

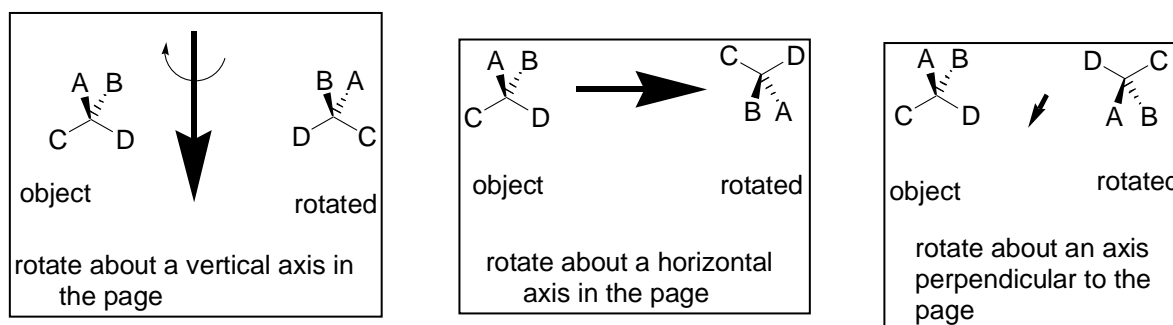
1. Visualization Skills
2. Chirality and Enantiomers
3. Diastereomers
4. Finding Meso

1. Visualization Skills

Proper use of stereochemical concepts requires an ability to perceive 3-dimensional objects rendered on a two dimensional sheet of paper or a board.

You need to be able to “see” how rotating a molecule in space changes the positions of groups around a stereocenter. You also need to “see” how reflecting a molecule in a mirror plane changes the relative positions of groups around a *stereocenter*. A *stereocenter* (also called a chiral center or stereogenic center) is an atom connected to four different groups.

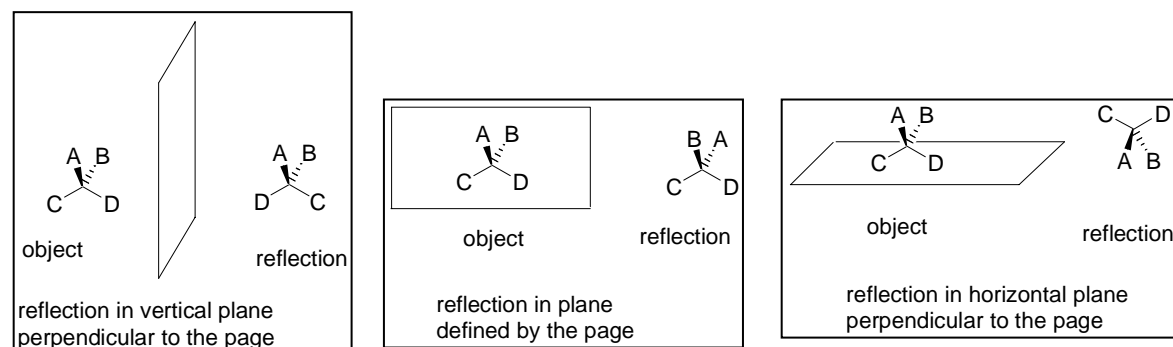
Rotate a molecule about an axis - changes the molecule’s orientation. Rotation about an axis does not change a molecule’s shape, conformation or any stereocenter’s configuration.



CONVINCE YOURSELF THAT

- ALL 3 ROTATED STRUCTURES ARE THE SAME AS THE OBJECT

Reflection a molecule in a plane – not a physically achievable motion (try to convert your left hand into your right hand). Reflection changes every stereocenter’s configuration.



CONVINCE YOURSELF THAT

- ALL 3 REFLECTED STRUCTURES ARE THE SAME

- ALL 3 REFLECTED STRUCTURES ARE NOT SUPERIMPOSABLE ON THE OBJECT

2. Chirality and Enantiomers

A *chiral* entity is not superimposable on its mirror image.

The above object and its reflection are chiral. Neither is superimposable on the other (its mirror image).

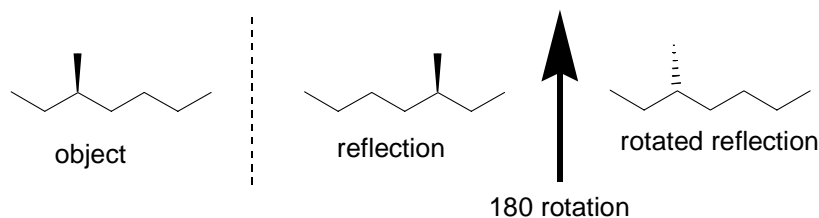
The above molecule (object) and its reflection are one example of *stereoisomers*.

Two molecules are *stereoisomers* if they have the same composition, constitution and connectivity but different 3-dimensional shapes that cannot be superimposed in any conformation without breaking bonds.

There are two main classes of stereoisomers: *enantiomers* and *diastereomers*.

Enantiomers: two molecules are enantiomers if they are stereoisomers and *mirror images*.

(Alternate definition: two molecules are enantiomers if they have the same connectivity, are mirror images but are non-superimposable).

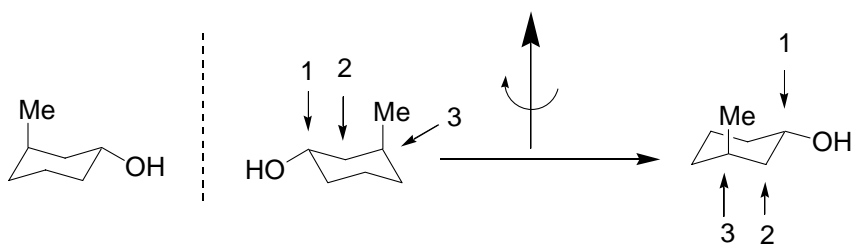


Starting with the object [(R)-3-methylheptane], reflection in the plane generates a new structure (reflection). A 180° rotation about a vertical axis generates the rotated reflection.

Although the heptane chain of the **object** and the **rotated reflection** can be perfectly overlaid, the 3-CH₃ group of the object points toward the viewer whereas the 3-CH₃ group of the rotated reflection [(S)-3-methylheptane], points away from the viewer. The third carbon is a stereocenter.

The object and the reflection (and rotated reflection) are *mirror images and non-superimposable*. Thus, they are enantiomers (and chiral by the previous definition).

Consider the two alcohol molecules below. Both have two stereocenters. The structure of the alcohol on the right was generated by reflecting the alcohol on the left in the dotted mirror plane. If the two molecules are not superimposable, they are enantiomers and each is chiral. To check whether they are superimposable, rotate the right structure by 180° about a vertical axis.

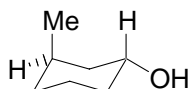


Note, this rotation moves carbons 2 and 3 from behind the page to in front of the page. If you compare the left and right most structures, the ring carbons and OH groups can be perfectly overlaid but

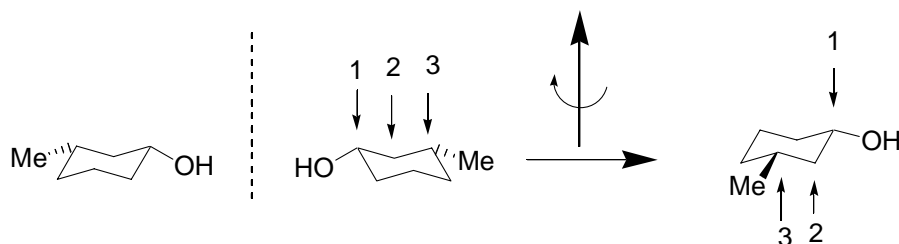
the methyl group (Me = CH₃) is in different places on the ring. Thus, the two molecules are not superimposable. The original molecule and its mirror image are enantiomers. (left most molecule is (1R,3R) 3-methylcyclohexanol. CONVINCe YOURSELF OF THIS.

3. Diastereomers

The Methyl and Hydroxyl (OH) group in the above two structures are *trans* to each other. If you can't see this, visualize the hydrogen atoms connected to the ring carbons bearing the Me and OH group. The Methyl group is above the hydrogen attached to the same carbon atom of the ring. The OH group is below the hydrogen attached to the same carbon atom of the ring. Two substituents are *trans* if one is above its partner H and the other is below its partner H. Two substituents are *cis* if both are above or both are below their partner H.

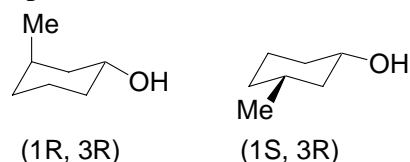


Let's look at 3-methylcyclohexanol in which the Me and OH groups are *cis*. Using a similar analysis as for the *trans* isomers, the reflected structure does not superimpose on the left most structure. Thus, these two structures are non-superimposable mirror images. They are each other's enantiomer.



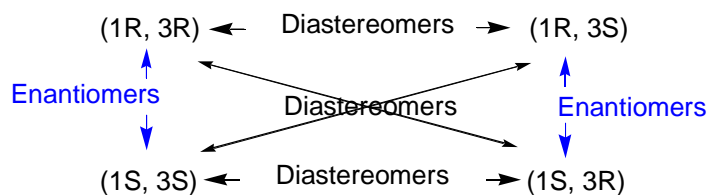
Convince yourself that the left most structure is (1R,3S) 3-methylcyclohexanol.

What is the relationship between the *cis* and *trans* molecules. If we put a *trans* isomer next to a *cis* isomer, can they be superimposed? Although, the ring carbons and the hydroxyl group overlay perfectly, the methyl groups are attached to different carbons. Furthermore, the Me group is axial in one isomer and equatorial in the other. Clearly, *cis* and *trans* isomers are not superimposable.

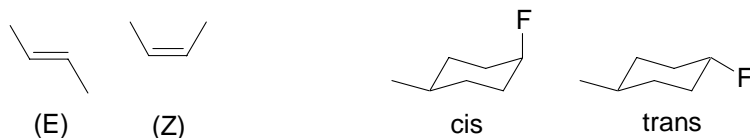


Are *cis* and *trans* isomers mirror images? I've rotated the right hand structure so that the ring carbons and hydroxyl group appear as object and mirror image (vertical plane perpendicular to the page). The Methyl groups on the two structures clearly do not exhibit a mirror image relationship.

These two molecules are *diastereomers*. Two molecules are diastereomers if they are stereoisomers but are not mirror images. (Alternate definition: two molecules are diastereomers if they have the same connectivity, are not superimposable and are not mirror images. We just tested the latter two characteristics.) In a structure with multiple stereocenters, the enantiomers have opposite configurations at all stereocenters. The diastereomers have opposite configurations at some, but not all, stereocenters. Check this below.



Two molecules can be diastereomers even if they have no stereocenters. These molecules constitute a special case of diastereomers called *geometric stereoisomers*. Two alkenes may be diastereomers if one is (Z) and one is (E). cis and trans 1,4-disubstituted cycloalkanes lacking stereocenters are diastereomers.



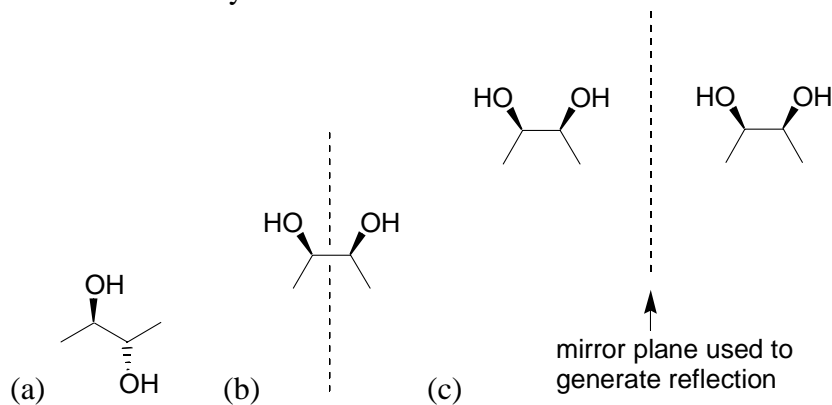
Pairs of diastereomers that lack stereocenters (geometric stereoisomers).

If a structure has N stereocenters, you will be able to generate a maximum of 2^N unique stereoisomers. If a structure is not *symmetrical*, there will be exactly 2^N stereoisomers and each stereoisomer will have one enantiomer.

4. Finding Meso



What happens if a structure is symmetrical? Well first, we have to define what we mean by the term. A simplistic definition says that an object is symmetrical if it can be cut into two mirror image parts by a plane passing through the molecule. Consider one stereoisomer of butan-2,3-diol (a). This molecule has two stereocenters. We can rotate the molecule into a high energy eclipsed conformation (b) in which the two methyl groups are eclipsed and the two hydroxyl groups are eclipsed. Can you see that the dotted plane in (b) cuts the molecule into two mirror image parts? This molecule is symmetrical.



If you compare the eclipsed conformer with its mirror image (c), you should be able to see that the two structures are superimposable. An object that is superimposable on its mirror image is not chiral. Instead of two enantiomers, there is only one symmetrical isomer. A structure that has

stereocenters but is not chiral (because it is symmetrical) is called a *meso compound*. Meso compounds reduce the number of unique stereoisomers below 2^N .

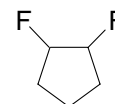
(A) How do you determine whether one of the stereoisomers of a particular structure will be a meso compound? In other words, how do you determine if a structure is symmetrical?

(B) How do you determine whether a specific stereoisomer is a meso compound?

Consider the following approaches and examples for the above two tasks:

Will any of the stereoisomers of 1,2-difluoropentane be a meso compound?

Draw the molecule as a flat, regular pentagon with two fluorines (no stereochemistry)



(A-1) Does this structure have more than one stereocenter? Although no stereochemistry is indicated in the flat structure, you should see that two carbons are each connected to four different groups. All meso compounds have more than one stereocenter.

(A-2) Is there a plane that divides this structure into two mirror image parts?

Yes. You can draw a vertical plane, perpendicular to the page that splits the upper C-C bond and passes through the lowest ring carbon. This plane divides the molecule into two mirror image parts. This tells you that a stereoisomer is a meso compound.

(A'-1) An alternative approach to determining whether a molecule is symmetrical: Can you identify two DIFFERENT carbons that, if selected as carbon # 1, give the same name for the compound?

For 1,2-difluoropentane:

Select the upper left carbon as number 1: the name is

1,2-difluoropentane

Select the upper right carbon as number 1: the name is

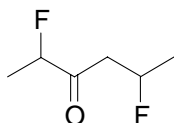
1,2-difluoropentane

These two names are the same. This structure is symmetrical. There will be a 1,2-difluoropentane that is a meso compound.

Try this for the following compounds:

2,5-difluorohexan-3-one

2,5-difluorohexan-4-one
symmetrical. **None of its**

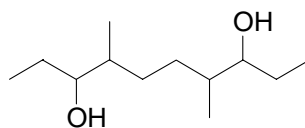


If you start numbering from the right end, the name is

These two names are different. This molecule is not **stereoisomers will be meso compounds.**

4,7-dimethyldecane-3,8-diol

the right, the methyl groups are numbered 3,8.
one of its stereoisomers will



If you start numbering from the left or are numbered 4,7 and the hydroxyl
This molecule is symmetrical. At least
be a meso compound.

Approaches (A-1,2) and (A'-1) should give you the same result.

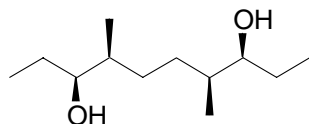
(B) How do you determine whether or not a specific stereoisomer is a meso compound?

For starters – if the molecule has one or fewer stereocenters, it can not be a meso compound.
For starters – the molecule must be symmetrical (A'-1) or (A-1,2).

(B-1). Draw the specific stereoisomer of interest and its mirror image. If possible, draw the molecules such that the carbon CHAIN or RING exhibits a mirror image symmetry. Carefully add in the substituents and functional groups. Pay special attention that you add the stereocenters correctly. Determine the original and mirror image superimpose. If they do, the two structures are the same and are a meso compound.

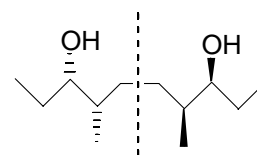
(B'-1). Determine the absolute configurations of the stereocenters. Name the compound, including absolute configurations, starting from the two chain ends or starting at two parts of the ring. If the absolute configurations associated with each number switches when you number the two different ways, the molecule is a meso compound. If the configuration associated with each number stays the same, the molecule is not a meso compound.

Example 1 :



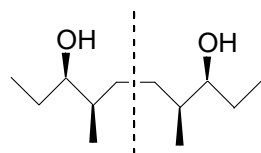
Approach B-1 Draw the molecule so that the carbon framework is symmetrical. Add the stereocenters carefully. Is the left half of the molecule a mirror image of the right half?

NO !! Both functional groups on the left point back. The corresponding groups on the right point forward. This molecule is not a meso compound.



Approach B'-1. Name starting at the left: (3S, 4S, 7S, 8S) 4,7-dimethyldecane-3,8-diol
Name starting at the right: (3S, 4S, 7S, 8S) 4,7-dimethyldecane-3,8-diol

The two names are the same – the molecule is not a meso compound.



How about the molecule to the left?

Approach B-1

The left and right halves are clearly mirror images.

Approach B'-1

Name starting with the left end carbon as #1: (3R, 4R, 7S, 8S) 4,7-dimethyldecane-3,8-diol

Name starting with the right end carbon as #1: (3S, 4S, 7R, 8R) 4,7-dimethyldecane-3,8-diol

The absolute configuration associated with every stereocenter (3, 4, etc.) switches when you start numbering at the left or at the right. The molecule appears to be its own enantiomer. That makes no sense. The molecule can not be chiral. The molecule is a meso compound.

Determine whether the following molecules are meso-compounds.

