

CH-211 Organic Chemistry I

Chapter 5: Stereoisomerism

By Ilari Filpponen

Textbook: Organic Chemistry, D.R. Klein. 4th ed. 2021 John Wiley & Sons, Inc.

Isomers – Overview / Two Types

- Isomers are different compounds that have the same formula
- There are two general types of isomers

Isomers

Constitutional isomers

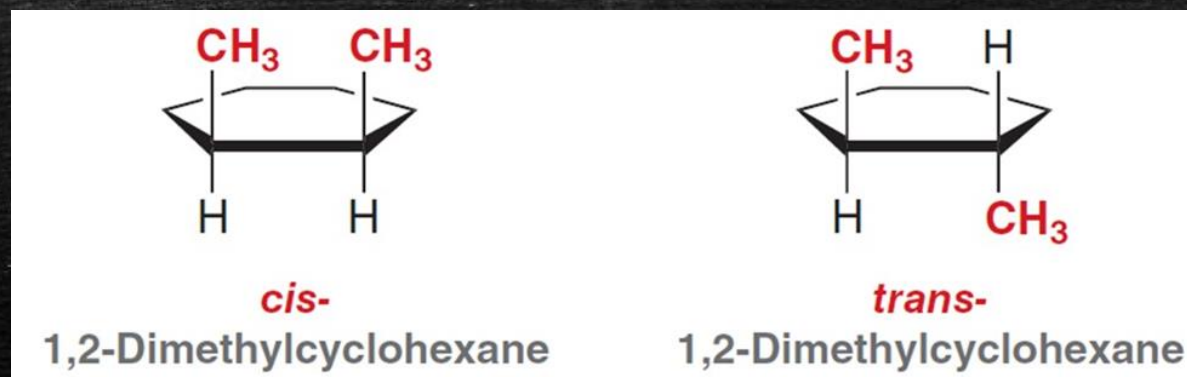
Same molecular formula but different constitution (order of connectivity of atoms)

Stereoisomers

Same molecular formula and constitution but different spatial arrangement of atoms

Isomers – Overview / Stereoisomers

- Although the two molecules below have the same connectivity, they are not identical. So they are **stereoisomers**



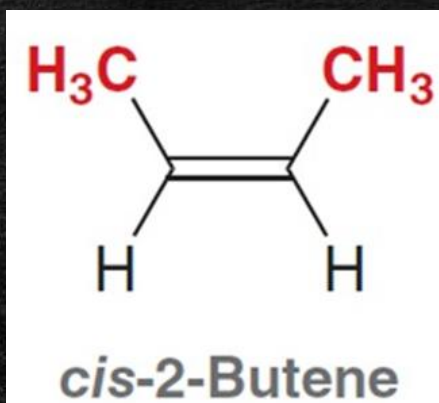
(Both groups on same side of ring)

(Both groups on opposite sides)

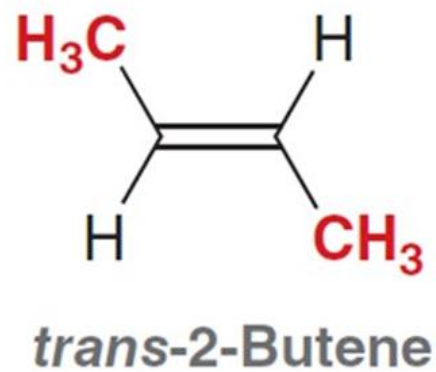
- In order to give these compounds unique IUPAC names, we use the *cis* and *trans* prefixes

Isomers – Overview / Examples

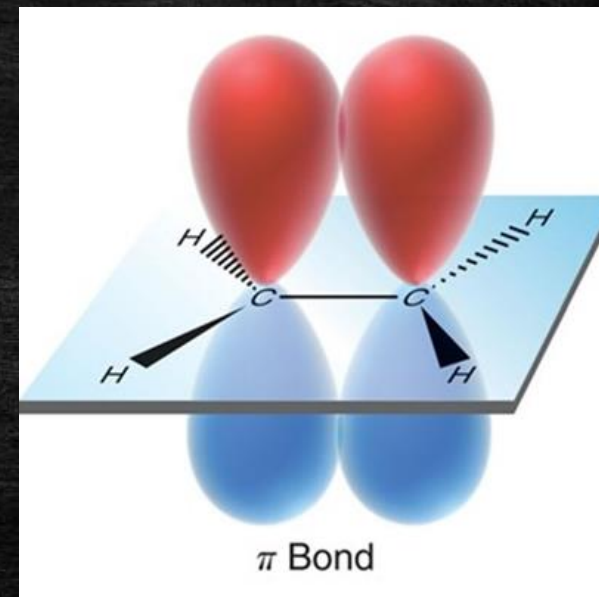
- To maintain orbital overlap in the pi bond, C=C double bonds cannot freely rotate.
- Although the two molecules below have the same connectivity, they are not identical... they are **stereoisomers**



*Groups on same
side of pi bond*

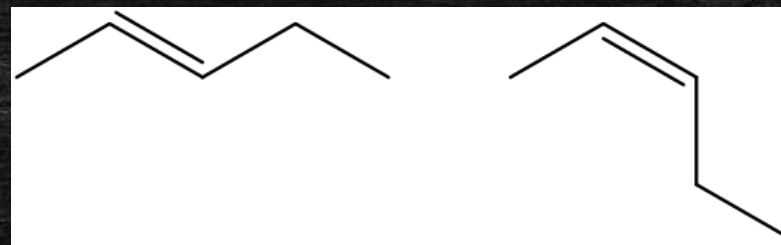
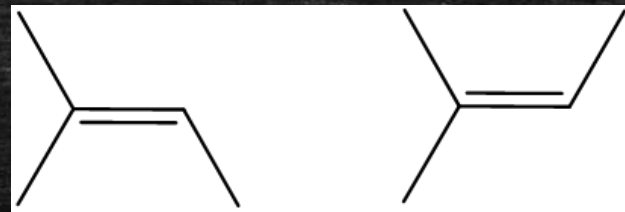
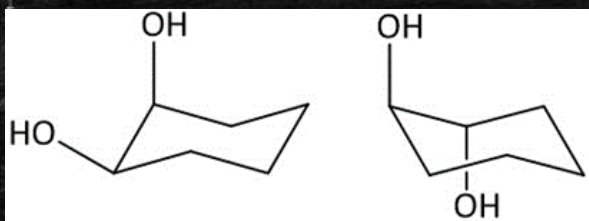


*Groups on
opposite sides*



Isomers – Overview / Practice

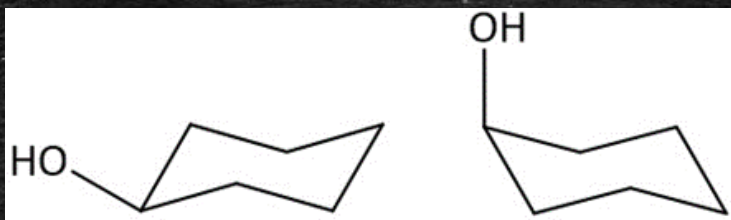
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures



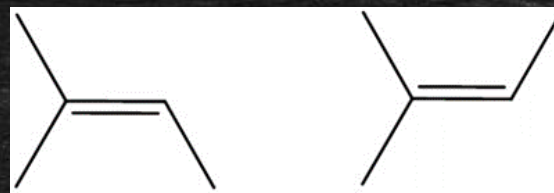
Answers on the next slide

Isomers – Overview / Practice Answers

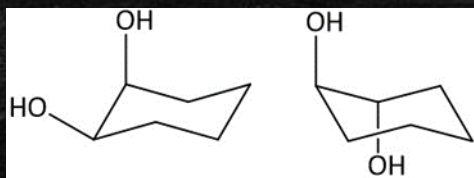
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures



identical



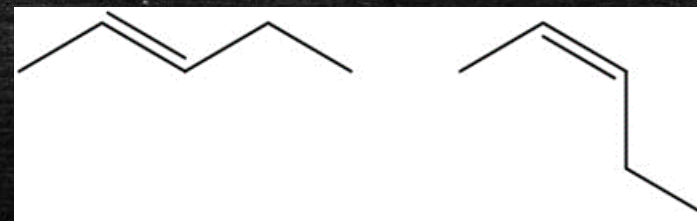
identical



stereoisomers



constitutional isomers



stereoisomers

Stereoisomers / Definition of a Chiral Molecule

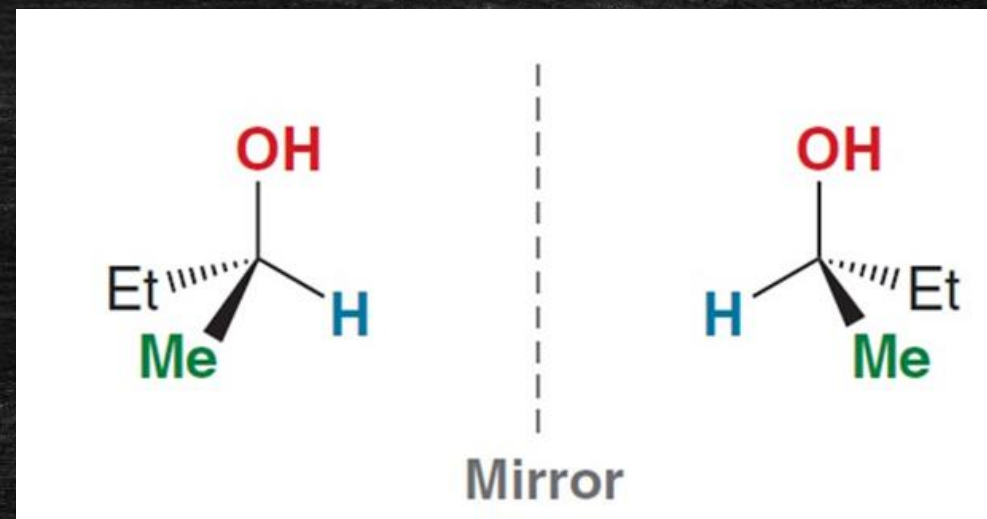
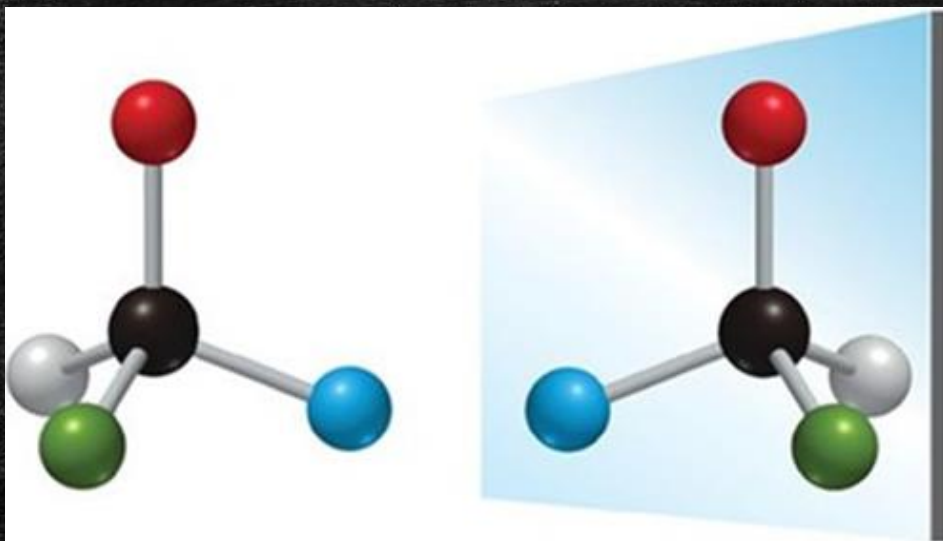
- *cis-trans* isomerism is only one type... there are other important stereoisomeric relationships
- To identify such stereoisomers, we must be able to identify **chiral** molecules
- A **chiral** object is **asymmetric**, which means it is not the same as its mirror image (i.e. **not superimposable** on its mirror image)
- You can test whether two objects are identical by seeing if they are **superimposable**.

Molecular Chirality

- Chirality is important in molecules
 - Because two chiral molecules are mirror images, they will have many identical properties, but because they are not identical, their **pharmacology** may be very different
- Visualizing mirror images of molecules and manipulating them in 3-D space to see if they are superimposable can be very challenging, so...
...it is **absolutely critical** that you **use handheld models** as visual aids

Stereoisomers / Mirror Images

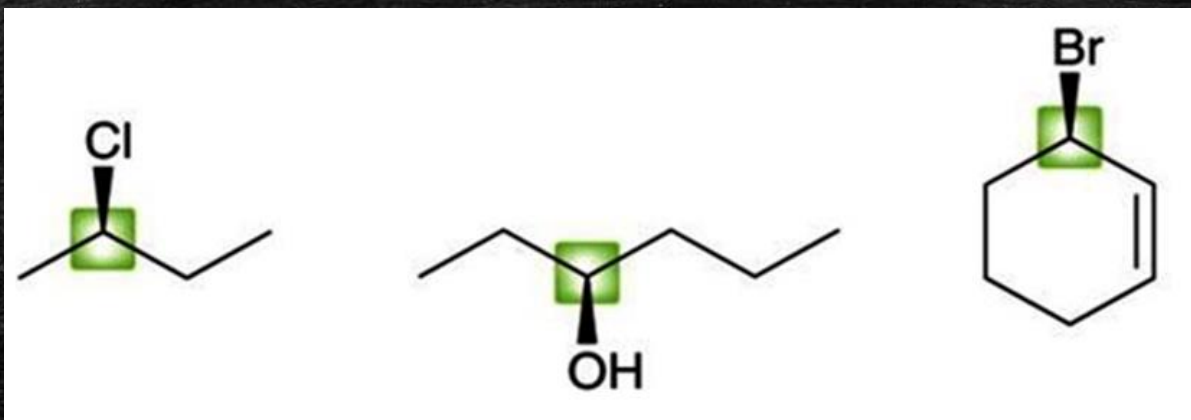
- Chirality most often results when a carbon atom is bonded to four unique groups of atoms.



- Make a handheld model to prove to yourself that they are not superimposable

Stereoisomers / Practice One

- When an atom (like carbon) forms a tetrahedral center with four different groups attached to it, it is called a chiral center
- Analyze the attachments for each chiral center below

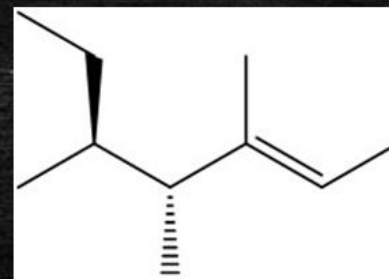
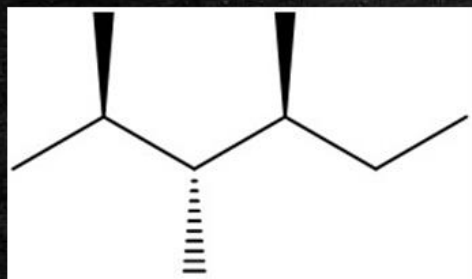
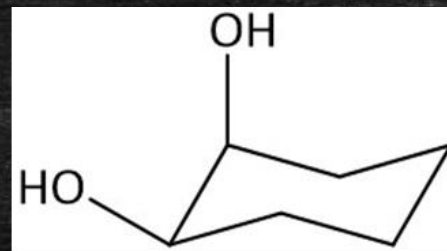
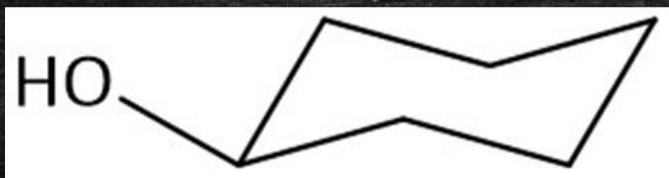


Each highlighted carbon is bonded to 4 different groups and is a chiral center

Practice with SkillBuilder 5.1 – Locating Chiral Centers.

Stereoisomers / Practice Two

- How many chiral centers are in each of the following compounds?



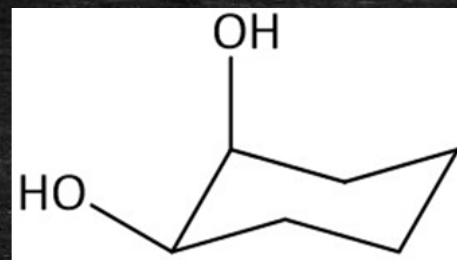
Answers on the next slide

Stereoisomers / Practice Two Answers

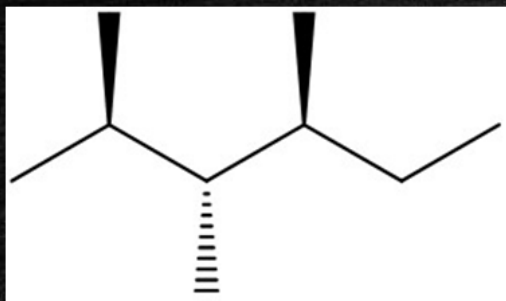
- How many chiral centers are in each of the following compounds?



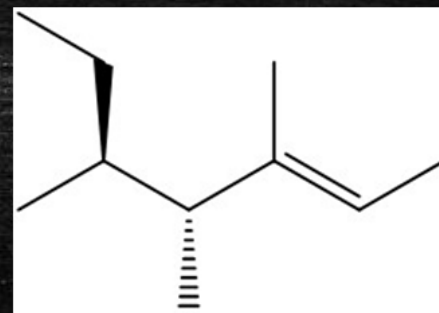
no chiral centers



two chiral centers



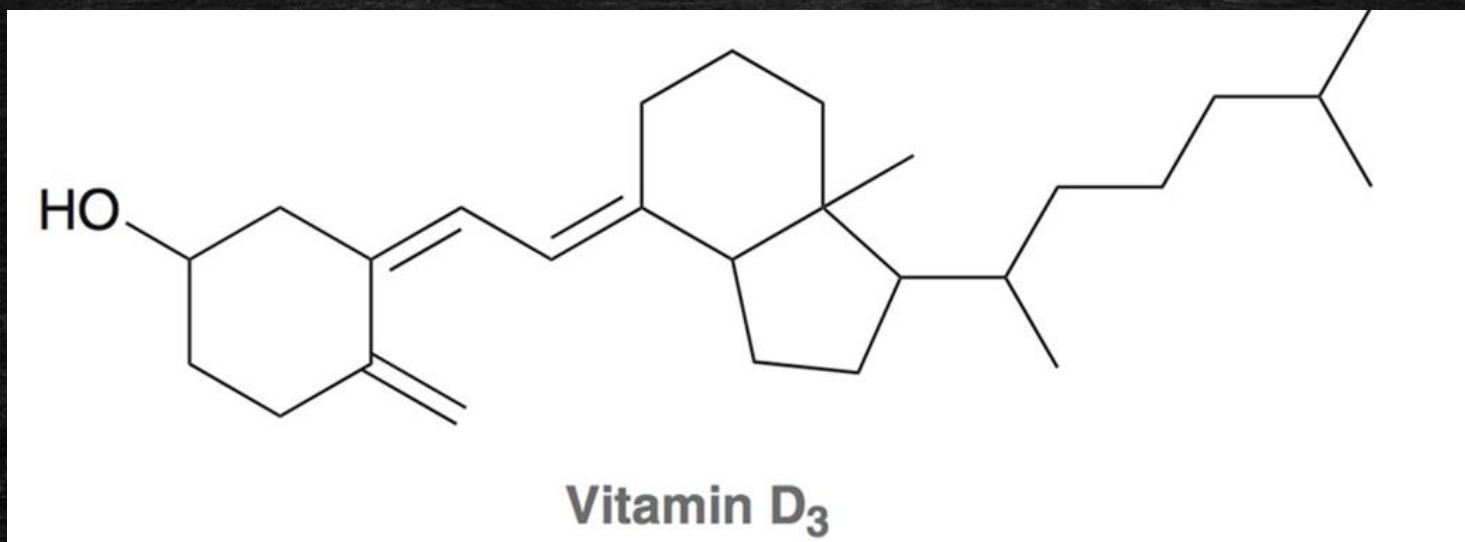
two chiral centers



two chiral centers

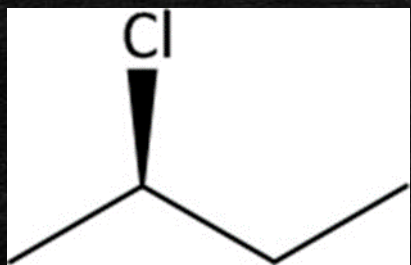
Stereoisomers / Practice Three

- **Practice the Skill 5.4** - Identify and label all the chiral centers in Vitamin D₃



Enantiomers / Definition of Enantiomers

- Some stereoisomers can also be classified as enantiomers
- **Enantiomers** are two molecules that are mirror images but are **not superimposable**, therefore **not identical**
- Only a chiral compound can have an enantiomer



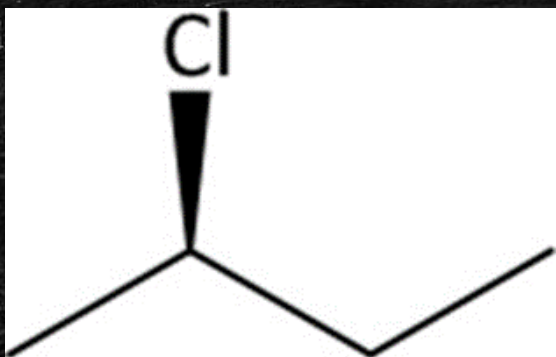
this is a **chiral compound**...



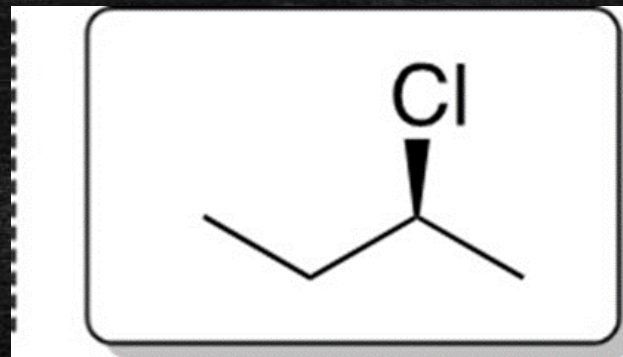
... the mirror image will be its **enantiomer**

Enantiomers / Example of Two Enantiomers

- Some stereoisomers can also be classified as enantiomers
- **Enantiomers** are two molecules that are mirror images but **are not superimposable**, therefore **not identical**
- Only a chiral compound can have an enantiomer



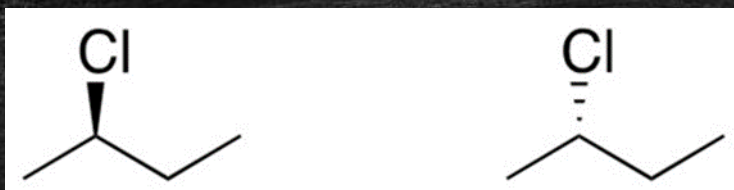
this is a **chiral compound**...



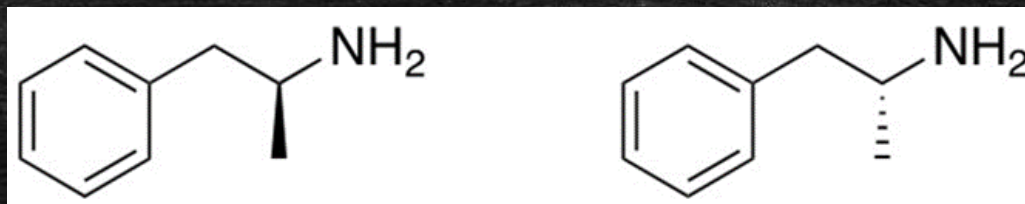
... the mirror image will be its **enantiomer**

Enantiomers / Drawing Enantiomers

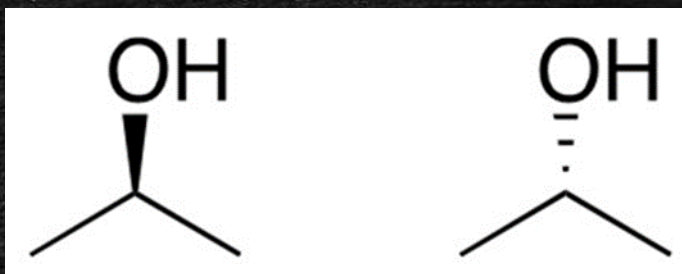
- Another, often easier way to draw the enantiomer of a chiral compound is to invert the dashes and wedges of a chiral center



enantiomers



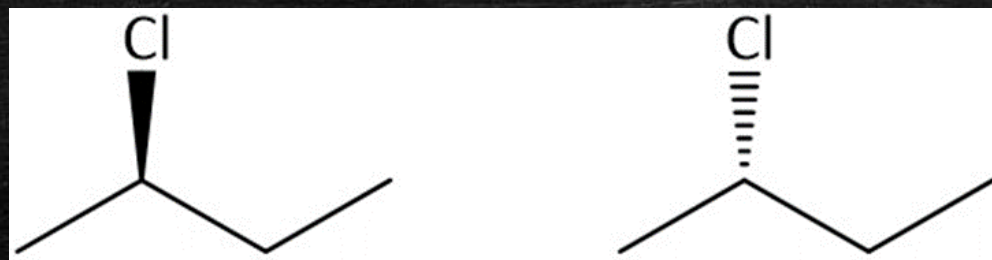
enantiomers



this is not a chiral compound, so inverting the dashes/wedges provides an identical structure!

Designating R vs. S Configuration / Introduction

- Enantiomers are different compounds, so they must not have identical names
- They have opposite configuration at their chiral center(s)



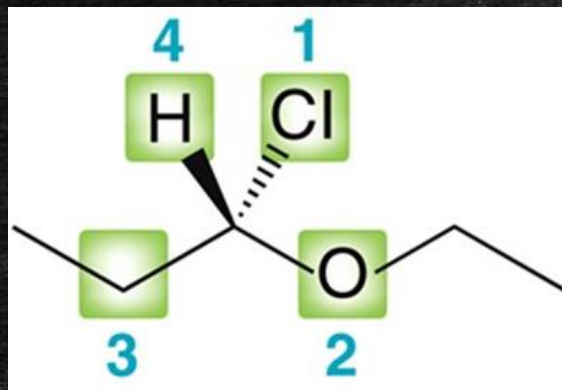
- We use the **Cahn-Ingold-Prelog system** to designate each chiral center as having either the "R" or "S" configuration.
- If a compound has the "R" configuration at a chiral center, then the enantiomer will have the "S" configuration

Designating R vs. S Configuration / Four Steps

- "R" or "S" is assigned to a chiral center using a stepwise procedure
 1. Using atomic numbers, prioritize the four groups attached to the chiral center (1, 2, 3 and 4)
 2. Arrange the molecule in space so the lowest priority group faces away from you
 3. Count the group priorities 1...2...3 to determine whether the order progresses in a clockwise or counterclockwise direction
 4. Clockwise = *R* and Counterclockwise = *S*
- A handheld model can be very helpful visual aid for this process

Designating R vs. S Configuration / Step One

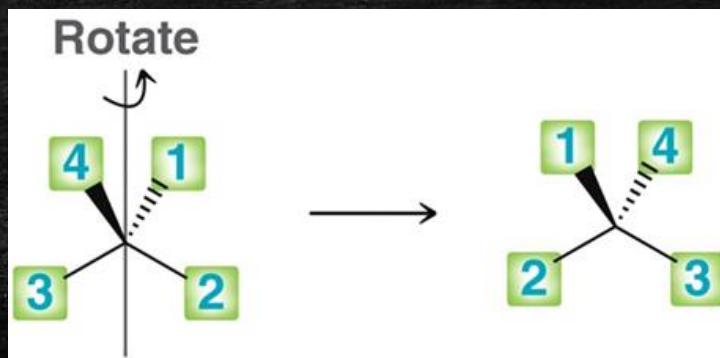
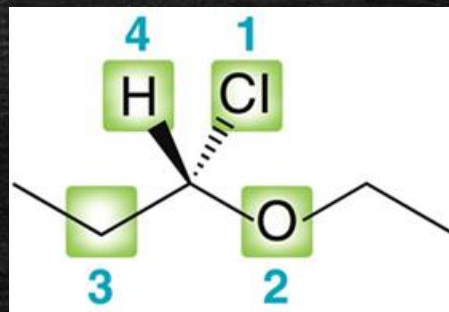
- The Cahn, Ingold and Prelog system
 1. Using atomic numbers, prioritize the four groups attached to the chiral center. The higher the atomic number, the higher the priority



- The atom with the largest atomic number is assigned the highest priority (1), and so on...

Designating R vs. S Configuration / Step Two

- The Cahn, Ingold and Prelog system end
 2. Arrange the molecule in space so the lowest priority group faces away from you

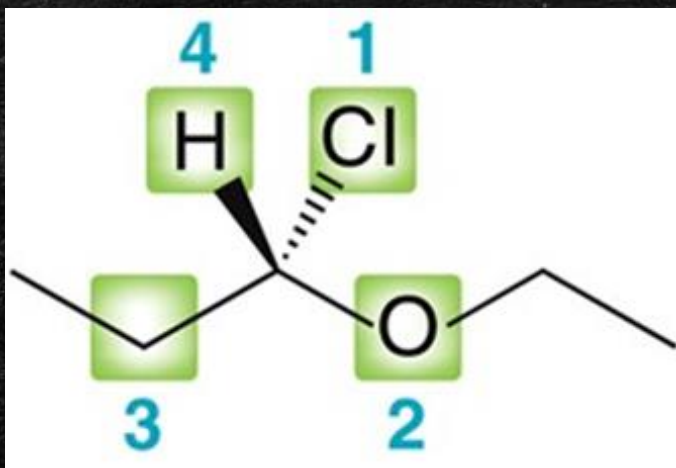


- ****This is the step where it is most helpful to have a handheld model**

Designating R vs. S Configuration / Step Three

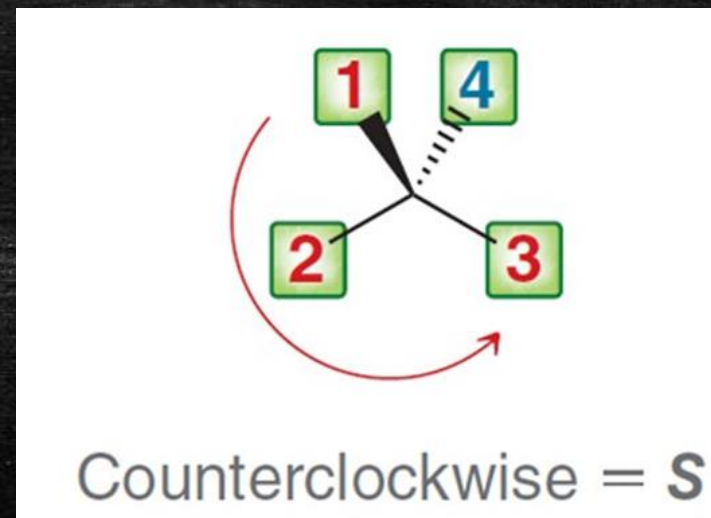
- The Cahn, Ingold and Prelog system
 3. Counting the other group priorities, 1...2...3, determine whether the order progresses in a clockwise or counterclockwise direction

Clockwise = *R*



and

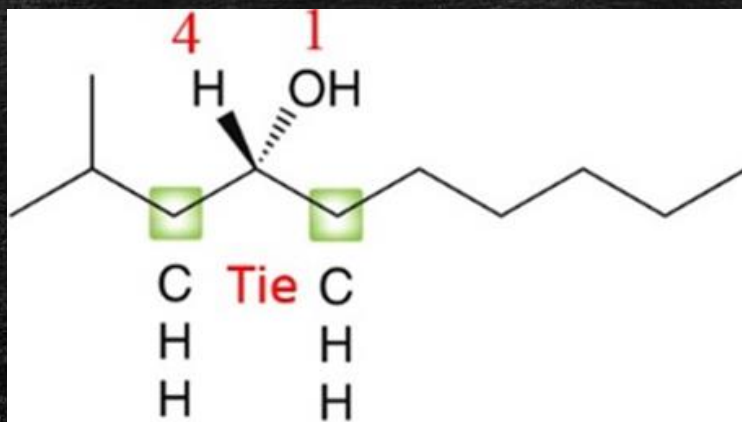
Counterclockwise = *S*



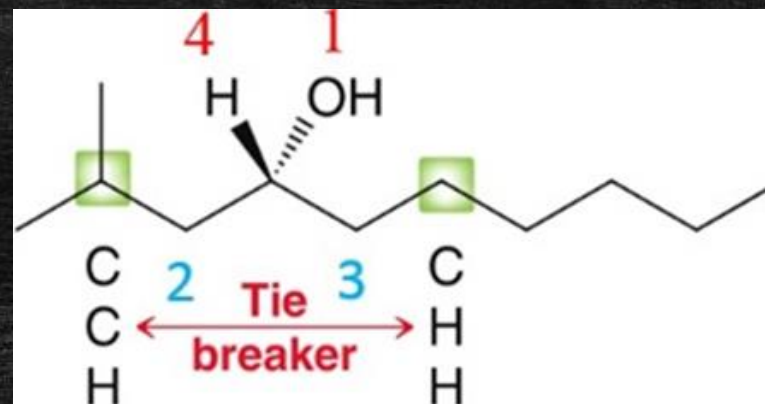
and so we just determined this chiral center has the (*S*) configuration

Designating R vs. S Configuration / Challenges

- When the groups attached to a chiral center are similar, it can be tricky to prioritize them
- Analyze the atomic numbers one layer of atoms at a time



The **1** and **4** groups are obvious, but there is a tie for priority **2** and **3**

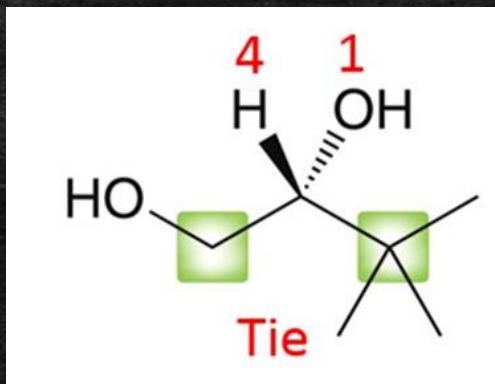


So we have to compare the atomic weights of the atoms bonded to each carbon to break the tie

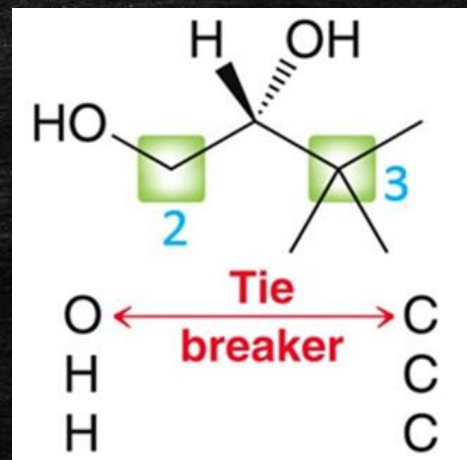
Designating R vs. S Configuration / First and Second Layers

- Analyze the atomic numbers one layer of atoms at a time

- **First layer**



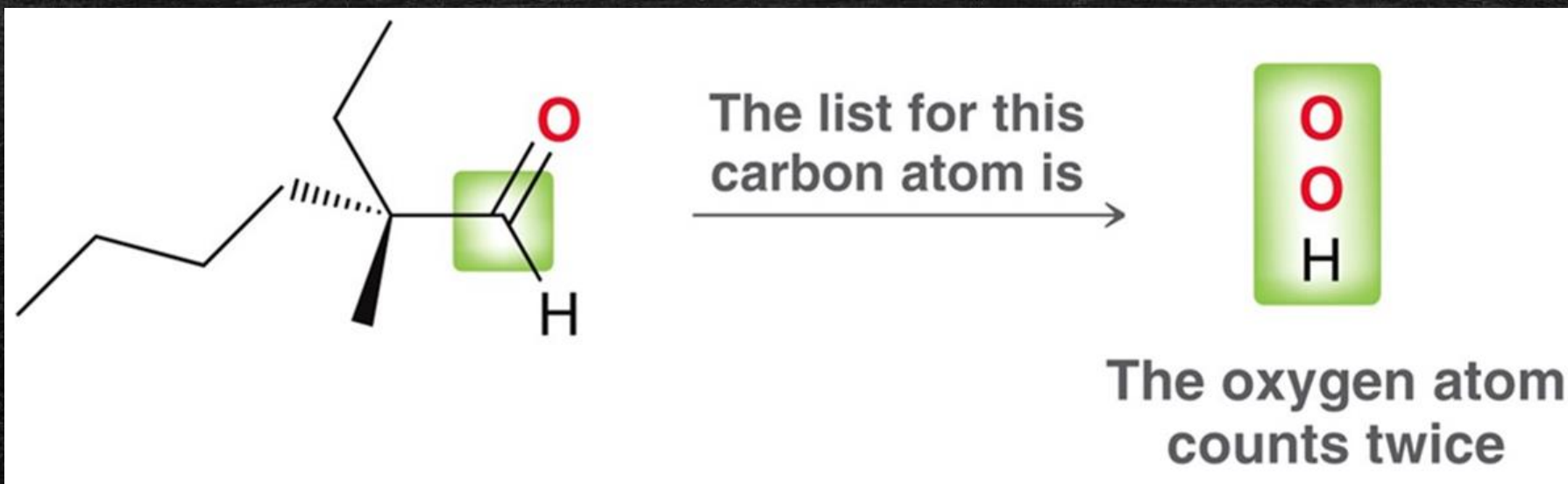
- **Second layer**



The priority is based on the first point of difference!

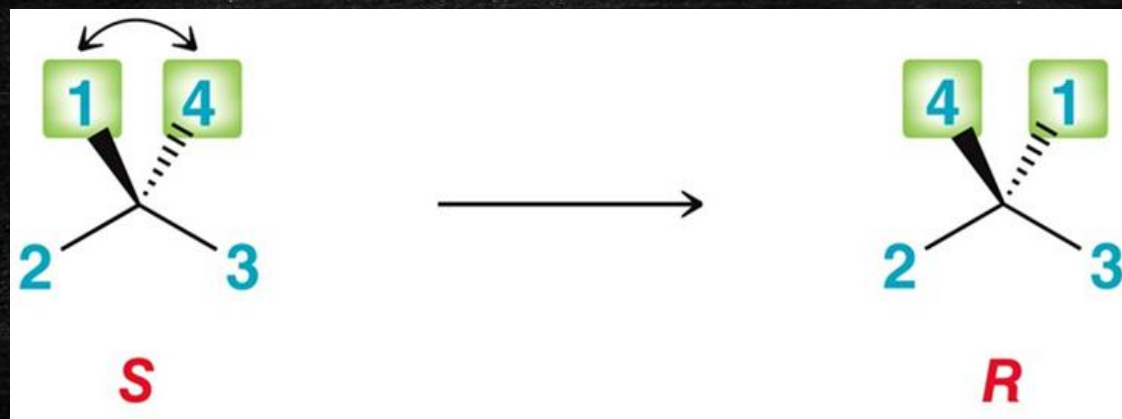
Designating R vs. S Configuration / Double Bonds

- When prioritizing for the Cahn, Ingold and Prelog system, double bonds count as two single bonds



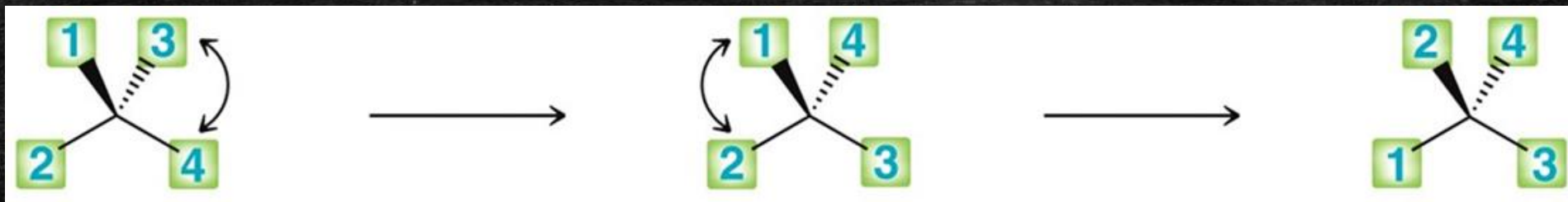
Rotating the Molecule / Useful Trick

- Handheld molecular models can be very helpful when arranging the molecule in space so the lowest priority group faces away from you
- Here are some other tricks that you can use
 - Switching two groups on a chiral center will produce its opposite configuration



Rotating the Molecule / More Useful Tricks

- Switching two groups on a chiral center will produce its opposite configuration
- You can use this trick to adjust a molecule so that the lowest priority group faces away from you.



- With the fourth priority group facing away, you can designate the configuration as *R*.
- Switching two of the groups, twice, returns the original configuration but allows us to put the priority 4 group pointing away.

CIP Rules Summary / Steps One - Three

- A review of Cahn-Ingold-Prelog rules: assigning the configuration of a chiral center

Step 1	Step 2	Step 3
Identify the four atoms directly attached to the chiral center.	Assign a priority to each atom based on its atomic number. The highest atomic number receives priority 1, and the lowest atomic number (often a hydrogen atom) receives priority 4.	If two atoms have the same atomic number, move away from the chiral center looking for the first point of difference. When constructing lists to compare, remember that a double bond is treated as two separate single bonds.

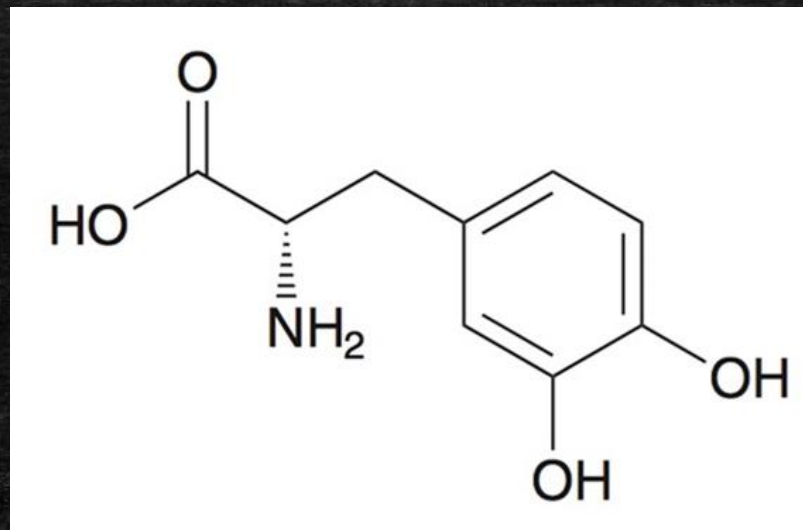
CIP Rules Summary / Steps Four and Five

- A review of Cahn-Ingold-Prelog rules: assigning the configuration of a chiral center

Step 4	Step 5
Rotate the molecule so that the fourth priority is on a dash (going behind the plane of the page).	Determine whether the sequence 1-2-3 follows a clockwise order (<i>R</i>) or a counter clockwise order (<i>S</i>).

Designating R vs. S Configuration

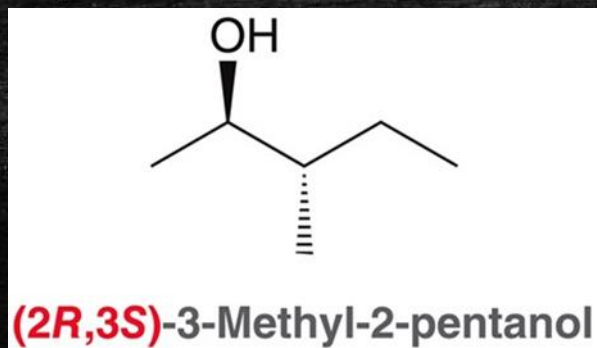
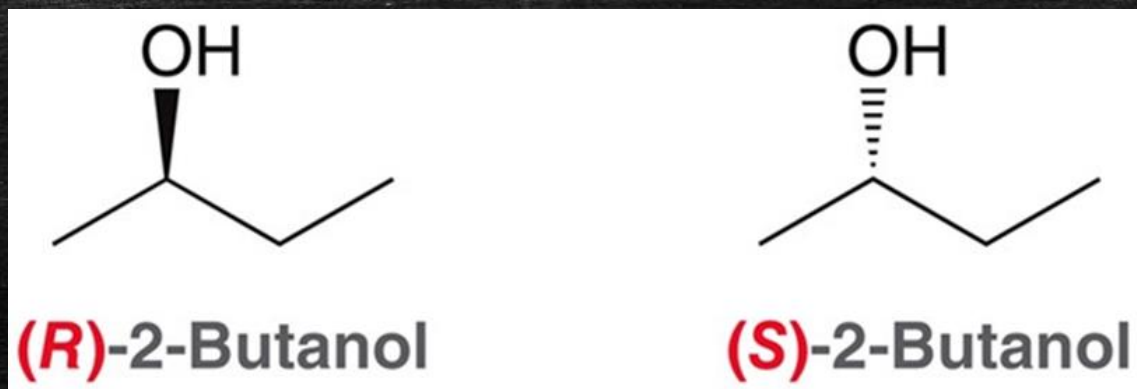
- **SkillBuilder 5.3** – Assign the configuration of the chiral center in the following compound



Get additional practice with **Practice the Skill 5.9**

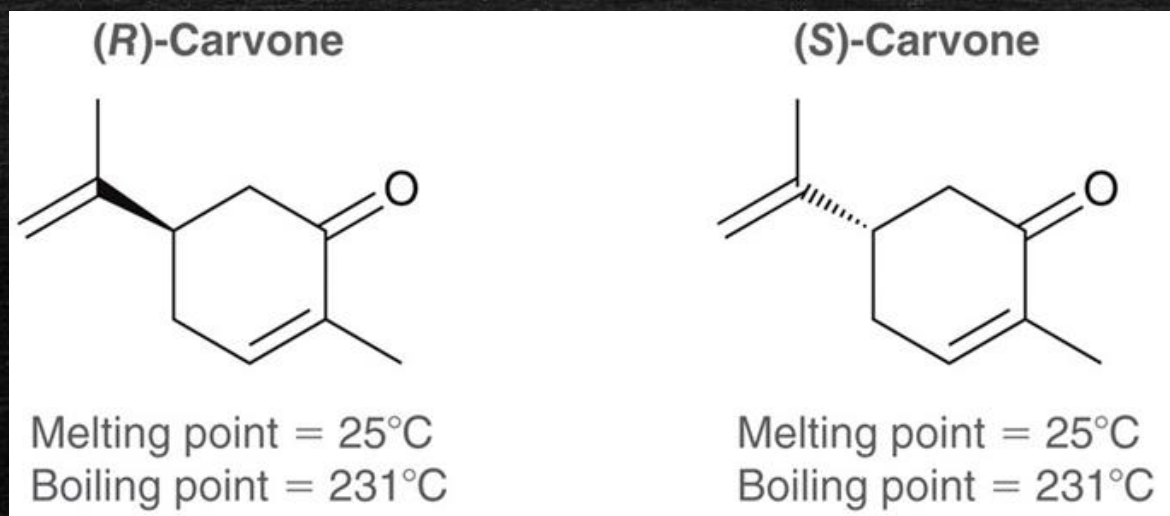
(R) and (S) in IUPAC Nomenclature

- The (*R*) or (*S*) configuration is used in the IUPAC name for a compound to distinguish it from its enantiomer



Optical Activity

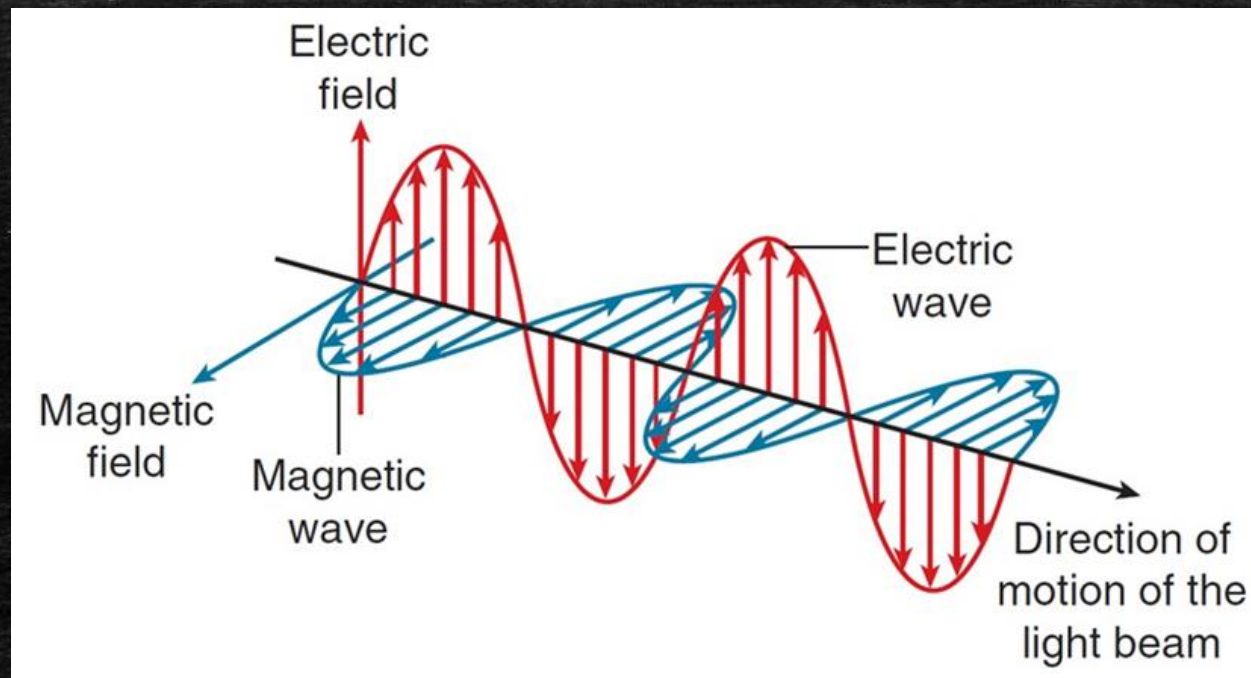
- Because the structures of enantiomers only differ in the same way your right hand differs from your left, they have the same physical properties.



- Enantiomers only differ in (1) **how they interact with other chiral compounds**, and (2) their **optical activity**

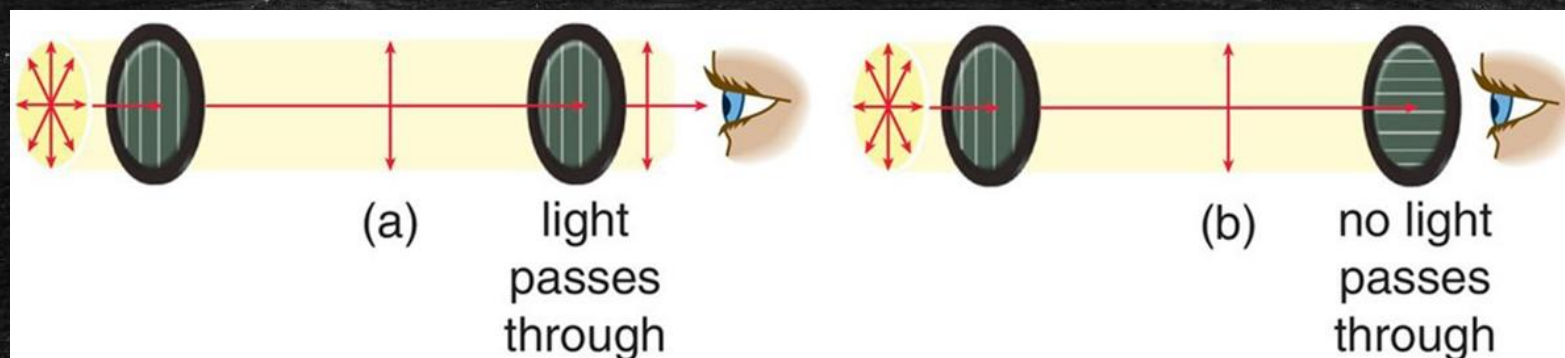
Optical Activity / Plane-Polarized Light

- Enantiomers have opposite configurations (*R* vs. *S*), and rotate **plane-polarized** light in opposite directions



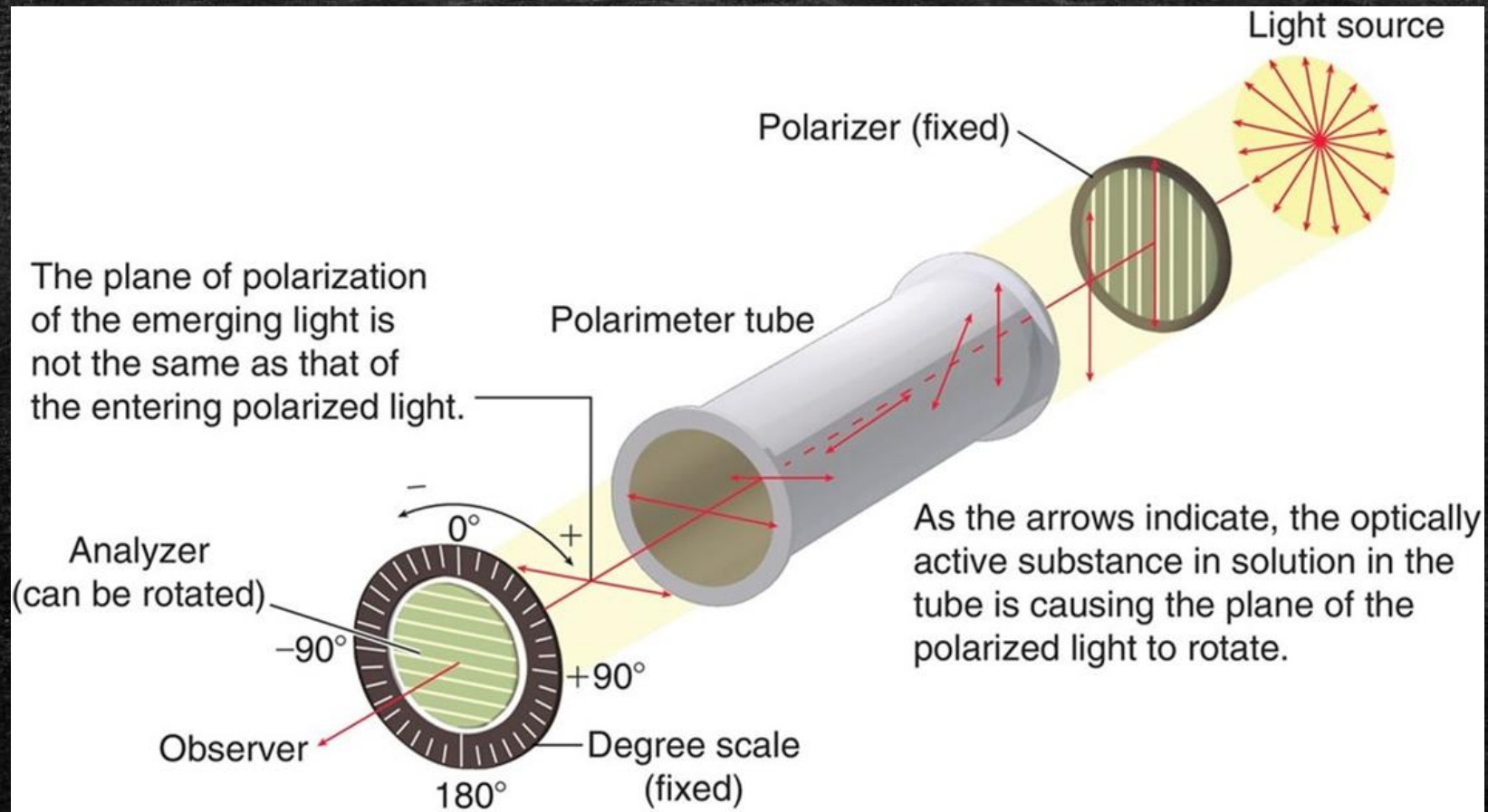
Optical Activity / Chiral Compounds

- To get light waves that travel in only one plane, light travels through a filter.



- When **plane-polarized light** is passed through a sample of chiral compound, the plane that the light travels on will rotate.
- Compounds that can **rotate plane-polarized light** are **optically active**. Only chiral compounds are optically active.

Optical Activity - Polarimeter



Optical Activity / Specific Rotation

- Enantiomers will rotate the plane of the light to equal degrees but in opposite directions
- The degree to which light is rotated depends on the sample concentration and the pathlength of the light
- Standard optical rotation measurements are taken with 1 gram of compound dissolved in 1 mL of solution, and with a pathlength of 1 dm for the light

Temperature and the wavelength of light can also affect rotation and must be reported with measurements that are taken

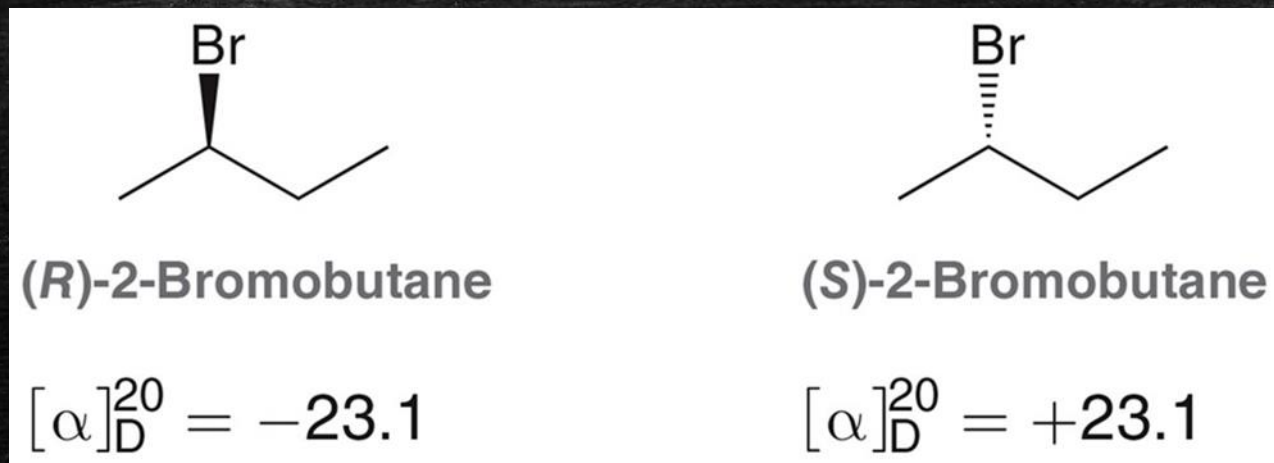
$$\text{Specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

$$[\alpha]_{\lambda}^{\text{temperature}}$$

wavelength

Optical Activity / Examples

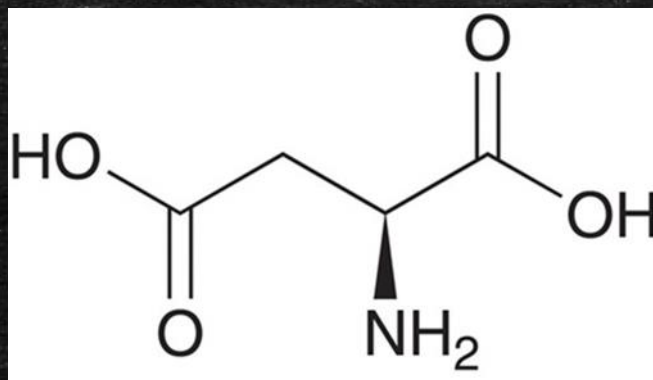
- Consider the enantiomers of 2-bromobutane



- (*R*) and (*S*) refer to the configuration of the chiral center
- (+) and (−) signs refer to the direction that the plane of light is rotated

Optical Activity / Dextrorotary and Levorotary

- (+) rotation is called **dextrorotary**, and (–) is **levorotary**
- The compound below has the (S) configuration



- Its optical rotation is levorotatory (–) at 20° C, but it is dextrorotatory (+) at 100 ° C
- **There is no correlation between R/S and +/ –**

Optical Activity / Racemic Mixtures

- The magnitude and direction of optical rotation cannot be predicted, and has to be measured experimentally
- However, we can predict the rotation of a racemic mixture to be 0° (the optical rotation of each enantiomer cancels each other).
 - **Racemic mixture:** 50/50 mixture of two enantiomers
- If one enantiomer is present *in excess*, relative to the other, then the mixture will have an optical rotation, but it will be less than the pure enantiomer.

Enantiomeric Excess

- For unequal amounts of enantiomers, the **enantiomeric excess (% ee)** can be determined from the optical rotation



- Suppose a mixture of (R) and (S) 2-bromobutane has a specific rotation of -4.6° . This allows us to determine the **% ee**

$$\% ee = \frac{|\text{observed } \alpha|}{\alpha \text{ of pure enantiomer}} \times 100\%$$

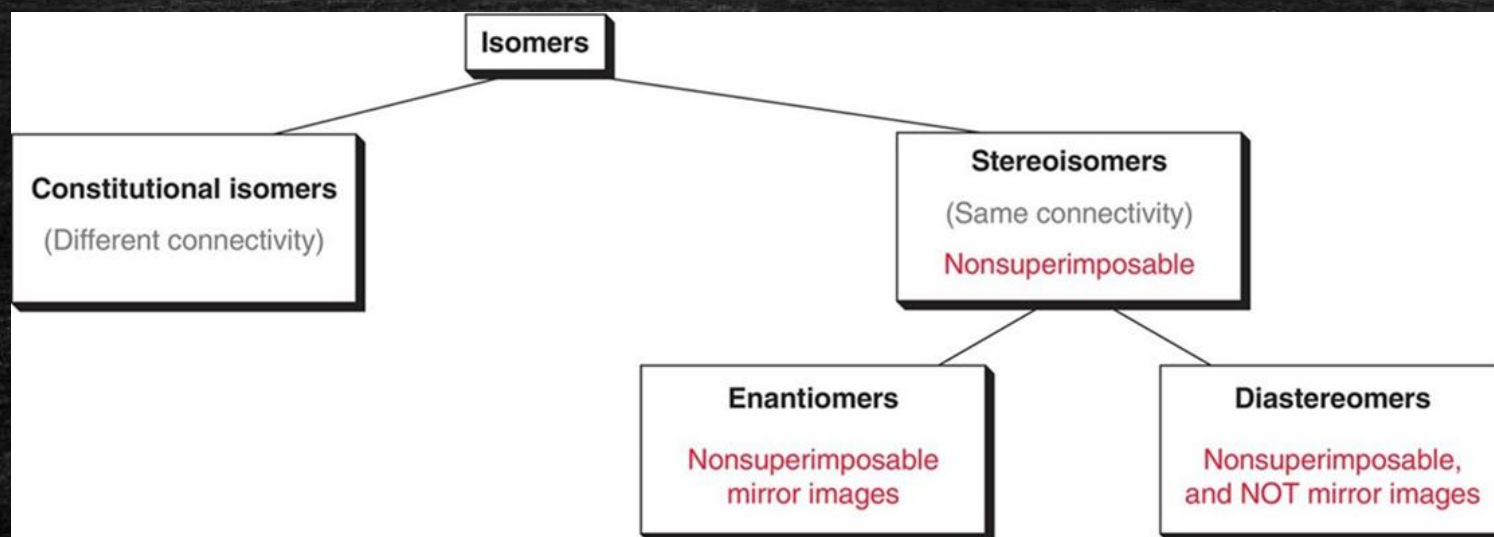
$$\frac{(-4.6)}{(-23.1)} \times 100\% = 20\% ee$$

Practice with SkillBuilder 5.5 – Calculating % ee.

Enantiomers and Diastereomers / Definitions

Categories of isomers

* there are two sub-categories of stereoisomers



- **Enantiomers:** stereoisomers that are mirror images
- **Diastereomers:** stereoisomers that are not mirror images

Enantiomers and Diastereomers / Examples

- Consider the structures of *cis*- and *trans*-2-butene.



- They are stereoisomers, but not mirror images of each other. So, they are **diastereomers!**
- Recall that enantiomers have identical physical properties.
- Diastereomers have different physical properties.**

Stereoisomeric Relationships / Introduction

- Consider a cyclohexane with three substituents



- There are three stereocenters here, and so there are eight possible stereoisomers (all drawn above). Consider the relationship among them (enantiomers vs. diastereomers)

Stereoisomeric Relationships / Eight Stereoisomers

- Notice these eight stereoisomers are comprised of four pairs of enantiomers



- You can think of this as a family where there are four pairs of twins, for a total of eight kids. Each kid has seven siblings, where one of them is their twin (i.e. enantiomer) and the other six are diastereomers

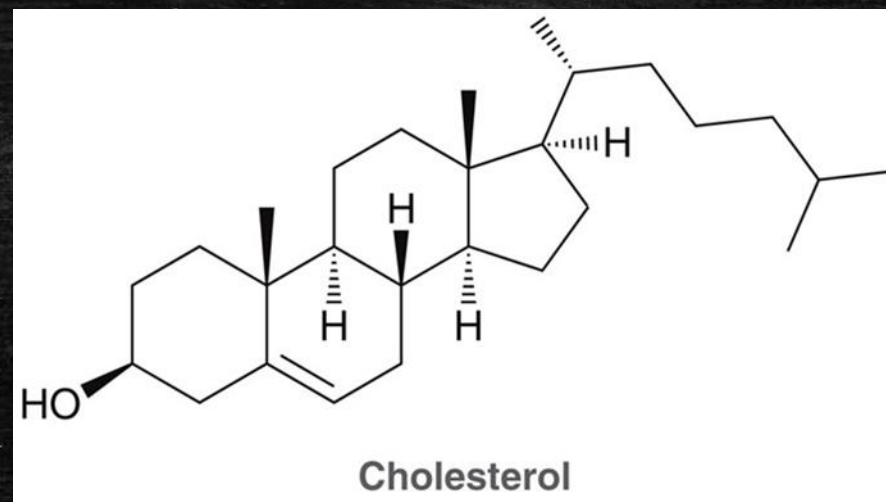
Stereoisomeric Relationships / Effect of Number of Chiral Centers

- The number of possible stereoisomers for a compound depends on the number of chiral centers (n) in the compound

$$\text{Maximum number of stereoisomers} = 2^n$$

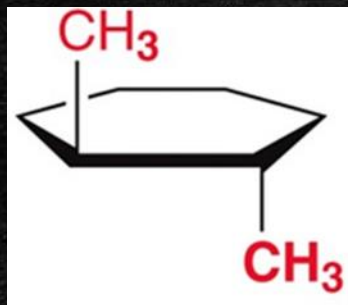
- What is the maximum number of possible cholesterol isomers?

- Practice with SkillBuilder 5.6 – Determining the Stereoisomeric Relationship.

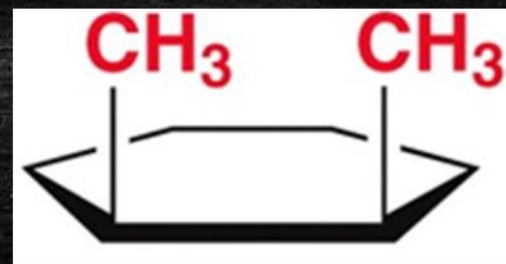


Symmetry and Chirality / Introduction

- Any compound with **only one chiral center will be a chiral compound**
- With more than one chiral center, a compound may not be chiral; it may have a plane of symmetry
- Consider the stereoisomers below, which possess TWO chiral centers:



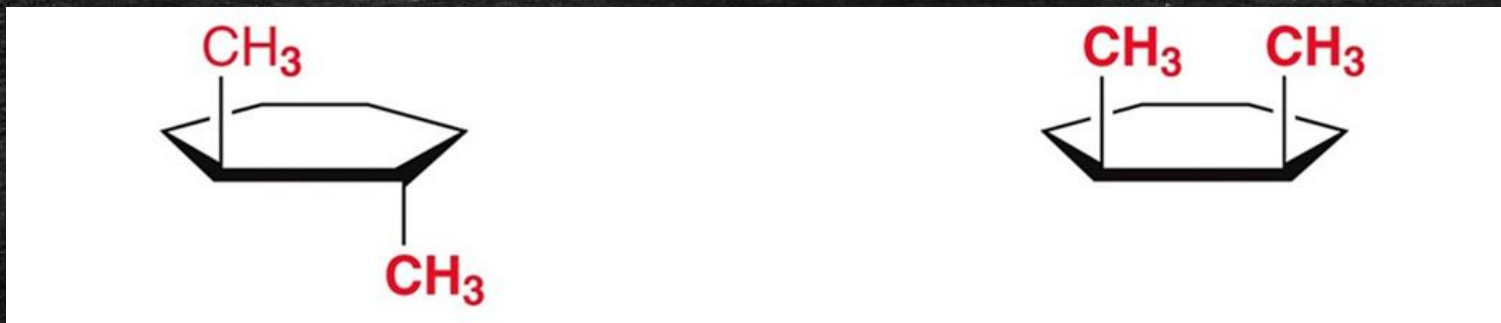
trans-1,2-dimethylcyclohexane



cis-1,2-dimethylcyclohexane

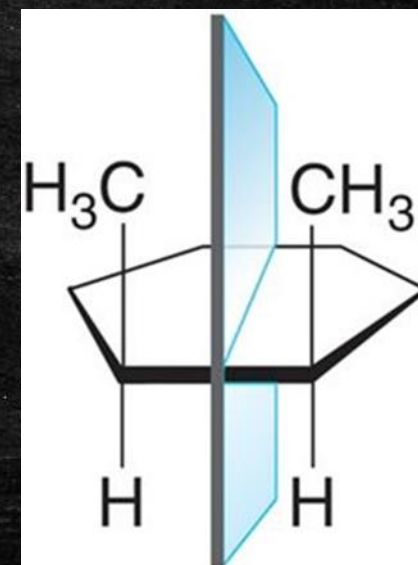
Symmetry and Chirality / cis vs trans

- The *trans* isomer is chiral, but the *cis* isomer is not (it is achiral)



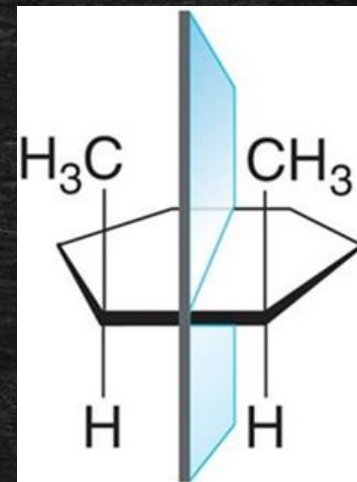
If a molecule has a plane of symmetry, it will be achiral

The *cis* isomer has a plane of symmetry, which means it will be superimposable on its mirror image, and is not a chiral compound



Symmetry and Chirality / Meso Compounds

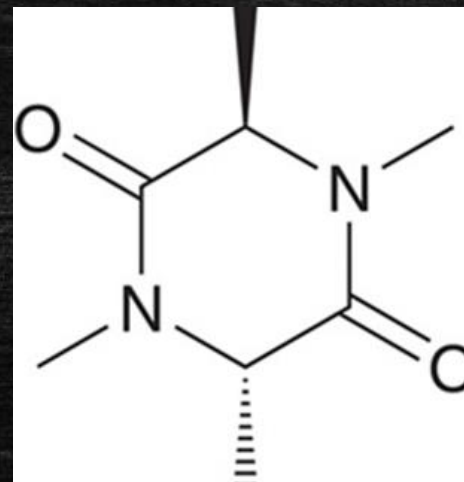
- Molecules with an even number of chiral centers that have a plane of symmetry are called **meso compounds**
- Another way to test if a compound is a **meso compound** is to see if it is identical to its mirror image
- Draw the mirror image of the *cis* isomer and show that it can be superimposed on its mirror image
- By definition, when a compound is identical to its mirror image, it is not chiral. It is achiral



Symmetry and Chirality / Achiral Compounds

- If a compound has a **plane of symmetry**, it is **achiral**
- But... a compound that lacks a plane of symmetry may still be an achiral compound... if it has reflectional symmetry through **inversion** about a central point in the molecule

- The molecule to the right has two chiral centers, and no plane of symmetry, but it is still achiral because of inversion

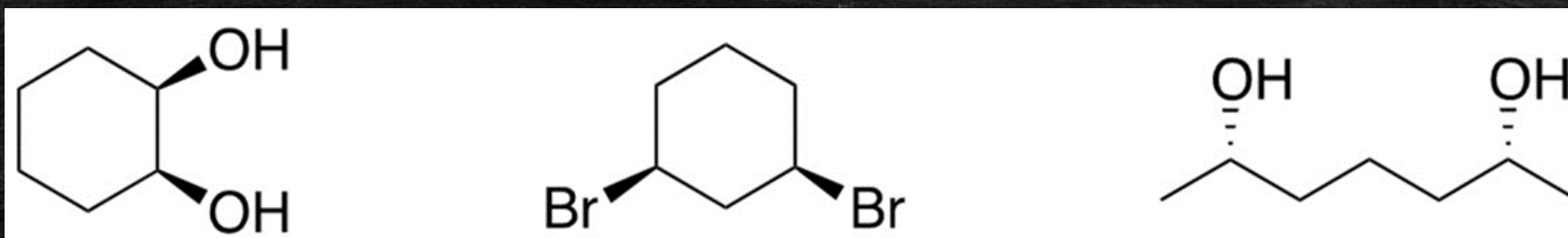


Symmetry and Chirality / Summary

- Overall:
 - The presence or absence of rotational symmetry is irrelevant to chirality.
 - A compound that has a plane of symmetry is achiral.
 - A compound without a plane of symmetry will *usually be chiral*, but there are exceptions (such as a compound with an inversion center).

Meso Compounds

- A compound with chiral centers, but is achiral because of symmetry is called a **meso compound**
- The molecules below are *meso* compounds:



- *meso* compounds have less than the predicted number of stereoisomers based on the $2^{(n)}$ formula
- Practice with SkillBuilder 5.7 – Identifying *Meso* Compounds.

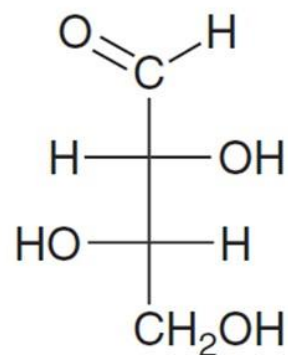
Fischer Projections / Introduction

- Fischer projections can also be used to represent molecules with chiral centers
- **Horizontal lines** represent attachments **coming out of the page**
- **Vertical lines** represent attachments going **back into the page**

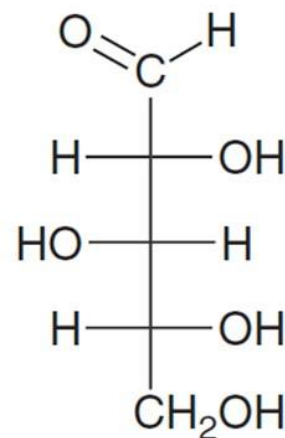


Fischer Projections / Examples

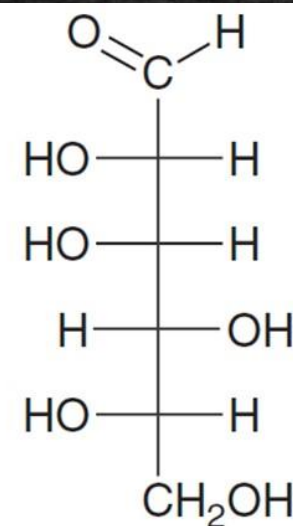
- Fischer projections are most useful when drawing molecules having multiple chiral centers (like sugars, shown below).



Two chiral centers



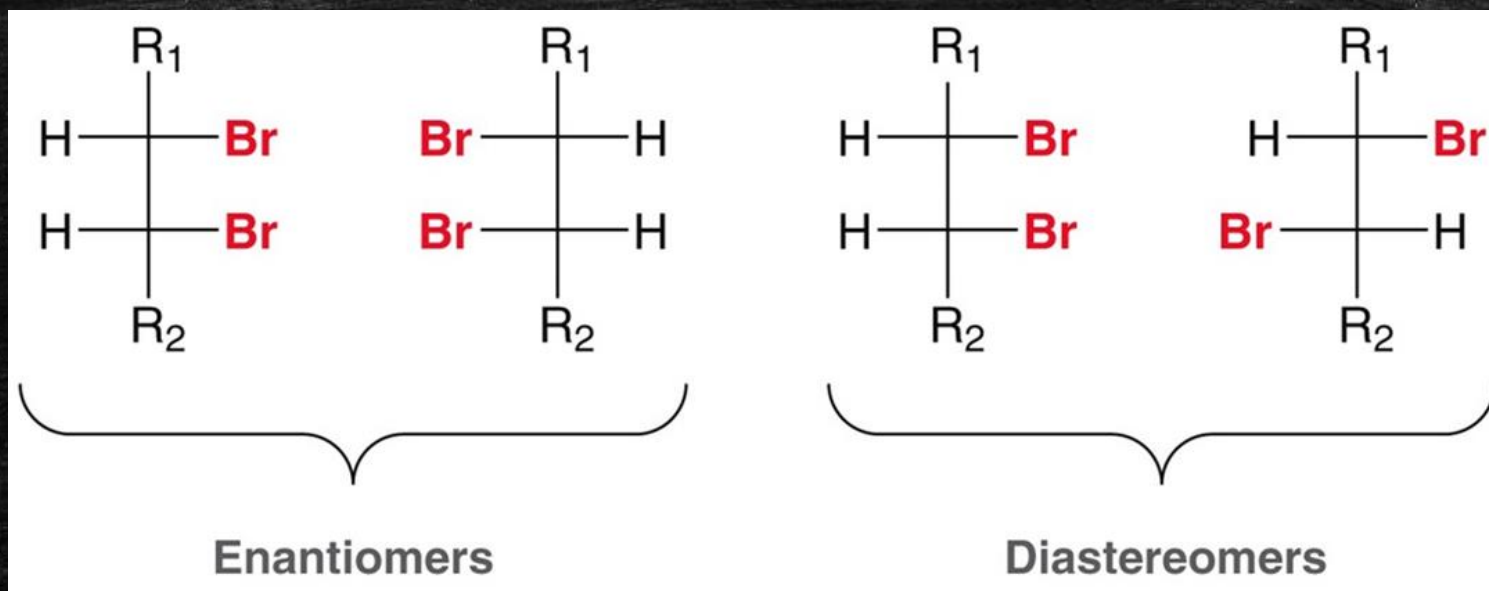
Three chiral centers



Four chiral centers

Fischer Projections / Enantiomers vs Diastereomers

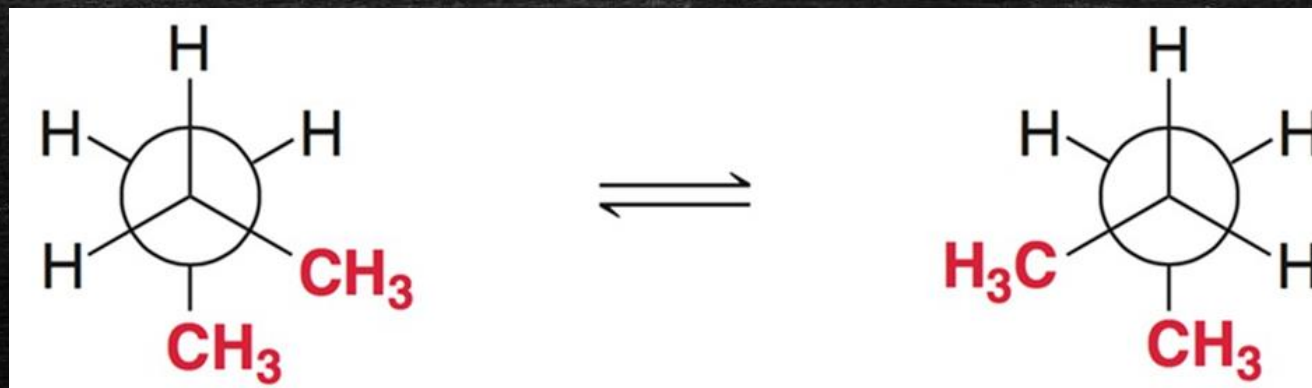
- Fischer projections are also useful to quickly assess stereoisomeric relationships



Practice with SkillBuilder 5.8 – Assigning Configuration.

Conformationally Mobile Compounds

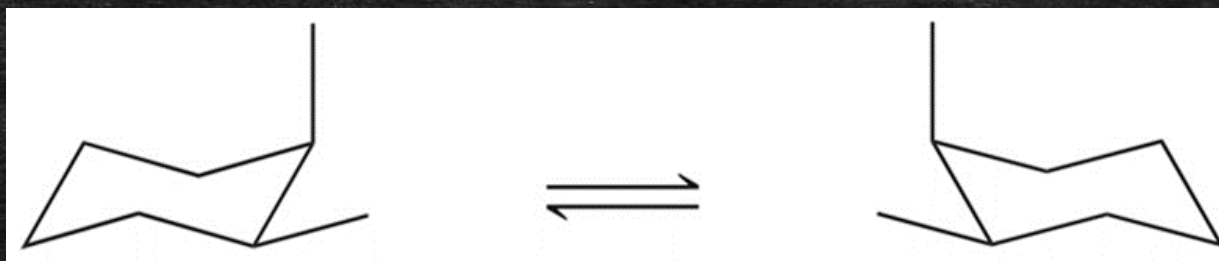
- Molecules can rotate around single bonds.
- Recall the *gauche* rotational conformations of butane.



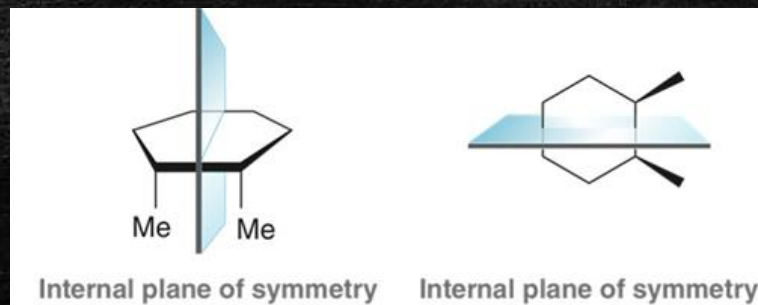
- Realize that these *conformations* are chiral and are actually enantiomeric.
- But, because these rotatomers are interchangeable via bond rotation, butane is not a chiral compound.

Interconverting Enantiomers

- Compare both possible chair conformations of (*cis*)-1,2-dimethylcyclohexane

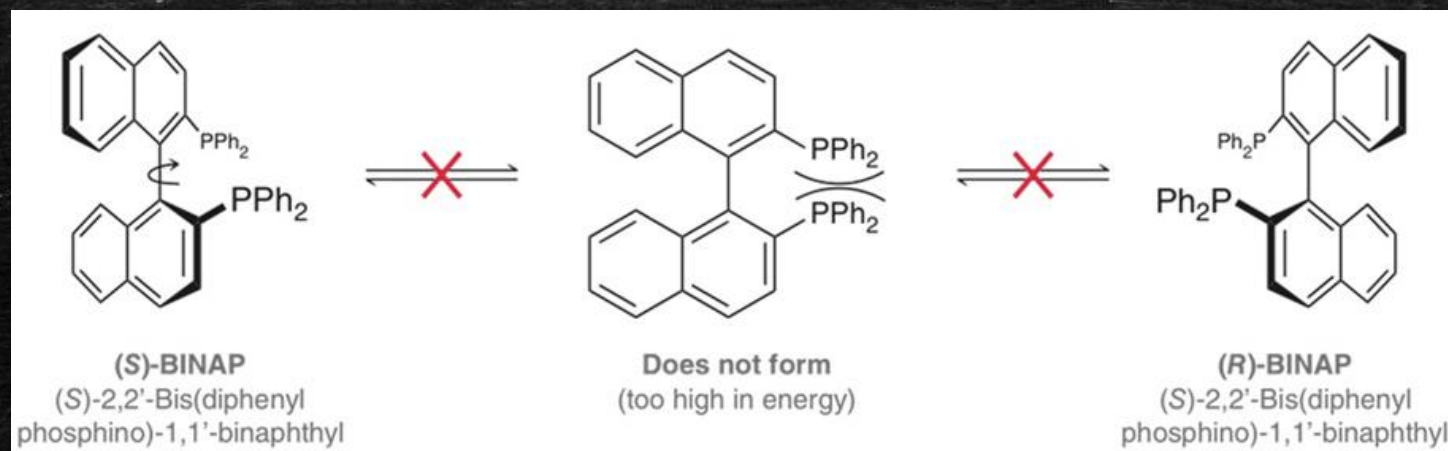


- These conformations are chiral, and also enantiomeric
- However, these conformations interconvert, and overall this is an achiral compound (possesses a plane of symmetry)



Chirality without Chiral Centers / Atropisomers

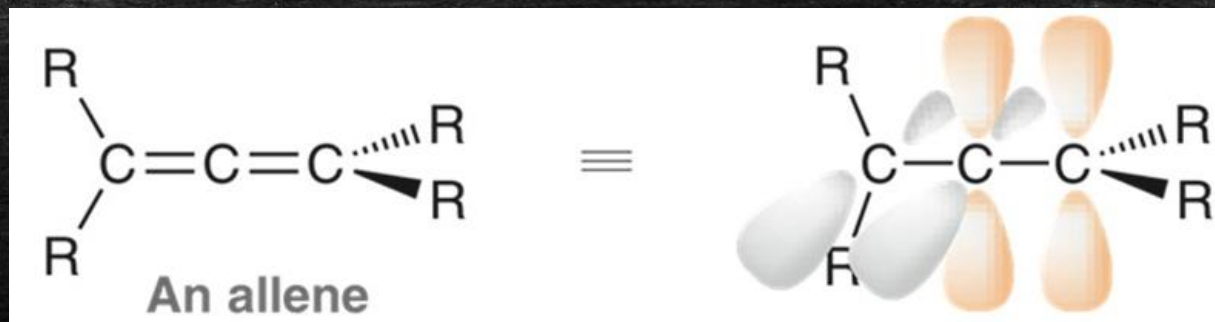
- **Atropisomers:** stereoisomers that would be interchangeable through the rotation of a sigma bond, but because the bond is unable to rotate, the different conformations are “stuck” and not interchangeable.



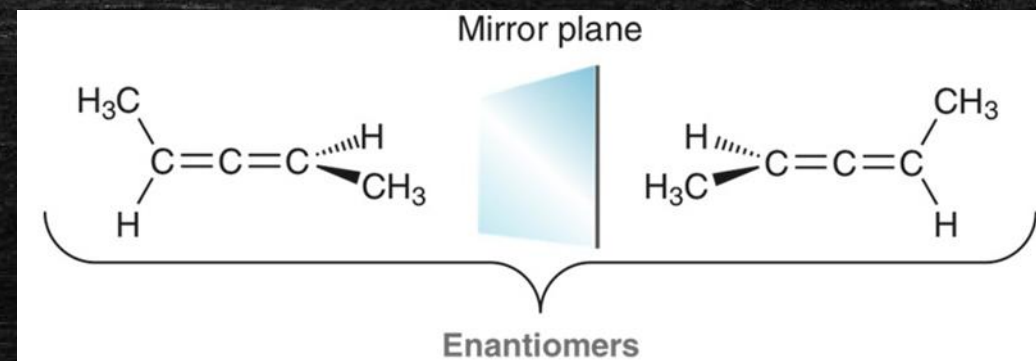
- (R) and (S)-BINAP are chiral, and enantiomers of one another, even though they do not have any chiral centers (they instead have an “axis of chirality.”)

Chirality without Chiral Centers / Allenes

- **Allenenes:** compounds that possess two adjacent C=C double bonds. They may or may not be chiral depending on the substituents



- The two groups on each end of the allene are different, then it will be a chiral compound

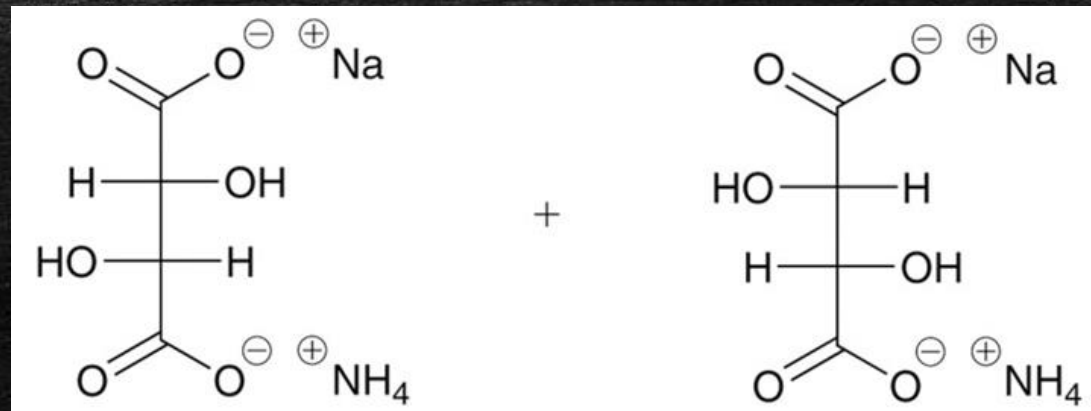


Resolution of Enantiomers / Challenge

- Most methods of separating compounds from one another take advantages of the compounds' different physical properties
 - Distillation– separates compounds with different boiling points
 - Recrystallization– separates compounds with different solubilities
- Such methods often don't work to separate one enantiomer from its racemate, because they have identical physical properties

Resolution of Enantiomers / Pasteur Method

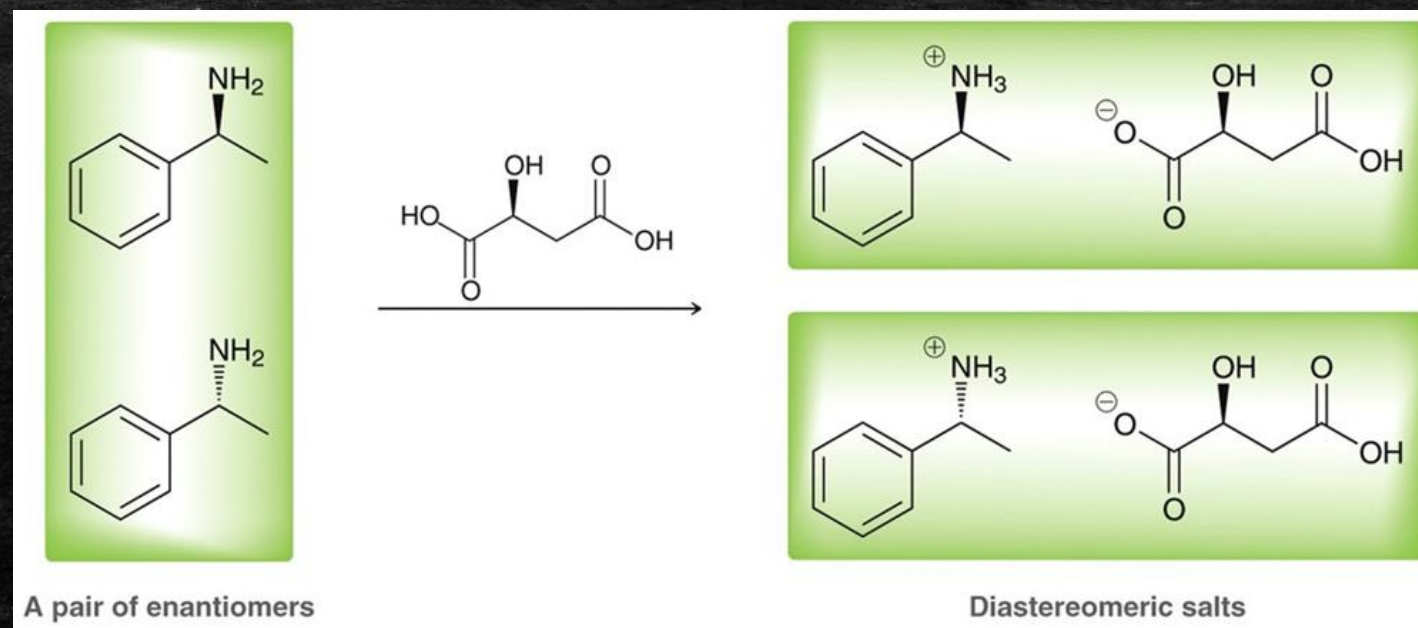
- In 1847, Pasteur performed the first resolution of enantiomers from a racemic mixture of tartaric acid salts



- The different enantiomers formed different shaped crystals that were separated by hand using tweezers
- However, this method doesn't work for most pairs of enantiomers

Resolution of Enantiomers / Resolving Agent

- Another method is to use a chiral resolving agent



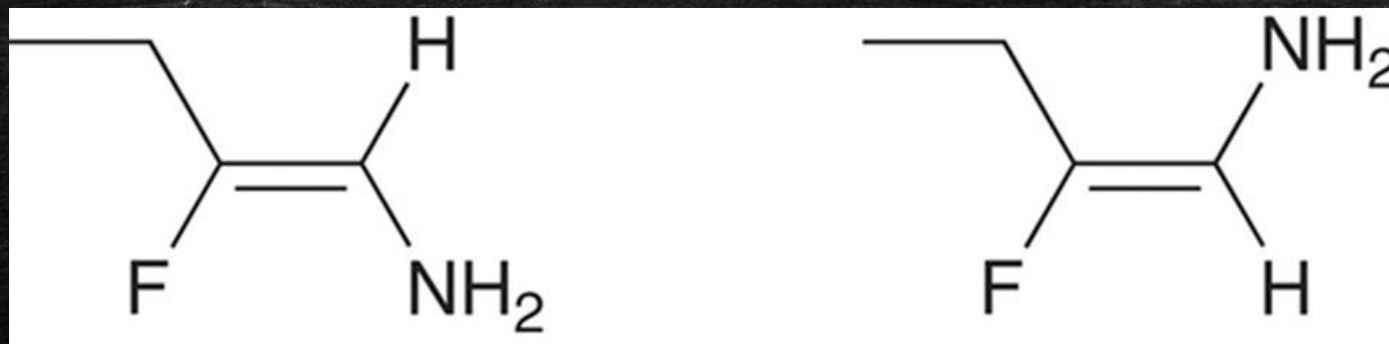
- The differing physical properties of diastereomers allow them to be more easily separated

Resolution of Enantiomers / Additional Methods

- Affinity chromatography is often used to separate compounds
- A glass column (or tube) is packed with a solid substance to act as an adsorbent, and a mixture is passed through it.
- If a **chiral adsorbent** is used, then enantiomers will interact with it differently, and travel through the column at different rates, allowing for their individual collection (thus separation).
- This is a very common way for resolving enantiomers

E and Z Designations for Alkenes / Introduction

- For molecules with different groups attached to the C=C double bond, the *E/Z* notation is used instead of *cis/trans* notation

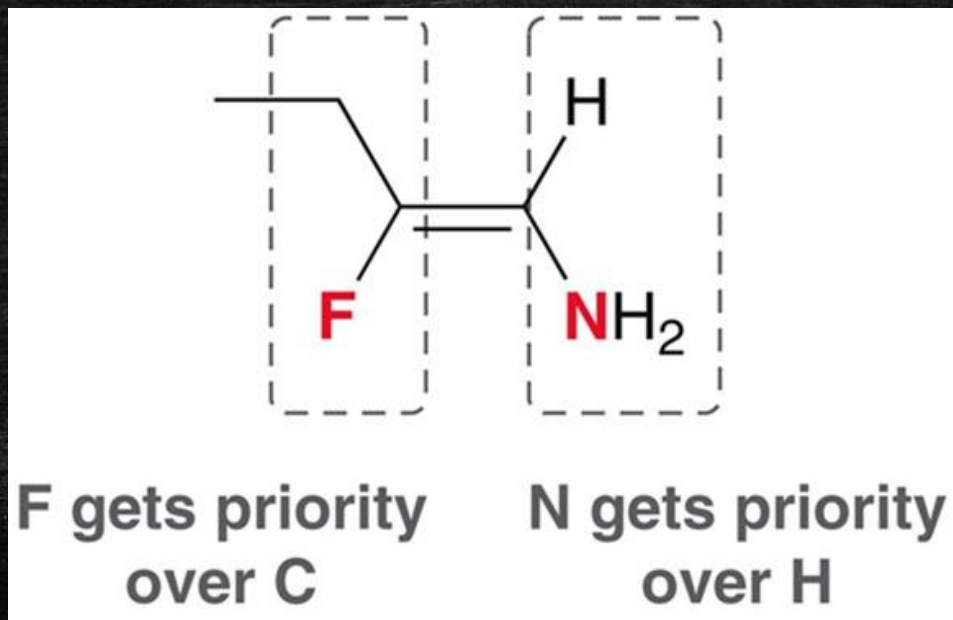


***Cis/trans* isn't adequate to differentiate between these two diastereomers**

- cis* and *trans* only works if there is a like group on each carbon of the alkene

E and Z Designations for Alkenes / Step One

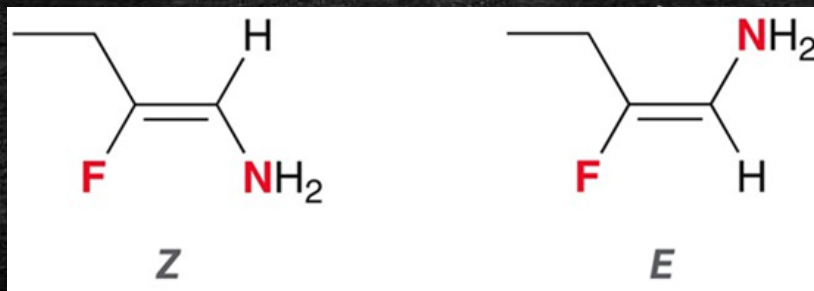
- Assigning *E* or *Z* to a C=C double bond:
 1. prioritize the groups attached to the C=C double bond based on atomic number



E and Z Designations for Alkenes / Step Two

- Assigning *E* or *Z* to a C=C double bond:
 1. prioritize the groups attached to the C=C double bond based on atomic number
 2. If the top priority groups are on the same side of the C=C double bond, it is *Z* (for zussamen, which means together)

If the top priority groups are on opposite sides of the C=C double bond, it is *E* (for entgegen, which means **opposite**)



- Practice with SkillBuilder 8.2 – Drawing an Enantiomer.