WILEY

Organic Chemistry

Third Edition

David Klein

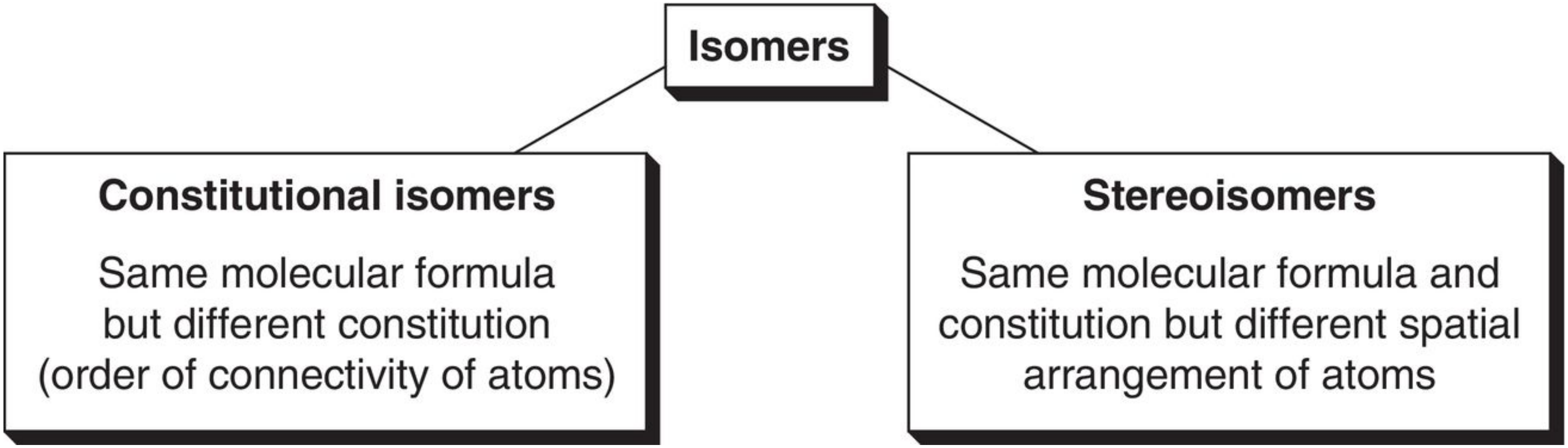
Chapter 5

Stereoisomerism

WILEY

5.1 Isomers - Overview

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



Isomers

Constitutional isomers

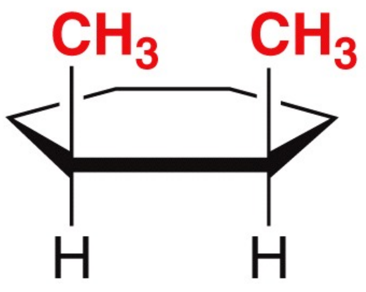
Same molecular formula but different constitution (order of connectivity of atoms)

Stereoisomers

Same molecular formula and constitution but different spatial arrangement of atoms

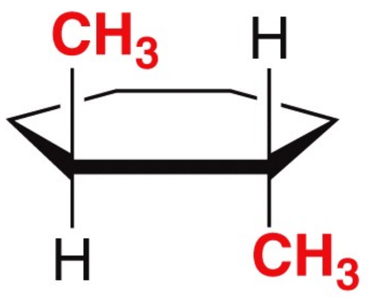
5.1 Isomers - Overview

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



***cis*-1,2-dimethylcyclohexane**

(both groups in same side of ring)



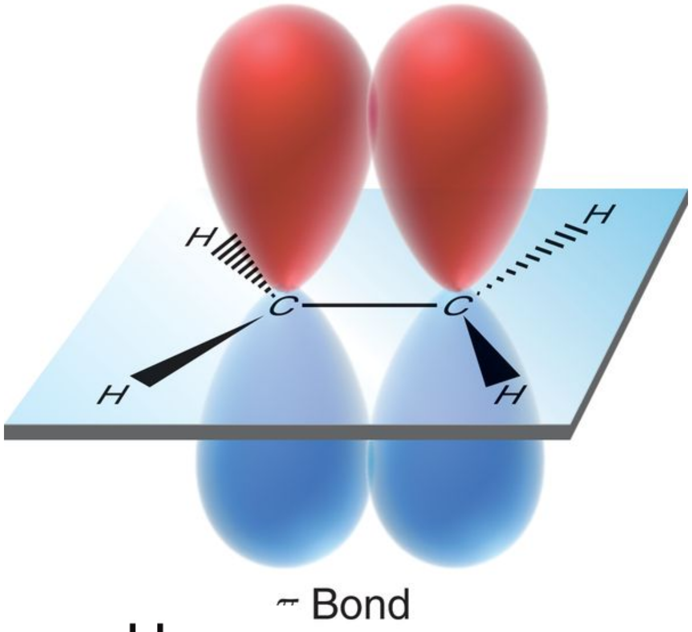
***trans*-1,2-dimethylcyclohexane**

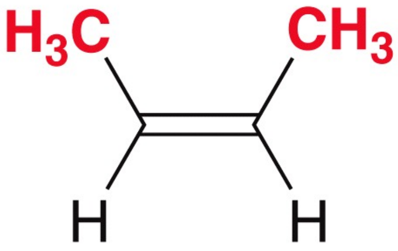
(Both groups on opposite sides)

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

5.1 Isomers - Overview

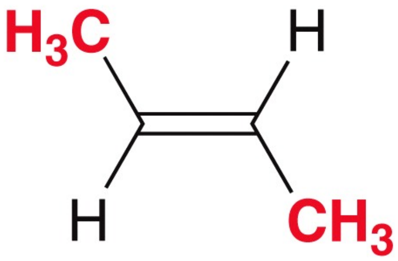
- To maintain orbital overlap in the pi bond, C=C double bonds can not freely rotate.
- Although the two molecules below have the same connectivity, they are NOT identical… they are **stereoisomers**





***cis*-2-butene**

Groups on same side of pi bond

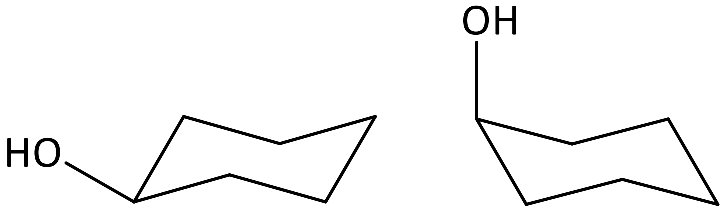


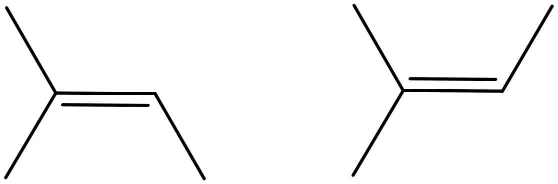
***trans*-2-butene**

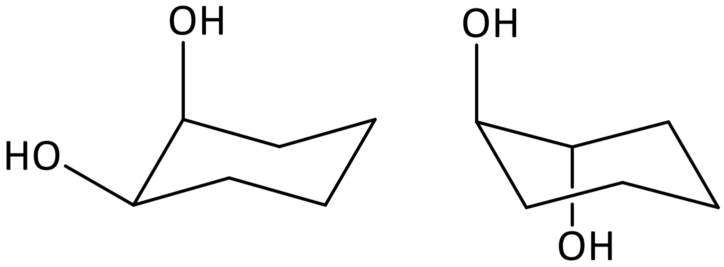
Groups on opposite sides

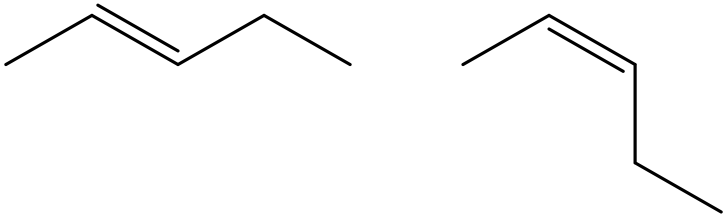
5.1 Isomers - Overview

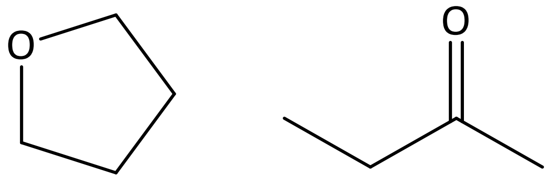
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures







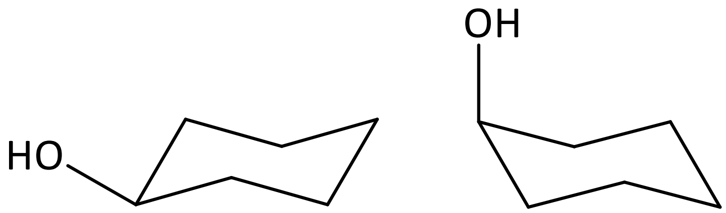




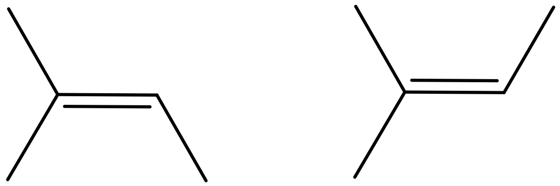
Answers on the next slide

5.1 Isomers - Overview

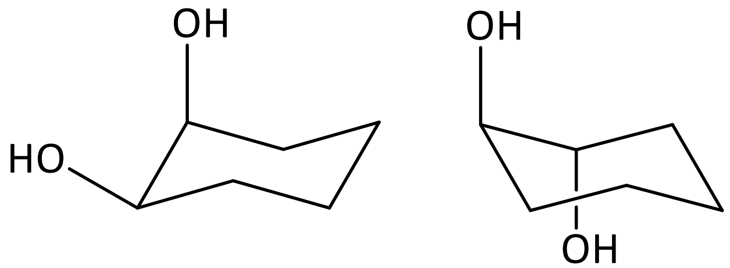
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures



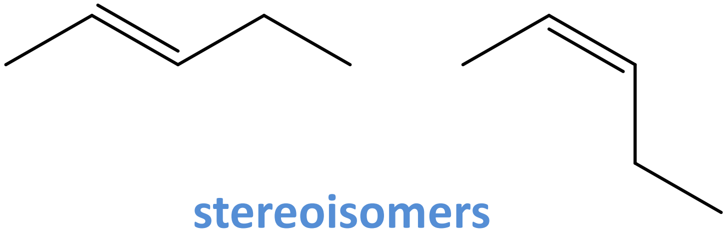
identical



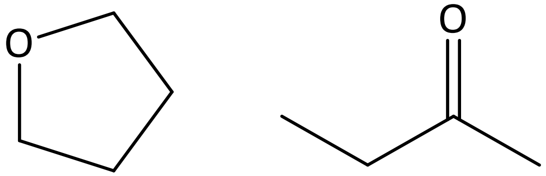
identical



stereoisomers



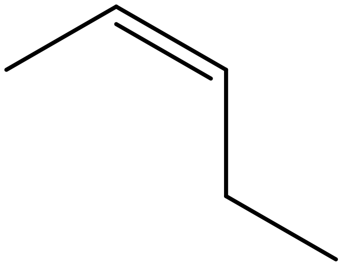
stereoisomers

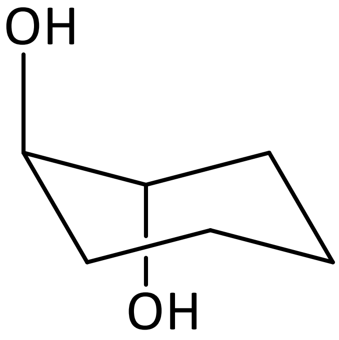


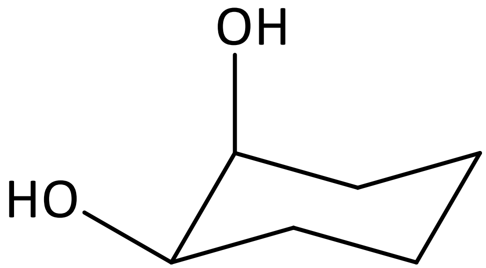
Constitutional isomers

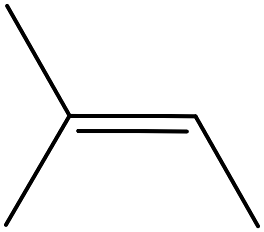
5.1 Isomers - Overview

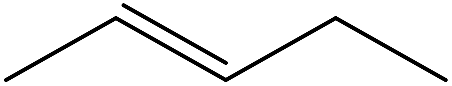
- Identify the following as either *cis*, *trans*, or neither.







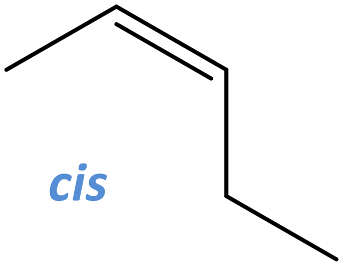




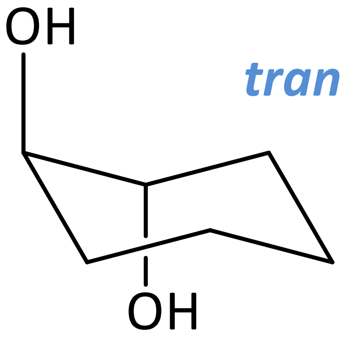
answers on next slide

5.1 Isomers - Overview

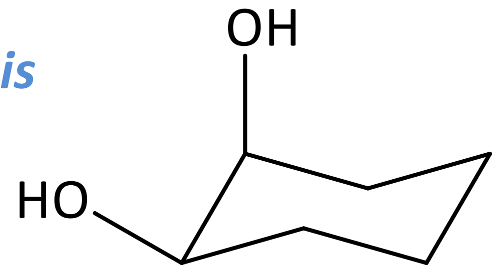
- Identify the following as either *cis*, *trans*, or neither.



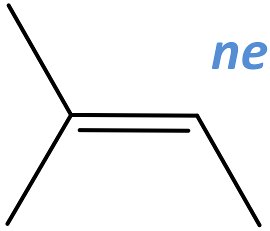
cis



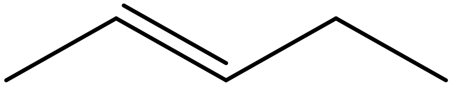
trans



cis



neither



trans

5.2 Stereoisomers

- *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**.

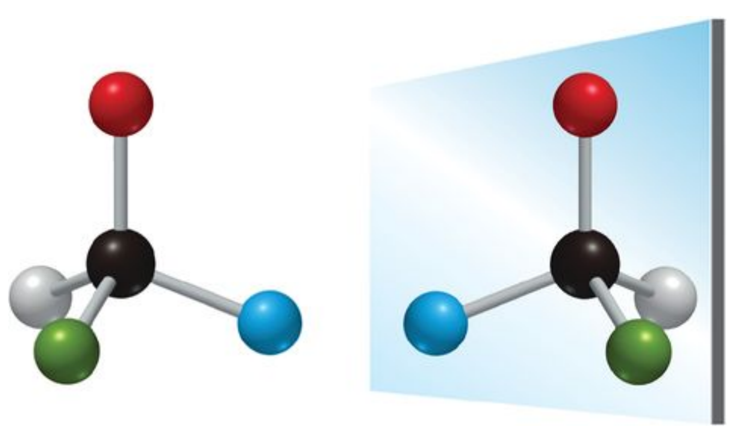
5.2 Molecular Chirality

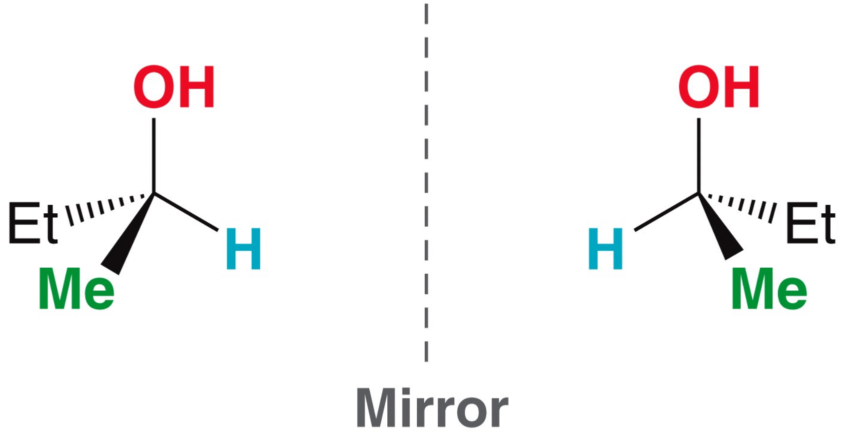
- Chirality is important in molecules.
  - Because two chiral molecules are mirror images, they will have many identical properties, but because they are not identical, their **pharmacology** may be very different
- Visualizing mirror images of molecules and manipulating them in 3D space to see if they are superimposable can be VERY challenging, so…

…It is **absolutely critical** that you **use handheld models** as visual aids

5.2 Stereoisomers

- Chirality most often results when a carbon atom is bonded to 4 unique groups of atoms.



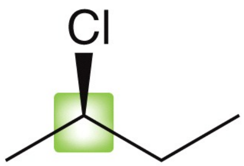


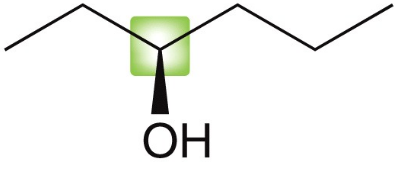
- Make a handheld model to prove to yourself that they are NOT superimposable

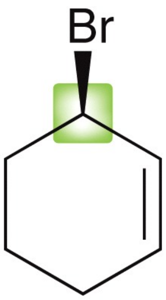
5.2 Stereoisomers

- When an atom (like carbon) forms a tetrahedral center with 4 different groups attached to it, it is called a chirality center

- Analyze the attachments for each chirality center below





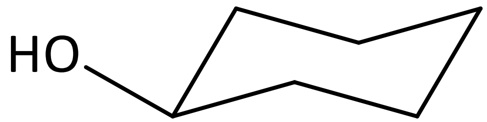


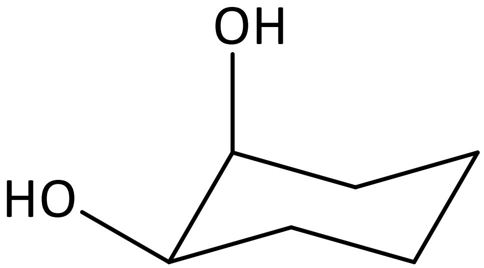
each highlighted carbon is bonded to 4 different groups, and is a chirality center

- Practice with SkillBuilder 5.1

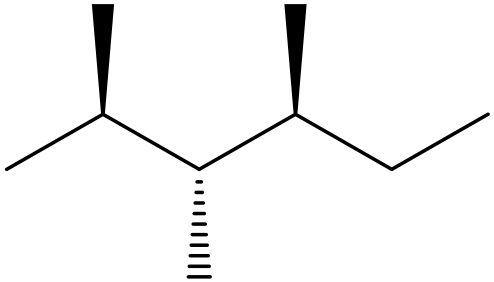
5.2 Stereoisomers

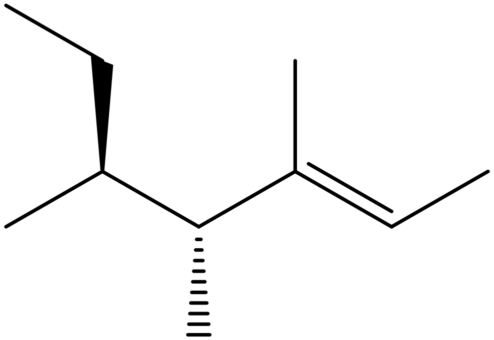
- How many chirality centers are in each of the following compounds?





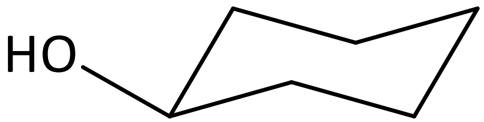
answers on next slide



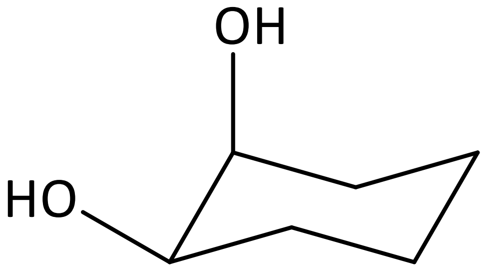


5.2 Stereoisomers

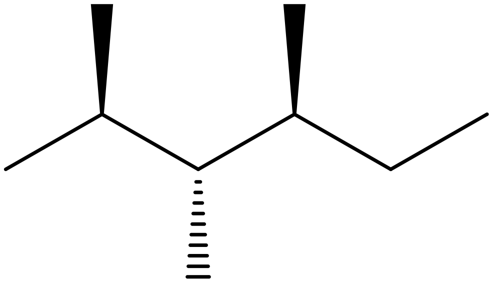
- How many chirality centers are in each of the following compounds?



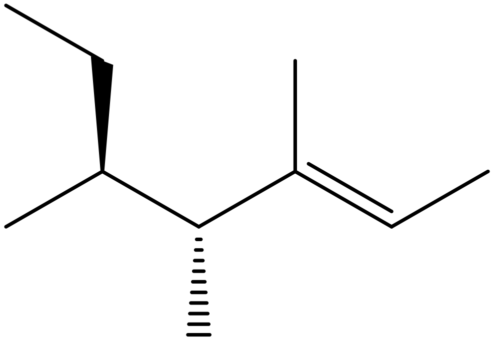
no chirality centers



two chirality centers



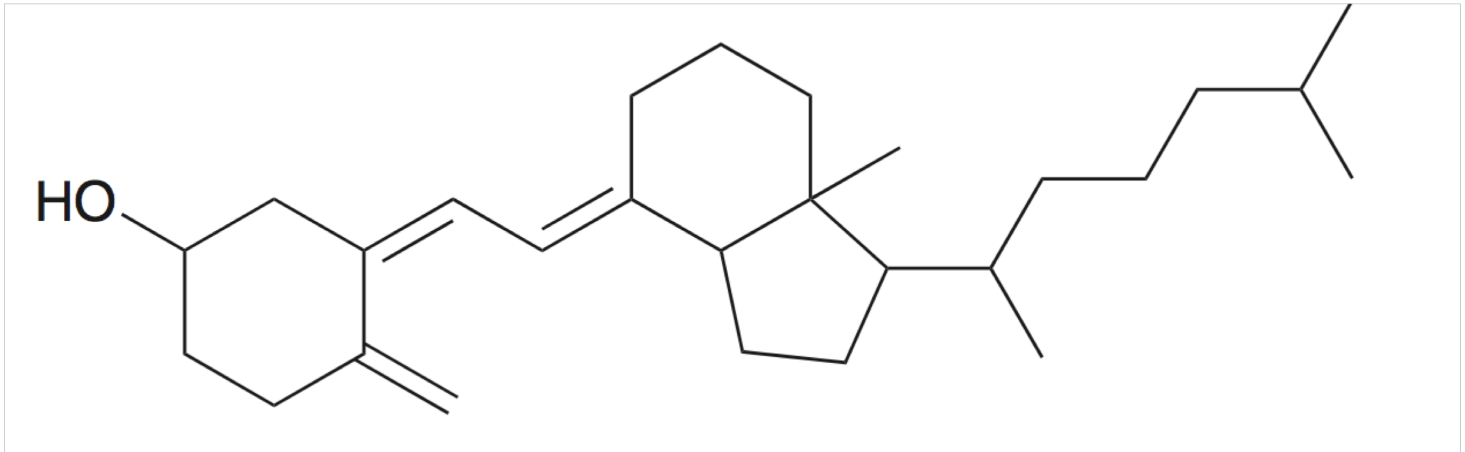
two chirality centers



two chirality centers

5.2 Stereoisomers

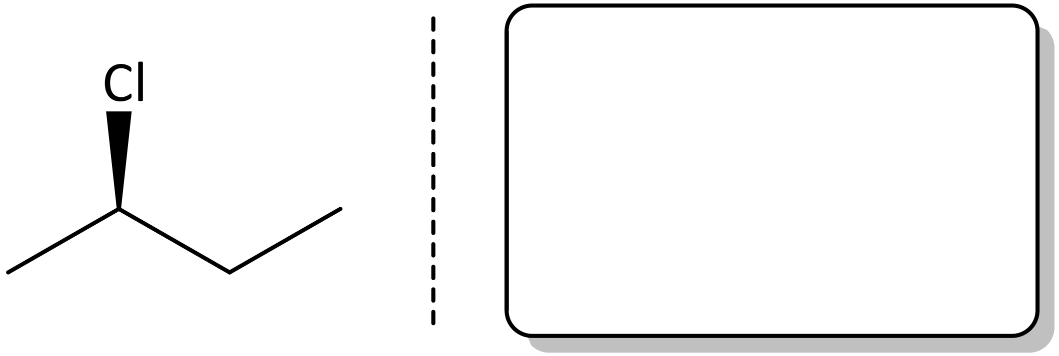
- **Practice the Skill 5.4 -** Identify and label all the chirality centers in Vitamin D_3



Vitamin D_3

5.2 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

5.2 Enantiomers

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- **Enantiomers** are TWO molecules that are MIRROR IMAGES but are **not superimposable**, therefore **not identical**
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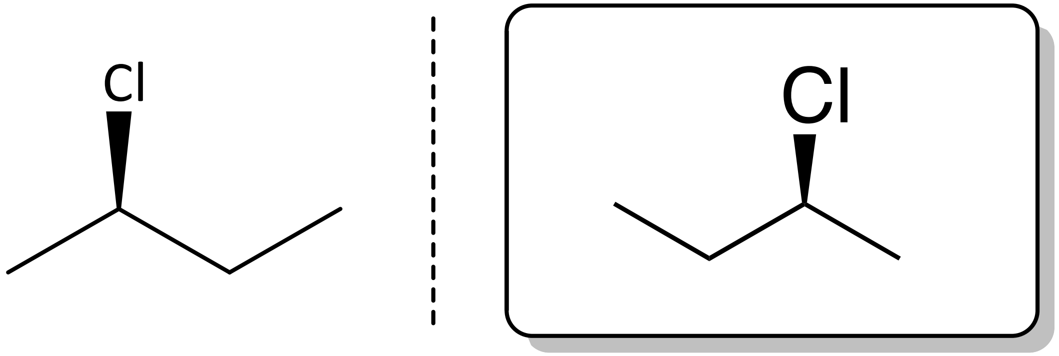


this is a chiral compound…

… the mirror image will be its enantiomer

5.2 Enantiomers

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

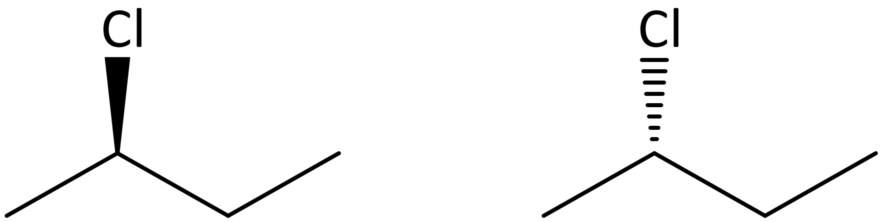
enantiomers

enantiomers

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

5.3 Designating R vs S configuration

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



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

5.3 Designating R vs S configuration

- "R" or "S" is assigned to a chirality center using a stepwise procedure

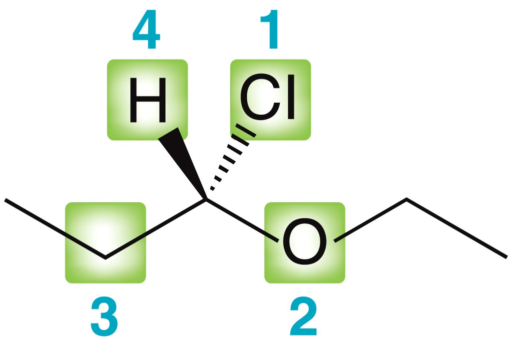
  1. Using atomic numbers, prioritize the 4 groups attached to the chirality center (1, 2, 3 and 4)
  2. Arrange the molecule in space so the lowest priority group faces away from you
  3. Count the group priorities 1…2…3 to determine whether the order progresses in a clockwise or counterclockwise direction
  4. Clockwise = *R* and Counterclockwise = *S*

- A handheld model can be very helpful visual aid for this process

5.3 Designating R vs S configuration

- The Cahn, Ingold and Prelog system

1. Using atomic numbers, prioritize the 4 groups attached to the chirality center. The higher the atomic number, the higher the priority

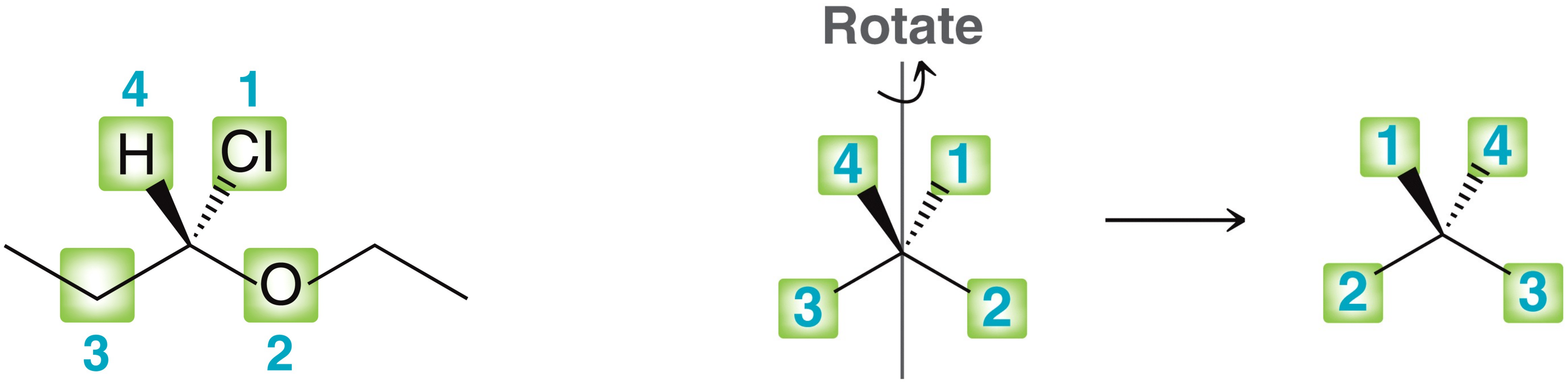


The atom with the largest atomic number is assigned the highest priority (1), and so on…

5.3 Designating R vs S configuration

- The Cahn, Ingold and Prelog system

2. Arrange the molecule in space so the lowest priority group faces away from you

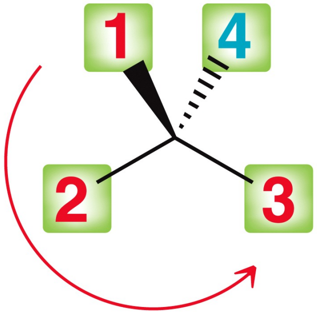


****This is the step where it is most helpful to have a handheld model**

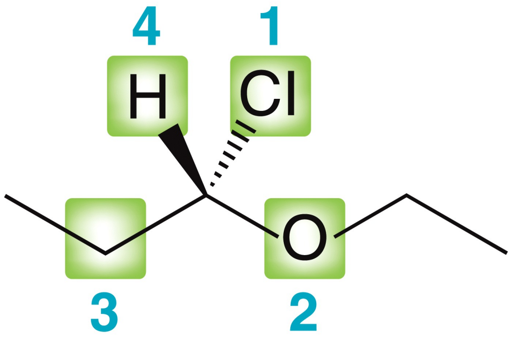
5.3 Designating R vs S configuration

- 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***



Counterclockwise = ***S***

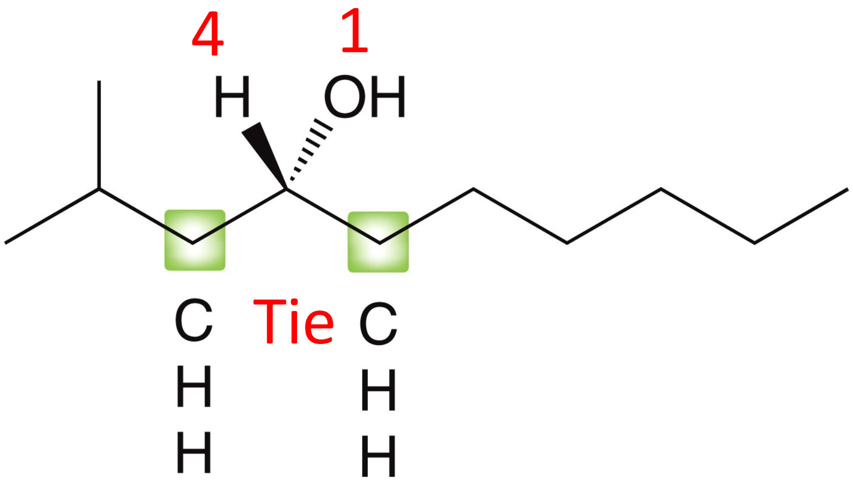


and so we just determined this chirality

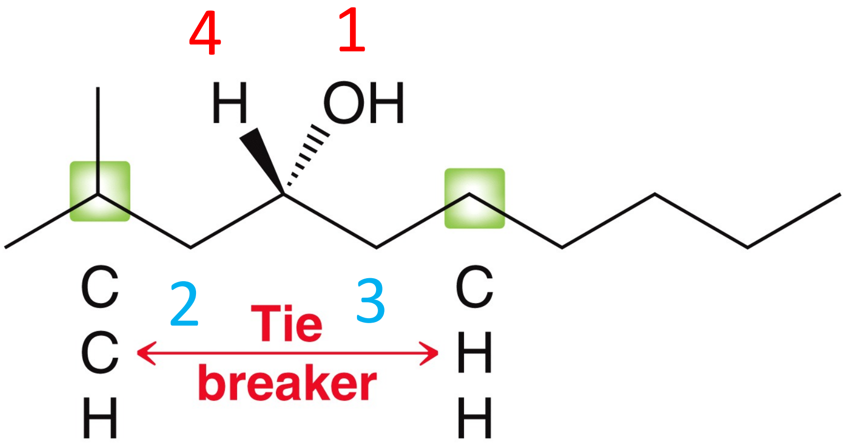
Center has the (S) configuration

5.3 Designating R vs S configuration

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



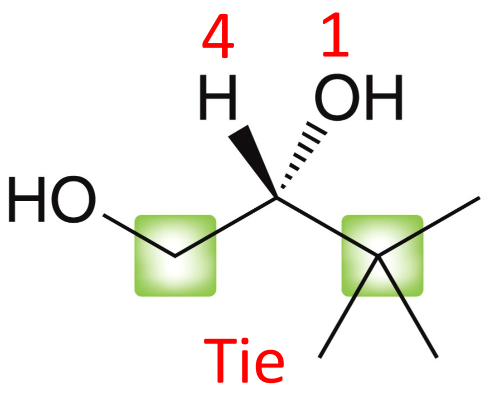
The 1 and 4 groups are obvious, but there is a tie for priority 2 and 3



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

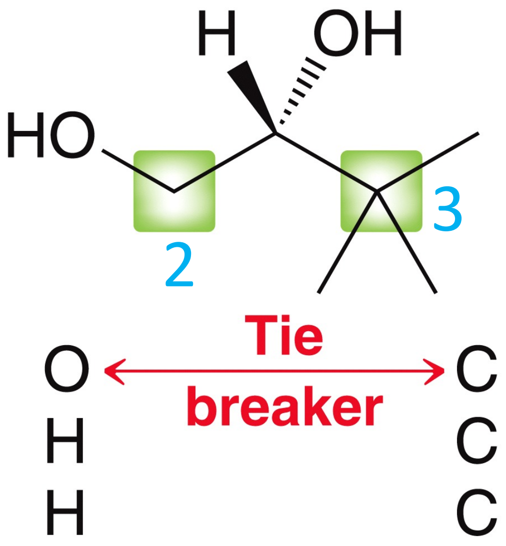
5.3 Designating R vs S configuration

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



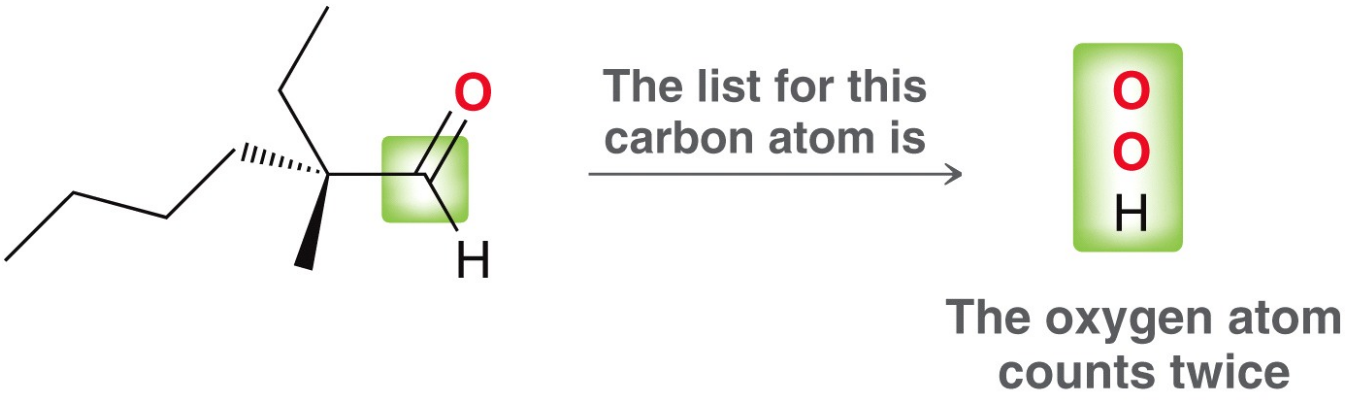
The priority is based on the first point of difference!

- Second layer



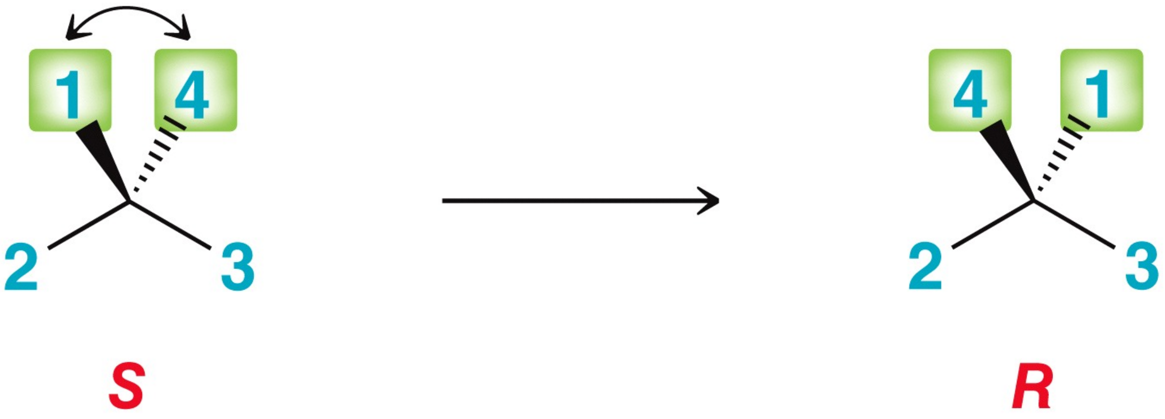
5.3 Designating R vs S configuration

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



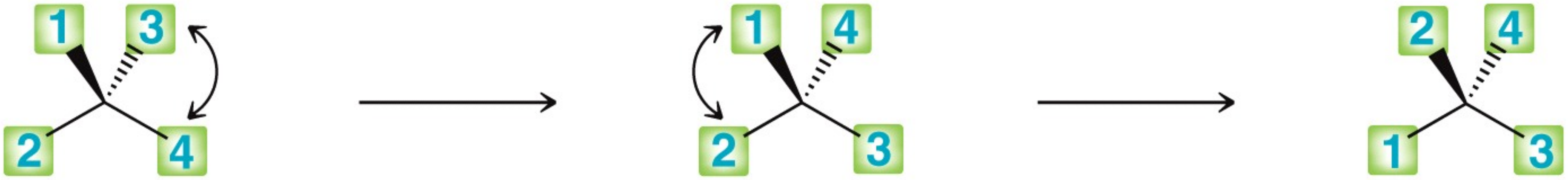
5.3 Rotating the Molecule

- 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 can use
  - Switching two groups on a chirality center will produce its opposite configuration



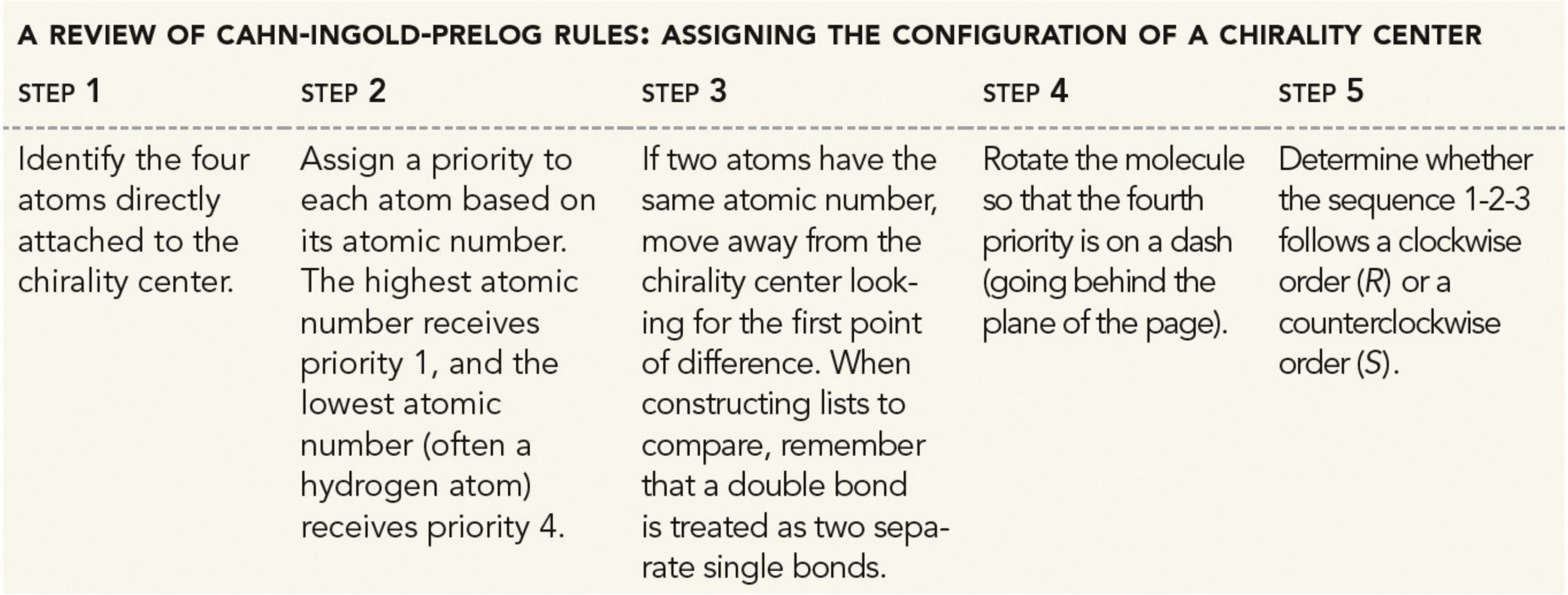
5.3 Rotating the Molecule

- Switching two groups on a chirality 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 4th 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 4 priority group pointing away.

5.3 CIP Rules Summary

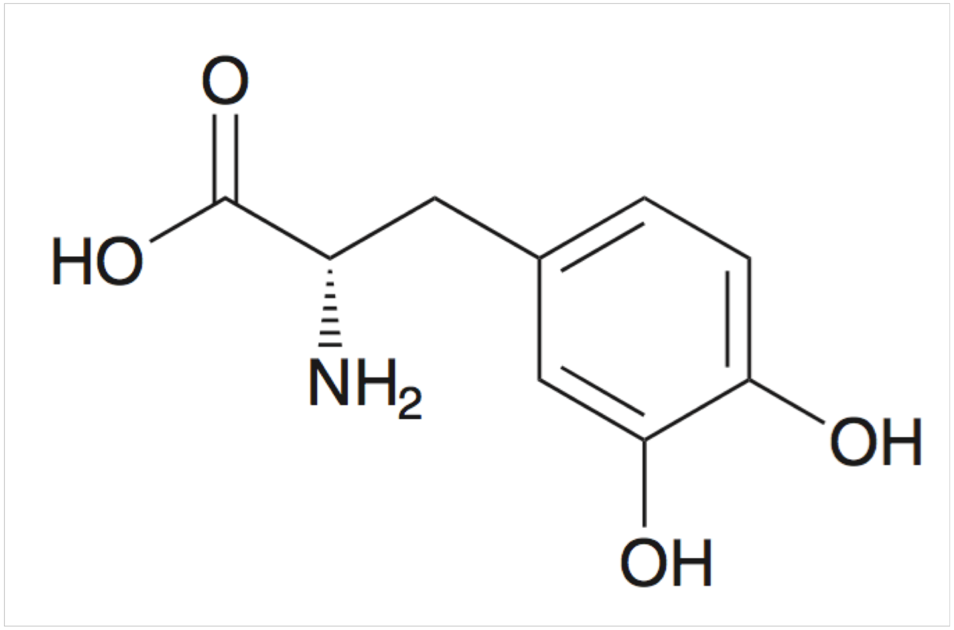


A REVIEW OF CAHN-INGOLD-PRELOG RULES: ASSIGNING THE CONFIGURATION OF A CHIRALITY CENTER

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Identify the four atoms directly attached to the chirality 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 chirality 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.	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 (*R*) or a counterclockwise order (*S*).

5.3 Designating R vs S configuration

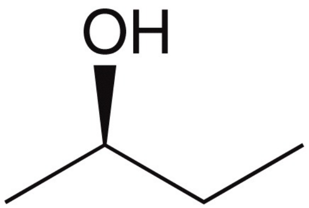
- **Skillbuilder 5.3 –** Assign the configuration of the chiral center in the following compound



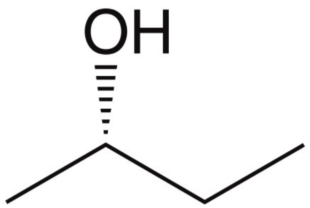
- Get additional practice with **Practice the Skill 5.9**

5.3 (R) and (S) in IUPAC Nomenclature

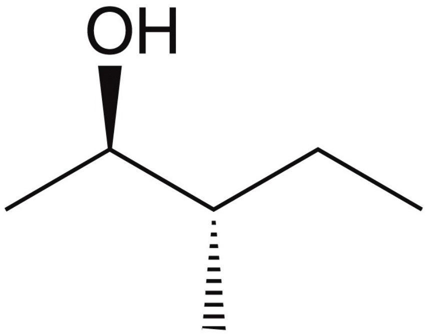
- The (*R*) or (*S*) configuration is used in the IUPAC name for a compound to distinguish it from its enantiomer



(*R*)-2-Butanol



(*S*)-2-Butanol

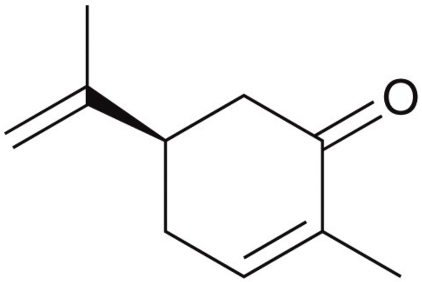


(2*R*,3*S*)-3-Methyl-2-pentanol

5.3 Optical Activity

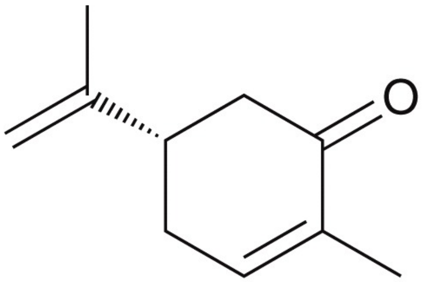
- Because the structures of enantiomers only differ in the same way your right hand differs from your left, they have the same physical properties.

(*R*)-Carvone



Melting point = 25°C
Boiling point = 231°C

(*S*)-Carvone

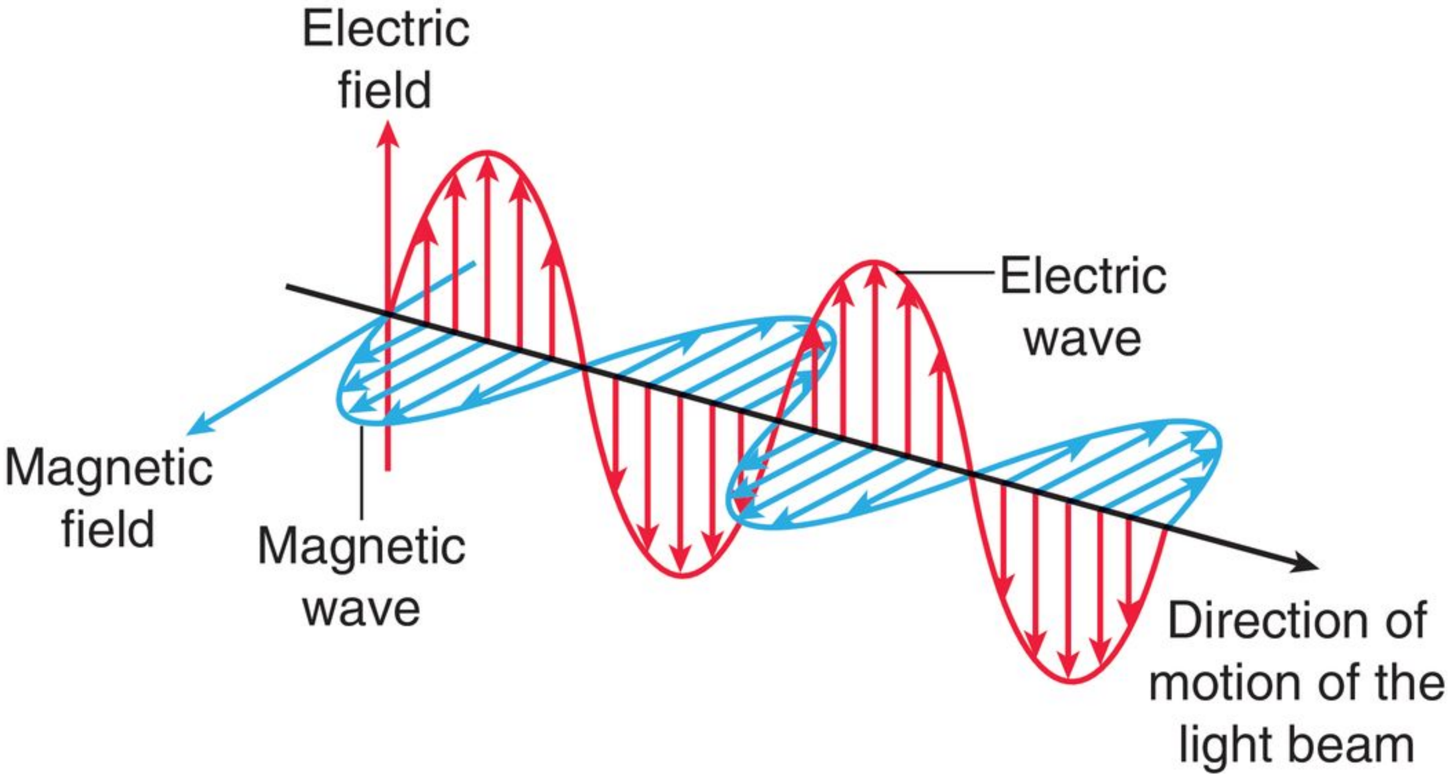


Melting point = 25°C
Boiling point = 231°C

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

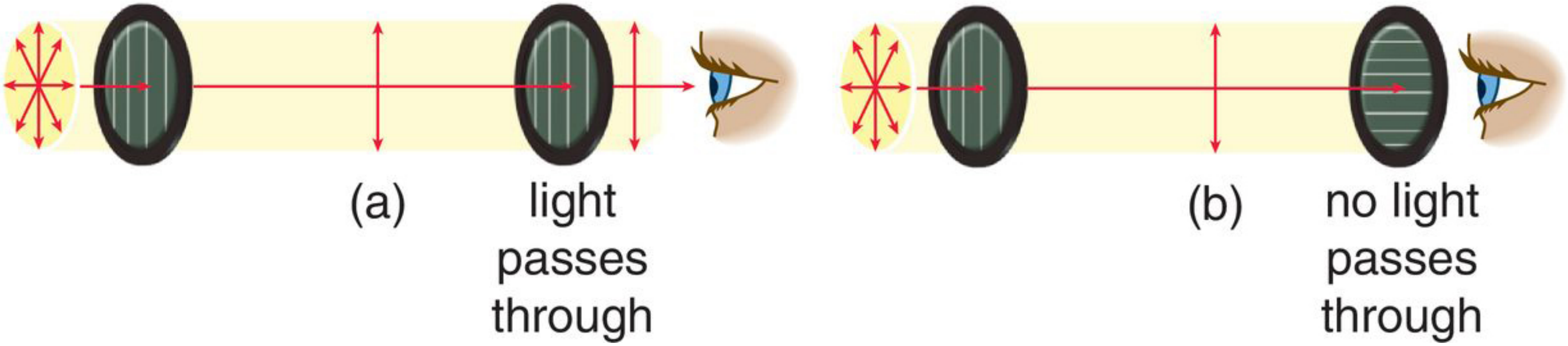
5.4 Optical Activity

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



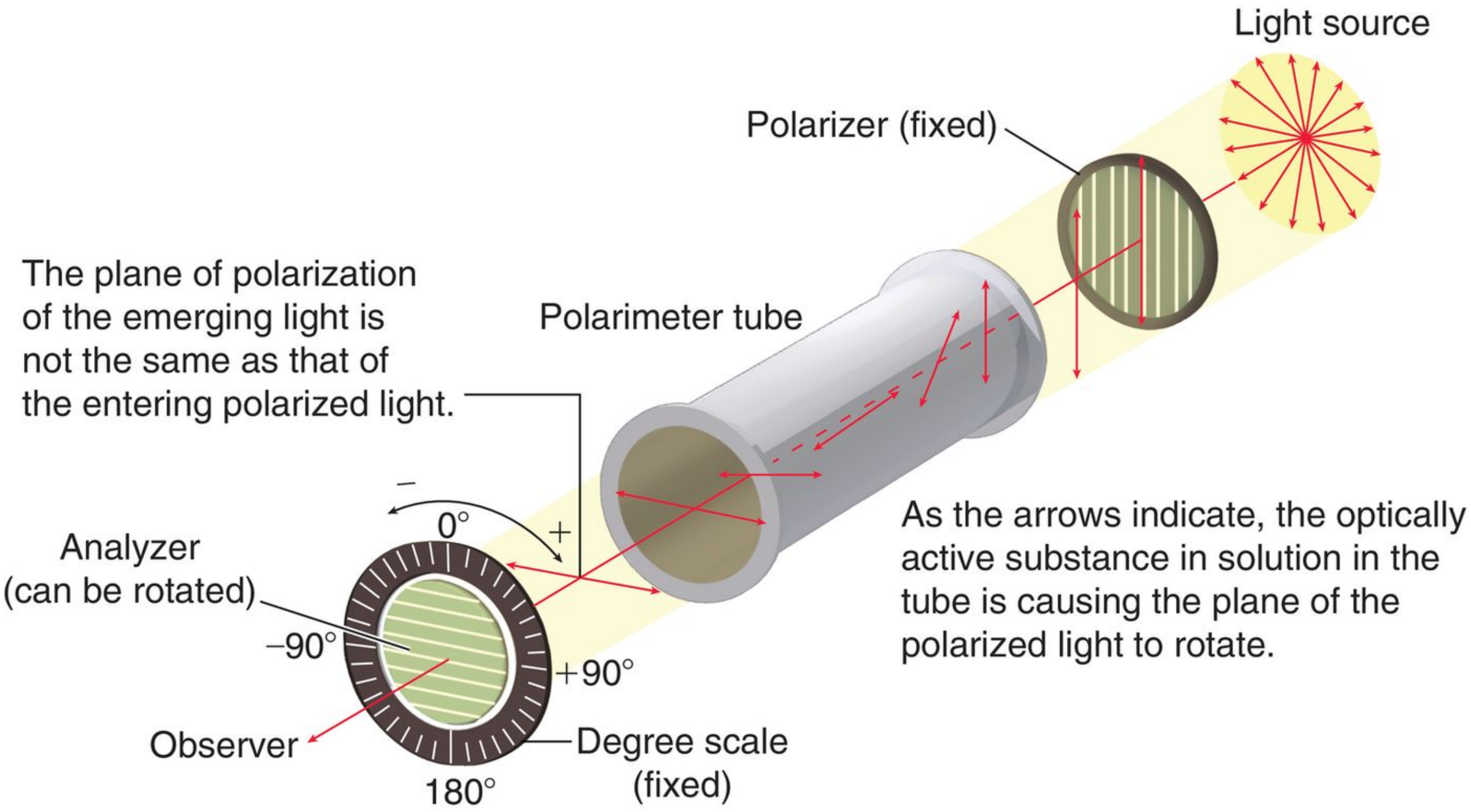
5.4 Optical Activity

- 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

5.4 Optical Activity - Polarimeter



The plane of polarization of the emerging light is not the same as that of the entering polarized light.

As the arrows indicate, the optically active substance in solution in the tube is causing the plane of the polarized light to rotate.

5.4 Optical Activity

- 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

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

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

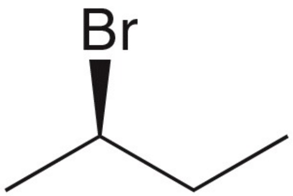
$$[\alpha]_{\lambda}^{T}$$

temperature

wavelength

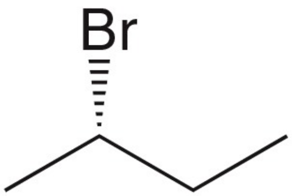
5.4 Optical Activity

- Consider the enantiomers of 2-bromobutane



(*R*)-2-Bromobutane

$[\alpha]_D^{20} = -23.1$



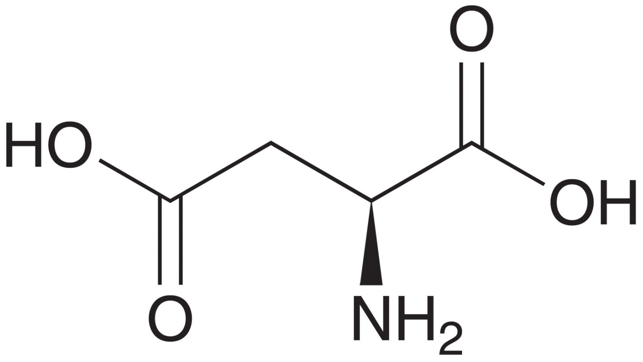
(*S*)-2-Bromobutane

$[\alpha]_D^{20} = +23.1$

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

5.4 Optical Activity

- **(+)** 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 +/-**

5.4 Optical Activity

- 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.

5.4 Enantiomeric Excess

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

$[\alpha]_D^{20} = -23.1$ $[\alpha]_D^{20} = +23.1$

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

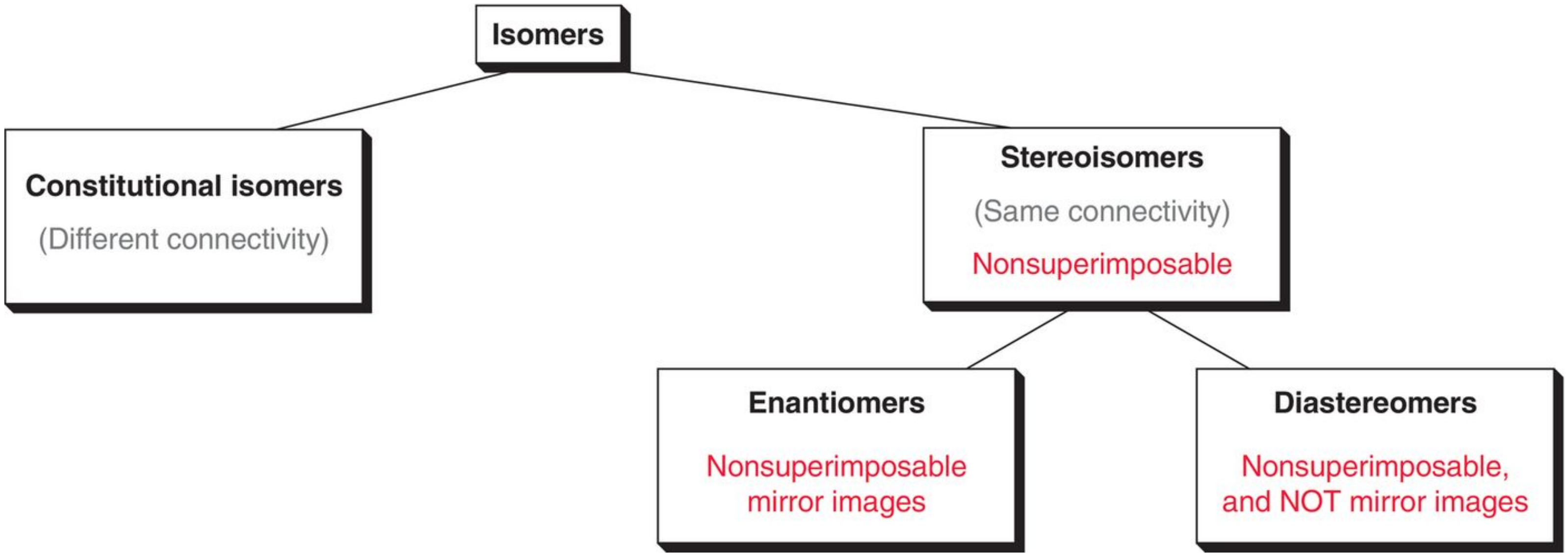
$$\% \; ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\%$$

- So, (-4.6) / (-23.1) x 100% = **20 % ee**
- Practice with SkillBuilder 5.5

5.5 Enantiomers and Diastereomers

- Categories of isomers

*** there are two sub-categories of stereoisomers**


Isomers

Constitutional isomers
(Different connectivity)

Stereoisomers
(Same connectivity)
Nonsuperimposable

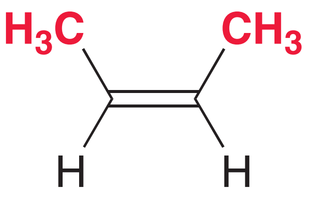
Enantiomers
Nonsuperimposable mirror images

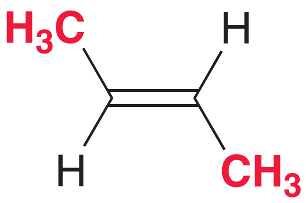
Diastereomers
Nonsuperimposable, and NOT mirror images

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

5.5 Enantiomers and Diastereomers

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


cis-2-Butene


trans-2-Butene

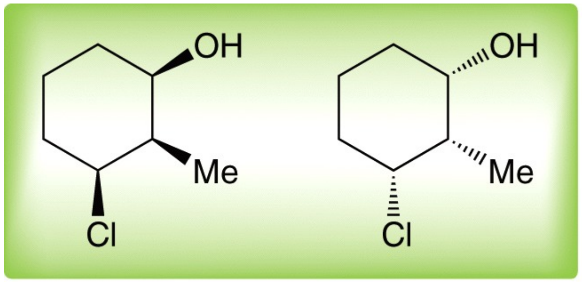
- They are stereoisomers, but not mirror images of each other. So, they are **diastereomers!**

- Recall that enantiomers have identical physical properties.

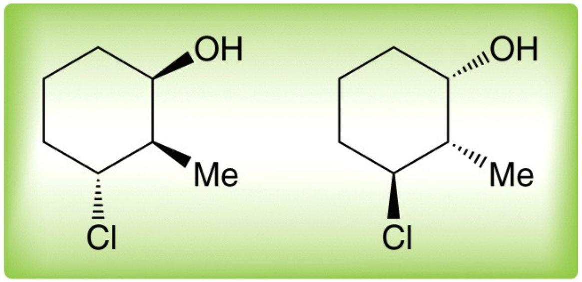
- **Diastereomers have <u>different</u> physical properties**

5.5 Stereoisomeric Relationships

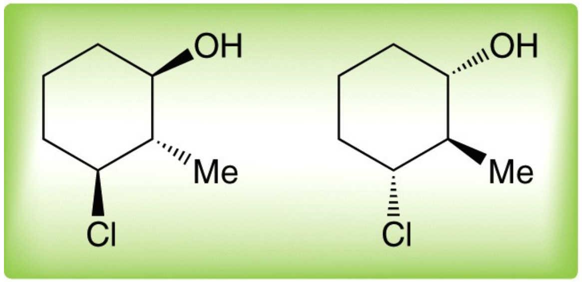
- Consider a cyclohexane with three substituents



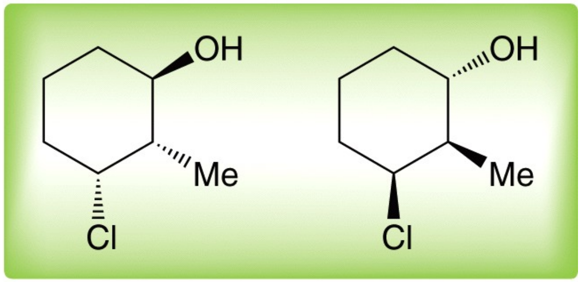
1*R*, 2*R*, 3*S* **1*S*, 2*S*, 3*R***



1*R*, 2*R*, 3*R* **1*S*, 2*S*, 3*S***



1*R*, 2*S*, 3*S* **1*S*, 2*R*, 3*R***

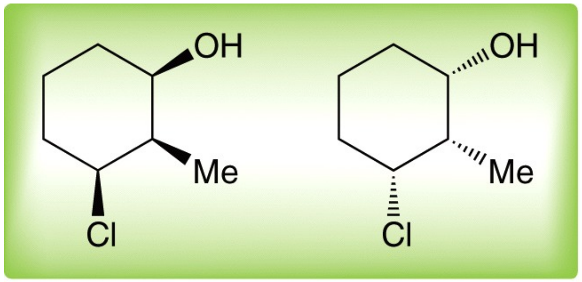


1*R*, 2*S*, 3*R* **1*S*, 2*R*, 3*S***

- There are three stereocenters here, and so there are 8 possible stereoisomers (all drawn above). Consider the relationship among them (enantiomers vs. diastereomers)

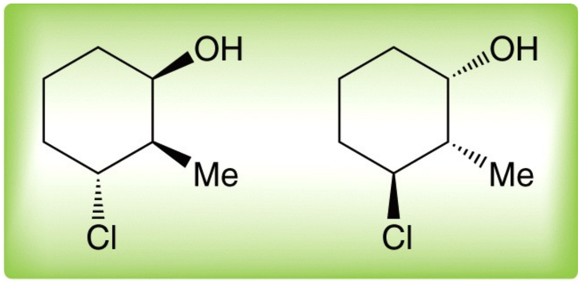
5.5 Stereoisomeric Relationships

- Notice these 8 stereoisomers are comprised of 4 pairs of enantiomers



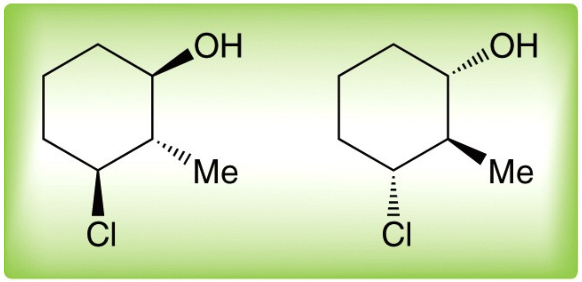
1*R*, 2*R*, 3*S*

1*S*, 2*S*, 3*R*



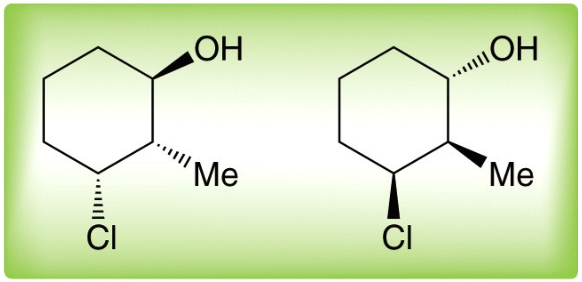
1*R*, 2*R*, 3*R*

1*S*, 2*S*, 3*S*



1*R*, 2*S*, 3*S*

1*S*, 2*R*, 3*R*



1*R*, 2*S*, 3*R*

1*S*, 2*R*, 3*S*

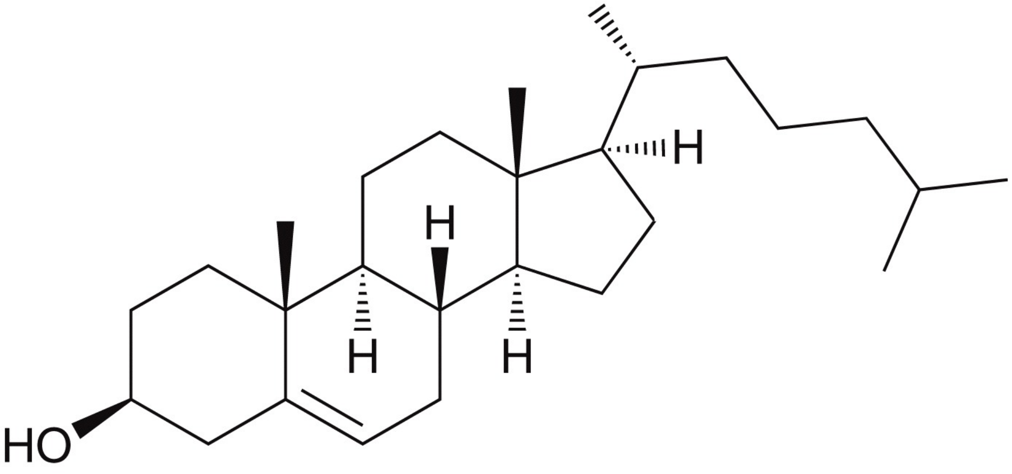
Can think of this as a family where there are 4 pairs of twins, for a total of 8 kids. Each kid has 7 siblings, where one of them is their twin (i.e. enantiomer) and the other 6 are diastereomers

5.5 Stereoisomeric Relationships

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

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

- What is the maximum number of possible cholesterol isomers?

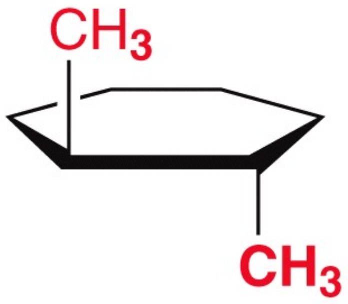


Cholesterol

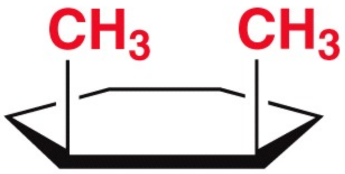
- Practice with SkillBuilder 5.6

5.6 Symmetry and Chirality

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



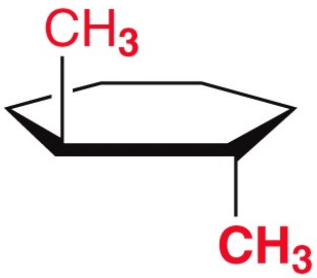
***trans*-1,2-dimethylcyclohexane**

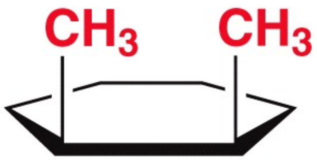


***cis*-1,2-dimethylcyclohexane**

5.6 Symmetry and Chirality

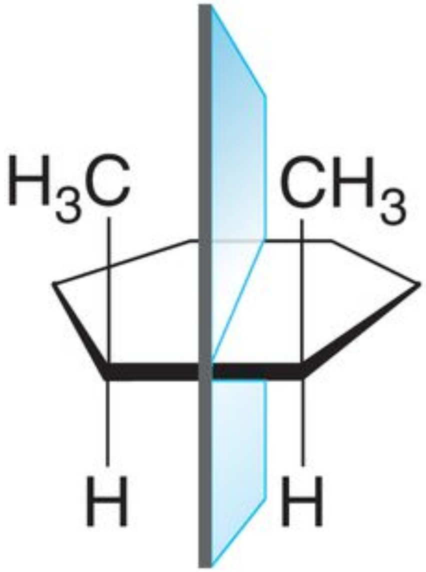
- The *trans* isomer is chiral, but the *cis* isomer is not (it is achiral)



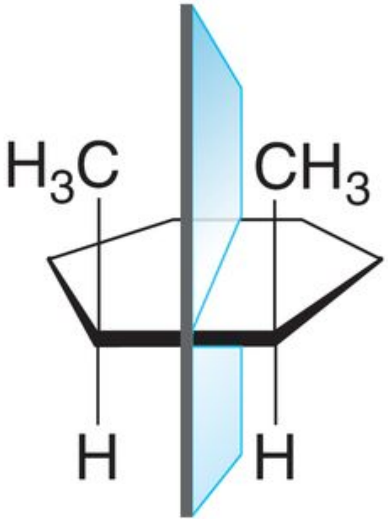


- If a molecule has a plane of symmetry, it will be achiral

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



5.6 Symmetry and Chirality



- Molecules with an even number of chirality centers that have a plane of symmetry are called ***meso* compounds**

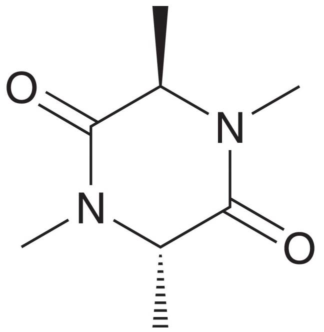
- Another way to test if a compound is a ***meso* compound** is to see if it is identical to its mirror image

- 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

5.6 Symmetry and Chirality

- 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 an reflectional symmetry through **inversion** about a central point in the molecule
- The molecule to the right has two chirality centers, and no plane of symmetry, but it is still achiral because of inversion



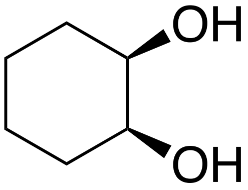
5.6 Symmetry and Chirality

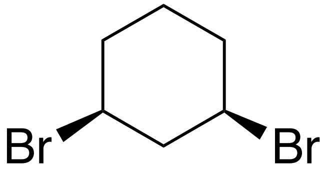
- OVERALL:
    - The presence or absence of rotational symmetry is irrelevant to chirality
    - **A compound that has a plane of symmetry is achiral**
    - **A compound without a plane of symmetry will *usually* be chiral**, but there are exceptions (such as a compound with an inversion center).

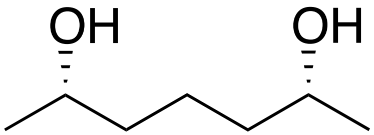
5.6 Meso Compounds

- A compound with chirality 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

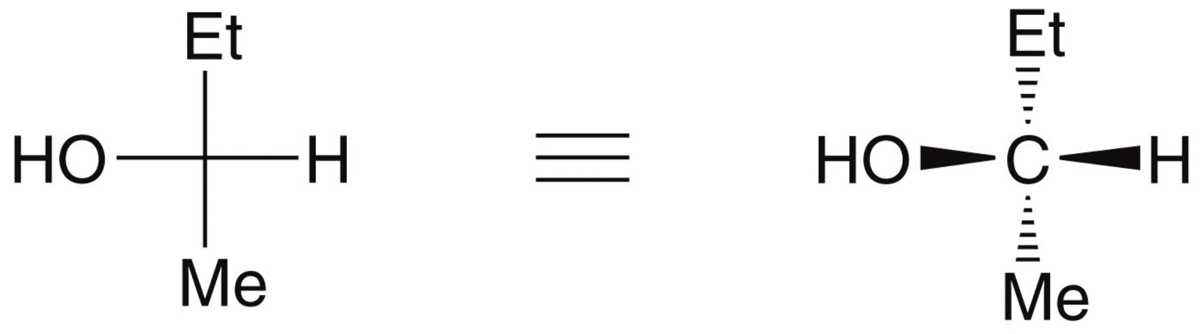
- Practice with Skillbuilder 5.7

5.7 Fischer Projections

- Fischer projections can also be used to represent molecules with chirality centers

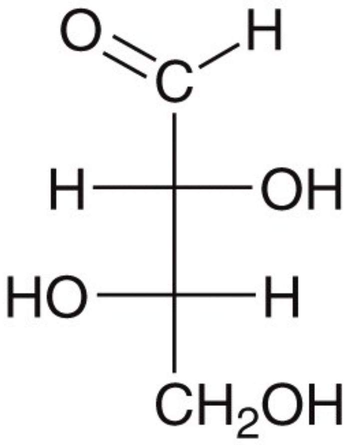
- **Horizontal lines** represent attachments **coming out of the page**

- **Vertical lines** represent attachments going **back into the page**

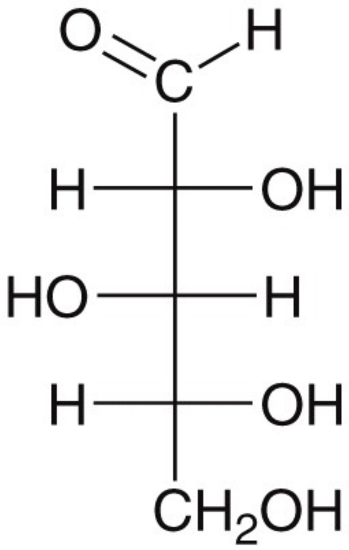


5.7 Fischer Projections

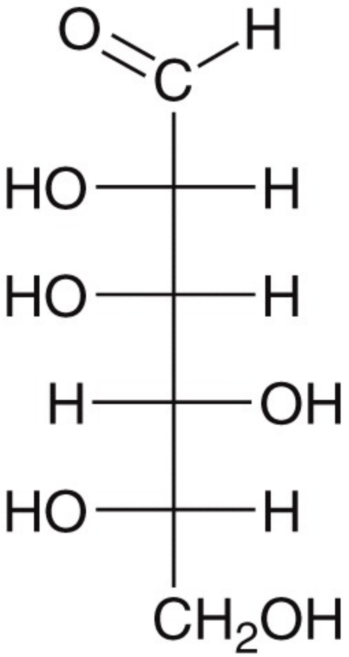
- Fischer projections are most useful when drawing molecules having multiple chirality centers (like sugars, shown below).



Two chirality centers



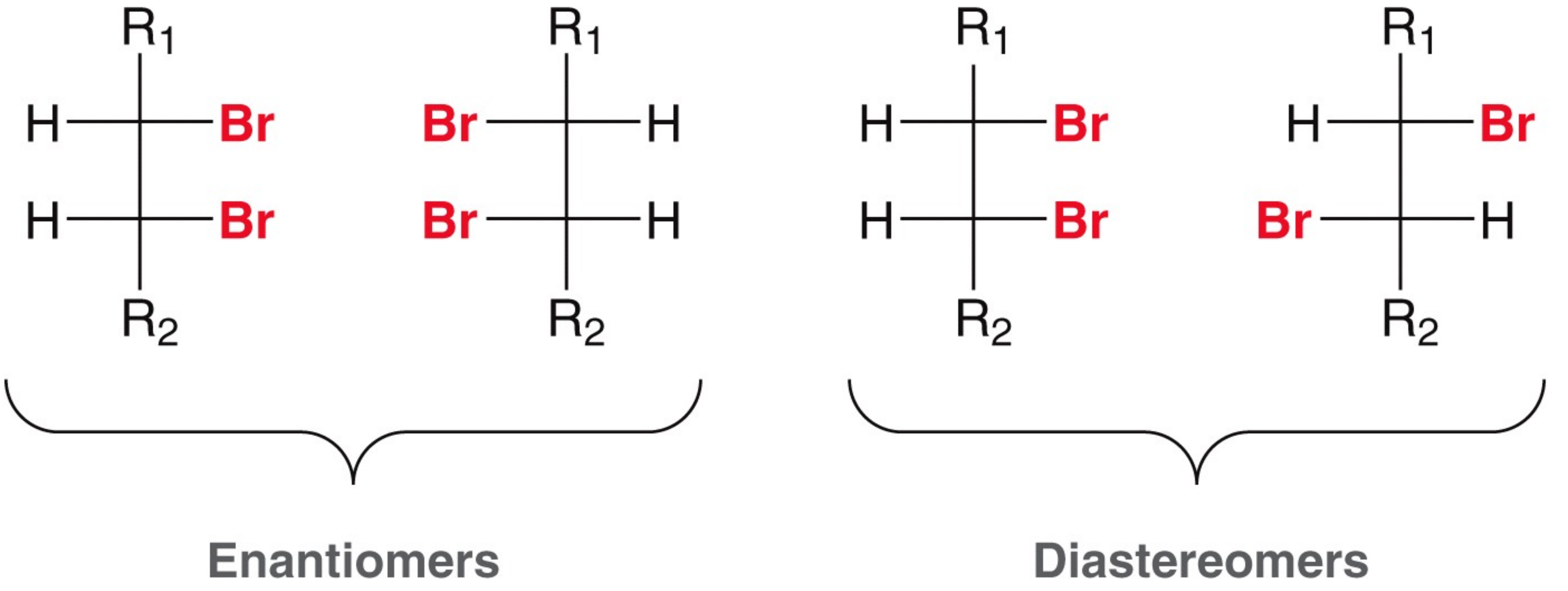
Three chirality centers



Four chirality centers

5.7 Fischer Projections

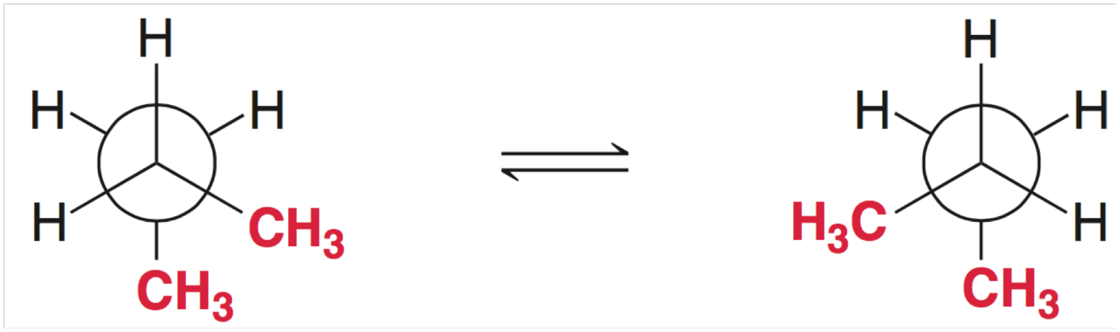
- Fischer projections are also useful to quickly assess stereoisomeric relationships



- Practice with SkillBuilder 5.8

5.8 Conformationally Mobile Compounds

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

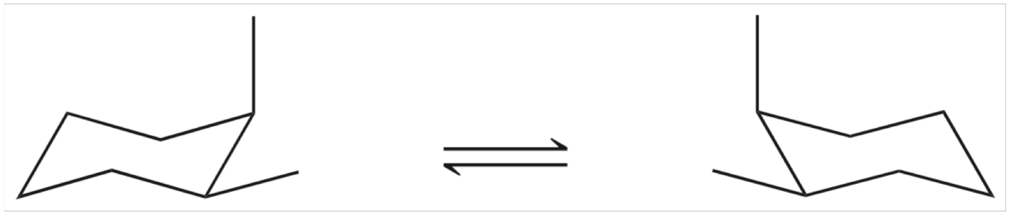


- Realize that these *conformations* are chiral, and are actually enantiomeric

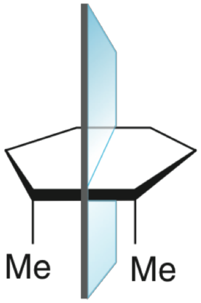
- But, because these rotatomers are interchangeable via bond rotation, butane is not a chiral compound.

5.8 Interconverting Enantiomers

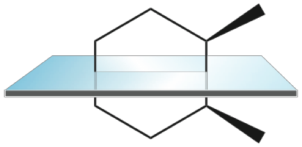
- Compare both possible chair conformations of (*cis*)-1,2-dimethylcyclohexane



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



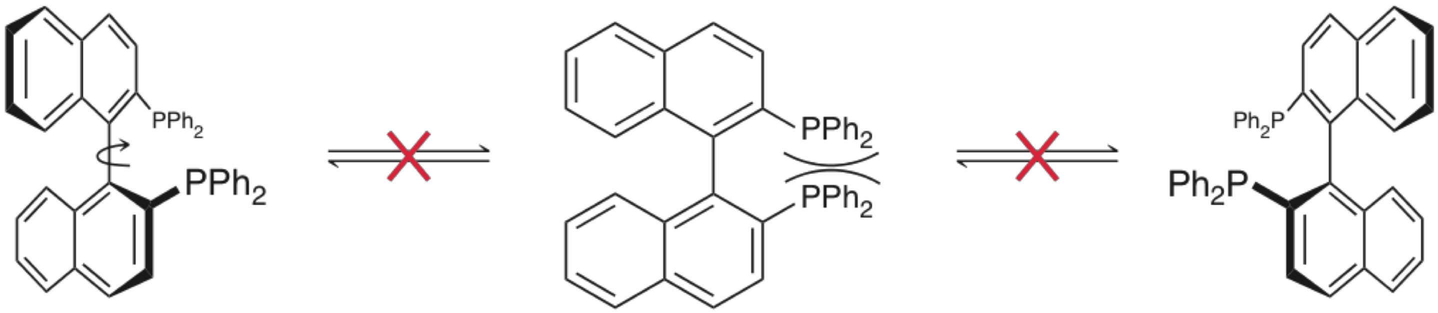
Internal plane of symmetry



Internal plane of symmetry

5.9 Chirality without Chirality Centers

- **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.



(*S*)-BINAP
(*S*)-2,2'-Bis(diphenyl
phosphino)-1,1'-binaphthyl

Does not form
(too high in energy)

(*R*)-BINAP
(*S*)-2,2'-Bis(diphenyl
phosphino)-1,1'-binaphthyl

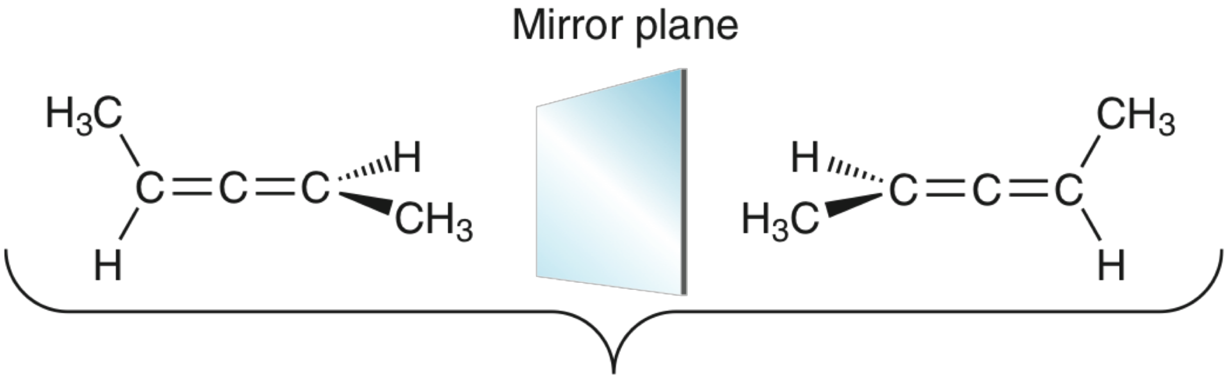
- (R) and (S)-BINAP are chiral, and enantiomers of one another, even though they do not have any chirality centers (they instead have an "axis of chirality."

5.9 Chirality without Chirality Centers

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

An allene

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



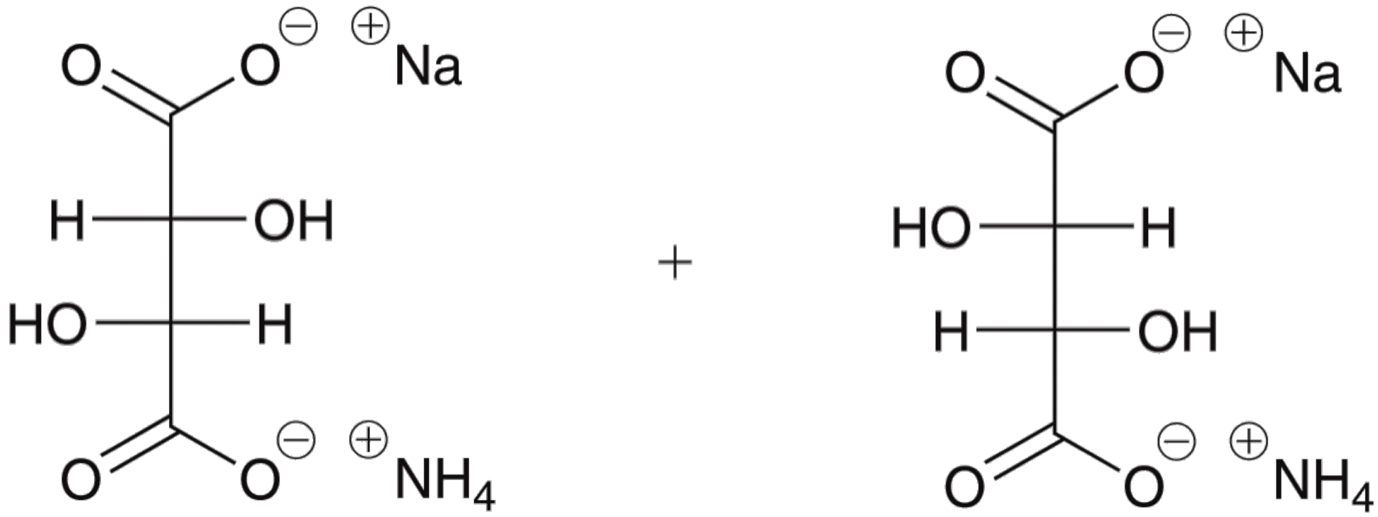
Enantiomers

5.10 Resolution of Enantiomers

- 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/

5.10 Resolution of Enantiomers

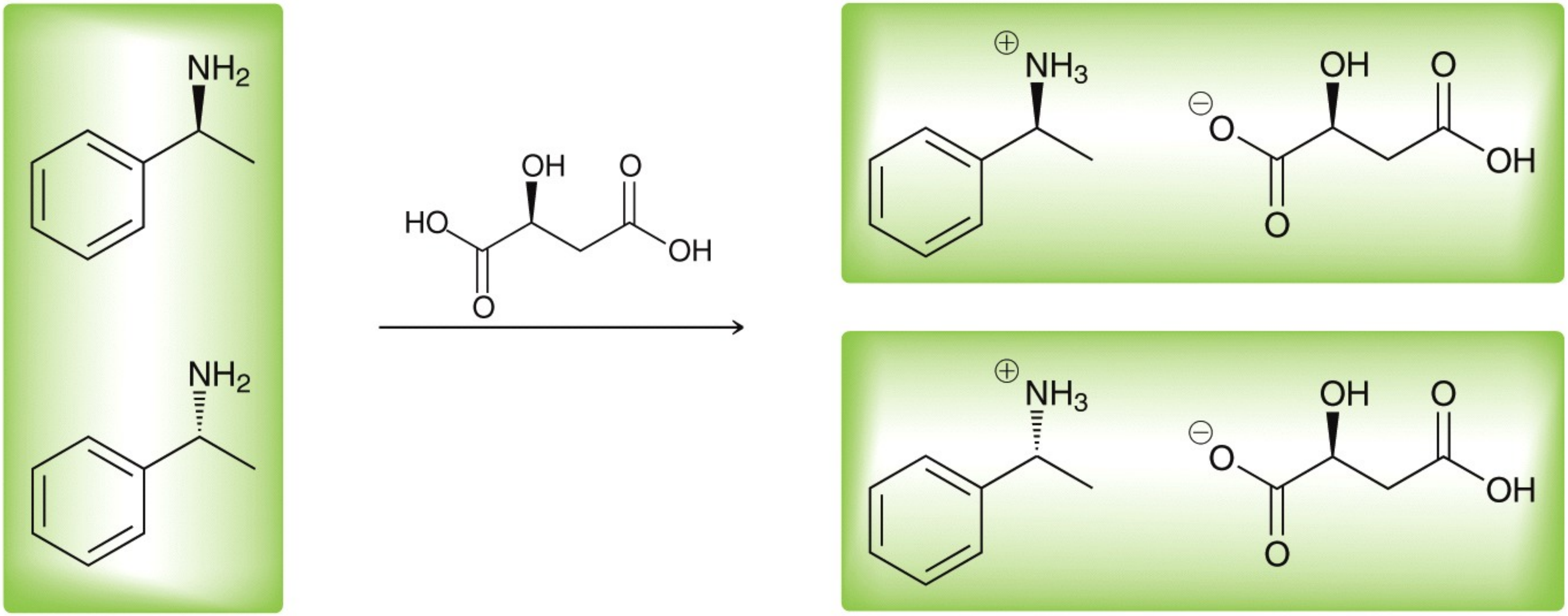
- In 1847, Pasteur performed the first resolution of enantiomers from a racemic mixture of tartaric acid salts



- 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

5.10 Resolution of Enantiomers

- Another method is to use a chiral resolving agent



A pair of enantiomers

Diastereomeric salts

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

5.10 Resolution of Enantiomers

- Affinity chromatography is often used to separate compounds

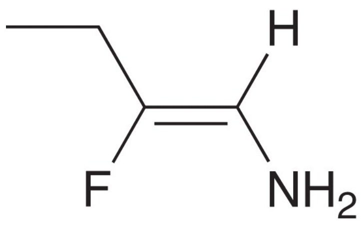
- a glass column (or tube) is packed with a solid substance to act as an adsorbent, and a mixture is passed through it.

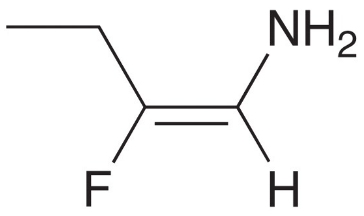
- If a **chiral adsorbent** is used, then enantiomers will interact with it differently, and travel through the column at different rates, allowing for their individual collection (thus separation).

- This is a very common way for resolving enantiomers

5.11 *E* and *Z* Designations for Alkenes

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



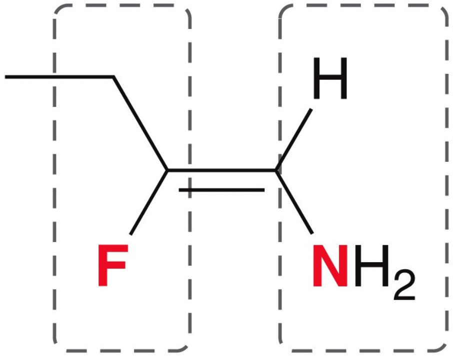


Cis/trans isn't adequate to differentiate between these two diastereomers

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

5.11 *E* and *Z* Designations for Alkenes

- 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



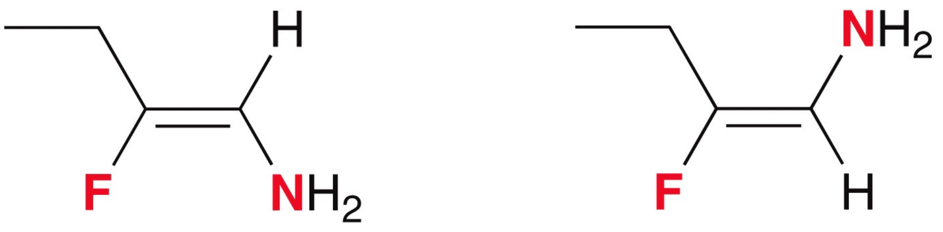
F gets priority over C

N gets priority over H

5.11 *E* and *Z* Designations for Alkenes

- 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)



Z　　*E*

- Practice with SkillBuilder 8.2