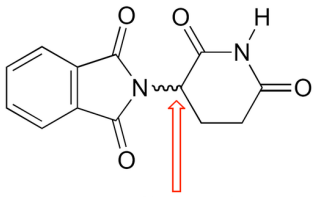
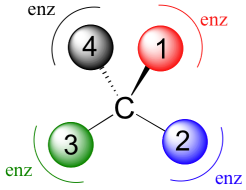
5.5: Stereogenic Centers in Cyclic Compounds

The thalidomide that was used in the 1960s to treat depression and morning sickness was sold as a 50:50 mixture of both the R and the S enantiomer – this is referred to as a **racemic mixture**. A 'squiggly' bond in a chemical structure indicates a racemic mixture - thus racemic (*R/S*) thalidomide would be drawn as:

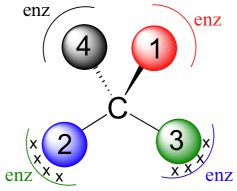


mixture of both R and S configurations at this stereocenter

The problem with racemic thalidomide, as we know, was that only the R enantiomer was an effective medicine, while the S enantiomer caused mutations in the developing fetus. How does such a seemingly trivial structural variation lead to such a dramatic (and in this case, tragic) difference in biological activity? Virtually all drugs work by interacting in some way with important proteins in our cells: they may bind to pain receptor proteins to block the transmission of pain signals, for instance, or clog up the active site of an enzyme that is involved in the synthesis of cholesterol. Proteins are chiral molecules, and are very sensitive to stereochemistry: just as a right-handed glove won't fit on your left hand, a protein that is able to bind tightly to (*R*)-thalidomide may not bind well at all to (*S*)-thalidomide (it will help to view a color version of the figure below).



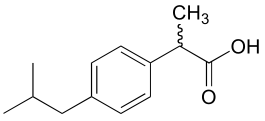
a protein that binds specifically to a chiral molecule . . .



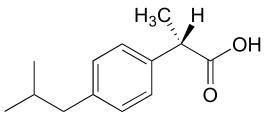
may not bind well at all to a different stereoisomer!

Instead, it seems that (*S*)-thalidomide interacts somehow with a protein involved in the development of a growing fetus, eventually causing the observed birth defects.

The over-the-counter painkiller ibuprofen is currently sold as a racemic mixture, but only the *S* enantiomer is effective.



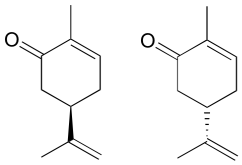
racemic ibuprofin



(S)-ibuprofin
(active enantiomer)

Fortunately, the *R* enantiomer does not produce any dangerous side effects, although its presence does seem to increase the amount of time that it takes for (*S*)-ibuprofen to take effect.

You can, with the assistance your instructor, directly experience the biological importance of stereoisomerism. Carvone is a chiral, plant-derived molecule that smells like spearmint in the *R* form and caraway (a spice) in the *S* form.



(R)-carvone (S)-carvone

The two enantiomers interact differently with smell receptor proteins in your nose, generating the transmission of different chemical signals to the olfactory center of your brain.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris) Template:HideTOC
