

SUPPLEMENTARY NOTES FOR STEREOCHEMISTRY

SOME IMPORTANT CONCEPTS IN STEREOCHEMISTRY

1. RELATIONSHIP BETWEEN SYMMETRY AND CHIRALITY

Asymmetric objects are chiral

Symmetric objects are achiral

2. RELATIONSHIP BETWEEN OBJECTS AND THEIR MIRROR IMAGES

Symmetric objects are superposable with their mirror images. They are one and the same.

Asymmetric objects are nonsuperposable with their mirror images. They are different objects.

In the case of molecules, chiral molecules and their mirror images are different molecules.

Chiral molecules and their mirror images are a kind of stereoisomers called enantiomers.

3. DEFINITIONS

Stereoisomers - Compounds that have the same molecular formula and the same connectivity, but different arrangement of the atoms in 3-dimensional space.

Stereoisomers cannot be converted into each other without breaking bonds.

Enantiomers - Nonsuperposable mirror images, or chiral molecules which are mirror images.

Chiral, or asymmetric carbon - A tetrahedral carbon atom bearing four different substituents.

Chirality centers, or stereocenters - Asymmetrically substituted atoms in a molecular structure.

The most common type encountered in this course will be the chiral carbon described above.

Diastereomers - Stereoisomers which are not enantiomers (or mirror images).

Meso compounds, or meso forms - Symmetric, or achiral molecules that contain stereocenters.

Meso compounds and their mirror images are not stereoisomers, since they are identical.

Optical activity - The ability of chiral substances to rotate the plane of polarized light by a specific angle.

Dextrorotatory - Ability of chiral substances to rotate the plane of polarized light to the right.

Levorotatory - Ability of chiral substances to rotate the plane of polarized light to the left.

Specific rotation - The measured angle of rotation of polarized light by a pure chiral sample under specified standard conditions (refer to textbook for a description of these).

Racemic mixture, racemic modification, or racemate - A mixture consisting of equal amounts of enantiomers. A racemic mixture exhibits no optical activity because the activities of the individual enantiomers are equal and opposite in value, thereby canceling each other out.

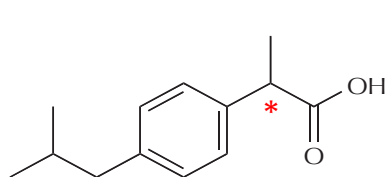
Optical purity - The difference in percent between two enantiomers present in a mixture in unequal amounts. For example, if a mixture contains 75% of one enantiomer and 25% of the other, the optical purity is $75 - 25 = 50\%$.

Absolute configuration - A description of the precise 3-dimensional topography of the molecule.

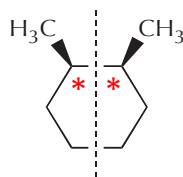
Relative configuration - A description of the 3-dimensional topography of the molecule relative to an arbitrary standard. Absolute and relative configurations may or may not coincide.

4. RELATIONSHIPS BETWEEN CHIRAL CENTERS AND CHIRAL MOLECULES - The term chiral center refers to an atom in the molecular structure. The term chiral molecule refers to the entire molecule.

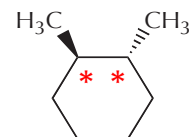
The presence of one chiral center renders the entire molecule chiral. The presence of two or more chiral centers may or may not result in the molecule being chiral. In the examples given below the chiral centers are indicated with an asterisk. The vertical broken line represents a plane of symmetry.



Ibuprofen. One chiral center renders the molecule chiral



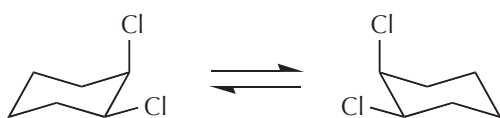
cis-1,2-dimethylcyclohexane is an achiral molecule



trans-1,2-dimethylcyclohexane is a chiral molecule

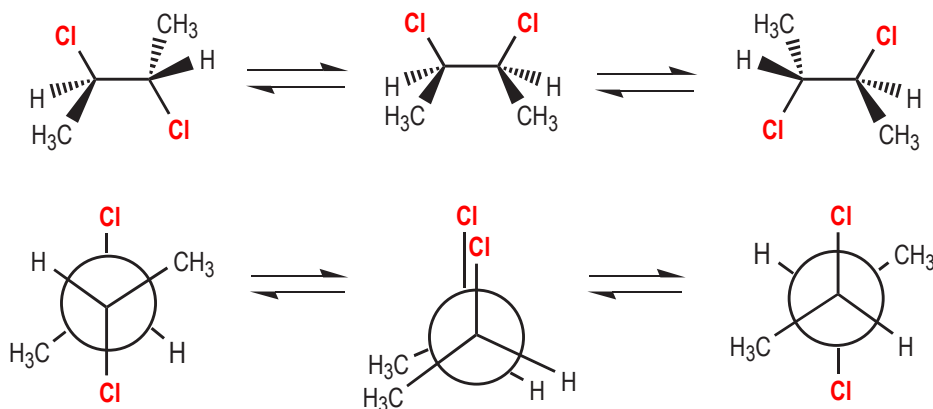
5. RELATIONSHIPS BETWEEN CONFORMATIONS AND CHIRALITY - The primary criterion to determine molecular chirality is the absence of any symmetry elements. However, some achiral molecules have chiral conformations. For example the chair conformations of 1,2-disubstituted cyclohexanes are chiral, yet the molecule as a whole is considered achiral. On the whole, we can apply the following criteria.

a) If the contributing conformations average out to an achiral conformation, then the molecule is considered achiral. Such molecules do not show optical activity. In the case of 1,2-disubstituted cyclohexanes the two most stable conformations are chiral. If we could freeze and isolate one of them, it would exhibit optical activity. But because they are mirror images in equilibrium, their optical activities cancel out and the sample is optically inactive. A similar example is illustrated by the conformations of (2R,3S)-1,2-dichlorobutane, which again is achiral, even though some of its conformations are chiral.

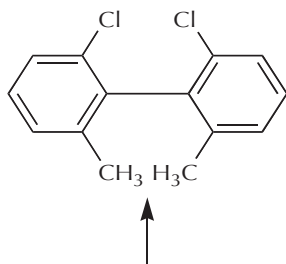


Chiral conformations in equilibrium.
The molecule is achiral

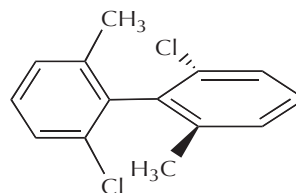
(2R,3S)-2,3-dichlorobutane



b) If a chiral conformation prevails over the others, then the molecule is considered chiral and it will show optical activity. The most common situations of this type involve molecules which are locked up into a chiral conformation due to steric interactions that impede free rotation around sigma bonds. In the example shown below, the two benzene rings cannot be coplanar because the steric interactions between the methyl and chlorine groups are too severe. The molecule is locked up in a conformation that has no symmetry, therefore it is chiral. Also notice that the molecule does not have any chiral centers. Its chirality is strictly due to a conformational effect.



Due to severe steric interactions between the substituents the molecule cannot be in this symmetric conformation.

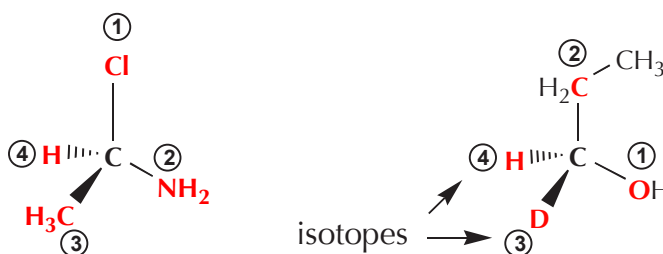


In the preferred conformation the benzene rings are perpendicular to each other. This relieves steric interactions but renders the molecule chiral.

R/S NOMENCLATURE SYSTEM (Cahn–Ingold–Prelog convention)

The complete set of rules is given in the textbook, but here are some things to keep in mind when assigning configuration to chirality centers.

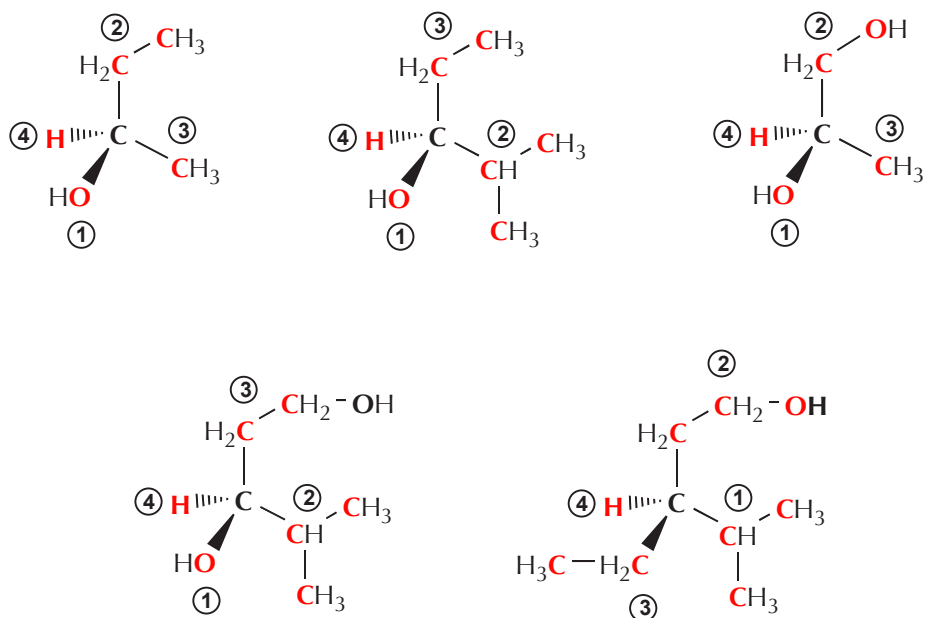
1. Make sure you have chiral centers in the molecule. The fact that a 3-dimensional formula is given does not imply that there are chiral centers.
2. Assign priorities to the atoms **directly attached to the chirality center**. The highest priority goes to the atom with the highest **atomic number**. In case there are isotopes, use the mass number instead, since they have the same atomic number.



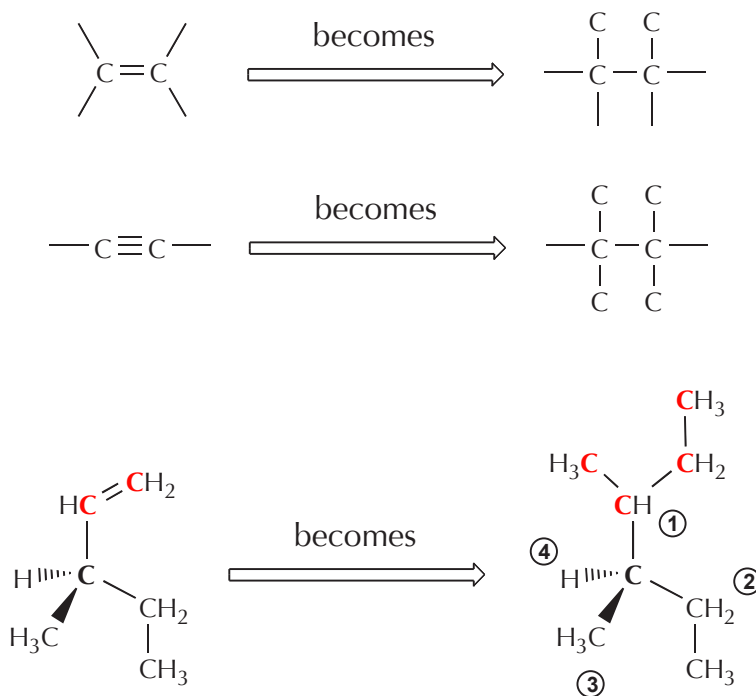
Notice that since the atomic number of hydrogen is 1, it will always be the lowest priority group, as long as it is present.

3. If two or more of the atoms directly attached to the chiral center are of the same type, look at the next atom to break the tie. Do not do this unless there is a tie. Repeat this process until the tie is broken.

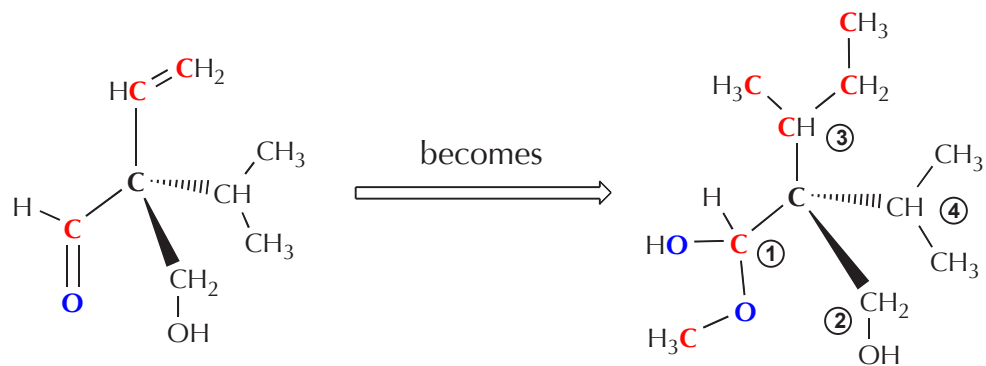
It is important to emphasize that in trying to break ties, one looks at the atoms **directly attached to the element under observation before looking at any others**. Study the examples on the following page very carefully to make sure this point is clear.



4. If there are atoms containing double or triple bonds, count them twice or thrice respectively. This holds for each of the atoms involved in the double or triple bonding.

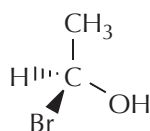


5. Although not obvious from the above examples, when duplicating the atoms involved in double or triple bonding they are also being crossed over at the same time. This only becomes apparent when the atoms involved in multiple bonding are not of the same kind, as in the examples shown on the following page.

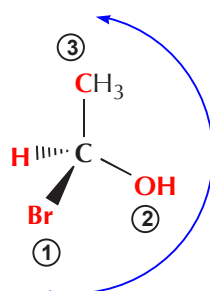


SHORCUTS FOR ASSIGNING ABSOLUTE CONFIGURATION ON PAPER

According to the Cahn-Ingold-Prelog convention, when assigning absolute configuration to a chiral carbon the lowest priority group that's attached to that carbon must be pointing away from an observer who is looking at the carbon in question. On paper, that usually means that if the observer is the person looking at the page, then the lowest priority group is pointing away from the observer, going behind the plane of the paper. In a 3-D formula this is indicated thus:



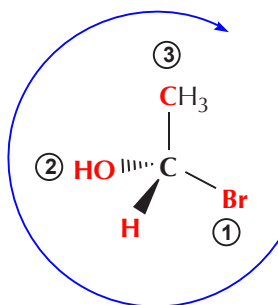
When the formula is given to us in this way, it's easy to assign configuration. All we have to do is assign priorities to the other three substituents and see if they are arranged clockwise or counterclockwise when the observer follows them in order of decreasing priorities. We don't have to mentally reposition either ourselves or the molecule in any way. In the example given above we can see that the central carbon has the (S) configuration.



If the lowest priority group is not presented to us already positioned towards the back of the chiral carbon, then it is useful to remember the following basic principle:

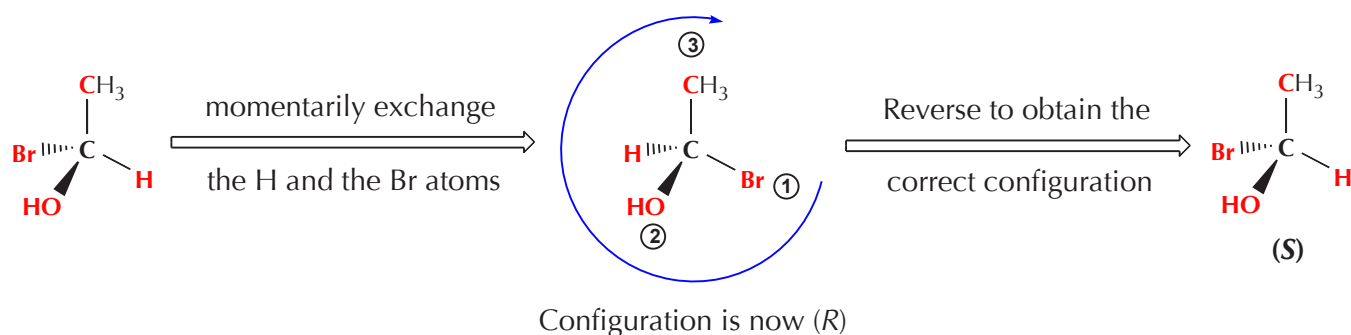
Every time any two substituents are exchanged, the opposite configuration results.

With this in mind, we can encounter two possible scenarios: Either the lowest priority group is positioned in front of the chiral carbon, or on the plane of the paper. If the lowest priority group is positioned in front of the chiral carbon (that is, opposite where it should be, according to the rules) we can still assign configuration by following the arrangement of the other three groups as given to us, but the configuration we obtain will be the opposite of the actual one. Following the same example given above we have:



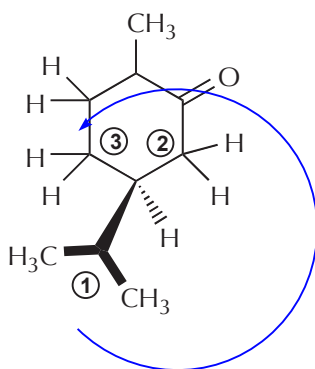
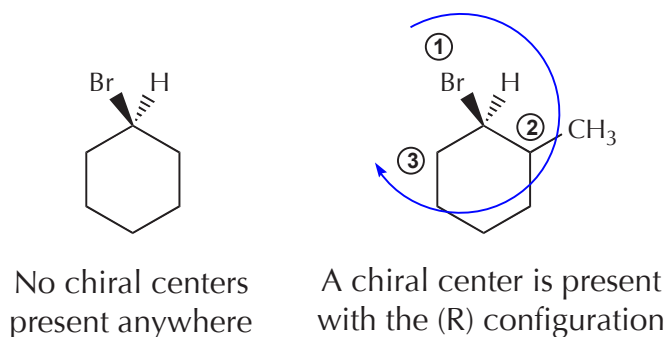
With the lowest priority group positioned in the front rather than towards the back, the central carbon appears to have the (R) configuration. The actual configuration is therefore (S). This is best seen when we rotate the molecule until the H atom is in the correct orientation.

If the lowest priority group is positioned on the plane of the paper, we can momentarily exchange it with whatever group happens to be positioned in the back, then assign configuration, then reverse it.



ASSIGNING ABSOLUTE CONFIGURATIONS IN CYCLIC MOLECULES

Cyclic molecules are frequently represented on paper in such a way that the ring atoms are all lying on the plane of the paper, and substituents are either coming out of the paper towards the front or towards the back. It is therefore easy to assign configuration to any chiral centers forming part of the ring, since the lowest priority substituent will be either pointing to the front or to the back. However, **always make sure there is in fact a chiral center present**. The fact that a 3-D representation is given does not necessarily mean there is a chiral center in the molecule.

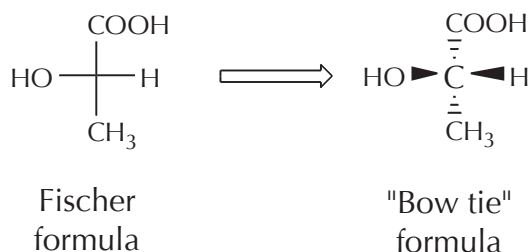


Although it may look cumbersome, sometimes it helps to spell out the structure in more detail to see the order of priorities clearly

ASSIGNING ABSOLUTE CONFIGURATIONS IN FISCHER FORMULAS

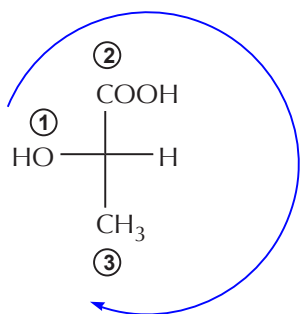
The key points to keep in mind regarding Fischer projection formulas are:

1. Horizontal lines represent bonds to the chiral carbon that are coming out of the plane of the paper towards the front, whereas vertical lines represent bonds going behind the plane of the paper towards the back. Thus, Fischer formulas are easily translated into "bow tie" formulas, which are 3-D formulas.



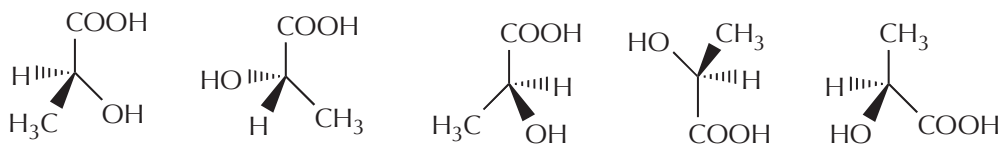
2. The lowest priority group bonded to the chiral carbon ***must always be shown as a horizontal bond***.

The process of assigning (*R*) or (*S*) configuration to the chiral carbon is the same as outlined before, but since the lowest priority group is pointing towards the front, **the configuration obtained directly from a Fischer formula is the opposite of the actual one.**



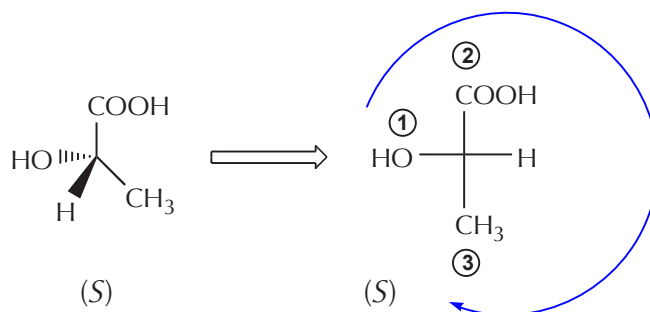
The order of priorities follows a clockwise direction in the Fischer formula. Therefore the actual configuration of this molecule is (*S*).

Once we know the actual configuration, we can represent the molecule in any of several possible ways using 3-D formulas. Thus the formulas shown below all represent the same molecule as given above in Fischer projection form. That is to say, all have the (*S*) configuration at the central carbon.

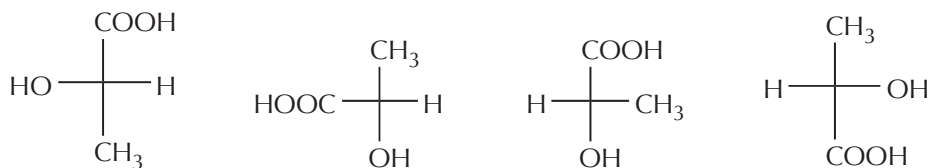


TRANSLATING 3-D FORMULAS INTO FISCHER FORMULAS

Once we become skilled at assigning configuration to chiral centers represented in 3-D notation, we can easily translate those into Fischer formulas. All we have to do is draw the cross with the four substituents attached to the chiral carbon, making sure the lowest priority group is lying on a horizontal line. At first we don't need to worry about where the groups are, for if it's wrong, all we have to do is exchange any two groups (make sure the lowest priority group remains on a horizontal line) to change configuration.



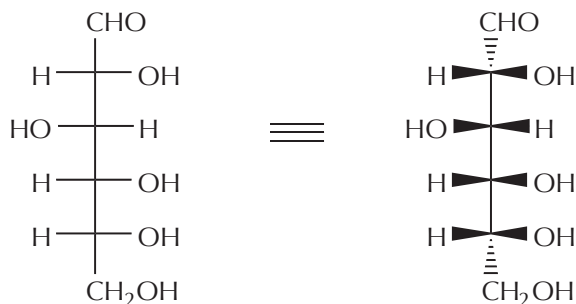
Just as was shown before using 3-D formulas, the same molecule can be represented in Fischer notation in several different ways, all showing the same molecule. In the example below all the compounds represent the same (*S*) isomer.



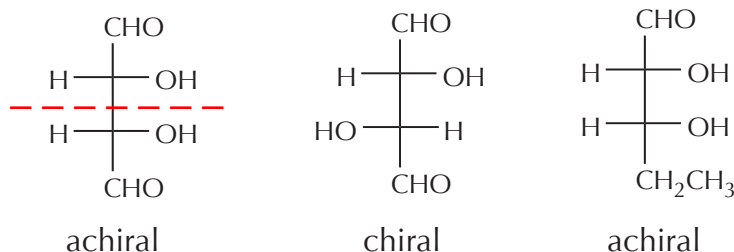
Notice that we did not forget to always put the lowest priority group on a horizontal bond.

FISCHER NOTATION OF MOLECULES CONTAINING TWO OR MORE CHIRAL CENTERS

Open chain molecules containing two or more chiral centers are traditionally represented in Fischer notation showing the main carbon chain in a vertical arrangement. The D-(+)-glucose molecule below illustrates this convention, shown in both Fischer projection and the bow tie equivalent. Notice that in the latter only the end atoms have bonds shown with broken wedge lines. Also notice that all the hydrogen atoms bonded to chiral carbons are shown lying along horizontal lines.

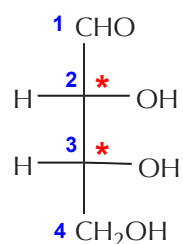


Identifying planes of symmetry in Fischer formulas is relatively easy, since they are planar representations. The following illustrations show examples of both chiral and achiral molecules.

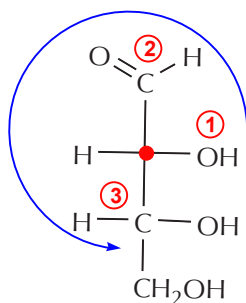


The process of assigning absolute configurations to the chiral centers in molecules containing two or more of them is basically an extension of the process followed for molecules containing only one. However, it helps to isolate the chiral centers and deal with one at a time to avoid confusion.

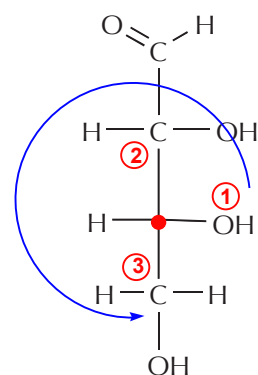
The following example illustrates this point. In this example we have numbered the carbon atoms in the main chain according to IUPAC rules that will be studied later. We have also marked the chiral carbons with asterisks.



Once the chiral centers have been identified, we focus on one at a time (shown as a red dot). First, we isolate carbon-2, then we assign priorities to the groups bonded to it, and assign configuration. In this case the configuration of carbon-2 turns out to be (*R*). A similar process for carbon-3 also leads to (*R*) configuration.



Carbon-2 (red dot) has the (*R*) configuration



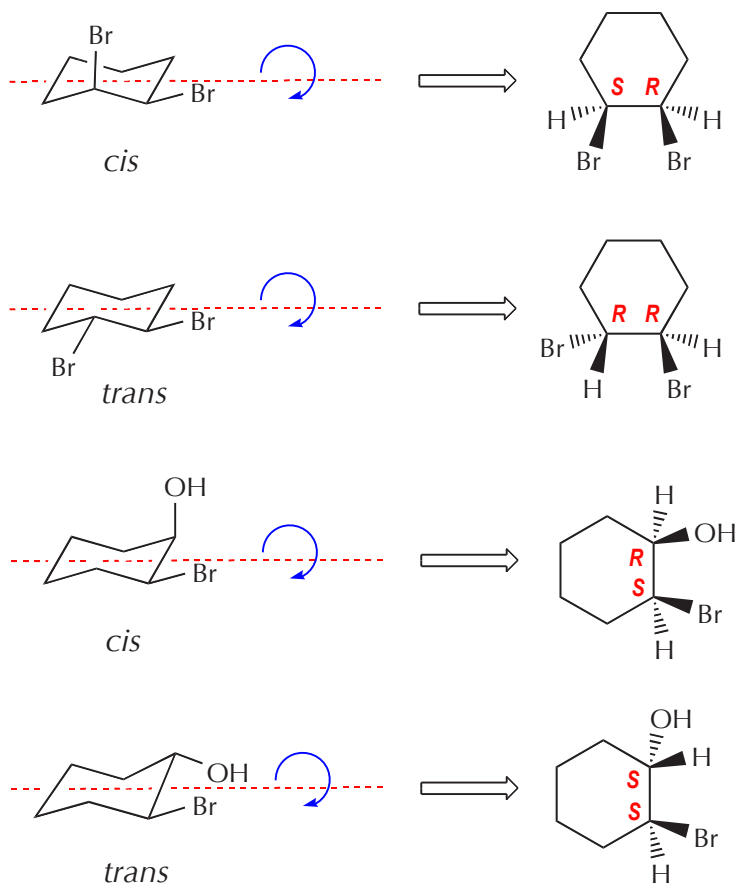
Carbon-3 (red dot) also has the (*R*) configuration

The IUPAC notation used to indicate the configurations at carbons 2 and 3 is therefore (*2R, 3R*).

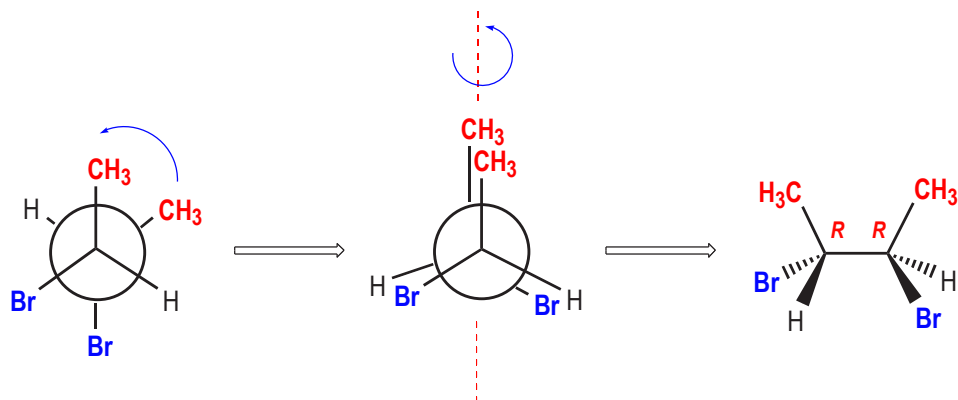
ASSIGNING CONFIGURATION TO CONFORMATIONALLY MOBILE SYSTEMS

This is probably one of the trickiest situations to deal with, especially when the molecule is shown to us in conformations such as a cyclohexane chair, or represented by Newman projections. It is a good idea in these cases to work with models, because one cannot help but to turn the molecule around until the of the lowest priority groups are positioned where they should be, and the priorities of the groups attached to the chiral centers can be clearly seen.

In the case of cyclohexane chairs and other rings, it's a good idea to flatten the ring and position it on the plane of the paper, with the lowest priority groups pointing towards the back when possible.

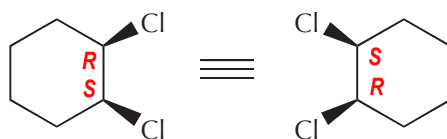


In the case of Newman projections, it helps to rotate one of the carbons around the C–C bond under consideration until as many similar groups as possible are aligned (eclipsing each other), then rotate the structure sideways to obtain a side view, rather than a projection, then assign priorities and configuration.



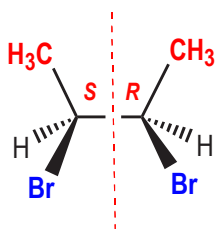
MOLECULES WITH 2 OR MORE CHIRAL CENTERS: DIASTEREOMERS AND MESO FORMS

As was stated before, molecules containing 2 or more chiral centers may or may not be chiral themselves. Let's consider the case of achiral molecules first. **Molecules that contain two or more chiral centers and at least one plane of symmetry are called meso forms.** *Cis*-disubstituted cyclohexanes are examples of meso forms. **Since these molecules have symmetry, they cannot have enantiomers. They are one and the same with their mirror images.**



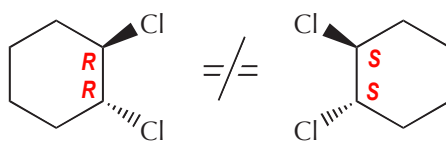
Cis-1,2-dichlorocyclohexane

Meso forms can also be open chain, as illustrated below.



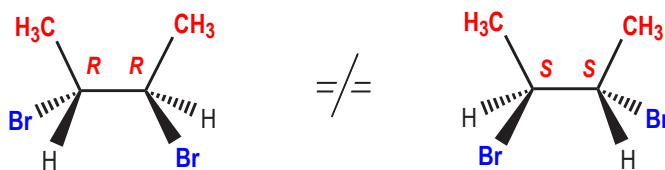
meso-2,3-dibromobutane

Now let's consider the case of **chiral** molecules that contain two or more stereocenters. Such molecules can have enantiomers because they are not the same as their mirror images.



Trans-1,2-dichlorocyclohexane.

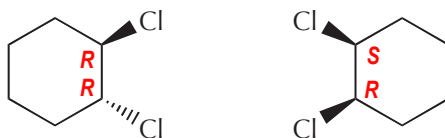
The mirror images are different compounds



(2*R*, 3*R*)-2,3-dibromobutane

(2*S*, 3*S*)-2,3-dibromobutane

Chiral molecules with two or more chiral centers can also have **stereoisomers which are not their mirror images**. Such sets of stereoisomers are called **diastereomers**. In the following example the two molecules shown are stereoisomers (same connectivity but different spacial arrangement of the atoms) but they are not mirror images. Their relationship is one of diastereomers.



Cis- and *trans*-1,2-dichlorocyclohexane.
are examples of **diastereomers**

As a corollary, we can state that ***cis/trans* pairs of disubstituted cyclohexanes (or any other rings for this matter) are always diastereomers**. Notice that we have referred to such sets before as **geometric isomers**. Geometric isomers are in fact a subcategory of diastereomers.

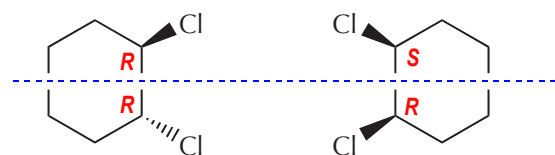
The following example is an illustration of open chain molecules with a diastereomeric relationship.



(2*R*, 3*R*)-2,3-dibromobutane

meso-2,3-dibromobutane

Also notice that in the above examples one of the members in each pair is chiral and the other is not. Diastereomeric sets are frequently made up of molecules where one of the molecules is chiral and the other is not. Also notice that although they are not mirror images, part of their structures do mirror each other. It is frequently the case that one half of one molecule mirrors one half of the other one, but the other halves are identical.



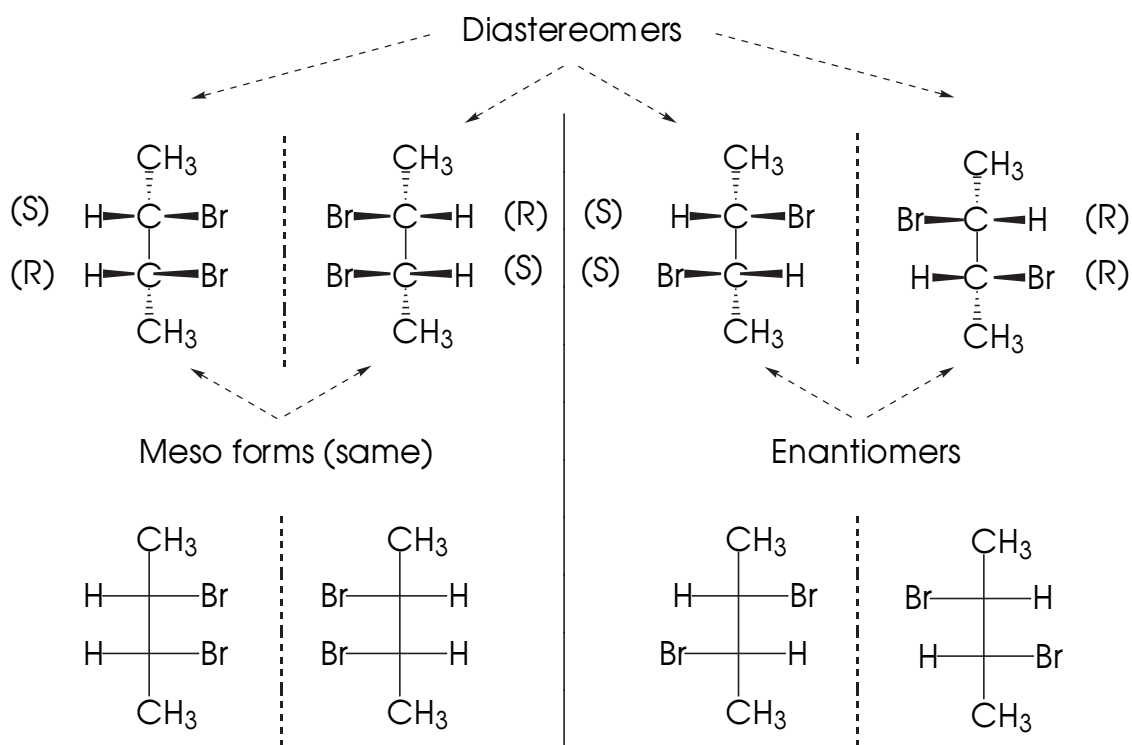
In this pair of *cis/trans* isomers, the top half of one molecule mirrors the top half of the other one (the chiral centers have opposite configurations), while the bottom halves are the same (the chiral centers have the same configuration).

SUMMARY OF RELATIONSHIPS BETWEEN MOLECULES WITH TWO OR MORE CHIRAL CENTERS

If n = number of chiral centers, the maximum possible number of stereoisomers is 2^n

n	1	2	3	4	5
2^n	2	4	8	16	32

EXAMPLE 1: Possible combinations for 2,3-dibromobutane.



EXAMPLE 2: Possible combinations for 2-bromo-3-chlorobutane.

