Organic Chemistry Chapter 7 Stereoisomerism & Configurations



Based on David Klein's Chemistry as a Second Language WILEY Klein, Organic Chemistry 3e

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7.0 Isomers - Overview

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





7.0 Isomers - Overview: Geometric Isomers

- Although the two molecules below have the "same connectivity", they are NOT identical. (Each carbon is attached to the same groups)
- So they are classified as a type of isomers called stereoisomers



CH₃ H H CH₃

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 like we did in Chapter 6 for our cyclohexane rings 7.0 Isomers - Overview: Geometric Isomers

- Why are these geometric isomers?
 - 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 geometric stereoisomers



cis-2-butene

Groups on same side of pi bond



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7.0 Isomers - Overview: Practice #1 Identifying Isomers

• Identify if any of the following molecules would require *cis*, *trans*, or neither in their name. (*This should be review from previous chapters!*)



7.0 Isomers - Overview: Practice #1 Identifying Isomers

• Identify if any of the following molecules would require *cis*, *trans*, or neither in their name.



7.0 Isomers - Overview: Practice #2 Identifying Isomers

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



7.0 Isomers - Overview: Practice #2 Identifying Isomers

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





identical - you could flip like a pancake and have the same molecule



stereoisomers - cis/trans versions



7.1 Finding Stereocenters



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- **<u>cis-trans isomerism</u>** is only one type *geometric isomers*... there are other important stereoisomeric relationships
 - To identify such stereoisomers, we must be able to identify chiral centers in molecules. Chiral is Greek for "hand" and we will later identify the chiral centers as R or S.
- 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 by building them with a model kit
 - <u>achiral</u> means it is not chiral, because it does not have a different mirror image. This means that it will have no stereocenters OR it does have a line of symmetry in the molecule. (This can be a little tricky!)



A Basic Comparison of Chiral Vs. Achiral



- There is another way to identify chiral compounds...
- Chirality most often results from a stereocenter.
 - a stereocenter occurs when a carbon is connected for 4 different "groups" (we are not looking at the immediate atoms attached, but rather the whole group)
 - This tetrahedral center with 4 different groups attached to it can also be called a <u>chirality center</u>





Examples of chiral centers and stereocenters



Tips to help identify stereocenters:

- Wedges and dashes <u>do not</u> necessarily mean it is a stereocenter. (But they can help!)
- Don't just look at the atoms directly attached to the stereocenter, follow out the group!
- 3. Watch out for hydrogen atoms that are not shown.
- 4. Double or triple bonds cannot be stereocenters.
- 5. Carbons attached to 2 hydrogens cannot be stereocenters

Watch these videos if you need extra help! \rightarrow





• How many chirality centers are in each of the following compounds? Circle or mark the stereocenters (chiral carbons).



answers on next slide



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



NOT Chiral center bc the "CH2" groups are the same the whole way around the ring



two chirality centers







two chirality centers



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• Chirality is important in molecules! Look at the different flavors we get from just a couple of these stereoisomers







- 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
- **Teratogenic** relating to, or causing malformations of an embryo or a fetus.



• Identify and label all the stereocenters each molecule



For practice with 7.1: READ pages 134 - 138 and complete problems 7.1 - 7.15 in the Klein Packet.

7.2 Determining the Configuration of a Stereocenter



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7.2 Determining the Configuration of a Stereocenter

- **Enantiomer** is the name given to the "pair" of mirror images
 - they are different compounds, so they must not have identical names
 - every stereocenter must be switched (inverted) if there is more than one stereocenter
 - enantiomers always exist in pairs (like twins! no more or less!)



- We use the Cahn-Ingold-Prelog system to designate each chirality center as having either the "R" or "S" configuration.
 - "R" meaning "Rectus" which is Latin for "Right-handed" and will rotate light in the clockwise direction
 7.2

7.2 Designating a Stereocenter as R or S

- "R" or "S" is assigned to a stereocenter using a stepwise procedure
 - 1. Using atomic numbers, prioritize the 4 groups attached to the chirality center (1, 2, 3 and 4)
 - #1 will be the largest, #4 will be the smallest
 - continue outward from the chiral center until the found! <u>Do not</u> look at the group as a "whole"



- 2. Arrange the molecule in space so the #4 priority group faces away from you (This is sometimes hard to do, see the trick on following slides!)
- 3. Count the group priorities $1 \rightarrow 2 \rightarrow 3$ to determine whether the order progresses in a clockwise or counterclockwise direction
- 4. Clockwise = *R* and Counterclockwise = *S*

READ pages 138-142 and complete practice problems 7.17 - 7.26 in the Klein Packet to get practice assigning #1-4 priorities.







Please fix! I made an oopsie!

- The Cahn, Ingold and Prelog system
 - 1. Assign the priorities to the atoms (#1 $\frac{\text{largest}}{\text{largest}} \rightarrow$ #4 $\frac{\text{smallest}}{\text{smallest}}$)
 - 2. Arrange the molecule in space so the lowest priority group faces away from you (#4 has to be on the dash). You can do this by "spearing" the molecule and rotating it.



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

Example continued on the next slide...

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7.2 Designating a Stereocenter as R or S

3. Counting the other group priorities, 1...2...3, determine whether the order progresses in a clockwise or counterclockwise direction (ignore #4)

S configuration

Clockwise = R and Counterclockwise = S3 counterclockwise



R configuration

clockwise

3



Looking back on the original model... we just determined this chirality Center has the (S) configuration

7.2 Designating a Stereocenter as R or S

More Help with Assigning Priorities for Groups

- 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, branching out from the stereocenter. Stop at the FIRST difference between the chains.





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

Help with assigning priorities continued...

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



<u>Tie</u> because both are C's attached to the stereocenter, so now we look at what THEY are attached to

Second layer

We look at all the atoms each of the C's is additionally attached to....



The priority is based on the first point of difference!

O is bigger than C's, so the left side wins. DO NOT look at total masses, just "who is attached to a bigger atom first"

A Solution for Multiple Bonds with respect to assigning priorities

- When prioritizing for the Cahn, Ingold and Prelog system, double bonds count as "two single bonds"
 - Think of it as counting that carbon as being attached to "two oxygens"

counts twice

Triple bonds would be handled similarly





7.2 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 look- ing for the first point of difference. When constructing lists to compare, remember that a double bond is treated as two sepa- rate 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 (<i>R</i>) or a counterclockwise order (<i>S</i>).



TIME FOR THE "HACK"!

- Handheld molecular models can be very helpful when arranging the molecule in space so the lowest priority group faces away from you, but that can take a lot of time!
- Here are some other hacks/tricks that can use
 - Switching two groups on a chirality ce opposite configuration



- So "swap" #4 with whatever is on the dustine to a second term of the second term of terms of the second term of terms of the second terms of terms of the second terms of ter
 - This will work every time, BUT you have to remember to switch your answer back at the end!!!!



Need 4 on a dash, so swap #'s with whatever is on the dash



Look at rotation of #1-3 to determine if R or S This one we would think is "S"



Remember you swapped #'s so your configuration isn't what you think! Our "S" is actually R!

7.2 Designating R vs S Configuration Practice #1

• Assign the configuration of the chiral center in the following compounds. Add H's as needed...



7.2 Designating R vs S Configuration Practice #2

• Assign the configuration of the stereocenters in the following compounds







Additional practice videos, if you need them!





READ pages 142-146 and complete practice problems #7.27 - 7.42 in the Klein Packet to get practice assigning R and S to stereocenters.

7.3 R/S and E/Z in IUPAC Nomenclature

Quick review of `stereochemical' ideas so far:



7.3 R/S and E/Z in IUPAC Nomenclature



- notice the E/Z and R/S go in parentheses ()'s
- If more than one stereocenter, the carbon number comes directly in front of the R or S (this would also apply for E/Z)
- There is a comma between multiple stereocenters or E/Z
- Add a dash/hyphen after the ()'s

Great Crash Course Overview Video!



7.3 R/S an	d E/Z in	IUPAC	Nomenc	lature
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Stereoisomerism	Substituents	Parent Chain	Unsaturation	Functional Group
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 For molecules with different groups attached to the C=C double bond, the <u>*E/Z* notation</u> is used instead of cis/trans notation



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

- cis and trans only works if there is the same group on <u>each</u> carbon of the alkene (double bonded carbons)
 - Z is for "zussamen", which means together
 - But we think "Zame Zide" for "same side", like cis
 - E is for "entgegen", which means opposite
 - but we this "Epposite Side" for "opposite side" like trans

Video with 2 practice problems, if needed



7.3 Steps for *E* and *Z* Designations of Alkenes 1. Prioritize the groups attached to the C=C double bond based on atomic number just like we did with prioritizing the 4 groups on stereocenters. *However, we only have to compare group "#1" and*

"#2" on each side.



If the top priority groups are on the same side of the C=C double bond, it is Z. If the top priority groups are on opposite sides of the C=C double bond, it is E



7.3 Nomenclature Practice Problems









READ pages 146-150 and complete practice problems #7.44-7.49 in the Klein Packet to get practice with R/S and E/Z nomenclature.

Stereoisomerism

Substituents

Parent Chain

Unsaturation

Functional Group
7.4 Enantiomers

when a molecule meet its enantiomer



Enantiomers be like









Learning about Enantiomers and found this funny

7.4 - Drawing Enantiomers

- Because a stereocenter allows the possibility of a molecule to have a mirror image of itself, we get two structures.
- These two structures would be considered enantioners of each other (like mirror image twins)

Some "rules" about enantiomers:

- Enantiomers **cannot** be superimposable
- Only a chiral compound can have an enantiomer
- There is always TWO of them! Like twins!
- If there are multiple stereocenters, then
 - **EVERY** stereocenter inverts
- There are 2 basic methods for drawing enantiomers



Y + STEREOCHEMI







7.4 - Drawing Enantiomers - 2 Methods

Method 1: Simply switch ALL wedges & dashes to the

opposite! Bonds will look like they are in exactly the same spaces. (You will NOT draw a mirror plane like in method 2)



Practice with the molecules below!





7.4 - Drawing Enantiomers - 2 Methods

Method 2: Draw the reflection in the mirror. Bonds will spread out symmetrically from the mirror plane (dotted line). Keep wedges as wedges and dashes as dashes.



... the mirror image will be its enantiomer



Practice with the molecules below!





READ pages 151-155 and complete practice problems #7.51-7.63 in the Klein Packet to get practice with drawing enantiomers.

Two types of stereoisocats





Categories of isomers Isomers Isomers Constitutional isomers (Different connectivity) Enantiomers Nonsuperimposable Ind NOT mirror images

- **Enantiomers**: stereoisomers that are mirror images (EVERY stereocenter has inverted, appear in pairs, like twins)
 - have identical physical properties
- **Diastereomers**: stereoisomers that are not mirror images (*This* occurs because they have 2 or more stereocenters and not eWerULEY stereocenter inverts) Like another sibling in the family, but not a

How to draw all the Enantiomers and Diastereomers:

- 1. Draw the first molecule. (Sometimes you are given this)
- 2. Draw the enantiomer of the molecule (invert ALL centers)
- 3. Then change ONE stereocenter, draw its enantiomer.
- 4. Continue this process of changing one stereocenter at a time and drawing it's enantiomer until all statistical possibilities of R & S combinations have occured.

• The max. number of stereoisomers is 2ⁿ, where n = # stereocenters We call these examples the "barn doors". It works nicely when you have 2 stereocenters!





1. What is the maximum # of possible cholesterol isomers?



1. Draw and label the "barn doors" and label them for a molecule of 1-ethyl-2methylcyclopropane



- **Consider a cyclohexane with three substituents.** There are statistically 8 ways to arrange wedges/dashes for all the stereocenters. This creates **4 pairs of enantiomers.**
 - 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



7.6 Meso Compounds





7.6 Meso Compounds

- We have talked about enantiomers which are mirror images BUT we can have a special case if a molecule with more than one stereocenter has a plane of symmetry. This is called a meso compound.
 - It does NOT have a non-superimposable mirror image. (aka it doesn't have an enantiomer - a "mirror twin")
 - it is it's own mirror image we say it is 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

A Basic Comparison of Molecules with the Property Brothers!







(Including molecules that are superimposable mirror images)



= the same molecule

Likewise, if these identical twins were molecules, they'd also be considered to be "the same":



7.6 Meso Compounds

- If a compound has a **plane of symmetry**, it is **ACHIRAL**
- If a compound as at least TWO stereocenters AND a plane of symmetry it is ACHIRAL, we specifically call it MESO

• But... There's more!

- a compound that lacks a plane of symmetry may still be an achiral compound... if it has an reflectional symmetry may still be an <u>inversion</u> 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
- Pro-tip: If you aren't sure draw what you *think* is the enantiomer and see if you can twist/rotate to superimpose it on the original structure, if you can - it's meso and achiral. If not, it's the enantiomer!

7.6 Meso Compounds

 Again, compound with chirality centers, but is achiral because of symmetry is called a meso compound

Internal plane of symmetry Internal plane of symmetry

• The molecules below are examples of meso compounds:



Me

Me

*Draw the line of symmetry for each!

meso compounds have less than the predicted number of stereoisomers based on the 2⁽ⁿ⁾ formula, thoy are their own "READ pages 157-160 and complete practice problems #7.72-7.74 in the Klein Packet to identify the meso compounds.



Fischer projections can also be useful to represent molecules with multiple consecutive stereocenters, instead of bondline drawings with wedges and dashes. (*The example below only has one*

stereocenter)



Horizontal lines represent attachments on WEDGES





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



• Fischer projections are also useful to quickly assess stereoisomeric relationships



• So how exactly does it work? Build the molecule and follow the steps!



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rotating it so that you are looking from the far side. We can see how the attached groups are coming off the left and right side.

- How to assign R and S to Fischer Projections
 - Keep one wedge and one dash attached to each stereocenter, assume the other 2 connections are straight lines. (It doesn't matter which ones you choose, you will get the correct answer as long as you follow the "horizontal = wedge & vertical = dash" rules!)

$$\begin{array}{cccc} \mathsf{CH}_3 & \mathsf{CH}_3 & \mathsf{CH}_3 & \mathsf{CH}_3 \\ \mathsf{HO} & & \mathsf{HO} & \mathsf{CH}_2 & \mathsf{CH}_3 \\ \mathsf{HO} & & \mathsf{HO} & \mathsf{CH}_2 & \mathsf{CH}_2 & \mathsf{CH}_2 & \mathsf{CH}_2 \\ \mathsf{CH}_2 \mathsf{CH}_3 & & \mathsf{CH}_2 \mathsf{CH}_3 & \mathsf{CH}_2 \mathsf{CH}_3 \\ \end{array}$$

2. Use your previously learned skills to assign values of 1-4 based on molar mass and determine the rotation of the 1-3 values. Use the trick if #4 isn't on a dash. *Keep in mind that you are looking for the FIRST difference between the atoms! See example below:*



• Practice assigning R and S to each stereocenter in the Fischer Projections





• Draw the enantiomer D-glucose.



Keep top/bottom in the same spot.



READ pages 160-165 and complete practice problems #7.76-7.81 in the Klein Packet to practice more with Fischer Projections.





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





Notice the enantiomers have the same melting and boiling points!

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

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



• To get light waves that travel in only one plane, light travels through



- 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

7.8 Optical Activity - Polarimeter





- **Enantiomers** will rotate the plane of the light to equal degrees but in <u>opposite</u> 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
- Consider the enantiomers of 2-bromobutane



- (*R*) and (S) refer to the <u>configuration</u> of the chirality center
 - Man-made designation to determine difference of molecules
- (+) and (-) signs refer to the <u>direction the plane of light is rotated</u>
 - Physical effect measured in a lab can flip with temperature!

R/S and +/- are NOT dependent upon each other!

- 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 both 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. 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

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

• So, (-4.6) / (-23.1) x 100% = **20 % ee**

Additional Info: Resolution of Enantiomers

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



- 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, so other methods have been created
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Additional Info: 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
 - Remember: diastereomers CAN have different MP & BR

Additional Info: 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



Here are some videos regarding column chromatography if you would like to learn more!







END of chapter 7 Notes **Student Version to** Follow



Organic Chemistry Chapter 7 Stereoisomerism & Configurations



David Klein

WILEY Klein, Organic Chemistry 3e

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• There are two general types of isomers

butanone

butanal





7.0 Isomers - Overview: Geometric Isomers

- Although the two molecules below have the "same connectivity", they are NOT identical. (Each carbon is attached to the same groups)
- So they are classified as a type of isomers called



CH₃ H H CH₃

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 like we did in Chapter 6 for our cyclohexane WILEY
7.0 Isomers - Overview: Geometric Isomers

- Why are these geometric isomers?
 - 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



H₃C CH₃ H H

cis-2-butene

Groups on same side of pi bond

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Klein, Organic Chemistry 3e

7.0 Isomers - Overview: Practice #1 Identifying Isomers

• Identify if any of the following molecules would require *cis*, *trans*, or neither in their name. (*This should be review from previous chapters*!)



7.0 Isomers - Overview: Practice #2 Identifying Isomers

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



_ is only one type - *geometric isomers*...

there are other important stereoisomeric relationships

To identify such stereoisomers, we must be able to identify
 in molecules. *Chiral is Greek for "____*

and we will later identify the chiral centers as R or S.

- A ______object is ______, which means it is not the same as its mirror image (i.e. ______ on its mirror image)
 - You can test whether two objects are identical by seeing if they are superimposable by building them with a model kit

means it is not chiral, because it does not have a different mirror image. This means that it will have no stereocenters OR it does have a line of symmetry in the molecule. (This can be a little tricky!)



11

A Basic Comparison of Chiral Vs. Achiral



- There is another way to identify chiral compounds...
- Chirality most often results from a _____

 a ______ occurs when a carbon is connected for 4 different "groups" (we are not looking at the immediate atoms attached, but rather the whole group)

 This tetrahedral center with 4 different groups attached to it can also be called a ______





Examples of chiral centers and stereocenters



Tips to help identify stereocenters:

- 1. Wedges and dashes <u>do not</u> necessarily mean it is a stereocenter. *(But they can help!)*
- 2. Don't just look at the atoms directly attached to the stereocenter, <u>follow out the group</u>!
- 3. Watch out for hydrogen atoms that are not shown.
- 4. Double or triple bonds cannot be stereocenters.
- 5. Carbons attached to 2 hydrogens cannot be stereocenters

Watch these videos if you need extra help! \rightarrow



• How many chirality centers are in each of the following compounds? Circle or mark the stereocenters (chiral carbons).



• Chirality is important in molecules! Look at the different flavors we get from just a couple of these stereoisomers



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 Because two chiral molecules are mirror images, they will have many identical properties, but because they are not identical, their

_____ may be very different

relating to, or causing malformations of an embryo or a fetus.



• Identify and label all the stereocenters each molecule



For practice with 7.1: READ pages 134 - 138 and complete problems 7.1 - 7.15 in the Klein Packet.

7.2 Determining the Configuration of a Stereocenter

- is the name given to the "pair" of mirror images
 they are different compounds, so they must not have identical names
 - every stereocenter must be switched (inverted) if there is more than one stereocenter
 - enantiomers always exist in pairs (like twins! no more or less!)



- We use the ______to designate each chirality center as having either the "*R*" or "*S*" configuration.
 - "R" meaning "Rectus" which is Latin for "Right-handed" and will rotate light in the clockwise direction
 7.2

- "R" or "S" is assigned to a stereocenter using a stepwise procedure
 - 1. Using atomic numbers, prioritize the 4 groups attached to the chirality center (1, 2, 3 and 4)
 - #1 will be the largest, #4 will be the smallest
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- 2. Arrange the molecule in space so the #4 priority group faces away from you (This is sometimes hard to do, see the trick on following slides!)
- 3. Count the group priorities $1 \rightarrow 2 \rightarrow 3$ to determine whether the order progresses in a clockwise or counterclockwise direction
- 4. Clockwise = *R* and Counterclockwise = *S*

READ pages 138-142 and complete practice problems 7.17 - 7.26 in the Klein Packet to get practice assigning #1-4 priorities.





- The Cahn, Ingold and Prelog system
 - 1. Assign the priorities to the atoms (#1 largest \rightarrow #4 smallest)
 - 2. Arrange the molecule in space so the lowest priority group faces away from you (#4 has to be on the dash). You can do this by "spearing" the molecule and rotating it.



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

Example continued on the next slide...

Once you learn the "trick" you won't want to think about it this way!

3. Counting the other group priorities, 1...2...3, determine whether the order progresses in a clockwise or counterclockwise direction (ignore #4)

S configuration

Clockwise = R and Counterclockwise = S3 counterclockwise



R configuration

clockwise

3



Looking back on the original model... we just determined this chirality Center has the (S) configuration

More Help with Assigning Priorities for Groups

- 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, branching out from the stereocenter. Stop at the FIRST difference between the chains.





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

Help with assigning priorities continued...

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



<u>Tie</u> because both are C's attached to the stereocenter, so now we look at what THEY are attached to

Second layer

We look at all the atoms each of the C's is additionally attached to....



The priority is based on the first point of difference!

O is bigger than C's, so the left side wins. DO NOT look at total masses, just "who is attached to a bigger atom first"

A Solution for Multiple Bonds with respect to assigning priorities

- When prioritizing for the Cahn, Ingold and Prelog system, double bonds count as "two single bonds"
 - Think of it as counting that carbon as being attached to "two oxygens"

counts twice

Triple bonds would be handled similarly





7.2 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 look- ing for the first point of difference. When constructing lists to compare, remember that a double bond is treated as two sepa- rate 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 (<i>R</i>) or a counterclockwise order (<i>S</i>).



TIME FOR THE "HACK"!

- Handheld molecular models can be very helpful when arranging the molecule in space so the lowest priority group faces away from you, but that can take a lot of time!
- Here are some other hacks/tricks that can use
 - Switching two groups on a chirality ce opposite configuration



- So "swap" #4 with whatever is on the dustine to a second term of the second term of terms of the second term of terms of the second terms of terms of the second terms of ter
 - This will work every time, BUT you have to remember to switch your answer back at the end!!!!



Need 4 on a dash, so swap #'s with whatever is on the dash



Look at rotation of #1-3 to determine if R or S This one we would think is "S"



Remember you swapped #'s so your configuration isn't what you think! Our "S" is actually R!

7.2 Designating R vs S Configuration Practice #1

• Assign the configuration of the chiral center in the following compounds. Add H's as needed...



7.2 Designating R vs S Configuration Practice #2

• Assign the configuration of the stereocenters in the following compounds







Additional practice videos, if you need them!





READ pages 142-146 and complete practice problems #7.27 - 7.42 in the Klein Packet to get practice assigning R and S to stereocenters.

7.3 R/S and E/Z in IUPAC Nomenclature



- notice the E/Z and R/S go in parentheses ()'s
- If more than one stereocenter, the carbon number comes directly in front of the R or S (this would also apply for E/Z)
- There is a comma between multiple stereocenters or E/Z
- Add a dash/hyphen after the ()'s

Great Crash Course Overview Video!



7.3 R/S and E/Z in IUPAC Nomenclature

Stereoisomerism	Substituents	Parent Chain	Unsaturation	Functional Group
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 For molecules with different groups attached to the C=C double bond, the ______ is used instead of cis/trans notation



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

• cis and trans only works if there is the same group on <u>each</u> carbon of the alkene *(double bonded carbons)*



7.3 Steps for *E* and *Z* Designations of Alkenes 1. Prioritize the groups attached to the C=C double bond based on atomic number just like we did with prioritizing the 4 groups on stereocenters. *However, we only have to compare group "#1" and*

"#2" on each side.



If the top priority groups are on the same side of the C=C double bond, it is Z. If the top priority groups are on opposite sides of the C=C double bond, it is E



7.3 Nomenclature Practice Problems









READ pages 146-150 and complete practice problems #7.44-7.49 in the Klein Packet to get practice with R/S and E/Z nomenclature.

Stereoisomerism

Substituents

Parent Chain

Unsaturation

Functional Group

7.4 - Drawing Enantiomers

- Because a stereocenter allows the possibility of a molecule to have a mirror image of itself, we get two structures.
- These two structures would be considered enantioners of each other (like mirror image twins)

Some "rules" about enantiomers:

- Enantiomers **cannot** be superimposable
- Only a chiral compound can have an enantiomer
- There is always TWO of them! Like twins!
- If there are multiple stereocenters, then
 - **EVERY** stereocenter inverts
- There are 2 basic methods for drawing enantiomers

Good video for overall stereochemistry practice!

Y + STEREOCHEMIS







7.4 - Drawing Enantiomers - 2 Methods

Method 1: Simply switch ALL wedges & dashes to the

opposite! Bonds will look like they are in exactly the same spaces. (You will NOT draw a mirror plane like in method 2)



Practice with the molecules below!





7.4 - Drawing Enantiomers - 2 Methods

Method 2: Draw the reflection in the mirror. Bonds will spread out symmetrically from the mirror plane (dotted line). Keep wedges as wedges and dashes as dashes.



... the mirror image will be its enantiomer



Practice with the molecules below!





READ pages 151-155 and complete practice problems #7.51-7.63 in the Klein Packet to get practice with drawing enantiomers.

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Two types of stereoisocats



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• **Enantiomers**: stereoisomers that are mirror images (EVERY stereocenter has inverted, appear in pairs, like twins)

have _____ physical properties

• **Diastereomers**: stereoisomers that are not mirror images (*This* occurs because they have 2 or more stereocenters and not eWeryLEY stereocenter inverts) Like another sibling in the family, but not a

How to draw all the Enantiomers and Diastereomers:

- 1. Draw the first molecule. (Sometimes you are given this)
- 2. Draw the enantiomer of the molecule (invert ALL centers)
- 3. Then change ONE stereocenter, draw its enantiomer.
- 4. Continue this process of changing one stereocenter at a time and drawing it's enantiomer until all statistical possibilities of R & S combinations have occured.

• The max. number of stereoisomers is 2ⁿ, where n = # stereocenters We call these examples the "barn doors". It works nicely when you have 2 stereocenters!





1. What is the maximum # of possible cholesterol isomers?



1. Draw and label the "barn doors" and label them for a molecule of 1-ethyl-2methylcyclopropane



- **Consider a cyclohexane with three substituents.** There are statistically 8 ways to arrange wedges/dashes for all the stereocenters. This creates **4 pairs of enantiomers.**
 - 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



7.6 Meso Compounds

 We have talked about enantiomers which are mirror images BUT we can have a special case if a molecule with more than one stereocenter has a ______. This is called a

compound.

- It does NOT have a non-superimposable mirror image. (aka it doesn't have an enantiomer - a "mirror twin")
- it is it's own mirror image we say it is 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

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A Basic Comparison of Molecules with the Property Brothers!







(Including molecules that are superimposable mirror images)



= the same molecule

Likewise, if these identical twins were molecules, they'd also be considered to be "the same":



7.6 Meso Compounds

- If a compound has a **plane of symmetry**, it is **ACHIRAL**
- If a compound as at least one stereocenter AND a plane of symmetry it is ACHIRAL, we specifically call it MESO

• But... There's more!

- a compound that lacks a plane of symmetry may still be an achiral compound... if it has an reflectional symmetry may still be an <u>inversion</u> 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
- Pro-tip: If you aren't sure draw what you *think* is the enantiomer and see if you can twist/rotate to superimpose it on the original structure, if you can - it's meso and achiral. If not, it's the enantiomer!
7.6 Meso Compounds

 Again, compound with chirality centers, but is achiral because of symmetry is called a meso compound

Internal plane of symmetry Internal plane of symmetry

• The molecules below are examples of meso compounds:



Me

Me

*Draw the line of symmetry for each!

meso compounds have less than the predicted number of stereoisomers based on the 2⁽ⁿ⁾ formula, thoy are their own "READ pages 157-160 and complete practice problems #7.72-7.74 in the Klein Packet to identify the meso compounds.



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Fischer projections can also be useful to represent molecules with multiple consecutive stereocenters, instead of bondline drawings with wedges and dashes. (*The example below only has one*

stereocenter)



Horizontal lines represent attachments on WEDGES





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



• Fischer projections are also useful to quickly assess stereoisomeric relationships



• So how exactly does it work? Build the molecule and follow the steps!



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rotating it so that you are looking from the far side. We can see how the attached groups are coming off the left and right side.

- How to assign R and S to Fischer Projections
 - Keep one wedge and one dash attached to each stereocenter, assume the other 2 connections are straight lines. (It doesn't matter which ones you choose, you will get the correct answer as long as you follow the "horizontal = wedge & vertical = dash" rules!)

$$\begin{array}{cccc} \mathsf{CH}_3 & \mathsf{CH}_3 & \mathsf{CH}_3 & \mathsf{CH}_3 \\ \mathsf{HO} & & \mathsf{HO} & \mathsf{CH}_2 & \mathsf{CH}_3 \\ \mathsf{HO} & & \mathsf{HO} & \mathsf{CH}_2 & \mathsf{CH}_2 & \mathsf{CH}_2 & \mathsf{CH}_2 \\ \mathsf{CH}_2 \mathsf{CH}_3 & & \mathsf{CH}_2 \mathsf{CH}_3 & \mathsf{CH}_2 \mathsf{CH}_3 \\ \end{array}$$

2. Use your previously learned skills to assign values of 1-4 based on molar mass and determine the rotation of the 1-3 values. Use the trick if #4 isn't on a dash. *Keep in mind that you are looking for the FIRST difference between the atoms! See example below:*



• Practice assigning R and S to each stereocenter in the Fischer Projections





• Draw the enantiomer D-glucose.



Keep top/bottom in the same spot.



READ pages 160-165 and complete practice problems #7.76-7.81 in the Klein Packet to practice more with Fischer Projections.

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





Notice the enantiomers have the same melting and boiling points!

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

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





- 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



- **Enantiomers** will rotate the plane of the light to equal degrees but in <u>opposite</u> 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
- Consider the enantiomers of 2-bromobutane



- (*R*) and (S) refer to the <u>configuration</u> of the chirality center
 - Man-made designation to determine difference of molecules
- (+) and (-) signs refer to the <u>direction the plane of light is rotated</u>
 - Physical effect measured in a lab can flip with temperature!

R/S and +/- are NOT dependent upon each other!

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- 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 both 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. 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

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

• So, (-4.6) / (-23.1) x 100% = **20 % ee**

Additional Info: 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 se
- However, this method doesn't work for most pairs of enantiomers, so other mean
- The differing physical properties of diastereomers allow them to be more easily separated
 - Remember: diastereomers CAN have different MP & BPs!
 - 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
 - ***Videos are on slide 65 on google classroom if you would like to learn more!***

