

Chapter 8 Chirality

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Tetrahedral theory of carbon atom was proposed in 1874, independently by Jacobus Henricus van't Hoff (1852-1911) and Joseph Achille Le Bel (1847-1930). The theory describes, in short, that methane is tetrahedral. According to this theory, the carbon atom in methane is located at the center of a tetrahedron and its four valences are directed to four edges of it. Louis Pasteur (1822-1895) achieved a successful resolution of a tartaric acid salt to cast light on the relation between the molecular structures and their properties. It is said that his finding opened the organic stereochemistry.

In the field of organic stereochemistry, a new field named conformational analysis was born that handles with the change of structure accompanied by the rotation about the single bond.

Stereochemistry is a study of three-dimensional arrangement of atoms in space, and is most important part of organic structure. One can say that the development of organic chemistry kept pace with that of organic stereochemistry. Organic stereochemistry is important not only as a means to understand properties, function and reactions, but also for the synthesis of organic compounds.

8.1 Stereochemistry of asymmetric carbon atom

(a) Asymmetric carbon atom

(1) Tetrahedral structure of carbon atoms

Two methane derivatives, bromochlorofluoromethane CHBrClF (A) and bromochlorofluoroiodomethane CBrClFI (B), substituted by different atoms are structurally interesting compounds. The carbon atoms of these compounds are **asymmetric carbon atoms** to which four different atoms or groups of atoms are bonded. Hence, they have a pair of mirror-image isomer (**enantiomer**) as is shown in Figure 8.1. The three-dimensional structure of these molecules can be represented by the perspective view. In a perspective view, all in-plane bonds are represented by solid lines, and bonds directed upwards, and those directed downwards are represented by solid wedges and wedges made of broken lines, respectively. By this drawing, three-dimensional structure of molecules is reproduced in two-dimensional surface of paper.

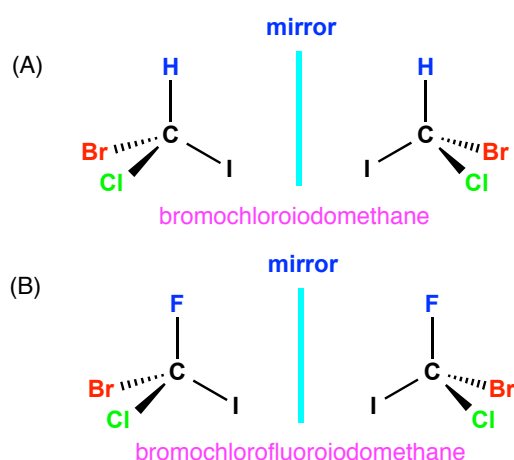


Figure 8.1 A perspective view of compounds with an asymmetric carbon atom.

When a compound and its mirror image are not superposable, the two form a pair of isomers named **enantiomers** (or enantio isomers; enantio means “reverse” in Greek). The relation between a pair of enantiomers is exemplified by the relation between right- and left- hands. The pairs have the same physical properties such as melting points, and the same chemical properties such as the acidity, and hence cannot be differentiated by conventional chemical methods but can be differentiated by the optical property.

Point: Asymmetric carbon atom

- (1) A carbon atom to which four different atoms or group of atoms are bonded is named an asymmetric carbon atom.
- (2) Compounds containing asymmetric carbon atoms form in most cases a pair of enantiomers.

(2) Optical activity

Light is polarized (the light vibrating in one particular plane) if it passes through a polaroid. The second polaroid will, if placed parallel to the first one, allow the polarized light to pass through it. When, however, the second polaroid is placed perpendicular to the first one, the polarized light is prohibited to travel (Figure 8.2).

Crystals or solutions of some compounds rotate the plane of polarized light to some extent. This

property is named **optical activity** and substances with this property are named **optically active substances**. Optically active substances form a pair of enantiomers. Historically pairs of enantiomers are named **optical isomers**. One of the well-known enantiomers is a pair of lactic acid.

The magnitude of rotation of the polarized plane depends not only the type of compounds but also the condition of measurements. The angle of rotation of the solution (1 g/1mL in a specific solvent) of a sample in a cell of 10 cm (1 dm) length at specific temperature with a light of specific wavelength is defined as **specific rotation** $[\alpha]_{\lambda}^t$ where t is the temperature at the measurement, λ represents the wavelength or type of the light employed. In most cases the D line of sodium is employed and hence in such cases D is used instead of λ

$$[\alpha]_{\lambda}^t = \frac{\text{experimental value of rotation } (^{\circ})}{\text{length of the sample (dm) x concentration (g ml}^{-1}\text{)}}$$

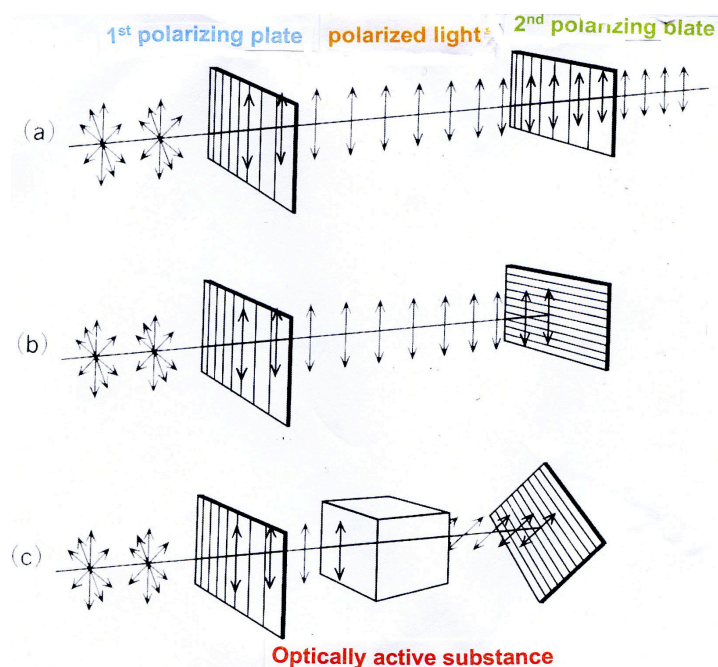


Figure 8.2 Polarized light and polaroid.

- (a), (b) The relation between the direction of polaroid and polarized light.
 (c) rotation of the plane of polarized light by optically active substance.

If one of the enantiomers rotates the plane of polarized light clockwise, this property is named **dextrorotatory**, and designated as (+). That of another enantiomer is **levorotatory**, with the symbol (-), meaning that the plane is rotated anticlockwise. Under the same condition a pair of enantiomers exhibits the same angle of rotation. As is indicated in Figure 8.3, the dextrorotatory lactic acid is named (+)-lactic acid, and the levorotatory one (-)-lactic acid.

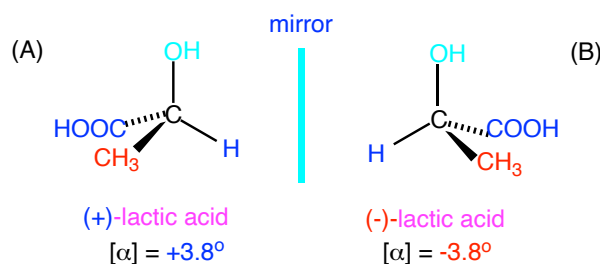


Figure 8.3 Enantiomeric pair of lactic acid.

Point: Optical activity

optically active substances: substances, as crystals or as solutions, rotate the plane of polarized light.

dextrorotatory: property to rotate the plane of polarized light clockwise (to the right); designated as (+)

levorotatory: property to rotate the plane of polarized light anticlockwise (to the left); designated as (-)

(b) Chirality

As will be discussed later, there are some compounds which are not optically active even though they have asymmetric carbon atoms, and there is another type of compounds which is optically active even though they do not have asymmetric carbon atoms. This means that whether a compound is optically active or inactive should be defined by a more general principle other than presence or absence of asymmetric carbon atoms. The new standard is the concept of “**chirality**”, which is a hand (cheir) in Greek.

A compound which forms a pair of enantiomers is necessarily chiral. It is impossible for a chiral molecule to superpose itself to its mirror image. A chiral molecule should have **a center of chirality**, **an axis of chirality** or **a plane of chirality**. Molecules without them are named achiral. Most popular center of chirality is asymmetric carbon atoms.

Exercise 8.1 Asymmetric carbon atom

If you find an asymmetric carbon atom in compounds shown below, give it an asterisk like C*.

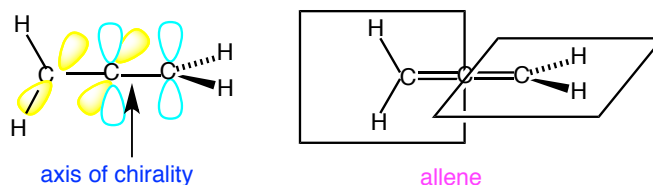
- (a) $\text{CH}_3\text{CHClCOOH}$
- (b) $\text{CH}_2\text{ClCH}_2\text{COOH}$
- (c) $\text{CH}_2\text{ClCHDCOOH}$
- (d) $\text{CH}_2\text{BrCH}_2\text{Cl}$
- (e) CHBrClCH_3

Answer

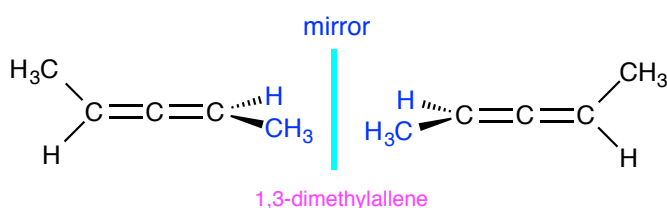
- (a) $\text{CH}_3\text{C}^*\text{HClCOOH}$
- (c) $\text{CH}_2\text{ClC}^*\text{HDCOOH}$
- (e) $\text{C}^*\text{HBrClCH}_3$

Allenes are the simplest of cumulenes with cumulative double bonds. In allene, the central carbon atom is sp hybridized and the two end-carbon atoms are sp^2 hybridized. Consequently, the left-half molecular plane and the right-half one is perpendicular each other. There is no rotation about carbon-

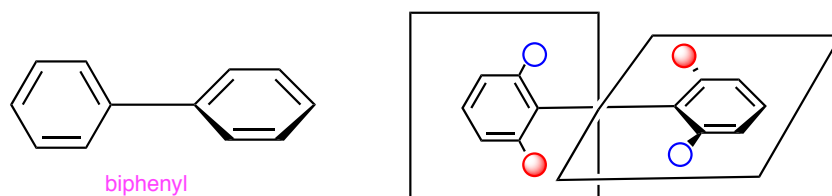
carbon bond since these are double bonds. Thus, the molecular axis of allenes can be an axis of chirality.



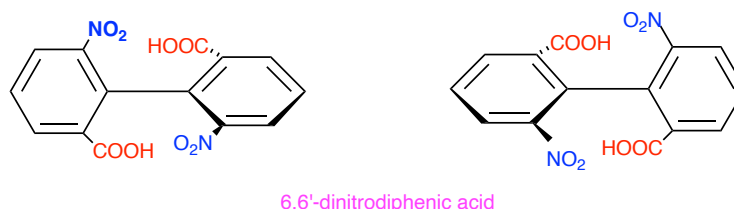
Allenes in which two different atoms or groups of atoms are bonded to the two end-carbon atoms, like 1,3-dimethylallene, have a pair of enantiomers. Though this compound does not have any asymmetric carbon atom, it does have an axis of chirality and hence optically active.



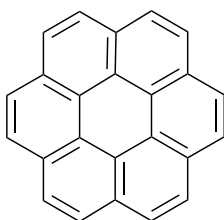
As was described in the previous chapter, two benzene rings of a biphenyl are twisted about 40° , and repulsion among *o*-protons is much too large in the planar structure. If four bulky groups are introduced in four *o*-positions, the rotation about the single bond is prohibited, and two planes each including one benzene ring become orthogonal. Accordingly, this compound has a pair of enantiomers like allenes.



A well-known example is 6,6'-dinitrodiphenic acid, which bears bulky nitro and carboxy groups in two *o*-positions of each benzene ring.

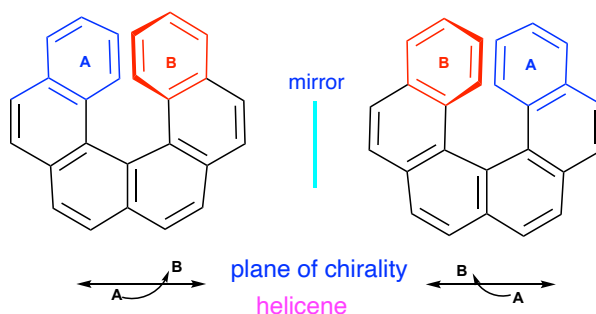


If benzene rings condense by sharing one edge to form a ring, a ring is completed by six benzene rings giving coronene. Coronene is a planar molecule.



coronene

If, however, the first (A) and the last (B) benzene rings are not condensed, there is a repulsion among protons of two rings A and B, two rings are twisted to give helicene. Helicene is a screw molecule; ring A proceed to ring B as a right screw or a left screw. In other words helicene is a chiral molecule to form a pair of enantiomers corresponding to right- and left-screw. In helicene the molecular plane acts as a plane of chirality.



Point: Chirality

type of chirality: center of chirality, axis of chirality, plane of chirality

chiral molecule; a molecule which does not superpose to its own mirror image.

achiral molecule: a molecule that not chiral

8.2 Stereochemical nomenclature

(a) Steric configuration (configuration)

The way of arrangements of atoms or groups of atoms around the center, the axis or the plane of chirality is named **configuration**. In this book, configuration around the center of chirality (in fact, asymmetric carbon atoms) is mainly discussed.

If we can by some means observe molecules directly, we can be sure that (+)-lactic acid has the configuration (A) as depicted in Figure. 8.3, but not (B). In fact, however, such observation was not possible until *ca.* 1950. Then chemists made a hypothesis that (+)-lactic acid has the configuration (A), and based on the results of interchange of optical activity, determined the configuration of other molecules. Configurations determined by this procedure is named **relative configuration**.

Around 1950, Johannes Martin Bijvoet (1892-1980) could obtain results equivalent to direct observations of molecular structure with the aid of abnormal X-ray scattering experiments. Configurations determined by this procedure are named **absolute configuration**. It is possible to visualize the configuration around an asymmetric carbon atom by use of perspective formulas as previously described. It would be even more convenient if the configuration can be represented by a symbol based on some rules and if this symbol can be incorporated into the name of the compound. Rules used to make such a symbol is named **stereochemical nomenclature**. The rule which is used to specify the absolute configuration is **(R)-(S) nomenclature**.

(b) (R)-(S) nomenclature.

(R)-(S) nomenclature is composed of two rules: one is the sequence rule which determines the priority of atoms or groups of atoms bonded to the asymmetric carbon atom, or in general, the center, the axis, and the plane of chirality, and the other which determines the stereochemical relation among these atoms and groups of atoms. The outline of (R)-(S) nomenclature to be used to compounds having asymmetric carbon atoms will be given below.

(1) Sequence rule

The sequence rule is used to determine the priority of four ligands around the asymmetric carbon atom.

Point: Sequence rule**Rule 1**

Priority is determined for four atoms bonded to the asymmetric carbon atoms (if the ligand is an atom, the atom itself; if the ligand is a group of atoms, the atom directly bonded to the asymmetric carbon atom) based on the decreasing order of their atomic number. In this book, the priority is expressed as:

$$L > M > S > s$$

Rule 1 supplement: For the isotopes, the one with larger mass number has higher priority.

Rule 2

When the priority is not determined by Rule 1, the second atoms of each ligand are compared. If priority is not determined by this procedure, the third (and fourth, *etc.*) atoms are to be compared.

Rule 3

When atom X and atom Y are double- or triple-bonded, X must be regarded to bond two (or three) Y in the context of sequence rule.

Let us apply the rule to alkyl halides treated in Ch. 8.1. In the case of bromochloriodomethane, the priority is $I > Br > Cl > H$. For bromochlorofluoriodomethane, the priority is $I > Br > Cl > F$.

As a little more complex example, the priority of lactic acid will be determined. It has four ligands, H, CH₃, COOH and OH.

[step 1] From rule 1, the one with the highest priority is O, and the one with lowest priority is H. Thus, $L = O$ and $s = H$.

[step 2] For two ligands (CH₃, COOH) the priority of which is not determined yet. Hence, rule 2 should be applied. The priority of the second atoms is compared. For CH₃, these are (H, H, H).

[step 3] Rule 3 is to be applied for the second atom of COOH. Three oxygen atoms are bonded to the second carbon atom (O, O, O). Thus, COOH (M) > CH₃(S).

[step 4] Thus, the priority is determined as $OH > COOH > CH_3 > H$.

Point: Determination of the priority of ligands of lactic acid

[step 1] OH(L), COOH, CH₃, H(s)

[step 2] OH(L), C(O,O,OH), C(H,H,H), H(s)

[step 3] OH(L) > COOH(M) > CH₃(S) > H(s)

(2) Determination of configuration

The procedure to determine the configuration ((*R*) or (*S*)) of an asymmetric carbon atom is as follows:

[step 1] The priority of four ligands bonded to the asymmetric carbon atom (hereafter C*) (previous section)

[step 2] You observe the molecule from the direction along the C*-s bond from the side of C* (see Figure 8.4)

[step 3] Look L, M and S in this order. If your eyes move anticlockwise as is shown in Figure 8.4(A), the configuration is defined as (*S*) configuration. If your eyes move clockwise as is shown in Figure 8.4 (B), the configuration is defined as (*R*) configuration.

The advantage of this nomenclature is obvious. As long as the sequence rule is correctly applied, there should be no ambiguity in determining the configuration.

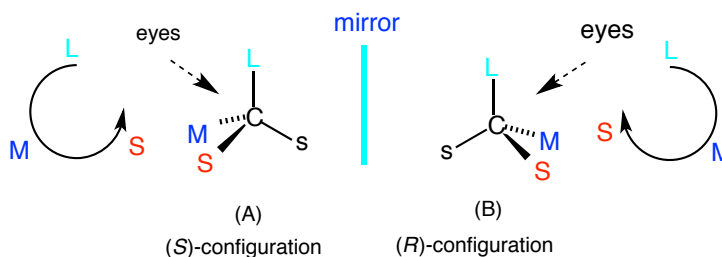
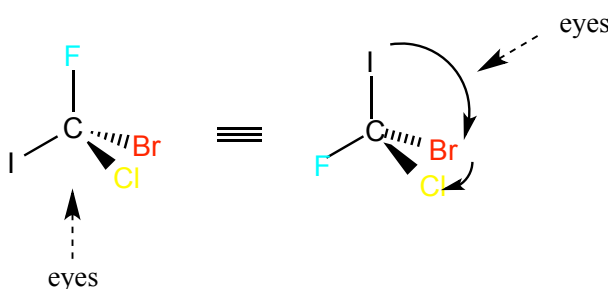


Figure 8.4 Determination of (*R*)-(*S*) configuration

Let us determine the configuration of one of the enantiomer of bromochlorofluoroiodomethane (Figure 8.1 (B)).



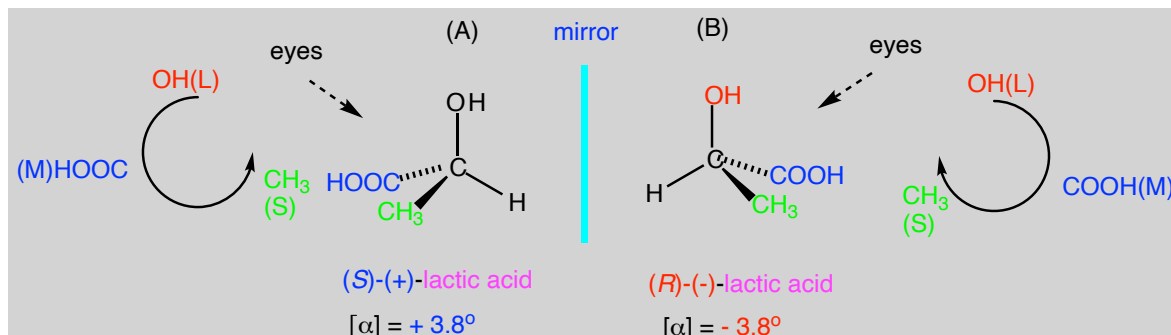
The priority is $I > Br > Cl$, and your eyes move anticlockwise. Thus, this enantiomer has (*S*) configuration.

Exercise 8.2 Determination of configuration

Determine the configuration of the enantiomeric pair of lactic acid shown in Figure 8.3.

Answer

(+)-lactic acid has (*S*) configuration and (-)-lactic acid has (*R*) configuration



You must notice that there is no relation between the sign of rotation (+ or -) and the configuration (*R* or *S*). There are dextrorotatory compounds with (*S*) configuration, and similarly, there are levorotatory compounds with (*R*) configuration.

Point: Determination of configuration

[step 1] Determine the priority of four ligands; $L > M > S > s$.

[step 2] Hold the C—s bond of the molecular model of the compound CLMSs so that you will face LMS plane.

[step 3] If your eyes move clockwise when you look at L, M and S in this order, the compound has (*R*) configuration. If anticlockwise, it has (*S*) configuration.

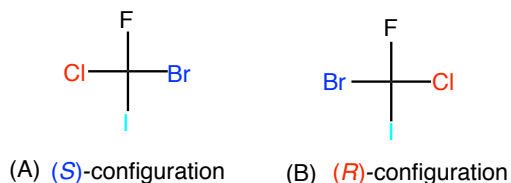
Both (*R*) lactic acid and (*S*) lactic acid are optically active, but a mixture of equal amounts of this enantiomeric pair has no optical activity. Though individual molecules are active, this activity is cancelled in the mixture. A mixture of equal amounts of enantiomers is named a **racemate**.

(c) Fischer projection formula

Hermann Emil Fischer (1852-1919) investigated sugars from the end of the 19th century to the beginning of the 20th century, and proved by experiments the tetrahedral theory of carbon compounds. During this investigation, Fischer and his coworkers devised a convenient method to express three dimensional structures in two dimensions. This drawing is named Fischer projection (formula). In this method, the asymmetric carbon atom and four bonds from it is represented by + (the carbon atom at the center) sign where the horizontal lines represent bonds towards upward from the plane of the paper, and the vertical lines represents bonds towards downward from the plane. The former corresponds to wedges while the latter to broken lines in the perspective view.



Fischer projections of the enantiomeric pair of bromochlorofluoriodomethane is shown below.



You must notice that there are other ways of drawing Fischer projection. If you look at the molecule from a different angle, you can draw a different Fischer projection. There is more than one Fischer projection for one enantiomeric compound. When you draw a different Fischer projection, you should be careful not to draw that of its other enantiomer. Note that by an exchange of a pair of ligands, the configuration is inverted to give the other enantiomer. By two exchanges, the original configuration is recovered.

In general, an even number of exchanges leads to the original configuration, and by an odd number of exchanges, the other configuration is obtained.

Though you may use any of possible Fischer projection, in the field of sugar and related chemistry, usually the carbon chain is drawn vertically, and a ligand such as carboxy or aldehyde groups which contains carbon atoms in higher oxidation states will be placed at the upper end of the chain.

Exercise 8.3 Fischer projection of lactic acid

By adding a hydroxy group and a hydrogen atom, make (A) to the Fischer projection of (*R*)-lactic acid, and (B) to the Fischer projection of (*S*)-lactic acid.



Answer



Point: Fischer projection

Of the four bonds of the carbon atom written on the surface of paper;

Horizontal bonds are directed upward from the surface of paper.

Vertical bonds are directed downward from the surface of paper.

Even-number exchanges of the position of a pair of two ligands recover the original configuration.

Odd-number exchanges of the position of a pair of two ligands invert the original configuration.

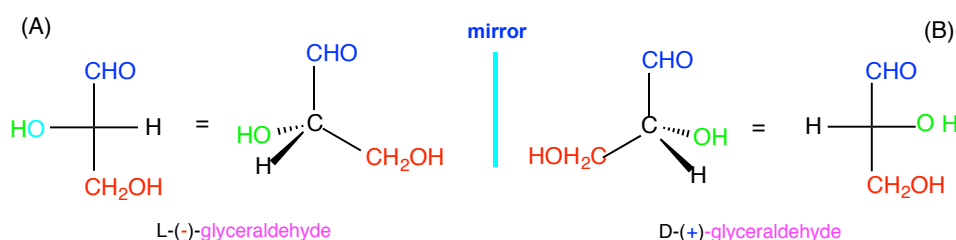
For sugars, the longest carbon chain is drawn vertically, and the ligand which contain the carbon atom with higher oxidation state will be placed at the upper end of the chain.

8.3 Stereochemistry of sugars

(1) Glyceraldehyde

When Fischer and his coworkers were investigating sugars, there was not yet available a means to determine the absolute configuration. Hence, they made a convention to determine the configuration of sugars with the aid of two hypotheses. Configurations determined by this convention is the relative configuration previously described

- (1) Glyceraldehyde (OHCCHOHCH₂OH; 2,3-dihydroxypropanal) is chosen as the standard of configuration.
- (2) It is assumed that (+)-glyceraldehyde has the configuration shown in (B). This configuration is defined as (D)-configuration. The configuration of its enantiomer is defined as (L)-configuration (A).



- (3) Any compound which can be derived from either D- or L-glyceraldehyde without changing configuration has D- or L-configuration.

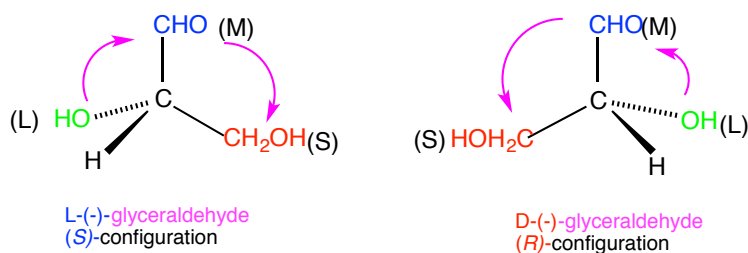
If the hypothesis is wrong, there is some possibility that relative configuration is different from the absolute configuration which is determined by experiments. Fortunately, two configurations agree with each other. Hence the system of relative configuration is not necessary. However, there are many literatures particularly on sugars which were written based on relative configuration. It is necessary to understand at least the relation between D-L nomenclature and (*R*), (*S*)-nomenclature.

Exercise 8.4 From D-L nomenclature to (*R*), (*S*)-nomenclature.

Name D- and L-glyceraldehydes by (*R*), (*S*)-nomenclature.

Answer

It is wise to examine the perspective view carefully. The priority of ligands is: OH > CHO(O, O, H) > CH₂OH (O, H, H) > H. Thus, D- and L-glyceraldehydes are (*R*)- and (*S*)-glyceraldehyde, respectively.

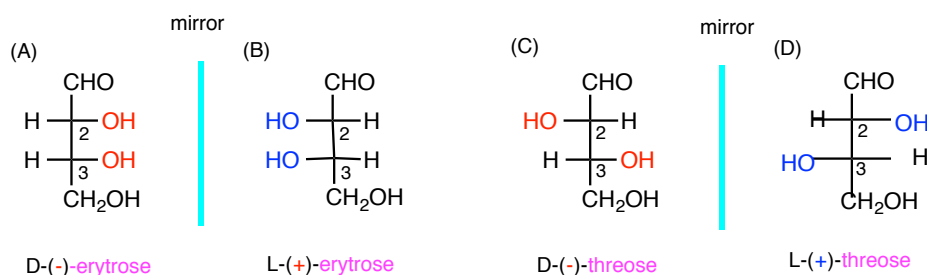


(b) Erythrose and threose

Some organic compounds have two or more than two asymmetric carbon atoms. Sugars with four carbon atoms, $\text{CH}_2\text{OH}(\text{CHOH})_2\text{CHO}$; 2,3,4-trihydroxybutanal) which has one more carbon atom than glyceraldehyde, the standard compound of sugar, is an example with two asymmetric carbon atoms. C^2 and C^3 are asymmetric carbon atoms, and the number of stereoisomers is $2^2 = 4$. Fischer projection of these isomers is shown below. The four isomers can be classified in two pairs of enantiomers, (A) and (B), and (C) and (D).

Trivial names, erythrose and threose, are given to these two pairs.

The relation between (A) and (C) or (A) and (D) is interesting. The same is true for the relation between (B) and (C) or (B) and (D). One of each pair does not superpose with the other member of pair, and hence these two are not identical. These two are not mirror image each other, and then these are not an enantiomeric pair.



A pair of stereoisomers which are not enantiomeric pair is **diastereoisomer** (or simply **diastereomer**) each other. This stereochemical relation is named **diastereoisomerism**. The physical and chemical properties of a pair of diastereomer are different. In this sense, diastereomers are different compounds and it is possible to separate diastereomers with the aid of conventional methods such as recrystallization or distillation. In this regard, diastereomers are completely different from enantiomers. The relation among (A)-(D) is summarized in Table 8.1.

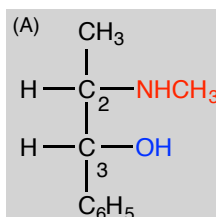
Table 8.1 The relation between erythrose and threose

	(A)	(B)	(C)	(D)
(A)	-	E	D	D
(B)	E	-	D	D
(C)	D	D	-	E
(D)	D	D	E	-

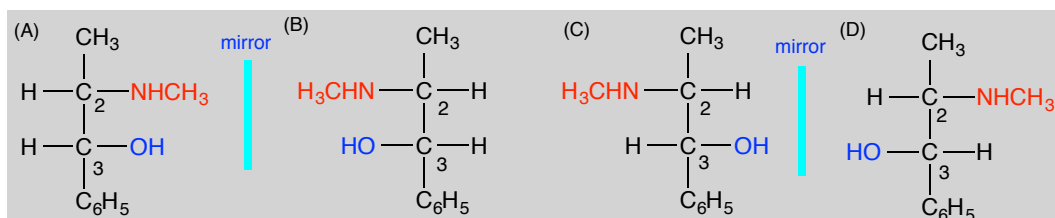
E: enantiomeric relation, D: diastereomeric relation

Exercise 8.5 Ephedrine

Ephedrine (A) is a widely used medicine. Draw Fischer projection of all possible stereoisomers, and indicate the stereochemical relation between (A) and its isomers.

**Answer**

Ephedrine (A) has three stereoisomers (B)-(D). The stereoisomers of (A) are (B), and (C) and (D) are enantiomers each other. The relations of other pairs are all diastereomers.

**(c) Resolution**

The pharmaceutical activity of the enantiomers of ephedrine is much inferior to that of ephedrine itself. This kind of selectivity is rather general for physiologically active compounds with asymmetric carbon atoms. Racemates in which equal amount of enantiomeric pair is included are generally formed when a synthesis of a compound with an asymmetric carbon atom is attempted. As a result, techniques to separate an enantiomeric pair into its component is very important.

Methods to separate racemates into their components are named **resolution**. There are three important methods for resolution.

- (1) physical resolution: if each of enantiomers crystallize with different crystal forms, these can be manually separated.
- (2) chemical resolution: Racemates are reacted with a chiral molecule (resolution reagent) to obtain a mixture of diastereomers. This mixture can be separated by means of conventional chemical methods. Each of pure enantiomers can be obtained by cleaving the resolution reagent from each diastereomer (Figure 8.5).

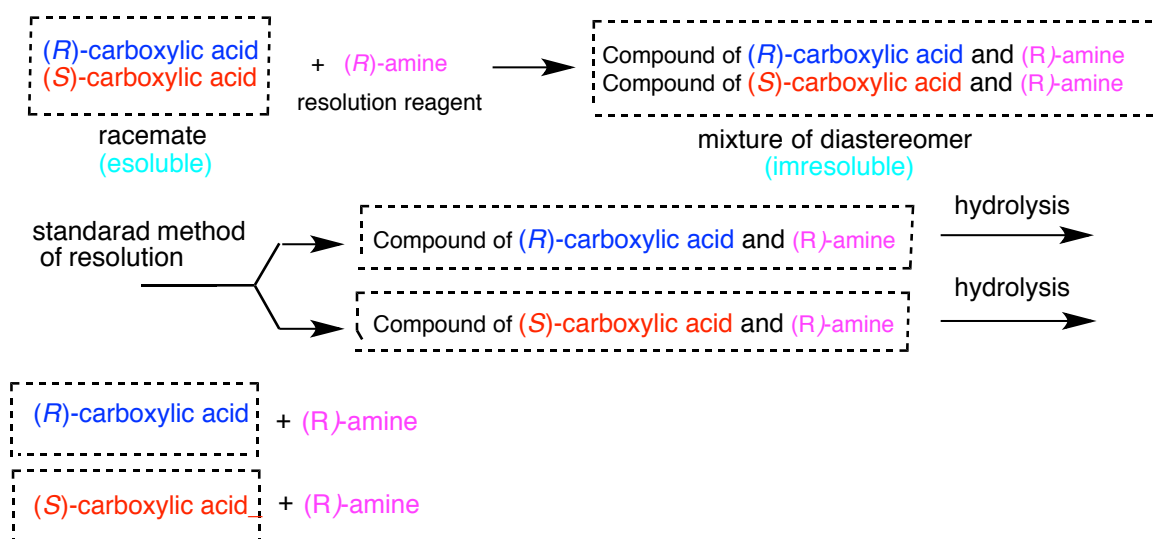


Figure 8.5 Flow chart of chemical resolution

An enantiomeric mixture of a carboxylic acid (R) and (S) is reacted with one of the enantiomeric pair of optically active amine, *e.g.*, (R') isomer, to obtain a mixture of compounds. These compounds are a mixture of diastereomeric (R)-(R'), and (S)-(R') compounds and can be chemically separated. By hydrolysis of each compound, pure (R)- and (S)-carboxylic acids are obtained.

(3) biological resolution: Use of specific enzymes which attack and consume one of the enantiomeric pair : It is not always easy to find such an enzyme which selectively attacks the unnecessary one out of the enantiomeric pair.

Point: Resolution of racemates

Racemates: a 1:1 mixture of enantiomeric pair.

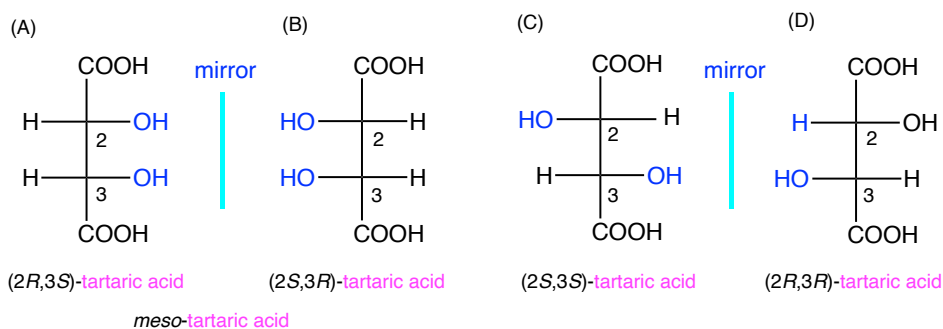
Resolution: process to separate a racemate into its component.

Three methods are used: physical resolution, chemical resolution, and biological resolution.

(d) Tartaric acid

Such compounds as threose and erythrose, or ephedrine which have two asymmetric carbon atoms have $2^2 = 4$ stereoisomers. Since tartaric acid is the oxidized product of erythrose and threose, it is expected that tartaric acid HOOCCHOHCHOHCOOH has also four isomers.

In the case of tartaric acid, four ligands bonded to C^2 and C^3 are the same set, with the priority order $\text{OH} > \text{COOH} > \text{half molecule} > \text{H}$. Will this situation influence the stereochemistry of tartaric acid? The configuration of C^2 and C^3 is given below.



The relation between (A) and (B) is to be discussed. First, C^2 and C^3 have the same set of ligands, and so, (A) and (B) are not an enantiomeric pair, but the same compound. Second, the configuration of C^2 and C^3 of (A) is opposite. So, if C^2 part of the molecule rotate the plane to a certain extent, the C^3 part rotates the plane by the same angle but to the reverse direction to cancel the rotation caused by C^2 part. Hence the molecule will be inactive.

This inactivity is caused by the fact that the molecule has a plane of symmetry which is perpendicular to the $C^2 - C^3$ axis. Such inactive compounds are named *meso* compounds. On the other hand, (C) and (D) are enantiomers each other. Table 8.2 lists the stereochemical relation among tartaric acid isomers.

Point: *Meso* compounds

Though two or more than two centers of chirality exist in the molecule, it is optically inactive because it has a plane of symmetry.

Table 8.2 The relation among tartaric acid isomers

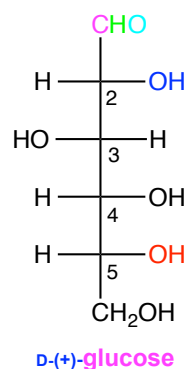
	(A) = (B)	(C)	(D)
(A) = (B)	-	D	D
(C)	D	-	E
(D)	D	E	-

E: enantiomeric relation, D: diastereomeric relation

(e) Glucose and its stereoisomers

(1) Configuration of glucose

Most interesting aspect of the study of chirality is the chemistry of glucose and its sixteen isomers. Glucose sometimes assumes a cyclic structure but first of all let us consider glucose in the chain structure. Naturally occurring glucose is dextrorotatory, and is represented by the following Fischer projection. Since the configuration of C^5 for glucose is identical with that of D-glyceraldehyde, it is named D-(+)-glucose.



Exercise 8.6 Configuration of glucose

Determine the configuration of four asymmetric carbon atoms of glucose.

Answer

Though this is not an easy question, you can obtain the correct answer by the correct use of sequence rule and sometimes with the help of molecular model.

C^2 : OH > CHO > lower half of the molecule > H \rightarrow (*R*) configuration

C^3 : OH > upper half of the molecule > lower half of the molecule > H \rightarrow (*S*) configuration

C^4 : OH > upper half of the molecule > lower half of the molecule > H \rightarrow (*R*) configuration

C^5 : OH > upper half of the molecule > CH₂OH > H \rightarrow (*R*) configuration

Some difficulty may be involved when you determine the configuration of C^3 and C^4 . Let us examine the C^3 case. It is impossible to determine the priority of the upper and lower half of the molecule because both C^2 and C^4 are substituted by (O, C, H) atoms. It is necessary to examine the substituted atoms at carbon atoms. The carbon C^1 bonded to C^2 has (O, O, H) while the carbon C^5 bonded to C^4 has (O, C, H). Hence the upper half has the higher priority.

Glucose has four asymmetric carbon atoms, and the number of stereoisomers is $2^4 = 16$. Conventionally, these sixteen compounds are classified into two groups, D- and L-series depending on whether the configuration of asymmetric carbon atom C^5 which is the furthest from the aldehyde group, is D or L. In Figure 8.6, eight compounds belonging to D-series are listed. Configuration of each asymmetric carbon atoms may be determined in a manner similar to that used for glucose.

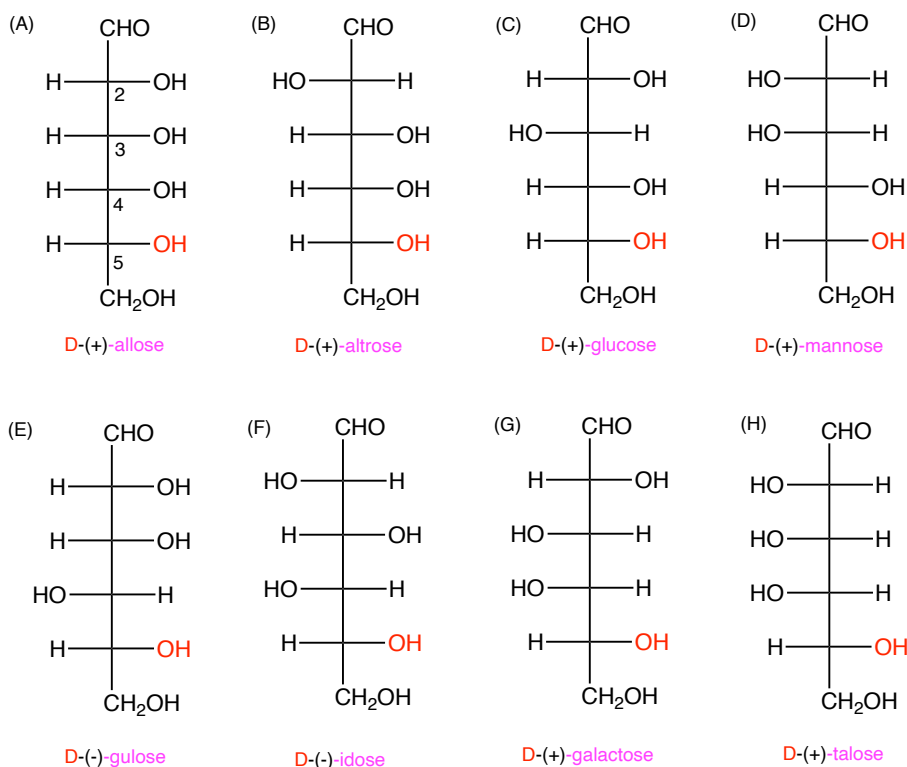


Figure 8.6 Stereoisomers of glucose (D-series)

Exercise 8.7 Stereoisomers of glucose

Draw the Fischer projection and sign of rotation of eight glucose isomers belonging to L-series.

Answer

Just exchange the positions of H and OH, and change the sign of rotation to obtain Figure 8.7. In the drawing below, atoms related to C⁵ are expressed in *italics* so that the difference between D- and L-series is clear.

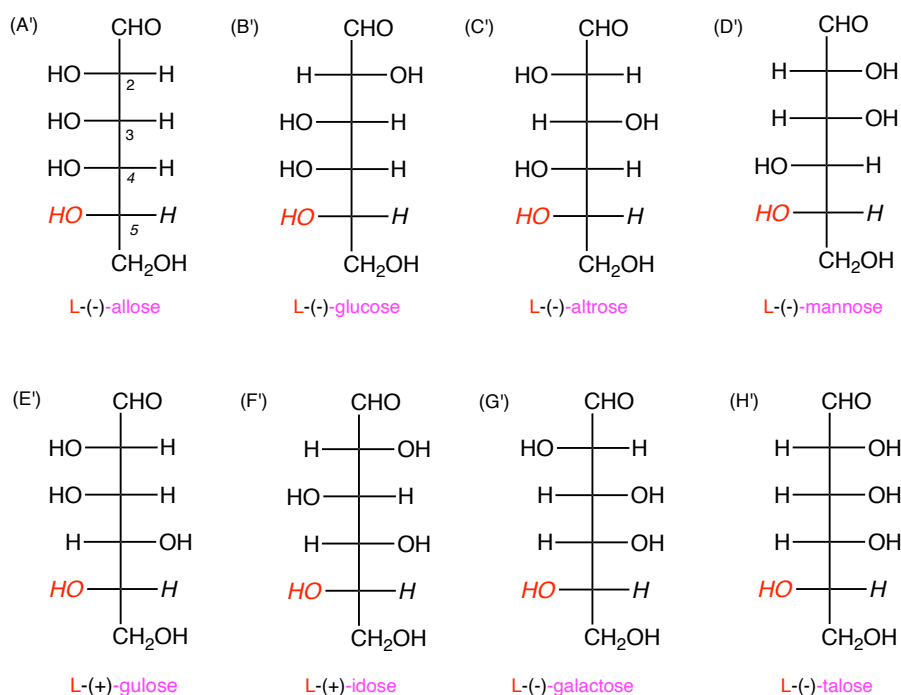


Figure 8.7 Stereoisomers of glucose (L-series)

(2) Mutarotation

If you dissolve crystalline glucose in water, its initial rotation, $[\alpha]_{\text{D}}^{20} = +111^\circ$, gradually changes and finally ceases to change at the rotation of $[\alpha]_{\text{D}}^{20} = +52.5^\circ$. This phenomenon is named **mutarotation**.

This phenomenon can be explained as below (Figure 8.8). Crystalline glucose takes a cyclic structure named α -form, not a chain structure. The specific rotation of this α -form is $+111^\circ$. In aqueous solution, the ring once opens to a chain, and the chain is again converted to two types of stereoisomeric rings, α -form and β -form. There is established an equilibrium among the chain structure (contribution of this structure is very small), α -, and β -forms. Since the specific rotation of the β -form is $+19.2^\circ$, the observed rotation, $+52.5^\circ$, is the weighted average of specific rotation of α - and β -forms.

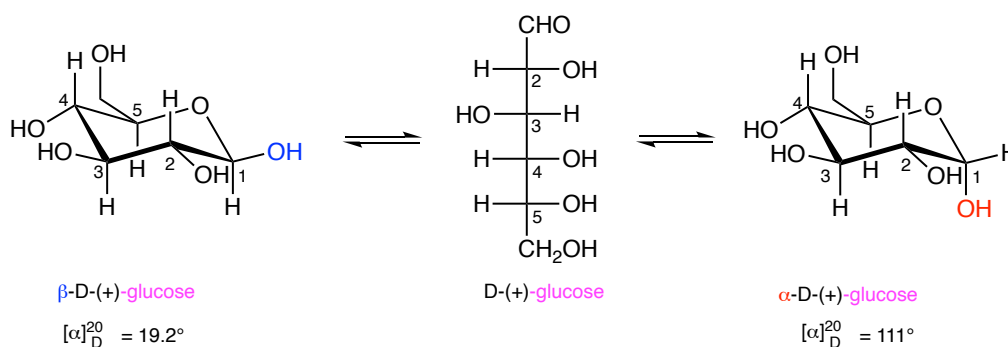


Figure 8.8 Mutarotation of glucose

Exercise 8.8 Mutarotation

Using the experimental results, determine the % ratios of α - and β -forms at equilibrium.

Answer

Put the % of α -form x . Then, $111x + 19.2(1-x) = 52.5$. $x = 0.36$ (36%)

Sometimes cyclic glucose is drawn as shown in Figure 8.9.

Cyclic glucose can be represented as below.

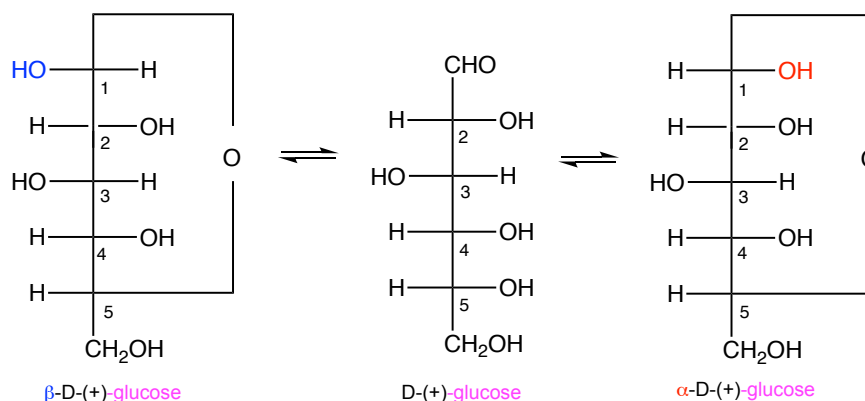


Figure 8.9 Representation of cyclic glucose

8.4 Stereochemistry of addition reactions

Based on the knowledge on asymmetric carbon atoms, you can obtain indirect, but decisive information on the invisible process of chemical reactions. Most persuasive example is the proof of the stereochemistry of addition reactions to alkenes (*trans* addition). The logic is as follows.

- [1] Choose an alkene which will give different stereoisomers depending on whether the addition proceeds in *trans* or *cis* mechanism.
- [2] Predict the products for each possible mechanism (*trans* addition or *cis* addition).
- [3] Carry out the experiment and compare the results with the prediction.

One possible compound to be tested is *trans*- and *cis*-2-butene. You may trace the process of *trans* addition of bromine to *trans*-2-butene with the aid of Figure 8.10. For simplicity's sake, let us assume Br^+ will add to the alkene. There are two cases for Br^+ to approach C^3 of the alkene.

In one case, Br^+ approaches from below the alkene plane (A) and the other case (B) from above the plane. Figure 8.10 shows the process of the addition by perspective view as well as Newman

projection. As a matter of fact, both approaches will give the same product, 2,3-dibromobutane. However, the stereochemistry will be different: case (A) will give (2*R*, 3*S*) while case (B) will give (2*S*, 3*R*).

It seems that cases (A) and (B) give stereoisomers. However, both compounds have the same set of four ligands for each asymmetric carbon atom, in other word, a *meso* compound, *meso*-2,3-dibromobutane, is formed.

Next, let us assume that a *cis* addition takes place. In this case also, there are two cases for Br⁺ to approach C³ of the alkene. In one case, Br⁺ approaches from below the alkene plane (A) and the other case (B) from above the plane. Figure 8.11 shows the process of the addition reaction by perspective view as well as Newman projection. The product is also 2,3-dibromobutane but the stereochemistry is different. Case (A) gives (2*S*, 3*S*) isomer while case (B) gives (2*R*, 3*R*) isomer. The two products form an enantiomeric pair.

The possibility that the case (A) takes place and the possibility that the case (B) takes place should be equal. Hence the actual product is a 1:1 mixture of enantiomeric pair, or racemate. This indicates that only inactive product is obtained regardless of the mechanism (*trans* or *cis*). However, *trans* addition should give a *meso* compound, but *cis* addition should give a racemate. In principle racemates can be resolved and hence by resolution can be differentiated from *meso* compounds. Finally, the mechanism (*trans* or *cis*) can be determined by experiments.

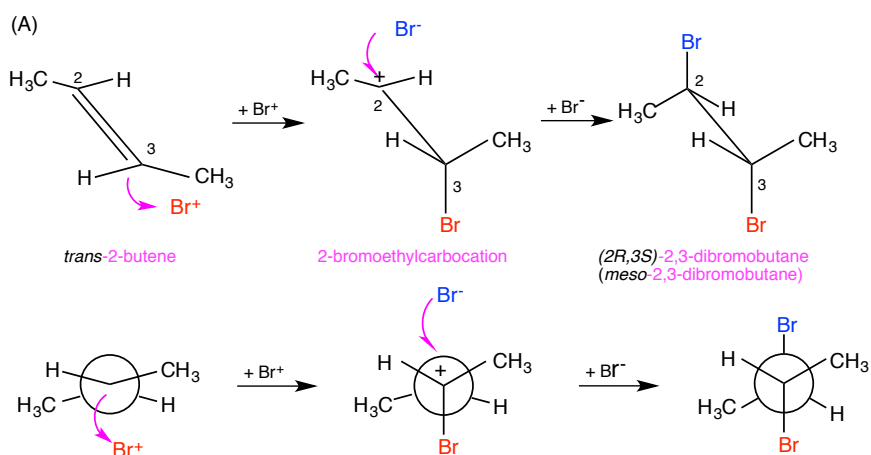


Figure 8.10 The *trans* addition of bromine to *trans*-2-butene.

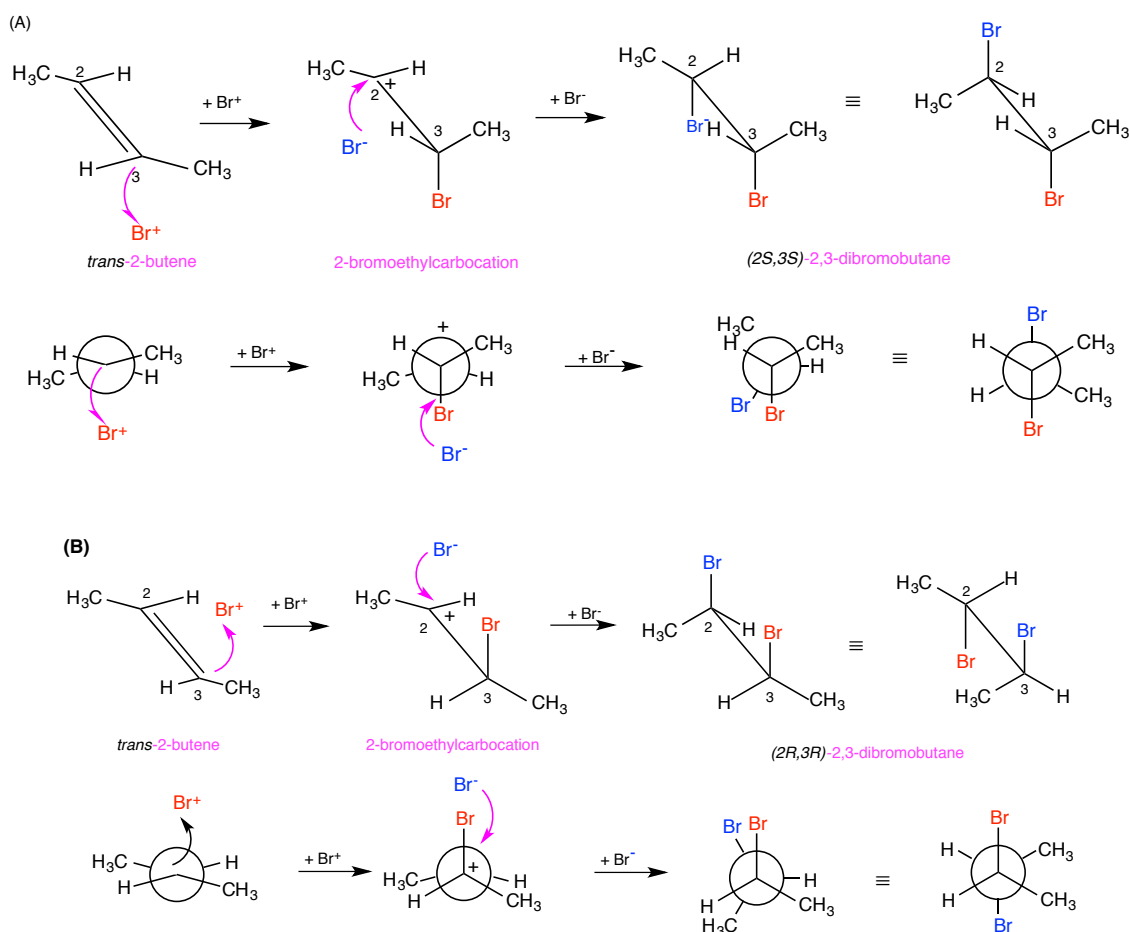
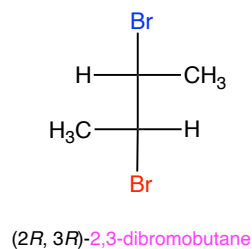
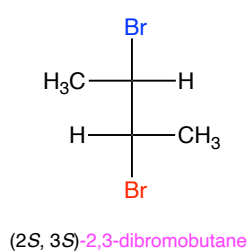
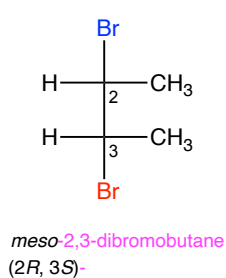


Figure 8.11 The *cis* addition of bromine to *trans*-2-butene.

Exercise 8.9 Stereochemistry of addition of bromine to *trans*-2-butene

Draw the Fischer projection of products of addition of bromine to *trans*-2-butene (see Figures 8.10 and 8.11).

Answer



Problems**8.1**

Determine whether the compounds below are chiral or achiral.

- 3-methylhexane
- 2,2-dimethylheptane
- 2,4-dimethylheptane
- 2-butanol
- glycine ($\text{H}_2\text{NCH}_2\text{COOH}$)

8.2

10 g of sucrose is dissolved in 100 mL of H_2O and its rotation is determined by D ray with a cell of 10 cm length.

- The angle of rotation of the polarized plane is $+6.39^\circ$. Determine the specific rotation of sucrose.
- The rotation of sucrose solution of unknown concentration under the same condition was $+3.95^\circ$. Determine its concentration (%).

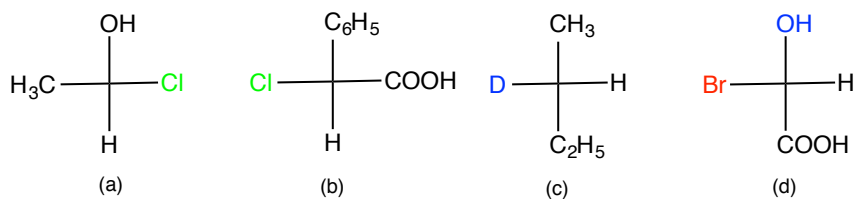
8.3

Determine the priority of each set of ligands.

- H-, CH_3 -, Cl-, D-
- H-, CH_3 -, $-\text{OCH}_3$ -, $-\text{SCH}_3$
- Br-, CH_2Br -, Cl-, CH_2Cl -
- $\text{CH}_3\text{CH}_2\text{CH}_2$ -, $(\text{CH}_3)_2\text{CH}$ -, CH_3CH_2 -, $(\text{CH}_3)_3\text{C}$ -

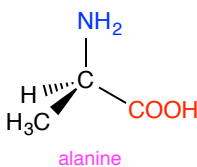
8.4

From the Fischer projection of the following compounds, determine their configuration in terms of (*R*), (*S*) nomenclature.

**8.5**

Based on the perspective view of alanine, answer the following questions.

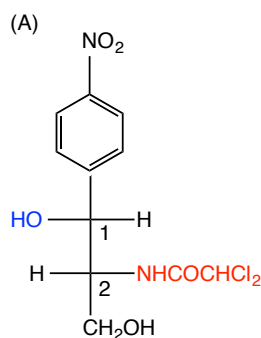
- Determine the configuration.
- Draw the Fischer projection.



8.6

The Fischer projection of a widely used antibiotics chloramphenicol (chloromycetin) (A) is shown below.

Determine the configuration of its two asymmetric carbon atoms, C¹ and C²,



Draw the Fischer projection of its all possible stereoisomers and explain the stereochemical relation of these isomers to (A).

8.7

If an alkene is oxidized with potassium dichromate KMnO_4 in basic media, 1,2-diol in which two hydroxy groups are attached is obtained.

- (1) Predict the configuration of the products butane-2,3-diol which is obtained by the oxidation of *cis*-2-butene under the similar condition.
- (2) Attempt the same experiment with *trans*-2-butene.

Answers**8.1**

(a) chiral (b) achiral (c) chiral (d) chiral (e) achiral

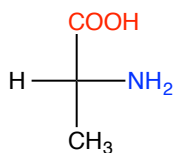
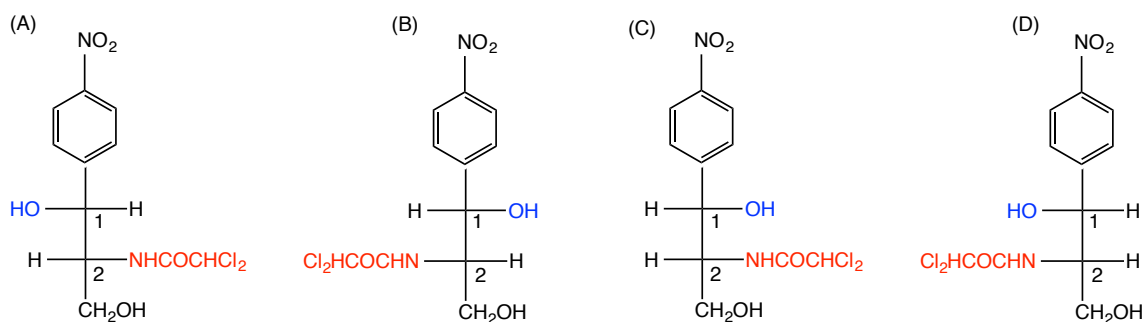
8.2

(1) $[\alpha]_D = (6.39^\circ \times 100)/(1 \times 10) = +63.9^\circ$

(2) $c = (3.95^\circ \times 10)/6.39^\circ = 6.18$; $x = 6.18 \times 100/(100 + 6.18) = 5.82(\%)$

8.3(a) $\text{Cl-} > \text{CH}_3\text{-} > \text{D-} > \text{H-}$ (b) $-\text{SCH}_3 > -\text{OCH}_3 > \text{CH}_3\text{-} > \text{H-}$ (c) $\text{Br-} > \text{Cl-} > \text{CH}_2\text{Br-} > \text{CH}_2\text{Cl-}$ (d) $(\text{CH}_3)_3\text{C-} > (\text{CH}_3)_2\text{CH-} > \text{CH}_3\text{CH}_2\text{CH}_2\text{-} > \text{CH}_3\text{CH}_2\text{-}$ **8.4**(a) *S* (b) *S* (c) *R* (d) *S***8.5**(1) The priority of substituents are: $\text{NH}_2 > \text{COOH} > \text{CH}_3 > \text{H}$. Hence the configuration is (*R*).

(2)

**8.6**

The pairs (A) and (B), and (C) and (D) are enantiomers each other. All other pairs are diastereomers each other.

8.7

The reaction can be explained by the same mechanism as that of the addition of bromine (see Ch. 8.4)