

Stereochemistry

Reading

- Brown and Foote Chapter 3
- Klein: Chapter 7

Suggested Text Exercises from Brown and Foote

- Chapter 3: 1–9, 11, 13–28, and 30–37

Lecture Supplement

- Stereochemistry

Optional Web Site Reading

- Chirality and Molecular Models (www.bluffton.edu/~bergerd/Models/home.html)
- The Life and Times of Louis Pasteur (<http://louisville.edu/library/ekstrom/special/pasteur/cohn.html>)
- Thalidomide (<http://en.wikipedia.org/wiki/Thalidomide>)
- Nitrogen Inversion (http://en.wikipedia.org/wiki/Nitrogen_inversion)

Related Tutorials from the Course Web Site

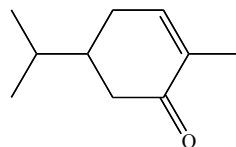
Stereochemistry: Vocabulary
Identifying Stereocenters
Determining Molecular Chirality
Classification of Isomers
Stereocenter Nomenclature: The *R/S* System
Drawing Enantiomers and Diastereomers

Concept Focus Questions

1. Briefly but precisely define each term.

(a) Absolute configuration	(e) Diastereomers	(i) Racemic mixture
(b) Achiral	(f) Enantiomer	(j) Stereocenter
(c) Cahn-Ingold-Prelog priority rules	(g) Meso compound	(k) Stereoisomer
(d) Chiral	(h) Optically active	
2. Jacobus van't Hoff proposed that compounds such as 2-chlorobutane that contain a carbon atom with four different attachments exists as two isomers. Draw both of these isomers for 2-chlorobutane and label each as *R* or *S*.
3. Tartaric acid has two stereocenters. What is the most number of stereoisomers it can have? Construct a diagram that shows all of these stereoisomers and their relationships to each other.
4. Explain why Pasteur was able to resolve racemic acid, but not mesotartaric acid.

5. Carvone exists as a pair of enantiomers. (*R*)-(-)-carvone smells like spearmint, whereas (*S*)-(+)-carvone smells like caraway. Why do these enantiomers have different smells (i.e., different biological activity)?



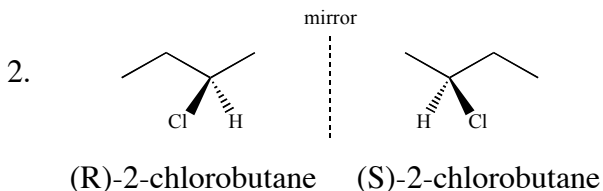
Carvone

6. Why are (*R*)-2-chlorobutane and (*S*)-2-chlorobutane not separable by simple means based on physical properties such as boiling point or solubility?
7. Why must enantiomers be converted to diastereomers before separation processes such as crystallization?

Concept Focus Questions Solutions

1. Illustrated definitions can be found at the Illustrated Glossary of Organic Chemistry available at the course web site.
- (a) Absolute configuration: The relative spatial position of substituents at a stereocenter. Assigned *R* or *S* based upon the Cahn-Ingold-Prelog priority rules.
- (b) Achiral: An object that is not chiral.
- (c) Cahn-Ingold-Prelog priority rules: Rules that assign priority to atoms or groups for various purposes such as labeling the absolute configuration of a stereocenter. Lowest priority is assigned to the atom or group with the lowest atomic number.
- (d) Chiral: An object that is not superposable upon its mirror image.
- (e) Diastereomer: A stereoisomer that is not an enantiomer.
- (f) Enantiomer: One of a pair of stereoisomers that are nonsuperimposable mirror images.
- (g) Meso compound: An achiral compound that contains two or more stereocenters.
- (h) Optically active: A substance that rotates plane-polarized light.
- (i) Racemic mixture: An equimolar mixture of enantiomers of the same molecule.
- (j) Stereocenter: A carbon atom bearing four different attachments. More broadly (and therefore a better definition): an atom bearing three or more different attachments whose juxtaposition leads to stereoisomers.

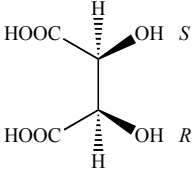
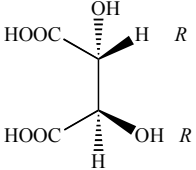
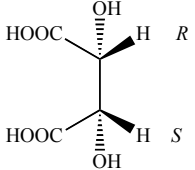
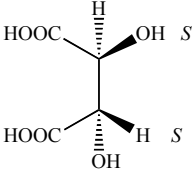
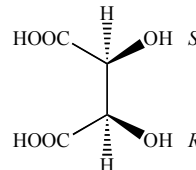
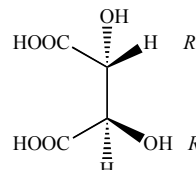
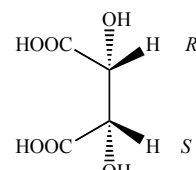
(k) **Stereoisomer**: One of a set of isomers of identical constitution (sequence of atomic attachments) but differing in the arrangement of their atoms in space and not interconvertible by rotation around a single bond.

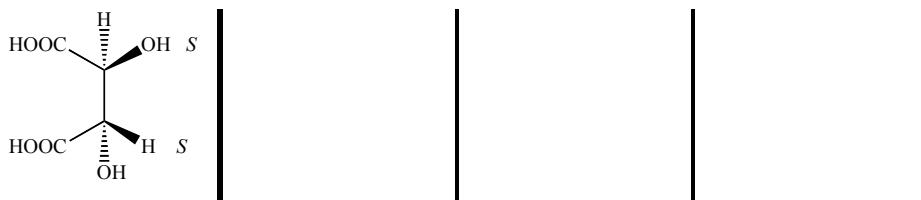


When drawing a molecule to show its stereochemistry, it is necessary to define the exact spatial relationship of all four groups attached to the stereocenter(s).

3. A compound with a single stereocenter can be *R* or *S* (two stereoisomers). A compound with two stereocenters can be *RR*, *SS*, *RS*, or *SR* (four stereoisomers). In general, a compound with *n* stereocenters can have at most 2^n stereoisomers. There may be less if the compound has meso forms.

Relationship of Tartaric Acid Stereoisomers

				
	-----	diastereomers	meso (identical)	diastereomers
	diastereomers	-----	diastereomers	enantiomers
	meso (identical)	diastereomers	-----	diastereomers
	diastereomers	enantiomers	diastereomers	-----



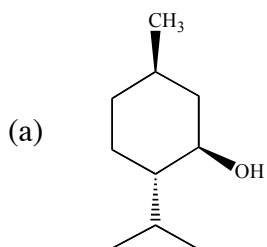
4. Racemic acid is a racemic mixture of (+)-tartaric acid and (-)-tartaric acid. As a mixture of enantiomers, racemic acid can be resolved into the two enantiomers. Mesotartaric acid is a meso compound, so it cannot exist as enantiomers, and therefore cannot be resolved.
5. Biological effects, such as smell, may occur when a compound interacts with an enzyme or receptor in the body. Enzymes and receptors are constructed from proteins or other biomolecules that have distinct three-dimensional shapes. An olfactory receptor may bind readily to (*R*)-(-)-carvone, thereby sending a specific signal (the spearmint smell signal) to the brain. This fit depends upon very specific shape and size of the receptor and the carvone. The (*S*)-(+)-carvone has a mirror image shape and thus does not fit as well into the same receptor. Instead, it binds strongly to a different olfactory receptor, resulting in a different signal to the brain. Thus, enantiomers may have different biological effects because they do not fit the same receptors of enzymes. Compare this to a lock and a key: a lock fits a specific key, but the same lock cannot fit the mirror image of the key. (Unless the lock or key is achiral, of course.)
6. Separation of compounds often depends upon some difference in physical property such as boiling point or solubility. The 2-chlorobutane stereoisomers shown above are enantiomers. The only difference in physical properties of enantiomers is the direction in which they rotate plane-polarized light. Thus, separation of 2-chlorobutane enantiomers by simple techniques based upon physical properties is not possible. Separation can be achieved if the compounds are converted to diastereomers by chemical reaction (or some other means).
7. Separation by crystallization requires the compounds undergoing separation to have different solubilities. Solubility is a physical property. The only difference in the physical properties of enantiomers is the direction in which they rotate plane-polarized light. Conversely, diastereomers have different physical properties, such as solubility. Thus, conversion of enantiomers (same solubility) into diastereomers (different solubility) is crucial for separation by crystallization.

OWLS Problems

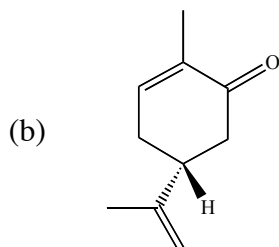
Molecular models are a great way to help visualize three-dimensional relationships of atoms within molecular structures. Their frequent use will assist you in mastering many aspects of organic chemistry, especially stereochemistry.

Please bring your model kit to discussion section this week.

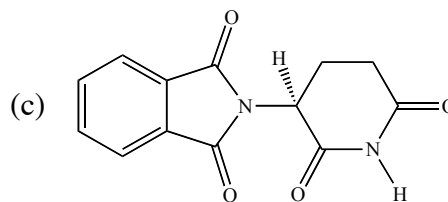
1. Label the stereocenter(s) in each molecule as *R* or *S*.



(-)-Menthol
*used in cough
drops*

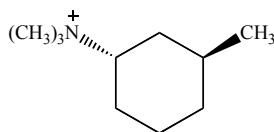


(-)-Carvone
*smells like
spearmint*



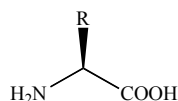
(+)-Thalidomide
teratogenic drug

2. Draw the structure of each molecule.
 - (a) (*R*)-2-chlorobutane
 - (b) (*S*)-3-hexanol
 - (c) (1*R*,3*S*)-1,3-diphenylcyclohexane
3. Build a model of the ammonium ion shown below. Pay careful attention to the absolute stereochemistry of the stereocenters. Answer the following questions.

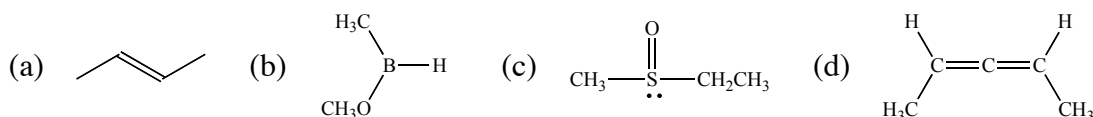


- (a) What is the most stable conformation of this molecule?
 - (b) Label the absolute configuration of the stereocenters as *R* or *S*.
 - (c) What is the stereochemical relationship between the two chair conformations (enantiomers, identical, etc.)?
 - (d) Change one of the ring attachments so that the equilibrium constant for the chair-chair equilibrium is much larger, but maintain the same *R* or *S* absolute configurations for the stereocenters.
4. Alter the structure of nicotine (from the Stereochemistry Lecture Supplement) so that:
 - (a) The rotation is (+),
 - (b) The molecule is optically inactive but not meso, and
 - (c) The molecule is optically inactive and has at least two stereocenters.

5. There are 21 standard amino acids, 20 of which are chiral. (See the Amino Acids, Peptides, and Proteins Lecture Supplement.) A generic amino acid structure is shown below. "R" is a common abbreviation for an alkyl group or other attachment.

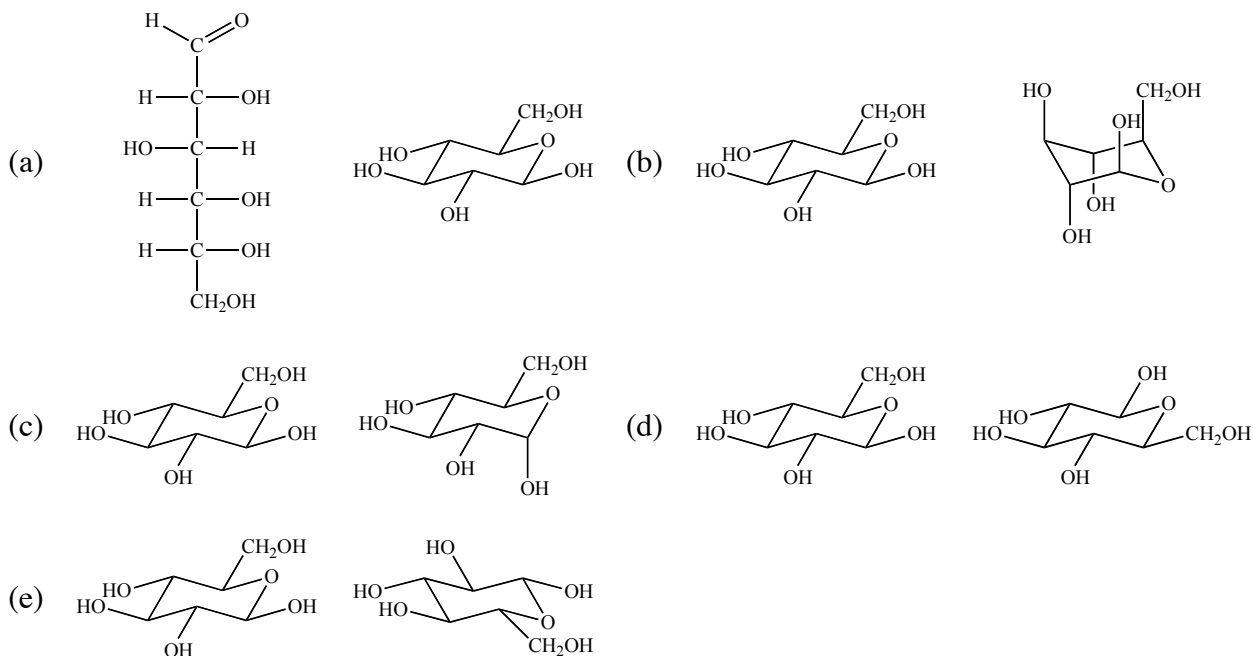


- (a) Draw the structure of the only achiral amino acid. Explain why it is achiral.
 (b) Build a model of alanine ($R = \text{CH}_3$). Is the stereochemical configuration (R or S) the same for all natural amino acids? Explain.
6. Label each structure as chiral or achiral. Hint: build a model of the molecule and its mirror image then test for superimposability. If the molecule is chiral draw its enantiomers.



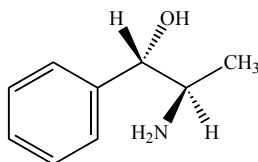
Practice Problems

1. Glucose is an important molecule that exists in a variety of isomeric forms. Label each pair of glucose isomers shown below as constitutional isomers, conformational isomers, stereoisomers, or identical. If the structures are stereoisomers, further label them as enantiomers or diastereomers. You may need to review the Classification of Isomers tutorial on the course web site first.

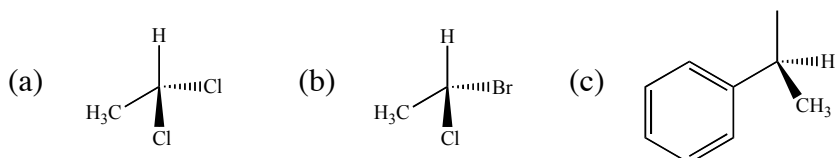


2. Draw (a) a pair of enantiomers, and (b) a pair of diastereomers.

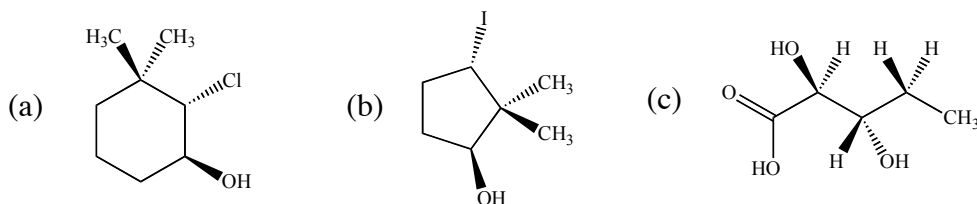
3. For the structure shown below draw: (a) an enantiomer, and (b) a diastereomer.



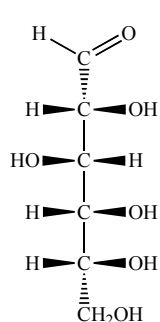
4. Explain why each compound shown below cannot be part of a set of diastereomers.



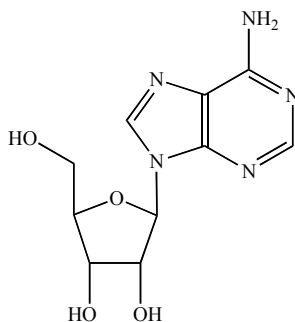
5. Label the stereocenters in each molecule as *R* or *S*.



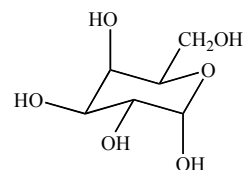
6. Label each stereocenter in the following biologically important molecules as *R* or *S*.
Models will be of great help!



D-Glucose

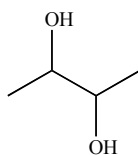


Adenylic acid



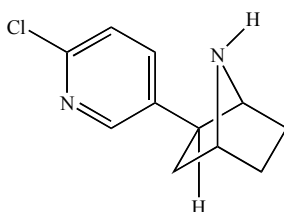
α -D-Galactopyranose

7. Of all the possible things that can be attached to a carbon that is a stereocenter, what thing has the lowest possible Cahn-Ingold-Prelog priority? Hint: start by thinking about the criteria used to define priority.
8. Draw a meso compound whose formula is $C_6H_{12}O_2$.
9. Draw all the possible stereoisomers of 2,3-butanediol. Label each stereocenter as *R* or *S*. Construct a table that shows the relationship of all of these stereoisomers.



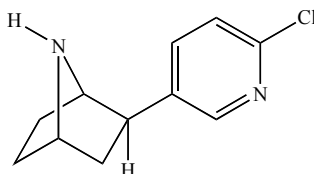
2,3-Butanediol

10. Epibatidine is an analgesic that is more powerful than morphine, but too toxic for human use. Much research is focused on finding analogs of epibatidine that are less toxic, but retain the analgesic activity. The sp^3 nitrogen atom of epibatidine is not a stereocenter because amines undergo a process of inversion that changes their stereochemistry many times per second (Vollhardt and Schore Chapter 21 section 2). Normally, we do not assign the configuration of the amine nitrogen as *R* or *S* unless there is no inversion. (Practice Problem 20 has more on this issue.)



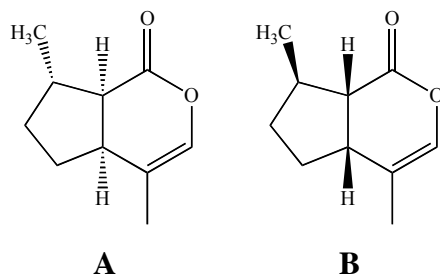
Epibatidine

- (a) Label each stereocenter of epibatidine as *R* or *S*. *A model is very useful!*
 (b) Draw a diastereomer of epibatidine.
 (c) Draw an enantiomer of epibatidine.
 (d) Do you expect your epibatidine enantiomer to have analgesic properties? Briefly explain your reasoning.
11. Answer the following actual student question: Is there is an error in the solution to part (c) of the previous question? The Thinkbook answer is wrong because the positions of the double bonds in the pyridine ring are switched. The correct answer is:

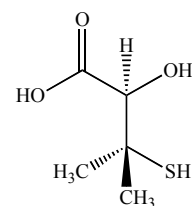


12. Consider the structure of thalidomide.
- (a) Draw (*R*)-thalidomide and (*S*)-thalidomide.
 (b) Why are the stereoisomers of thalidomide not separable by ordinary physical means such as differences in solubility?
 (c) Briefly but thoroughly explain why one stereoisomer of thalidomide is a sedative, while the other stereoisomer is a teratogen?

13. Catnip is a plant that upon ingestion has obvious effects on some cats, causing them to exhibit unusual, uninhibited play behavior (i.e. it makes them “stoned”). Two structures for nepetalactone, the active component of catnip, are shown below.
- What one term best describes the relationship of compounds **A** and **B**?
 - Compound **A** causes the “stoned” behavior cats whereas molecule **B** is inactive. Based on what we have discussed in lecture, suggest a reasonable explanation for this fact.

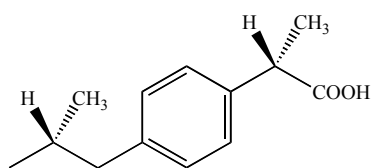


14. Answer these questions about molecule **C**.
- Label the stereocenters as *R* or *S*.
 - Draw an enantiomer of this compound.
 - Can this compound be optically active?
 - Can this compound be resolved by crystallization?



Molecule **C**

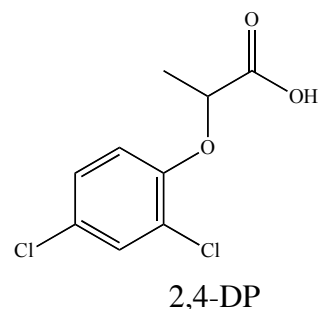
15. Imagine that you run a factory that manufactures ibuprofen, an analgesic and anti-inflammatory found in many over-the-counter drugs such as Motrin.



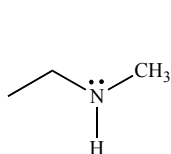
Ibuprofen

- Label all the ibuprofen stereocenters as *R* or *S*.
- Draw an enantiomer of ibuprofen.
- Draw a diastereomer of ibuprofen.
- Your factory currently makes racemic ibuprofen, but new FDA laws do not allow you to sell a racemic product because the enantiomers may have different biological effects. What is the biological reason(s) that ibuprofen enantiomers may have different drug effects? Be as specific as possible.
- Very briefly outline a plan to resolve the ibuprofen racemic mixture. Details on specific chemical reactions are not needed.

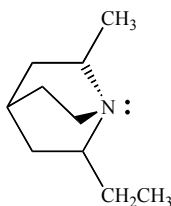
16. (a) Draw the *R* enantiomer of 2,4-DP.
 (b) What is the relationship of the melting points of the two enantiomers of 2,4-DP?
 (c) A herbicide is a chemical that is used to kill plants. Do you expect the *R* and *S* enantiomers of 2,4-DP to have the same or different herbicidal properties? Explain.



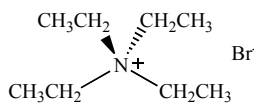
17. Why are many drugs sold as single enantiomers and not as a racemic mixture, despite the fact that it is usually less expensive to manufacture a racemate than a single enantiomer?
18. Butane has an infinite number of conformations. All of the conformations except two are chiral, yet butane is not optically active.
 (a) Show that the gauche conformation is chiral.
 (b) What conformations are achiral?
 (c) Explain why butane is not optically active.
19. Draw a pair of alkenes that differ only in that they are *E* and *Z* isomers. Label each as *E* or *Z*.
20. Nitrogen atoms with four different attachments are frequently encountered in biologically important molecules.
 (a) In which of the following molecules is the nitrogen atom a stereocenter?



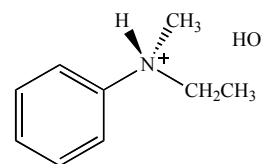
D



E



F

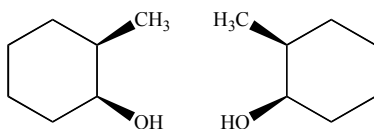


G

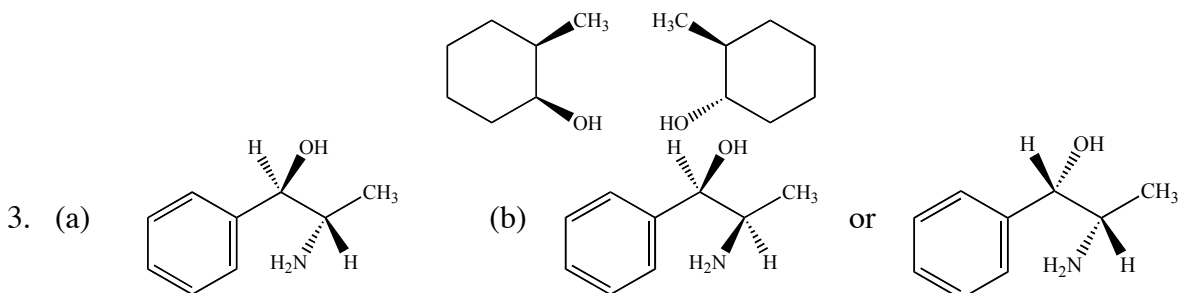
- (b) What is the Cahn-Ingold-Prelog priority for a lone pair?
 (c) For each molecule in part (a) that is optically active, assign the absolute configuration of the nitrogen atom as *R* or *S*.

Practice Problems Solutions

1. (a) Constitutional isomers; (b) conformational isomers; (c) stereoisomers (diastereomers); (d) stereoisomers (enantiomers); and (e) identical
2. (a) Enantiomers are molecules that are nonsuperimposable mirror images. Any pair of enantiomers is acceptable. For example:



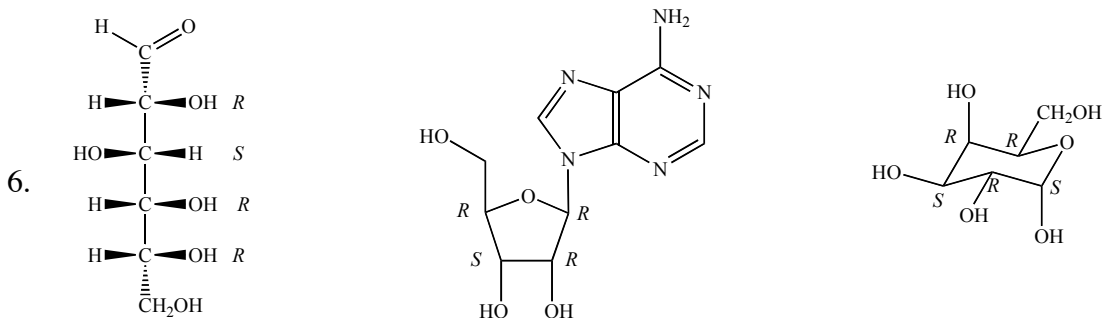
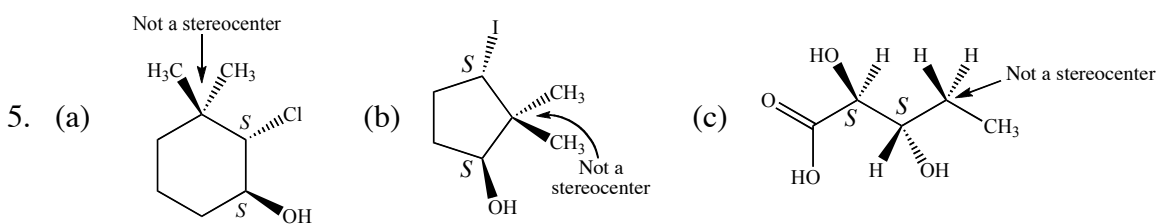
(b) Diastereomers are stereoisomers that are not enantiomers. Any pair of diastereomers is acceptable. For example:



4. (a) The structure lacks a stereocenter, so it cannot be any sort of stereoisomer, let alone a diastereomer.

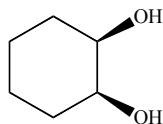
(b) The molecule has a single stereocenter. Therefore it cannot have a stereoisomer which is not an enantiomer.

(c) The molecule does not have a stereocenter therefore it cannot have any diastereomers. (Recall that a “stick” represents a methyl group. Also recall that the wedge and broken wedge notation is used to indicate the relative position of groups in space. It does not indicate the presence of a stereocenter.)



7. In the Cahn-Ingold-Prelog priority system, things with lower atomic number have lower priority. Hydrogen has an atomic number of one, but a lone pair has an atomic number of zero. Therefore a lone pair is lowest possible priority attachment.

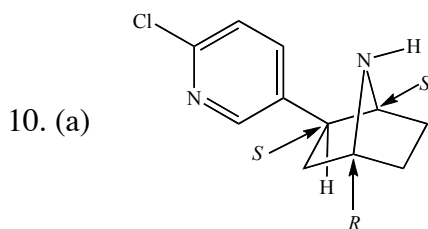
8. A meso compound is an achiral molecule bearing stereocenters. Any meso compound with the correct formula is an acceptable answer. For example:



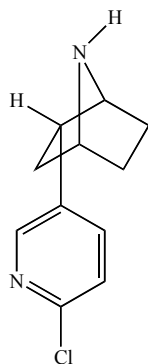
9. This molecule has two stereocenters, so it can have at most $2^2 = 4$ stereoisomers.

Stereoisomers of 2,3-Butanediol

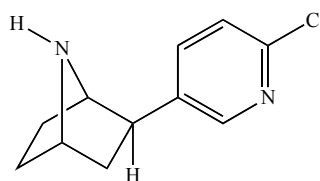
	 (2 <i>R</i> , 3 <i>R</i>)	 (2 <i>R</i> , 3 <i>S</i>)	 (2 <i>S</i> , 3 <i>R</i>)	 (2 <i>S</i> , 3 <i>S</i>)
(2 <i>R</i> , 3 <i>R</i>)	-----	diastereomers	diastereomers	enantiomers
(2 <i>R</i> , 3 <i>S</i>)	diastereomers	-----	identical (meso)	diastereomers
(2 <i>S</i> , 3 <i>R</i>)	diastereomers	identical (meso)	-----	diastereomers
(2 <i>S</i> , 3 <i>S</i>)	enantiomers	diastereomers	diastereomers	-----



- (b) Several diastereomers are possible. The most obvious one is shown below.



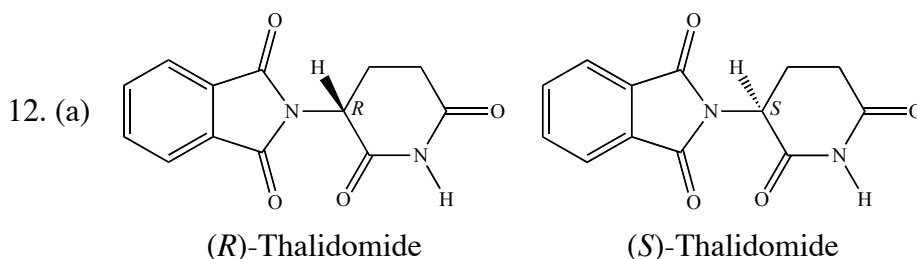
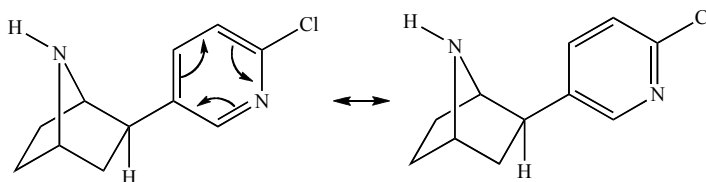
Epibatidine diastereomer



Epibatidine enantiomer

- (c) Enantiomers exist in pairs, so for a given molecule, there can only be one enantiomer. The enantiomer of epibatidine is shown above.
- (d) Biological properties of a molecule are controlled by how well the molecule fits into a receptor site, such as an enzyme pocket. These receptor sites are chiral because they are built from chiral molecules (amino acids). There is usually a "lock and key" relationship between the receptor (the lock) and the molecule(s) that the receptor responds to (the keys). Molecules that fit well into the receptor activate that receptor strongly. Molecules that do not fit well do not activate the receptor. Molecules that are enantiomers or diastereomers often do not fit into the same receptor and therefore do not have the same biological properties. Alternately, the stereoisomers may both fit the same receptor, but one fits well and the other poorly, invoking different levels of response from this receptor. Therefore, we expect the different stereoisomers of epibatidine to have different biological properties. While epibatidine is a strong but toxic analgesic, the enantiomer may be a weaker analgesic or induce some biological response that is altogether different.

11. This is not an error. The two structures are resonance contributors, which are alternate representations of the same molecule.

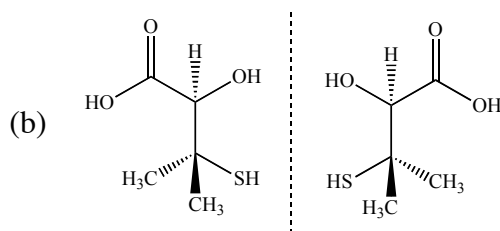
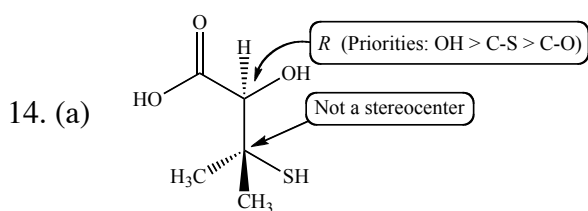


- (b) Thalidomide has only one stereocenter, so the stereoisomers must be a set of enantiomers. The physical properties of enantiomers such as solubility or melting point are identical except for the direction in which they rotate plane-polarized light. Thus the enantiomers of thalidomide cannot be separated by means that depend on their physical properties alone.
- (c) Many drugs act by binding to enzymes or receptor sites. These binding sites have a certain three-dimensional shape that fits a specific arrangement of atoms in space. The binding site may fit one enantiomer of thalidomide, producing a certain biological effect. The other enantiomer has a mirror image shape, so the

arrangement of atoms in space is different. This different arrangement of atoms may not fit the same binding site, but instead may fit into a separate binding site, resulting in a different effect. This is analogous to a lock and key arrangement. A lock has a very specific shape that only fits one key. The mirror image of the key cannot fit into this lock and cannot open the same door.

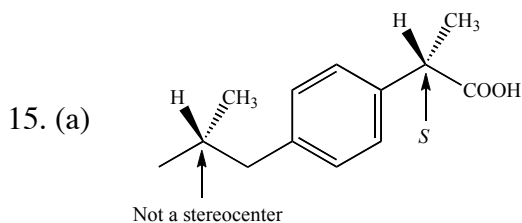
13. (a) Enantiomers.

(b) The biological effect of any compound depends upon what enzyme or active site it triggers. Triggering requires the molecule to fit into the enzyme pocket or active site. Because these structures have different three-dimensional details, enantiomers may not fit them equally well. Thus, enantiomers may have different biological effects because they have different interactions with receptors, etc.

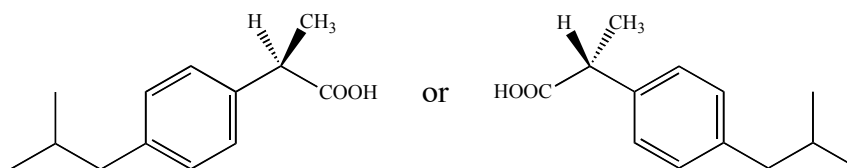


(c) This structure is nonsuperimposable on its mirror image. It is chiral and therefore can be optically active.

(d) Resolution by crystallization requires that the compounds being resolved have different physical properties (solubility in this case). This compound can exist only as enantiomers, which do not differ in any physical except the rotation of plane-polarized light. Therefore this compound cannot be resolved by crystallization. Alternate reasoning: As drawn, this compound is a single enantiomer. Since resolution involves separation of different enantiomers, this compound cannot be resolved.

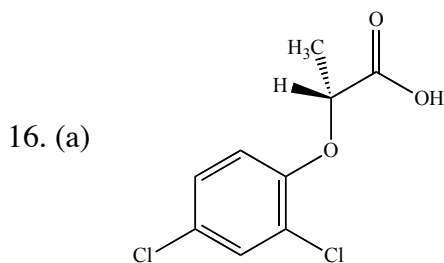


- (b) Any molecule can have at most one enantiomer. Two views of this enantiomer are presented.



- (c) Ibuprofen has a single stereocenter, so it cannot have a diastereomer.
- (d) Drug effects may be due to interaction with a biological structure such as a receptor or enzyme. These structures have distinct three-dimensional shapes (the lock of the lock and key analogy, or the glove of the glove and hand analogy used in lecture). The ibuprofen enantiomer also has a distinct three-dimensional shape (key or hand) that fits well into a specific receptor or enzyme. The other ibuprofen enantiomer does not fit this same receptor or enzyme as well. This difference in fit is the cause of different drug effects.
- (e) Recall the resolution of methamphetamine from lecture. Using the same idea for ibuprofen, the resolution might be achieved by this three-step process.
- Step 1: Convert racemic mixture of enantiomers (identical physical properties) to diastereomers (different physical properties) by reacting ibuprofen (an acid) with an optically active amine (a base).
 - Step 2: Separate diastereomers based on their different physical properties.
 - Step 3: Convert separated diastereomers back into enantiomers.

Resolution is the process of separating enantiomers by any means necessary. It is a common student misconception that every resolution requires conversion to diastereomers. This is a false restriction. For example, Pasteur separated tartaric acid enantiomers solely based on the shape of the crystals. No diastereomers were involved.



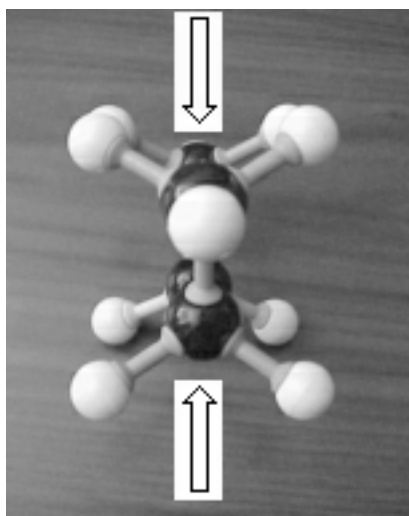
When drawing a molecule to show its stereochemistry, it is necessary to define the exact spatial relationship of all four groups attached to the stereocenter(s).

- (b) The only difference in physical properties of enantiomers is the direction in which they rotate plane-polarized light. Thus the melting points of the two enantiomers of 2,4-DP are equal.

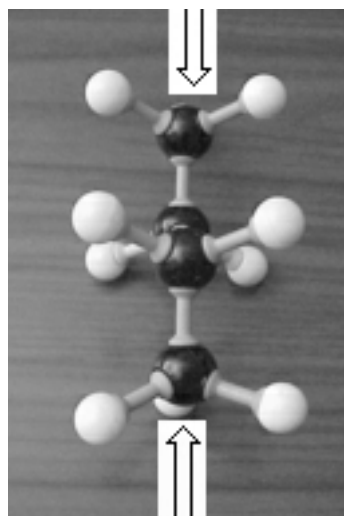
- (c) Herbicidal action is a biological effect. Such biological effects are often brought about by interaction with a biological structure such as an enzyme or receptor. These structures have distinct three-dimensional shapes because they are made of chiral building blocks such as amino acids. One enantiomer of 2,4-DP might fit well into an enzyme or receptor, whereas the other enantiomer may not fit as well. Enantiomers that bind differently cause different biological effects. As an analogy, recall the lecture demonstration with hands and gloves: the right hand fits well into a right-handed glove, but not a left-handed glove. If the right hand is an enantiomer of 2,4-DP it would activate the right glove enzyme but not the left glove enzyme. The left hand (corresponding to the opposite enantiomer of 2,4-DP) would activate the left glove enzyme but not the right glove enzyme.

In practice, plants died when exposed to one enantiomer of 2,4-DP but were immune to the other enantiomer. Other studies found no noticeable toxicity in birds, but significant toxicity to fish and aquatic invertebrates.

17. A racemate is a mixture of enantiomers. One enantiomer may have the desired drug properties, while the other may have harmful properties.
18. (a) The gauche conformation is chiral because it is not superposable upon its mirror image. This is easily explored using molecular models.
- (b) The syn-periplanar and anti-periplanar conformations are achiral because they both have an internal plane of symmetry. (In the structures shown the mirror plane is represented with the arrows.) Because of this, both of these conformations are superposable with their mirror images and hence achiral. This fact can be easily verified with molecular models.

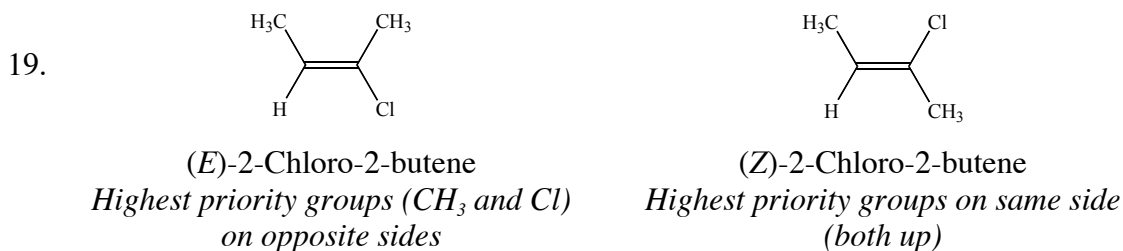


Syn-periplanar



Anti-periplanar

- (c) One might expect butane to be optically active because it has chiral conformations. However, each chiral conformation has an enantiomer. Enantiomers have equal energy and are thus populated equally. In other words, in a sample of butane there are an equal number of “left” and “right” gauche conformations. The enantiomeric conformations rotate plane-polarized light in equal amounts but in opposite directions, resulting in no optical activity for the sample as a whole.



20. (a) Molecule **D**: The nitrogen atom has four different attachments (ethyl, hydrogen, methyl, and lone pair) but is not a stereocenter due to nitrogen inversion (Brown and Foote section 23.3).

Molecule **E**: The nitrogen atom has four different attachments. Strain prevents nitrogen inversion. Therefore the nitrogen atom is a stereocenter.

Molecule **F**: The nitrogen atom does not have four different attachments and therefore cannot be a stereocenter.

Molecule **G**: The nitrogen atom has four different attachments. Nitrogen inversion does not occur in the absence of a lone pair (or if the lone pair is highly delocalized due to resonance). This nitrogen atom is a stereocenter.

- (b) Cahn-Ingold-Prelog priority is based on atomic number (the number of protons in the nucleus). A lone pair has no protons (or a nucleus!) so its priority is always lowest.
- (c) Molecules **D** and **F** lack stereocenters, and therefore are not optically active. The nitrogen atoms of molecule **E** and **G** are both *R*.