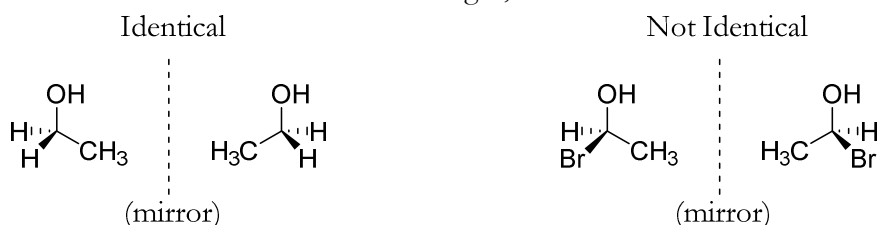


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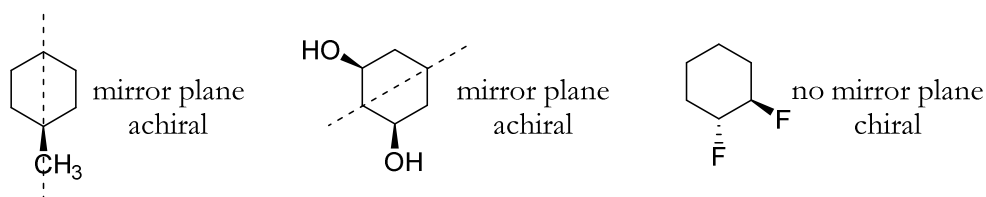
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This entire chapter has to do with the relationship between stereoisomers (molecules that have the same connectivity, but a different spatial arrangement). We've already seen one type of stereoisomerism with cis/trans and E/Z alkenes, but there are many other types. Since so much of this chapter looks at three-dimensional shapes, model kits are essential!

Some molecules are identical to their mirror images, and some are not.



In this second case, the two molecules are noncongruent mirror images of each other. This makes them **enantiomers** of each other. Every molecule that has an enantiomer is **chiral** (from the Greek word for hand), because it has a “handedness” or “**chirality**” to it. The easiest way to check whether a molecule is chiral is to look for an **internal mirror plane of symmetry** – a place where you can cut the molecule in half so that each half reflects perfectly into the other. If it exists, then the molecule is not chiral (in other words, it is **achiral**). Some examples are shown below. The last molecule has no mirror plane because you can't reflect a bold bond onto a dashed bond.



The part of the molecule that gives it chirality is often, but not always, an **asymmetric carbon**. This is a carbon with four different groups attached to it. Asymmetric carbons are one example of a **stereocenter** – a part of the molecule where swapping any two groups converts the molecule to a different molecule.

Absolute Configuration

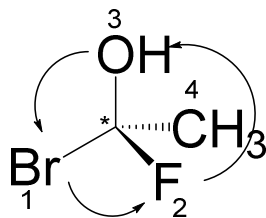
Since there are multiple possible arrangements at an asymmetric carbon, we need a way to describe the absolute configuration. We use the R/S designation to do this. To determine if a particular asymmetric carbon is R or S:

- 1) Find each asymmetric carbon in the molecule and mark it with an asterisk or star. To save time, you can rule out many of the carbons: if a C has two or three Hs, there's no way it can have four different groups on it.
- 2) For each asymmetric carbon, assign priorities to the four groups around it, using the same CIP rules that you used for assigning E or Z to an alkene. Start at the asymmetric carbon, move out one step at a time, and compare groups. Higher-atomic-number atoms have priority, and multiple bonds to an atom count as multiple copies of that atom.
- 3) Orient the molecule so that group 4, the lowest priority group, is pointing away from you. Then travel in a circle from group 1 to 2 to 3, back to 1. If you traveled in a clockwise circle, your molecule is R. If you went counterclockwise your molecule is S.

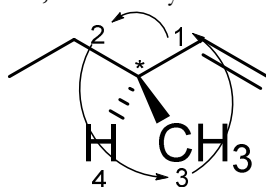
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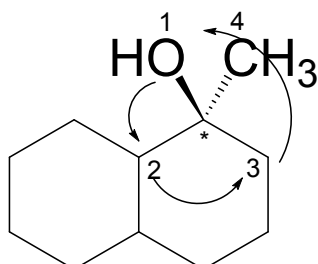
Here are some examples:



In this example, the asymmetric carbon is marked with an asterisk. The four groups attached to it are OH, Br, H, and CH₃. Since each of these has a different atom at the first point of attachment, they are easy to rank: Br > OH > CH₃ > H, so we label them 1-4 in that order. Group 4, the H, is already pointing away from us. Now we just go from Br to OH to CH₃ back to Br. We went counterclockwise, so this asymmetric carbon is S.



In this one, we compare C vs. C vs. C vs. H. The H immediately takes lowest priority. Then, moving one step out, we compare a C with one other bond to C, vs. a C with two other bonds to C, vs. a C with no other bonds to C. This lets us assign priorities 1, 2, and 3. Moving around these goes counterclockwise, so it's S.



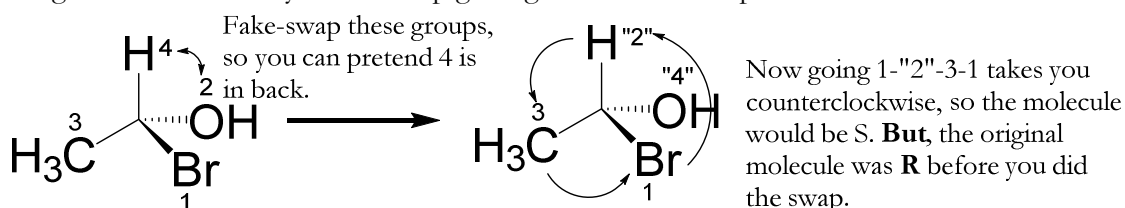
In this example, there are several asymmetric carbons (both the Cs at the places where the rings join together), but we'll only look at the one labeled with an asterisk. Moving one step out from the asymmetric carbon gives us four groups: one with an O, and the others all with Cs. The oxygen immediately takes first priority. Comparing the other groups, one of the carbons has two other bonds to C and one to H (C,C,H), one of the carbons has one other bond to C and two Hs (C,H,H), and one of the carbons has only three Hs (H,H,H). They are prioritized in that order. Once we've labeled each group, we check that group 4 is in the back, then move from 1 to 2 to 3 to 1. This is again counterclockwise, so S.

How do you handle cases where group 4 is not in the back? There are several options: you can build a model of the molecule and rotate it around so it's oriented correctly. If your visualization skills are good, you can do the same thing mentally. One other option is to use a trick based on an interesting fact: swapping any two groups at an asymmetric carbon converts the carbon from R to S, or vice versa. If you take a molecule and pretend you're swapping group 4 with whatever group is in back, you can avoid having to rotate the molecule. (You don't even have to redraw the groups – just swap the priority numbers

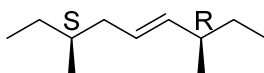
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temporarily.) Then, since you swapped two groups, the original molecule was the opposite designation from what you ended up getting. Here's an example:



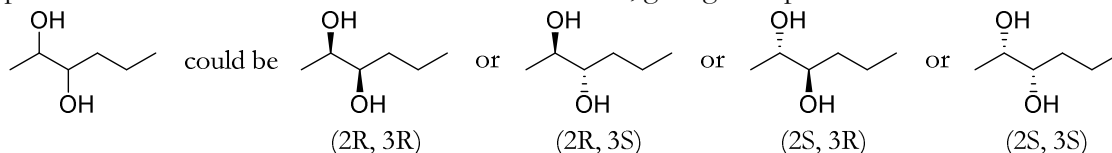
If a molecule has multiple stereocenters, you have to assign each one individually as R or S, following the rules listed above. Once you've figured out R/S for each stereocenter in the molecule, put them in parentheses at the front of the name, along with a number specifying the location of each stereocenter.



This molecule is R at carbon 3 and S at carbon 7. Its name is (3R, 7S)-3,7-dimethyl-4-nonene. (You can also throw the E/Z descriptors for alkenes into the same parentheses, sorting everything by location. So to be completely thorough, you would call this molecule (3R, 4E, 7S)-3,7-dimethyl-4-nonene.) Note that even though we aren't showing the Hs at the stereocenters, they are implied to be there, and to be on dashed bonds, since the bold-bond position is already taken up by a CH₃ group in both cases.

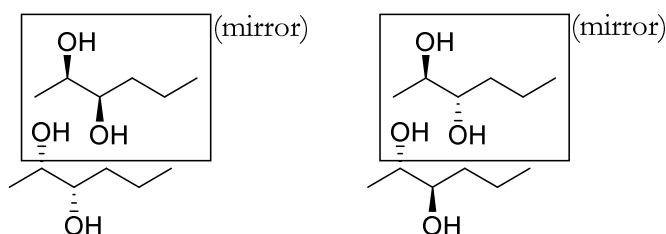
Diastereomers

When molecules have more than one stereocenter, there are more than just two molecules possible. Each individual stereocenter can be R or S, giving four possible stereoisomers:



For a given structure with n stereocenters, there will be a maximum of 2^n possible stereoisomers. There can sometimes be fewer than this, if some of the compounds are meso (see below).

Some of these structures are mirror images of each other. If you imaging a mirror in the plane of the page, the reflection of the (2R, 3R) stereoisomer looks exactly like the (2S, 3S) stereoisomer, and the reflection of the (2R, 3S) stereoisomer looks exactly like the (2S, 3R) stereoisomer.

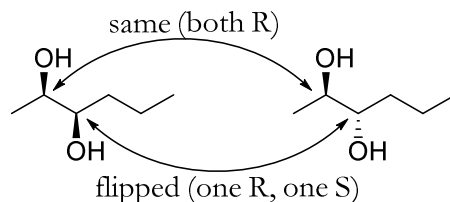


This means that the (2R, 3R) and the (2S, 3S) are enantiomers of each other. But how can we describe the relationship between, for instance, the (2R, 3R) and the (2R, 3S)? These do not reflect into each other at all, so they are **diastereomers** – nonsuperimposable non-mirror images that still have the same connectivity as each other. The easiest way to figure

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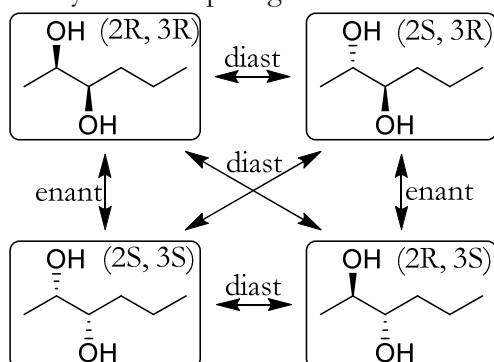
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out the relationship between two molecules is to compare the stereocenters between the two molecules.



- If all stereocenters are the same (R stays R, S stays S), the molecules are identical.
- If all stereocenters are flipped (R on one molecule is S on the other or vice versa), the molecules are enantiomers.
- If some stereocenters are flipped and some are the same, the molecules are diastereomers.
- Be careful! These rules don't always work if the molecule is capable of being meso (see below)

It's important to remember that "identical", "enantiomer" and "diastereomer" describe the relationship between molecules. A given molecule can be any of these things, depending on what you're comparing it to.



- How many enantiomers total? 4.
- How many diastereomers total? 4.
- How many enantiomers does (2S, 3S) have? 1.
- How many diastereomers does (2S, 3S) have? 2.

Now we can put together a hierarchy of similarity between any two molecules.

- Different formula? Not related.
- Same formula but different connectivity? Constitutional isomers.
- Same formula and connectivity, but not mirror images or identical? Diastereomers.
- Same formula and connectivity, mirror images of each other, but not identical? Enantiomers.

This can also be applied to E/Z isomerism in alkenes:



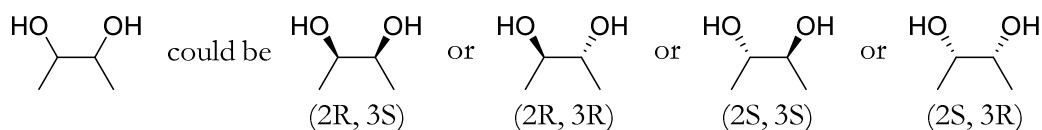
These molecules have the same formula and connectivity, but are not mirror images, so they must be diastereomers. This is true for any E/Z pair of alkenes. Remember, any place where swapping two groups gives you a different molecule is a stereocenter, so each carbon of this alkene is a stereocenter.

Meso Compounds

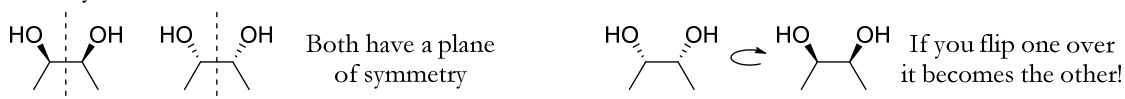
Some compounds have a plane of symmetry, even though they have stereocenters.

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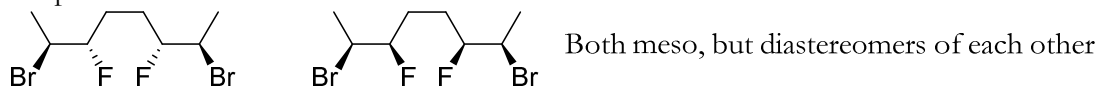
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Of these compounds, the (2R, 3S) and the (2S, 3R) have an internal plane of symmetry and should be achiral. In fact, if we flip one of the molecules over, we can see that they're actually both the same molecule.



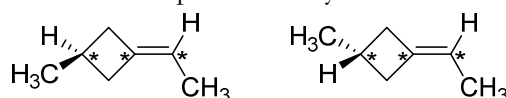
These molecules are described as **meso**. The formal definition for meso is an achiral compound with chiral diastereomers. In a set of stereoisomers, each meso molecule decreases the total number of stereoisomers by one. In this case, there's one meso molecule, so the total number of stereoisomers is $2^2 - 1 = 3$. More complicated molecules can have multiple different meso forms:



This molecule, with 4 stereocenters, should have $2^4 = 16$ stereoisomers. But it has two different meso forms, so really there are only 14 possible stereoisomers.

Chirality without Asymmetric Carbons

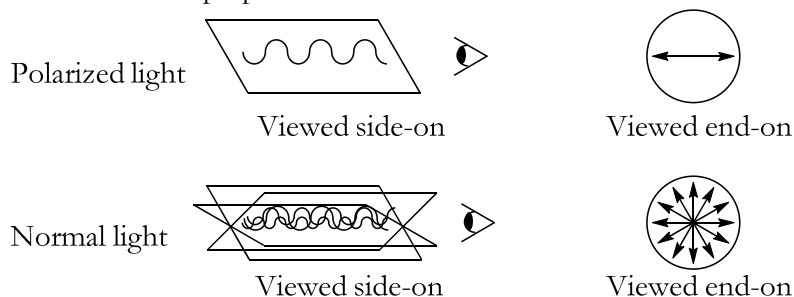
There are other types of stereocenters apart from asymmetric carbons and alkenes.



In these molecules, the stereocenters are marked with asterisks. Swapping two groups at any of these locations converts one molecule into the other. (Try this with a model set – it's a little hard to see this for the middle carbon.)

Optical Activity

Two enantiomers will have identical physical properties – melting point, boiling point, solubility, heat of formation, etc. – except optical activity. (Diastereomers have different physical properties to each other, because the spatial relationships between atoms of the molecule are different.) Optical activity is the ability to rotate plane-polarized light: light that's confined to vibrating in a single plane. Normal light contains a mixture of all vibrational directions that are perpendicular to the direction of travel.

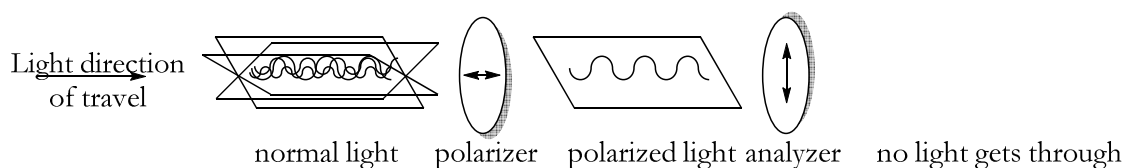
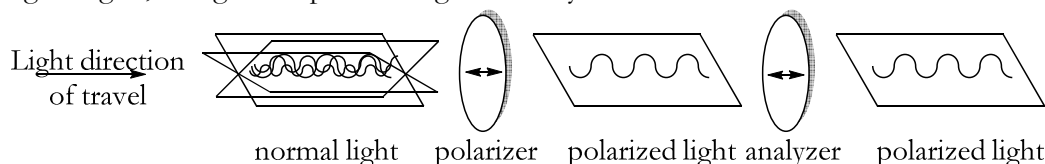


We can use polarized filters to block most of the components of normal light and only allow through one direction of polarization. When we use two filters in series, the first one is

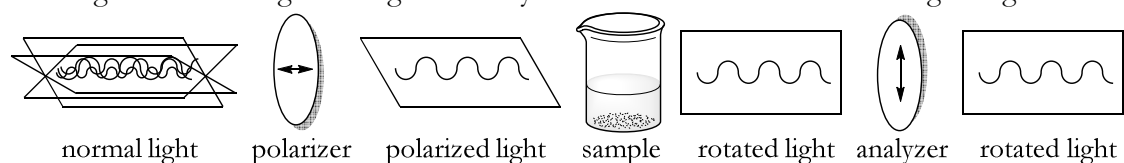
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called the polarizer (because it converts the light to polarized light) and the second is called the analyzer (because it allows you to analyze the light you just polarized). If the polarizer and analyzer are parallel to each other, the polarized light gets through fine. But if they're at right angles, no light can pass through the analyzer.



Since optical activity gives a compound the ability to rotate plane-polarized light, we can put a sample of the compound in between the polarizer and analyzer. This will rotate the light, allowing some of it to get through the analyzer even when the filters are at right angles.



If you want to measure how much the polarized light has been rotated by the sample, you can rotate the analyzer to find the angle where the most light gets through. The difference in angle is equal to the **optical rotation** of the sample. If the light plane was rotated clockwise (in the “positive” direction), the sample is **dextrorotatory or (+)**; if the light plane was rotated counterclockwise (in the “negative” direction), the sample is **levorotatory or (-)**. You can describe optical rotation with this equation:

$$\alpha = [\alpha]cl$$

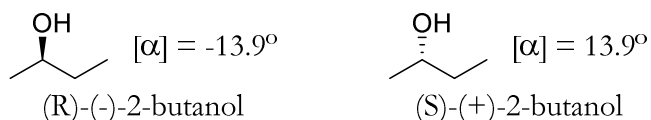
- $[\alpha]$ is the specific rotation. This is an inherent property of a material, and stays constant regardless of concentration.
- α is the optical rotation of a particular sample, and is what you're actually measuring.
- c is the concentration, given in g/mL.
- l is the path length, given in dm. A longer path through the sample will result in the light being rotated further.

For example, say you take a sample of a compound with a concentration of 0.5 g/mL and put it in a tube that's 10 cm (or 1 dm) long. You measure an optical rotation of 100°. In this case, you can calculate the specific rotation to be 200°mL/g·dm, although the number is traditionally given in units of ° only. You would say that this compound has a specific rotation of 200°.

Enantiomers can be distinguished because they always have the same size of optical rotation, but a different sign. If one molecule happens to have a specific rotation of 35°, then its enantiomer will have a specific rotation of -35°. You can put the sign of rotation in the compound's name:

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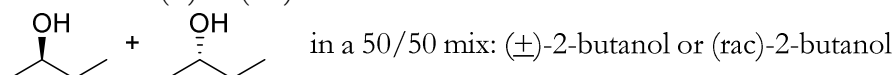
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Unfortunately, there's no way to look at a structure on paper and tell whether it's (+) or (-). Some structures have R as (+) and S as (-), and some have it the other way around. They are totally different systems: R and S describe a formal naming system, while (+) and (-) describe a physical property of the material, determined by the way electron clouds move back and forth around the molecule in response to light. The only thing you can say for certain is that if you have a molecule that happens to be (+), then its enantiomer will always be (-), regardless of which is R and which is S.

Racemic Mixtures

If you mix together equal quantities of a pair of (+) and (-) enantiomers, you will get a sample that doesn't rotate light at all – it is **optically inactive**. This is called a **racemic mixture** or **racemate**. Since one compound is trying to rotate light clockwise and the other is trying to rotate light counterclockwise, they cancel out each other's effects. These mixtures are often written with (\pm) or (rac) in front of their name.



Racemic mixtures have different physical properties from either pure enantiomer, because the (+) and (-) form interact differently with each other than they would with pure (+) or pure (-).

Summary

There are several important terms in this chapter that you need to keep straight:

- Chiral: the molecule lacks an internal mirror plane of symmetry
- Asymmetric carbon: a carbon with four different groups attached (a type of stereocenter)
- Stereocenter: any place where swapping two groups gives you a different molecule
- Optically active: rotating the plane of polarized light

These four things often go together (a molecule with stereocenters will usually have asymmetric carbons and be chiral and optically active), but there are cases when a sample can have some of these attributes but not others.

