Stereochemistry I

Stereochemistry and Stereoisomerism

The science of organic chemistry is based on the relationship between molecular structure and properties. That part of the science which deals with structure *in three dimensions* is called **stereochemistry** (Gr.: stereos, solid).

One aspect of stereochemistry is stereoisomerism. Isomers are different compounds that have the same molecular formula. The particular kind of isomers that are different from each other only in the way the atoms are oriented in space (but are like one another with respect to which atoms are joined to which other atoms) are called stereoisomers.

Pairs of stereoisomers, despite their close similarity, one isomer of such a pair may serve as a nourishing food, or as an antibiotic, or as a powerful heart stimulant, and the other isomer may be useless.

Optical Activity

There are an infinite number of planes passing through the line of propagation, and ordinary light is vibrating in all these planes. **Plane-polarized light** *is light whose vibrations take place in only one of the possible planes* (Figure 7-1). Ordinary light is turned into plane-polarized light by passing it through a lens made of the material known as Polaroid or more traditionally through pieces of calcite (a particular crystalline form of CaCO3) so arranged as to constitute what is called a *Nicol prism*.

An **optically active** ***substance*** *is one that rotates the plane of polarized light.* When polarized light, vibrating in a certain plane, is passed through an optically active substance, it emerges vibrating in a different plane.

Figure 7-1 Schematic representation of *(a)* ordinary light and *(b)* plane polarized light.

The plane-polarized light can be detected and measured by the **polarimeter** (Figure 7-2), which consists of a light source, two lenses (Polaroid or Nicol), and between the lenses a tube to hold the substance that is being examined for optical activity. These are arranged so that the light passes through one of the lenses (*polarizer*), then the tube, then the second lens (*analyzer*), and finally reaches our eye.When the tube is empty, we find that the maximum amount of light reaches our eye when the two lenses are so arranged that they pass light vibrating in the same plane. If we rotate the lens that is nearer our eye, say, we find that the light dims, and reaches a minimum when the lens is at right angle to its previous position.

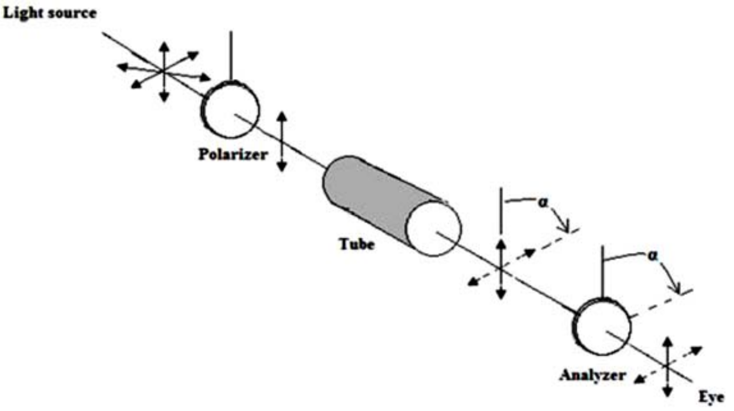


Figure 7-2 Schematic representation of a polarimeter. Solid lines: before rotation. Broken lines: after rotation. α is the angle of rotation.

Let us adjust the lenses so that a maximum amount of light is allowed to pass. (In practice, it is easier to detect a minimum than a maximum; the principle remains the same). Now let us place the sample to be tested in the tube. If the substance does not affect the plane of polarization, light transmission is still at a maximum and the substance is said to be **optically inactive**, if, on the other hand, the substance rotates the plane of polarization, then the lens nearer our eye must be rotated to conform with this new plane if light transmission is again to be a maximum, and the substance is said to be **optically active**. If the rotation of the plane, and hence our rotation of the lens, is to be right (clockwise), the substance is **dextrorotatory** (Latin: dexter, right); if the rotation is to the left (counterclockwise), the substance is **levorotatory** (Latin: laevus, left).

We can determine not only that the substance has rotated the plane, and in which direction, but also *by how much*. The amount of rotation is simply the number of degrees that we must rotate the lens to confirm with the light. The symbols + and – are used to indicate rotations to the right and to the left, respectively.

Specific Rotation

The amount of rotation depends upon how many molecules the light encounters in passing through the tube. The light will encounter twice as many molecules in a tube 20 cm long as in a tube 10 cm long, and the rotation will be twice as large. If the active compound is in solution, the number of molecules encountered by the light will depend upon the concentration. For a given tube length, light will encounter twice as many molecules in a solution of 2 g per 100 cc of solvent as in a solution containing 1 g per 100 cc of solvent, and the rotation will be twice as large. When allowances are made for the length of tube and the concentration, it is found that the amount of rotation, as well as its direction, is a characteristic of each individual optically active compound.

Specific rotation is the number of degrees of rotation observed if a 1-decimeter tube is used, and the compound being examined is present to the extent of 1 g/cc. This is usually calculated from observation with tubes of other lengths and at different concentrations by means of the equation:

$$[\alpha] = \frac{\alpha}{l \times d}$$

$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/cc}}$$

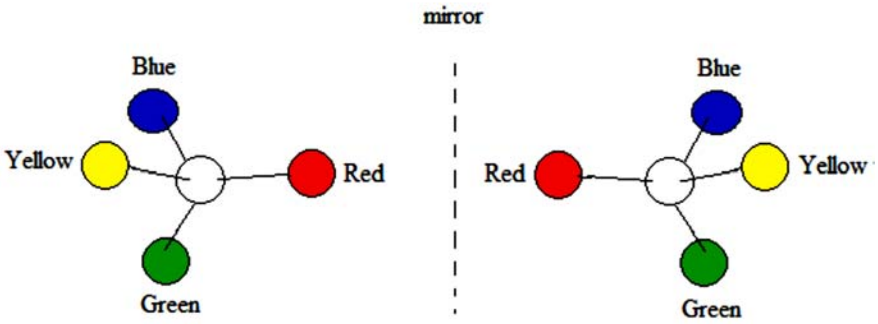
where d represents density for a pure liquid or concentration for solution.

Enantiomerism

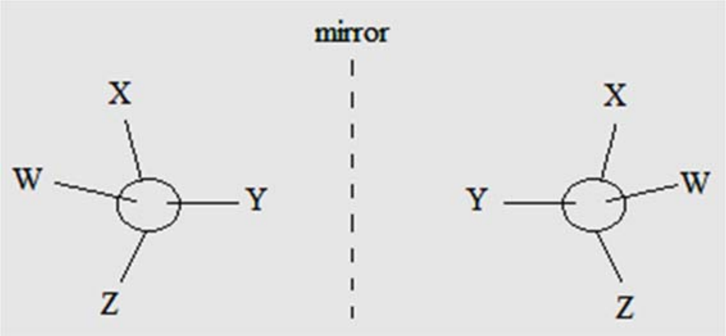
Louis Pasteur found that optically active sodium ammonium tartrate existed as a mixture of two different kinds of crystals, which were *mirror images* of each other. Using a hand lens and a pair of tweezers, he carefully and laboriously separated the mixture into two tiny piles, one of right-handed crystals and the other of left-handed crystals. Now, although the original mixture was optically inactive, each set of crystals dissolved in water was found to be *optically active*. Furthermore, the specific rotations of the two solutions were exactly *equal, but of opposite sign*; that is to say, one solution rotated plane-polarized light to the right, and the other solution an equal number of degrees to the left. In all other properties the two substances were identical.

Since the difference in optical rotation was observed *in solution*, it is characteristic, not of the crystals, but of the *molecules*. Like the two sets of crystals themselves, the molecules making up the crystals were *mirror images of each other*. There are two isomers whose structures differ only in being mirror images of each other, and whose properties differ only in the direction of rotation of polarized light.

Starting with the actual, tetrahedral arrangement for methane, let us make a model of a compound CWXYZ, using a ball of a different color for each different atom or group represented as W, X, Y, and Z. Let us then imagine that we are holding this model before a mirror, and construct a second model of what its mirror image would look like. We now have two models which look something like this:



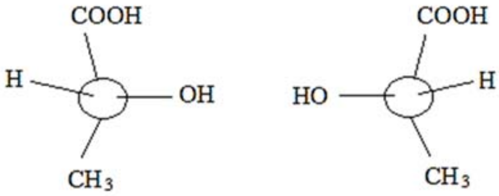
which are understood to stand for this:



Not superimposed: isomers

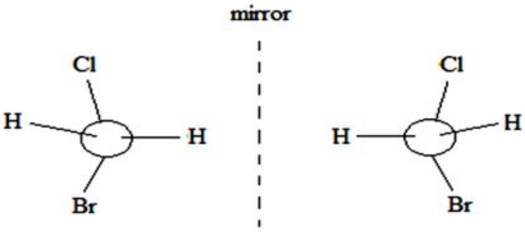
Are these two models superimposed? *No*. We may twist and turn them as much as we please (so long as no bonds are broken), but although two groups of each may coincide, the other two do not. The models are not superimposable, and therefore must represent two isomers of formula CWXYZ.

As predicted, mirror-image isomers do indeed exist, and thousands of instances besides the tartaric acids are known. There are, for example, two isomeric lactic acids:



Lactic acid

Most molecules, however, are superimposed on their mirror images, as, for example, bromochloromethane, and do not show this mirror-image isomer.



Bromochloromethane

Superimposed: no isomerism

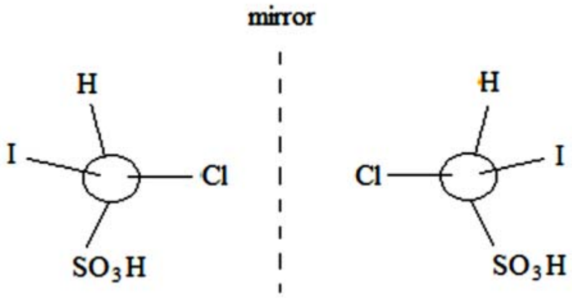
Mirror-image isomers are called *enantiomers*. Since they differ from one another only in the way the atoms are oriented in space, enantiomers belong to the general class called *stereoisomers*.

Stereoisomers that are not mirror images of each other called *diastereomers*. *Any two stereoisomers are thus classified either as enantiomers or as diastereomers, depending upon whether or not they are mirror images of each other*.

Chirality

Molecules that are not superimposable on their mirror images are **chiral**.

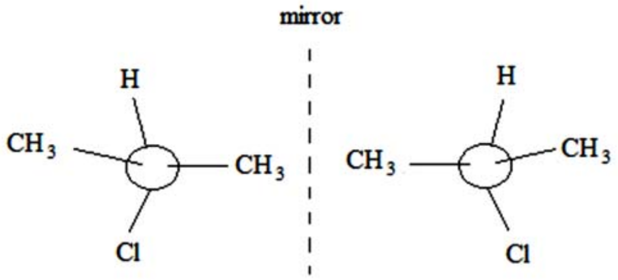
Chirality is the necessary and sufficient condition for the existence of enantiomers. That is to say: *a compound whose molecules are chiral can exist as enantiomers; a compound whose molecules are achiral (without chirality) cannot exist as enantiomers.* Some compounds are not superimposable on their mirror images, like these:



Chloroiodomethanesulfonic acid

Not superimposable: enantiomers

These molecules are chiral, and we know that chloroiodomethanesulfonic acid can exist as enantiomers, which have the structures we have just made or drawn. Others, we find, are superimposable, like these:



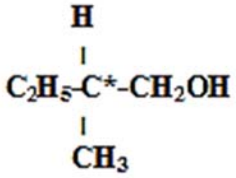
Isopropyl chloride

Superimposable: no enantiomers

These molecules are achiral, and so we know that isopropyl chloride cannot exist as enantiomers.

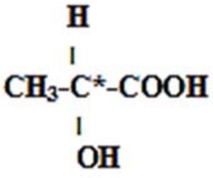
The Chiral Center

So far, all the chiral molecules we have talked about happen to be of the kind CWXYZ; that is, in each molecule there is a carbon (C*) that holds four different groups.



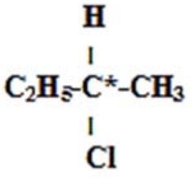
$$\begin{array}{c} H \\ | \\ C_2H_5\text{-}C^*\text{-}CH_2OH \\ | \\ CH_3 \end{array}$$

2-Methyl-1-butanol



$$\begin{array}{c} H \\ | \\ CH_3\text{-}C^*\text{-}COOH \\ | \\ OH \end{array}$$

Lactic acid



$$\begin{array}{c} H \\ | \\ C_2H_5\text{-}C^*\text{-}CH_3 \\ | \\ Cl \end{array}$$

***sec*-Butyl chloride**

A carbon atom to which four different groups are attached is a **chiral center**.

Many, *but not all*, molecules that contain a chiral center are chiral. Many, *but not all*, chiral molecules contain a chiral center. There are molecules that contain chiral centers and yet are achiral. There are chiral molecules that contain no chiral center. The chiral center is located where the lines cross. Chemists have agreed that such a diagram stands for a particular structure: *the horizontal lines represent bonds coming toward us out of the plane of the paper, whereas the vertical lines represent bonds going away from us behind the plane of the paper*.

The Racemic Modification

A mixture of equal parts of enantiomers is called a **racemic modification**. A racemic modification is optically inactive: when enantiomers are mixed together, the rotation caused by a molecule of one isomer is exactly canceled by an equal and opposite rotation caused by a molecule of its enantiomer.

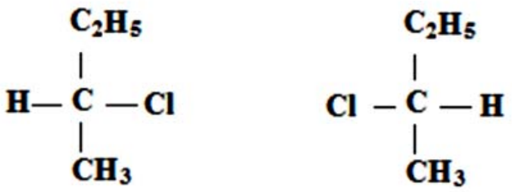
The prefix ± is used to specify the racemic nature of the particular sample, as, for example, (±)-lactic acid or (±)-2-methyl-1-butanol.

It useful to compare a racemic modification with a compound whose molecules are superimposable on their mirror images, that is, with an achiral compound. They are both optically inactive, and for exactly the same reason. Because of the random distribution of the large number of molecules, for every molecule that the light encounters there is a second molecule, a mirror image of the first, aligned just right to cancel the effect of the first one. In a racemic modification this second molecule happens to be an isomer of the first; for an achiral compound it is not isomer, but another, identical molecule.

Configuration

The arrangement of atoms that characterizes a particular stereoisomer is called its **configuration**.

Using the test of superimposability, we conclude, for example, that there are two stereoisomers *sec*-butyl chloride; their *configurations* are I and II.



$$\begin{array}{c}C_2H_5\\|\\H-C-Cl\\|\\CH_3\end{array}\qquad\begin{array}{c}C_2H_5\\|\\Cl-C-H\\|\\CH_3\end{array}$$

I II

sec-Butyl chloride

Compound I rotate the plane of polarized light to the right, and the other to the left.

Specification of Configuration: R and S

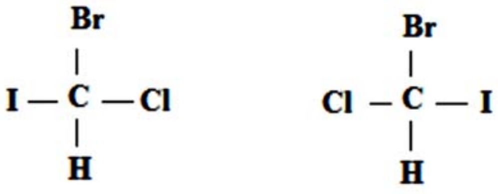
Now, a further problem arises. How can we specify a particular configuration in some simpler, more convenient way than always having to draw its picture?

Step1. Following a set of *sequence rule*, we assign a sequence of priority to the four atoms or group of atoms attached to the chiral center.

In the case of CHClBrI, for example, the four atoms attached to the chiral center are all different and priority depends on atomic number, the atom of higher number having higher priority:

Priority: I^{53}, Br^{35}, Cl^{17}, S^{16}, P^{15}, O^{8}, N^{7}, C^{6}, H^{1}

Thus, in our example, the priority is I, Br, Cl, H.

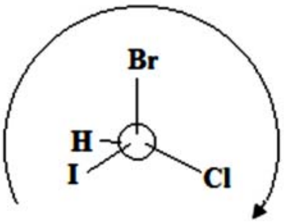


$$\begin{array}{c} \mathrm{Br} \\ | \\ \mathrm{I}-\mathrm{C}-\mathrm{Cl} \\ | \\ \mathrm{H} \end{array} \qquad \begin{array}{c} \mathrm{Br} \\ | \\ \mathrm{Cl}-\mathrm{C}-\mathrm{I} \\ | \\ \mathrm{H} \end{array}$$

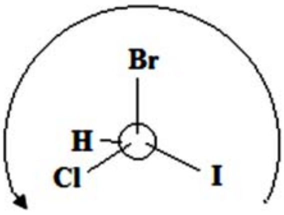
I **II**

Bromochloroiodomethane

Step 2. We visualize the molecule oriented so that the ligand of lowest priority is directed away from us, and observe the arrangement of the remaining ligands. If, in proceeding from the ligand of highest priority to the ligand of second priority and thence to the third, our eye travels in a clockwise direction, the configuration is ***R*** (Latin: rectus, right); if counterclockwise, the configuration is ***S*** (Latin: sinister, left).



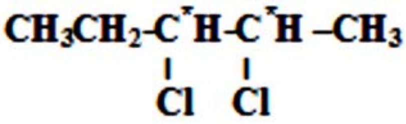
R



S

Diastereomers

We must learn what stereoisomers are possible for compounds whose molecule contain, not just one, *but more than one chiral center*. Let us start with 2,3-dichloropentane. This compound contains two chiral centers, C-2 and C-3.

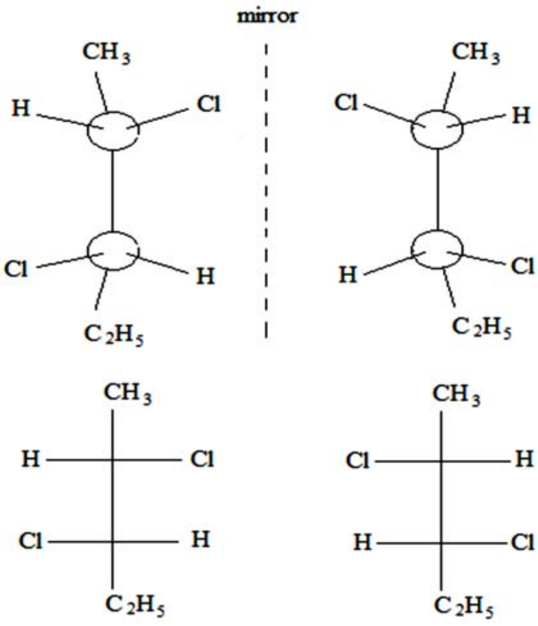


$$CH_3CH_2\text{-}\underset{Cl}{\underset{|}{C^*H}}\text{-}\underset{Cl}{\underset{|}{C^*H}}\text{-}CH_3$$

2,3-Dichloropentane

Using models, let us first make structure I and its mirror image II, and see if these are superimposable. We find that I and II are not superimposable, and hence must be enantiomers.

Next, we try to interconvert I and II by rotations about carbon-carbon bonds. We find that they are not interconvertible in this way, and hence each of them is capable of retaining its identity and, if separated from its mirror image, of showing optical activity.



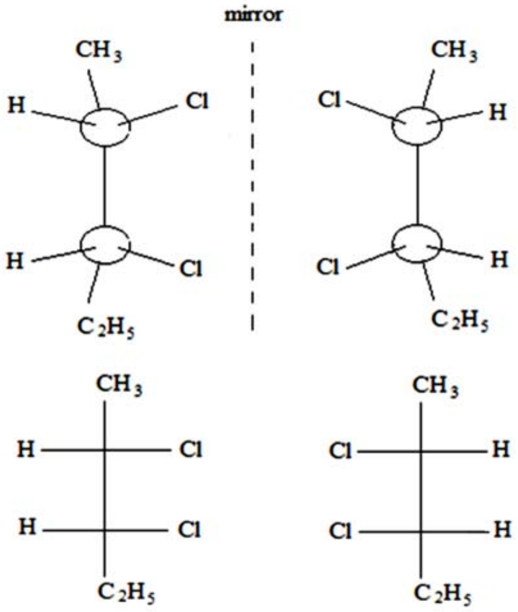
I **II**

Not superimposable

Enantiomers

Are there any other stereoisomers of 2,3-dichloropentane? We can make structure III, which we find to be non-superimposable on either I or II: it is not, of course, the mirror image of either. What is the relationship between III and I? Between III and II? They are stereoisomers but not enantiomers. *Stereoisomers that are not mirror images of each other are called* **diastereomers**. Compound III is a diastereomers of I, and similarly of II.

Now, is III chiral? Using models, we make its mirror image, structure IV, and find that this is not superimposable on (or interconvertible with) III. Structures III and IV represent a second pair of enantiomers. Like III, compound IV is a diastereomers of I and II.



III **IV**

Not superimposable

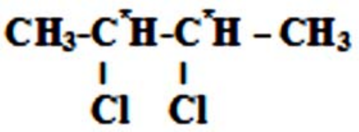
Enantiomers

Diastereomers have similar chemical properties, since they are members of the same family. Their chemical properties are *not identical*, however. In the reaction of two diastereomers with a given reagent, neither the two sets of reactants nor the two transition states are mirror images, and hence, except by sheer coincidence, will not be of equal energies. **Diastereomers have different physical properties**, different melting points, boiling points, solubilities in a given solvent, densities, refractive indexes, and so on. Diastereomers differ in specific rotation; they may have the same or opposite signs of rotation, or some may be inactive. As a result of their differences in boiling point and in solubility, they can, in principle at least, be separated from each other by fractional distillation or fractional crystallization; as a result of differences in molecular shape and polarity, they differ in adsorption, and can be separated by chromatography.

Thus the presence of two chiral centers can lead to the existence of as many as four stereoisomers. The maximum number of stereoisomers that can exist is equal to 2n, where *n* is the number of chiral centers.

Meso structures

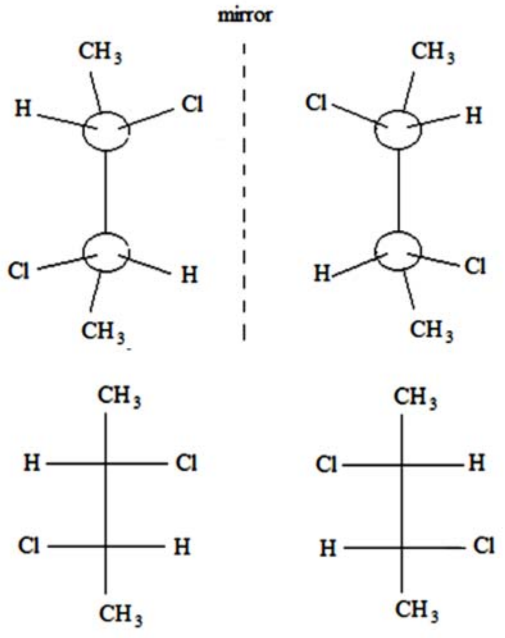
Now let us look at 2,3-dichlorobutane, which also has two chiral centers. Does this compound, too, exist in four stereoisomers forms?



$$\mathrm{CH_3\text{-}\underset{\underset{Cl}{|}}{\overset{*}{C}}H\text{-}\underset{\underset{Cl}{|}}{\overset{*}{C}}H-CH_3}$$

2,3-Dichlorobutane

Using models as before, we arrive first at the two structures V and VI.



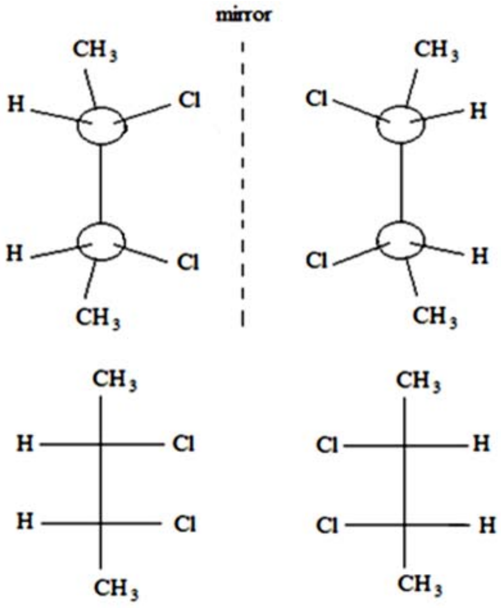
V **VI**

Not superimposable

Enantiomers

These are mirror images that are not superimposable or interconvertible; they are therefore enantiomers, and each should be capable of optical activity.

Next, we make VII, which we find to be a diastereomer of V and of VI. We now have three stereoisomers; is there a fourth? No. If we make VIII, the mirror image of VII, we find the two to be superimposable; turned end-for-end, VII coincides in every respect with VIII. In spite of its chiral center, VII is not chiral. It cannot exist in two enantiomeric forms, and it cannot be optically active. It is called a meso compound.



VII **VIII**

Superimposable

A meso compound

A **meso compound** *is one whose molecules are superimposable on their mirror images even though they contain chiral centers.* A *meso* compound is optically inactive for the same reason as any other compound whose molecules are achiral: the rotation caused by any one molecule is cancelled by an equal and opposite rotation caused by another molecule that is the mirror image of the first.

We can often recognize a meso structure on sight by the fact that (in at least one of its conformations) one half of the molecule is the mirror image of the other half. This can be seen for *meso*-2,3-dichlorobutane by imagining the molecule to be cut by a plane lying where the dotted line is drawn. The molecule has *a plane of symmetry*, and cannot be chiral. If we do not see a plane of symmetry, however, this does not necessarily mean that the molecule is chiral.