When we talk about stereochemistry, we are not always talking about chiral compounds and chiral centers. Consider *cis*- and *trans*-2-butene:

![cis-2-butene](image1) ![trans-2-butene](image2)

Each can be superimposed on its own mirror image, and neither is chiral (also, note the lack of a chiral center!) However, they both have the same molecular formula and the same bonding connectivity, so by definition they are stereoisomers of each other. Because they are not mirror images, they must be diastereomers. An alkene group which can exist in two stereoisomeric forms is referred to as **stereogenic**.

Alkene groups in natural unsaturated fatty acids are normally *cis*, but *trans*-fatty acids (which are thought to be associated with heart disease and other health problems) are found in some food products.

![cis and trans fatty acids](image3)

Retinal is a light-sensitive molecule, derived from vitamin A, that is found in the rod cells of the eye. When light enters the eye through the retina, one form of retinal is converted to a diastereomer when a *cis* double bond is converted to *trans* (we'll learn how this happens in chapter 13). This changes the shape of the molecule and the way that it binds to the vision protein rhodopsin, which in turn initiates a chain of events that leads to a signal being sent to the vision center of the brain.

![11-cis retinal and all-trans retinal](image4)

While the terms *cis* and *trans* are quite clear in the examples above, in some cases they can be ambiguous, and a more rigorous stereochemical designation is required. To unambiguously designate alkene stereochemistry, it is best to use
the designators ‘E’ and ‘Z’ rather than trans and cis. To use this naming system, we first decide which is the higher priority group on each carbon of the double bond, using the same priority rules that we learned for the R/S system. If the higher-priority groups are on the same side of the double bond, it is a Z-alkene, and if they are on the opposite side it is an E-alkene. A memory device that many students find helpful is the phrase ‘Z = zame zide’.

Shown below is an example of an E-alkene: notice that, although the two methyl groups are on the same side relative to one another, the alkene has E stereochemistry according to the rules of the E/Z system because one of the methyl groups takes a higher priority (relative to a hydrogen) and the other takes lower priority (relative to a primary alcohol). The cis/trans terms would be ambiguous for this compound.

\[
\text{[Diagram of E-alkene with labels for higher priority groups.]}\]

Not all alkenes can be labeled E or Z: if one (or both) of the double-bonded carbons has identical substituents, the alkene is not stereogenic, and thus cannot be assigned an E or Z configuration. Terminal alkenes, in which one of the alkene carbons is bonded to two hydrogen atoms, are the most commonly seen type of nonstereogenic alkene.

\[
\text{[Diagram of terminal alkenes.]}\]

Natural rubber is a polymer composed of five-carbon isoprenoid building blocks linked with Z stereochemistry. The same isoprenoid building blocks can also be connected with E stereochemistry, leading to a polymer that is a precursor to cholesterol and many other natural isoprenoid compounds found in all forms of life.

\[
\text{[Diagram of natural rubber polymer with isoprene units.]}\]

Alkenes located inside a five- or six-membered ring, such as in cyclohexene, are not generally labeled E or Z, simply because the closed geometry of the ring allows for only one stereochemical possibility. (E)-cyclohexene is not physically possible, so it is not necessary to include the (Z) designator for cyclohexene. Larger rings, however, can hypothetically have E or Z alkene groups: two actual examples are included in exercise 3.26 below.
As a general rule, alkenes with the bulkiest groups on opposite sides of the double bond are more stable, due to reduced steric strain. The *trans* (*E*) diastereomer of 2-butene, for example, is slightly lower in energy than the *cis* (*Z*) diastereomer, as seen by their relative heats of hydrogenation to butane (see section 2.2C for a reminder of the meaning of 'heat of hydrogenation'.)

![Diagrams of alkenes and hydrogenation reactions](image)

**Exercise 3.25**

Label the alkene groups below as *E*, *Z*, or *N* (for a nonstereogenic alkene).

a) ![Alkene a]

b) ![Alkene b]

c) ![Alkene c]

d) ![Alkene d]

**Exercise 3.26**

The compounds shown below were all isolated from natural sources and their structures reported in a 2007 issue of the *Journal of Natural Products*, an American Chemical Society publication. Label all alkene groups that are not inside 5- or 6-membered rings as *E*, *Z*, or *N* (for a nonstereogenic alkene).

![Compounds](image)

From marine sponge  

From algae  
*J. Nat. Prod.* **2007**, *70*, 596
How many possible stereoisomers?

How do we know how many stereoisomers are possible for a given structure? There is actually a straightforward way to figure this out. All we need to do is count the number of chiral centers and stereogenic alkene groups, the use this following rule:

\[
\text{number of stereoisomeric forms} = 2^n
\]

\ldots where \( n \) = the number of chiral centers plus the number of stereogenic alkene groups

*(the rare exception to this rule is when a meso form is possible - in this case, the rule becomes } 2^{n-1})*

Consider for example a molecule with two chiral centers and one stereogenic alkene. By the rule stated above, we know right away that there must be eight possible stereoisomers. Drawing out all the possibilities, we see:

We see that, for example, \( RRE \) has one enantiomer, the \( SSE \) compound. The six other stereoisomers are all diastereomers of \( RRE \).

It needs to be stressed that the enantiomer of the \( RRE \) compound is the \( SSE \) compound, \textbf{not} the \( SSZ \) compound. Remember, the \( E/Z \) relationship is diastereomeric, not enantiomeric. Use models to convince yourself that the \( RRE \) and the \( SSE \) isomers are mirror images of each other, while \( RRE \) and \( SSZ \) compounds are not. In general, to get the enantiomer of a compound, we invert all chiral centers \textit{but leave all stereogenic alkenes the same}.

**Exercise 3.27**

Draw the enantiomer of each the compounds below, and assign configurations to all chiral centers and stereogenic alkenes. How many diastereomers are possible for each of the structures you drew?
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