
glycoside bond

Goals of this chapter

After you master this chapter successfully, you will be able to do the following:

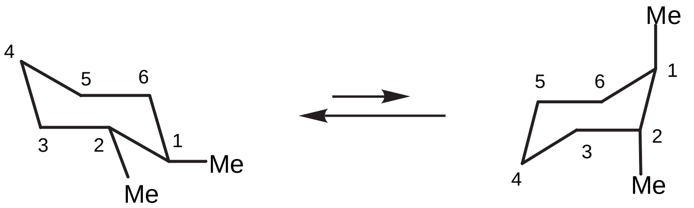
1. to understand that disubstituted cyclohexanes are involved not only in conformational problems (*e.g.*, ring inversion) but also in configurational problems. In other words, some compounds may have enantiomers.
2. to predict the number of stereoisomers of fused cyclohexanes, and to understand that there are two series, the 5α-androstane series and the 5β-androstane series in steroids.
3. to confirm that there are two configurational isomers, an α anomer and β anomer, for the glucopyranose formed by the ring closure of D-glucose.
4. to understand the difference in the structures of disaccharides and polysaccharides formed by the condensation of α isomers and these formed by the condensation of β isomers.

7.1 Configuration of substituted cyclohexanes and condensed cycloalkanes

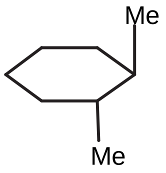
Dimethylcyclohexane

There are two stereoisomers for 1,2-dimethylcyclohexane; one is the *trans* isomer **1** in which two methyl groups are *trans*, and the other is the *cis* isomer **2** in which two methyl groups are *cis*.

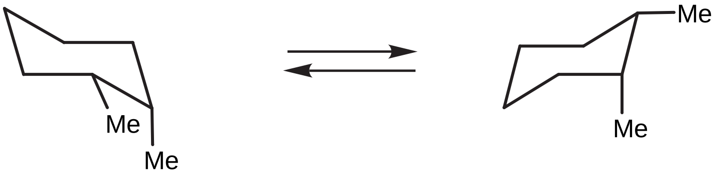
There are two *trans* isomers **1**aa and **1**ee and these isomers are convertible by ring inversion. Similarly, there are two *cis* isomers **2**ea and **2**ae and these are convertible by ring inversion. Hence these are conformers. The stereochemical relation between **1**aa and **1**ee is discussed in Q7.1.



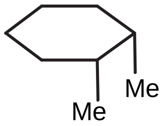
1ee **1**aa



trans-**1**



2ea **2**ae



cis-**2**

Q7.1

The carbon atoms C1 and C2 of **1**, to each which a methyl group is bonded, are asymmetric. Determine the configuration of C1 and C2 of **1**. Try the same for **2**.□

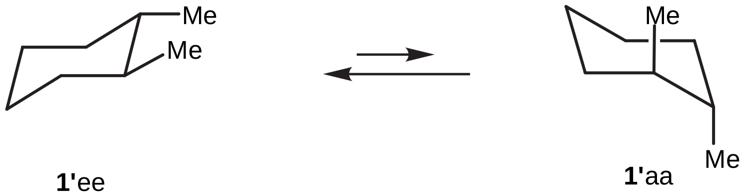
Q7.2

Can you say that **1** and **2** are optically active based on the information obtained from Q7.1?□

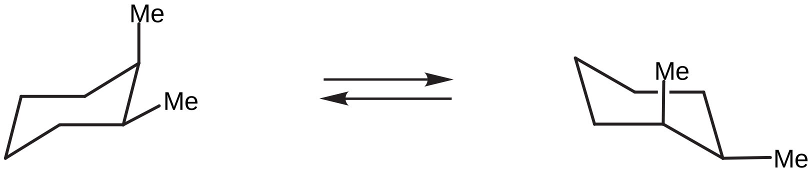
A7.1

1: C1 *R*, C2 *R*. **2**: C1 *S*, C2 *R*. The priority is as follows: $CHCH_3 > CH_2CH_2 > CH_3 > H$. The second group of atoms of the first three ligands are CCH > CHH > HHH. It is important to remember that the ring inversion does not affect the configuration.□

A7.2



1'ee **1'**aa



2'ea **2'**ae

□

1 is optically active. **1** and its enantiomer (*S*, *S*) should exist in a 1:1 ratio. Hence 1,2-dimethylcyclohexane exists as a racemate. However, **2** is a *meso* compound since **2**ea≡**2**'ae, **2**ae≡ **2**'ea. The planar drawing of **2** in the previous page seems to indicate the presence of a plane of symmetry.

Q7.3

Make a table which shows the stereochemical relation among conformers of **1** and **2**. You can find an example of this kind of table in A6.3. You may omit **2**'ea and **2**'ae from the table for simplicity's sake.□

It will be very instructive if you try the same exercise with 1,3- and 1,4-dimethylcyclohexanes.

A7.3

1ee and **1**ae are stereoisomers but not enantiomers. Thus, these two are diastereomers. The stereochemical relation among these isomers are tabulated.

	1ee	**1**aa	**1**’ee	**1**’aa	**2**ea	**2**ae
1ee	-	D	E	D	D	D
1aa	D	-	D	E	D	D
1’ee	E	D	-	D	D	D
1’aa	D	E	D	-	D	D
2ea	D	D	D	D	-	E
2ae	D	D	D	D	E	-

E; enatiomer; D; diastereomer

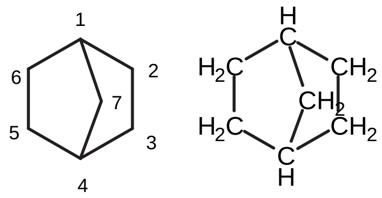
☐

Fused cycloalkanes

Naphthalene is made of two fused benzene rings that share one edge. In nature, there exist many organic compounds in which such cycloalkanes as cyclopentanes or cyclohexanes are fused. Conformation of such fused cycloalkanes is sometimes different from that of monocyclic compounds.

Q7.4

3 is the perspective view of norbornane, written in two ways, which forms the skeleton of important compounds such as camphor or borneol. Identify and describe the structure of cyclohexane unit in **3**.

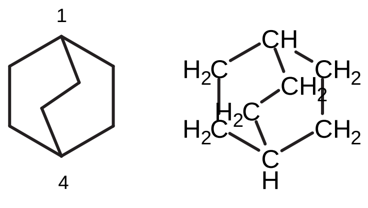


3

☐

Q7.5

Identify and describe the structure of the cyclohexane unit in bicyclo[2.2.2[octane **5**.

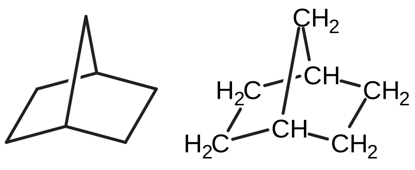


5

☐

A7.4

Boat form. If the cyclohexane ring assumes a chair, the distance between C1 and C4 is too far to make a bridge between C1 and C4. The perspective view **4** of norbornane will show you more clearly the boat form of the cyclohexane ring.



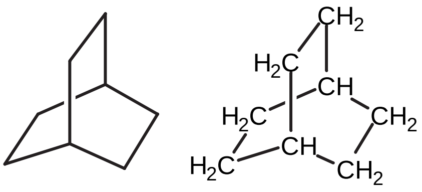
4

Q7.6

Describe the stereochemistry of the norbornane derivative(s) obtained by substituting for one of the hydrogen atoms bonded to C2.□

A7.5

Boat form. The situation is the same with norbornane. The perspective view of **5** is given as **6**.

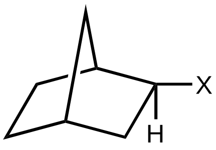


6

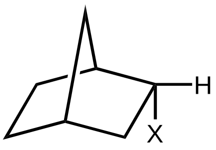
□

A7.6

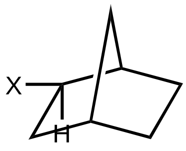
In the case of the fused system, ring inversion is sometimes impossible because the ring is fixed. Two hydrogen atoms bonded to C2 are also fixed; one in the ***exo*** (outer) position and the other the ***endo*** (inner) position. Hence there are two isomers; *exo* isomer *exo*-**7** and *endo* isomer *endo*-**7**.



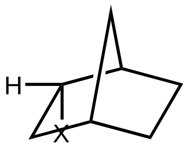
exo-**7**



endo-**7**



exo-**8**



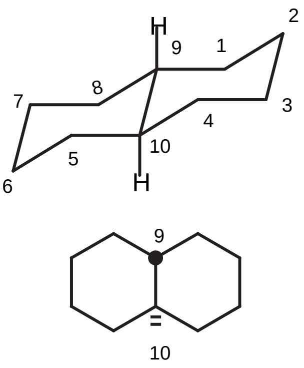
endo-**8**

Though the pair *exo*-**7** and *endo*-**7** are stereoisomers, these are not enantiomers. Their enantiomers are *exo*-**8** and *endo*-**8**, respectively.□

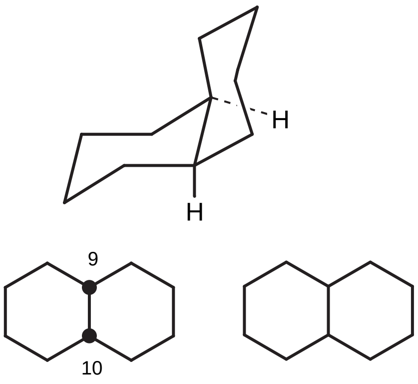
Decalins

We have learned in Ch. 6 that there are two stereoisomers, *trans*-decalin **9** and *cis*-decalin **10** for decalin, and **9** is fixed while **10** is flexible. A ring inversion is possible for **10**.

There is a convention in the field of natural product chemistry to differentiate *trans* and *cis* junction. When two cycloalkanes are fused, the stereochemistry of the fused part (*i.e.*, *trans* or *cis*) is designated as ●—• or ●—● (or •—•), respectively, as shown below in the structural formula.



9



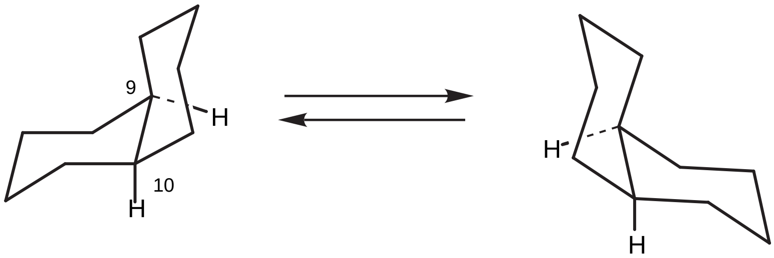
10

Q7.7

Are **9** and **10** optically active?□

A7.7

9 is inactive since there is a center of symmetry at the middle of C9-C10 bond. **10** is chiral.



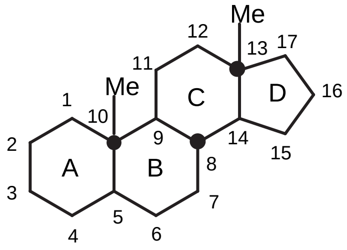
10a **10**b

☐

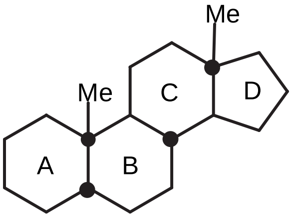
The configuration of C9 and C10 in **10**a is *S* for both, but that in **10**b is *R* for both. Thus, both **10**a and **10**b are optically active. Since the equilibrium **10**a $\rightleftarrows$ **10**b is exactly 1:1, **10** exists as a racemate. The barrier for the equilibrium is expected ro be very low, and resolution of the racemate must be impossible. Of the two structurally identical but conformationally different ligands, the axial one has higher priority than the equatorial one.

7.2 Steroids

Steroids form a very important class of naturally occurring organic compounds. Steroids include sex hormones and adrenal cortical hormones (cortison is one example), cardiac glycosides, and bile acids. Because of their very important physiological activity and because of the very challenging complexity of their structure and reactions, the study of steroids has been and is even now, one of the most attracting areas of organic chemistry. Many Nobel laureates were engaged in the chemistry of steroids.



11



12

The skeleton of steroids consists in three fused cyclohexane rings and one cyclopentane ring. Each of the four rings is given an alphabet; the cyclohexane ring at the left edge is A and the cyclopentane ring at the right edge is D.

There are two types for the skeletons of steroids, **11** and **12**. For both compounds, the stereochemistry of B-C ring fusion and C-D ring fusion is *trans* but that of the A-B ring is *trans* for **11** and *cis* for **12**. Most steroids have a methyl group at C10 and C13 as shown in the plane structure above. **11** and **12** are called 5α-androstane and 5β-androstane, respectively. The prefix 5α or 5β indicates the stereochemistry of A-B ring fusion.

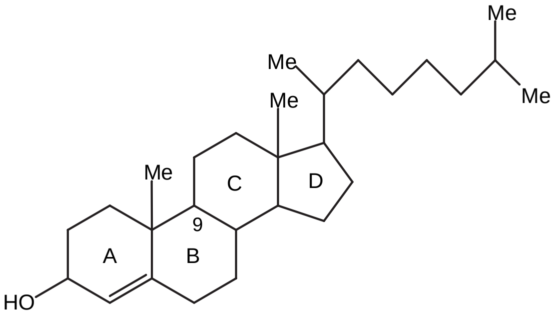
Q7.8

Draw the perspective view of **11** and **12**.☐

Their perspective views will clearly show the difference.

Q7.9

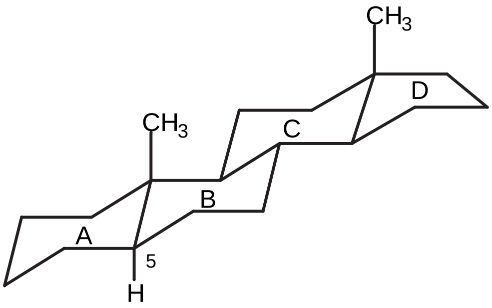
The plane drawing of cholesterol **13** is given below. Draw its perspective view and if possible build the molecular model of it.

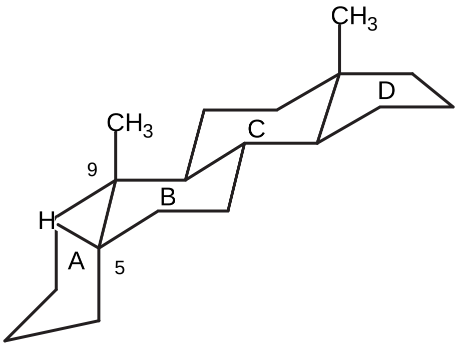


13

☐

A7.8





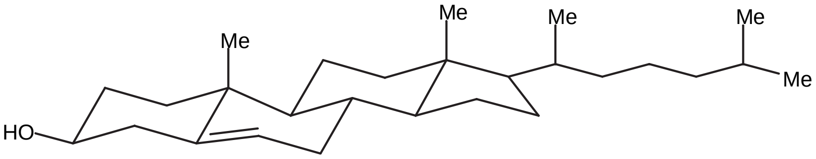
11

12

☐

Cholesterol is very notorious as the substance deposited on the walls of arteries and as the chief constituent of gallstones. Hypercholesterolemia is one of the representative adult diseases.

A7.9



13 cholesterol

☐

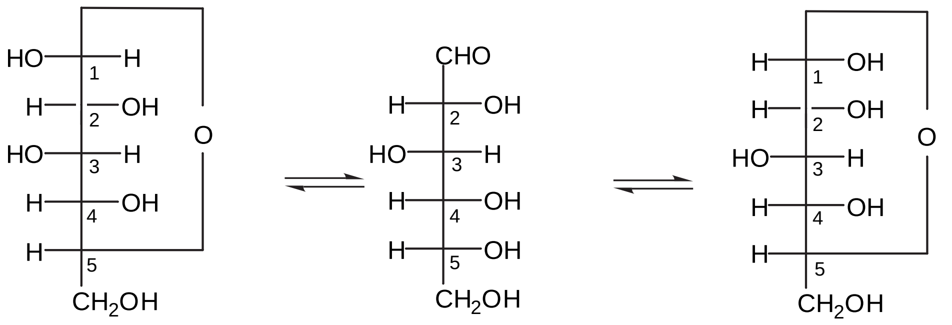
Because the C4-C5 bond of cholesterol is a double bond, there is no stereochemical problem concerning the A-B fusion

7.3 Sugars

Glucopyranose and glucofuranose

When glucose, a representative monosaccharide, is dissolved in water, its specific rotation $[\alpha]^{20}_{D}$ is +111°, but it gradually changes to +52.5° and stabilizes. This phenomenon is called the **mutarotation**.

A change of rotation should be accompanied by some structural change. This structural change is explained in terms of equilibrium between two cyclic structures α-D-glucose (α-D-glucopyranose) **14** and β-D-glucose (β-D-glucopyranose) **15** *via* acyclic glucose **16**.



β-D(+)-glucose **14**
(glucopyranose)

D(+)-glucose **16**

α-D(+)-glucose **15**
(glucopyranose)

When dissolved, glucose existed as cyclic α-D-glucose **14**. In aqueous solution, a ring opening of **14** takes place to yield acyclic intermediate **16**. When a ring closure of **16** takes place, both **14** and **15** are formed. Since the specific rotation of **15** is different from that of **14**, the specific rotation of the solution is necessarily different from that of **14**. You will learn the structures of **14** and **15**, and the significance of α and β isomerism later.

Q7.10

The specific rotation of α-D-glucose **14** is $[\alpha]^{20}_{D}$ = +111° and that of β-D-glucose **15** is $[\alpha]^{20}_{D}$ = +19.2°. When the aqueous solution reaches the equilibrium, the rotation is +52.5°. Calculate the populations of the two isomers.□

Q7.11

D(+)-Glucose **16** has four asymmetric carbon atoms (C2, C3, C4 and C5). How many asymmetric carbon atoms are there in **14** and **15**?□

A7.10

α-isomer 36%, β-isomer 64%. If the proportion of α-isomer is x, then $111x + 19.2(1 - x) = 52.5$, $\therefore x = 0.36$.□

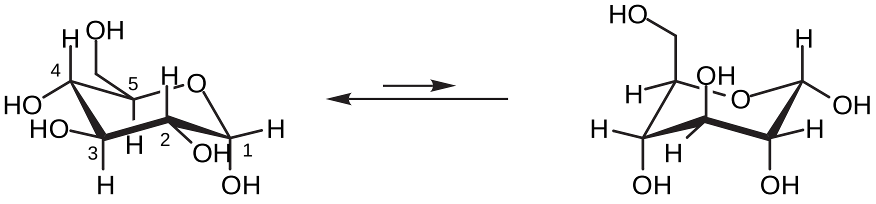
Q7.12

It is known that glucopyranose (six-membered) ring assumes a cyclohexane-like structure and its stable form is a chair. Draw the perspective views of **14** and **15**. Draw also the isomers of **14** and **15** obtained by ring inversion.□

A7.11

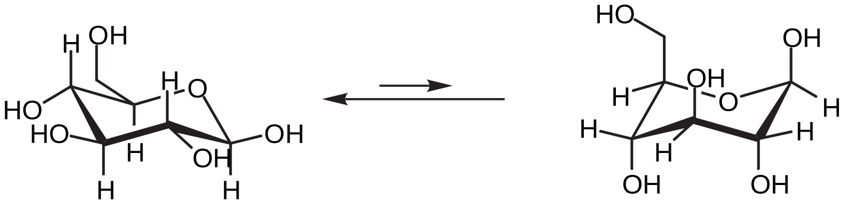
Five for both **14** and **15**. Note that C1 is now asymmetric.□

A7.12



α-D(+)-glucose **14**

14'



β-D(+)-glucose **15**

15'

□

It is interesting to know the reason why mutarotation takes place. C1 of **16** is in the sp^2 hybridized state. By ring closure, a new bond is formed between C1 and the hydroxy oxygen bonded to C5. The oxygen can approach C1from topside or bottom side of the sp^2 plane to give α and β isomers.

You should notice that both **14** and **15** are much more stable than their conformers **14**’ and **15**’ because in **14** and **15**, all ligands (on C2, C3 C4 and C5) are equatorial, except the hydroxy group bonded to C1.

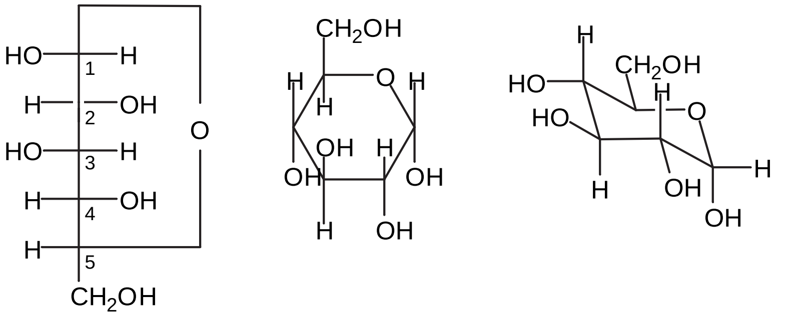
Furthermore, cyclohexane-like structure of glucose clearly shows the difference between α and β isomer. In glucopyranose, the newly formed asymmetric carbon atom C1 is called the **anomeric** position, and isomers due to the difference in the stereochemistry of the anomeric position are called **anomers**. Hence **14** is an α anomer and **15** is a β anomer.

Q7.13

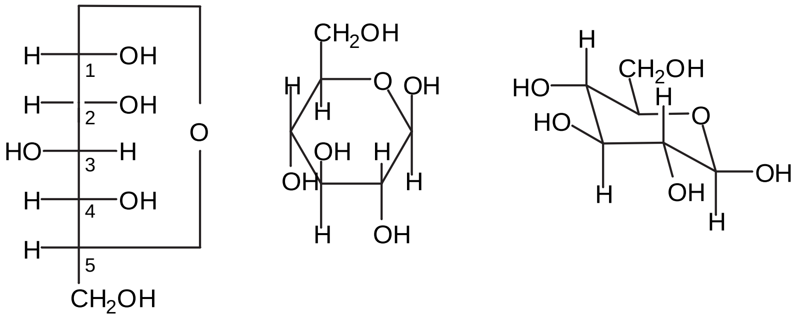
Determine the configuration of C1 of **14** and **15**. Based on this, define their stereochemical relation.□

We have seen two different drawings of glucose. In practice, the 3rd method, plane drawing is also employed, which will be summarized below as S7.1

S7.1 Various drawings of glucose

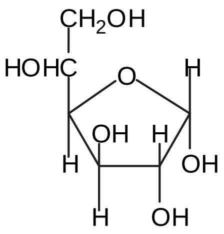


α-D(+)-glucose (glucopyranose) **14**

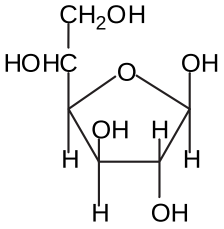


β-D(+)-glucose (glucopyranose) **15**

A six-membered glucopyranose is formed when C1 and the hydroxy group bonded to C5 makes a new bond. It is possible that C1 makes a new bond with the hydroxy group bonded to C4. In that case a five-membered ring, a glucofuranose ring, is formed. Similarly with the glucopyranose system, glucofuraose system also has α and β anomers. Glucofuranose is important as a constituent of sucrose (sugar).



α-D(+)-glucofuranose **16**



β-D(+)-glucofuranose **17**

Disaccharides

Disaccharides are condensation[a)] products of two monosaccharides. The most popular disaccharide is sucrose (sugar) **18;** it is composed of one mole of glucose and one mole of fructose (a furanose). Details of the formation of **18** from glucose and fructose are given in Figure 7.1. The newly formed sugar-O-sugar bond is referred to as the **glycoside bond**.

[a)] a reaction between two compounds to give a compound which contains most of the two compounds and a small molecule like water.

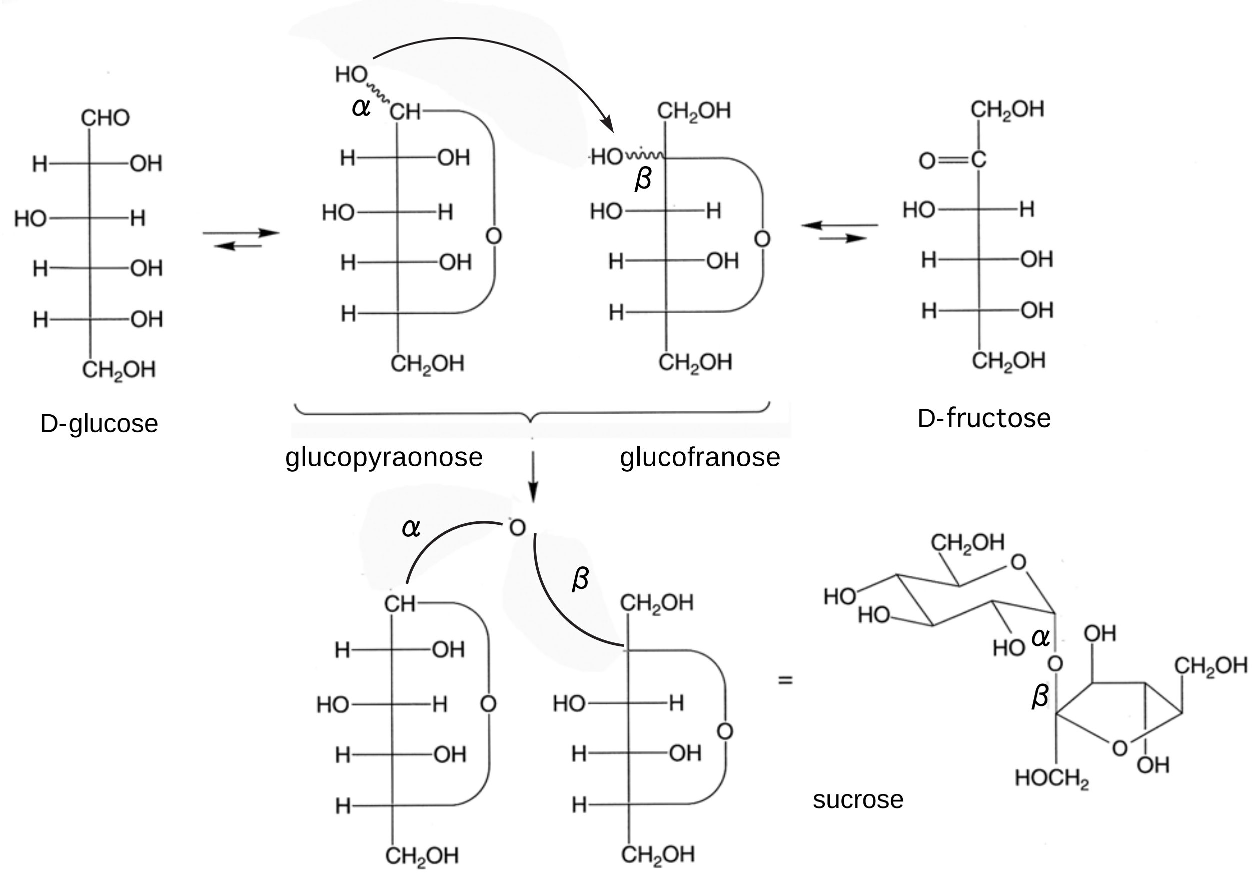


Figure 7.1. Formation of sucrose from glucose and fructose

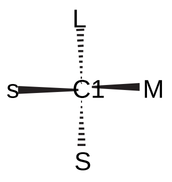
Disaccharides made of two glucose units are also very important. Condensation products of two glucose units may be various since glucose has many hydroxy groups. Most important ones are the condensation between the hydroxy groups on C1 of one molecule of glucose and that on C4 of the other molecule of glucose (1,4-glycoside bond formation).

Q7.14

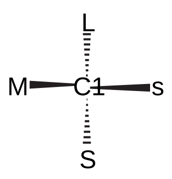
Suppose the hydroxy group on C1 of α-D(+)-glucose reacts with the hydroxy group on C4 of the second α-D(+)-glucose. Draw the perspective view and plane picture of the product.□

A7.13

The priority is as follows. OC5 > OH > C > H. Thus, **14** and **15** are not enantiomer, but diastereomers.



14 (*S*)



15 (*R*)

□

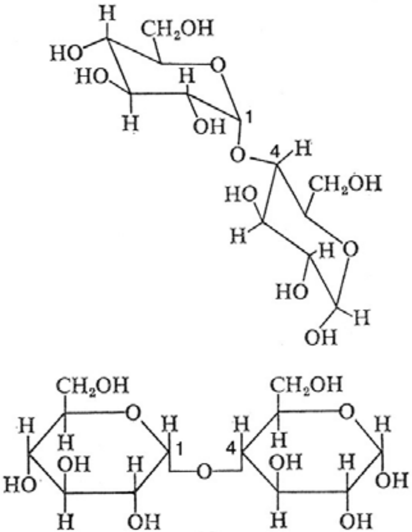
Q7.15

Draw the perspective view and plane picture of the disaccharide cellobiose **20** made of two molecules of β-D(+)-glucose. Make the molecular model of **20** and compare with that of **19**.□

A7.14

The disaccharide thus formed is called maltose **19**. Maltose is contained in malt.

You had better make a molecular model of maltose and keep it to compare with that of cellobiose (Q7.15). You need not make a "perfect" model. If the atoms and bonds (of the model) are not enough to build the target molecule, you can omit hydrogens and hydroxy groups which are not involved in condensation.

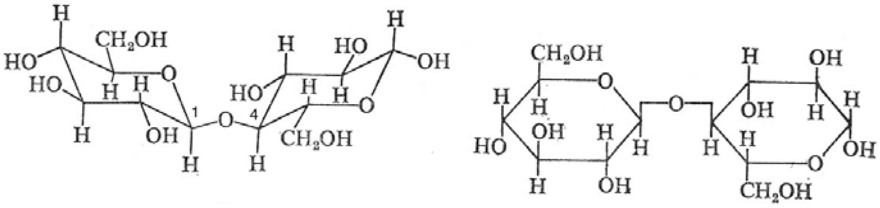


19

☐

A7.15

The crucial point is that in **20**, the hydroxy group on C1 is equatorial.



20

☐

If the condensation of **14** proceeds smoothly in a same fashion (*i.e.* 1,4-glycoside bond formation), finally a polymer, amylose **21**, will be obtained (Fig. 7.2).

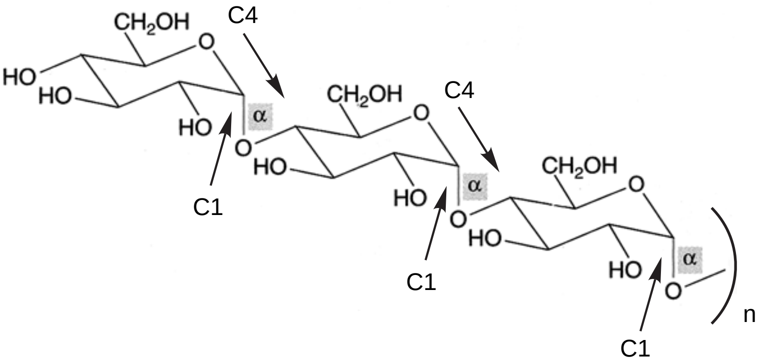


Figure 7.2 Schematic drawing of amylose **21**

Amylose is a main constituent of starch, one of the most familiar and most important organic compounds. If the condensation of **15** proceeds in a similar manner, a polymer will be obtained which is none other than cellulose **22** (Fig. 7.3).

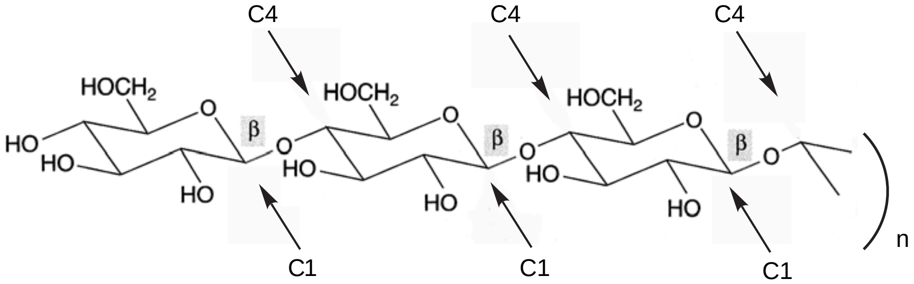
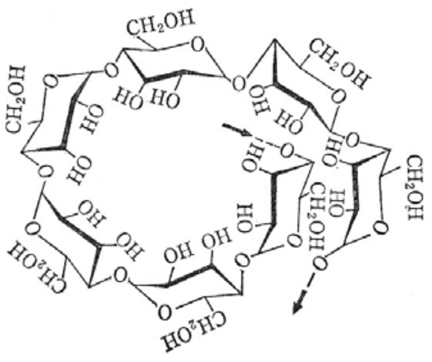
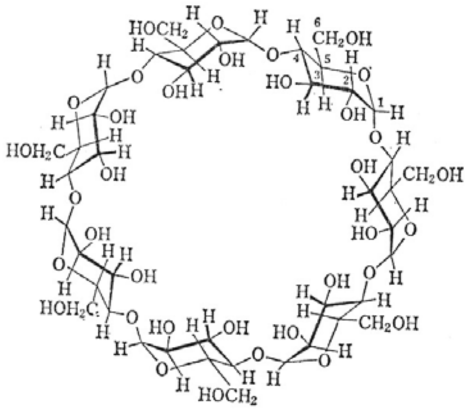


Figure 7.3 Schematic drawing of cellulose **22**

The formation of a circular or spiral from **14** will be more clearly demonstrated in the next figure in which the spiral structure of **21** and the formation of cyclic compound γ-cyclodextrin **23** is shown.



amylose **21**



γ-cyclodextrin **23**