11. Chirality of conformationally mobile systems – ring compounds

Monosubstituted cycloalkanes cannot have an asymmetric carbon in the ring, because there is a plane of symmetry. Disubstituted cycloalkanes are different; we consider them on a case-by-case basis, depending on a) the pattern of substitution, b) the ring size, and c) the particular geometric isomer we are considering with. For the purpose of evaluating symmetry you may assume that the rings are flat.

i. 1,2-Disubstituted cyclohexanes have two stereocenters; if the substituents are different, neither of the two geometric (cis- and trans-) isomers has a plane of symmetry. The trans-isomers are enantiomers of each other; the cis-isomers are enantiomers of each other; the two cis-stereoisomers shown on top are diastereomers of the two trans-isomers shown on the bottom. These features are general for all 1,2-disubstituted cycloalkanes.

Please, note that you need not draw chair conformers for assessing the absolute configuration of cyclohexane derivatives; hexagon structures will serve you just as well.
For 1,2-disubstituted cyclohexanes with two identical substituents, the cis-isomer is a meso form, whereas the trans-isomer exists as a pair of enantiomers; there are three stereoisomers (see section 9, above). This feature is general for all 1,2-disubstituted cycloalkanes.

ii. 1,3-Disubstituted cyclohexanes, with different substituents also have two cis-enantiomers and two trans-enantiomers. If the two substituents are identical the cis-isomer has a plane of symmetry; it is a meso form and is optically inactive. trans-1,3-disubstituted cyclohexanes have two stereo-isomers, they are enantiomers of each other; they lack a plane of symmetry; each of them shares one stereocenter with the cis-isomer: both are diastereomers of the cis-isomer. Can you assign the absolute configuration of the two trans-1,3-dimethylcyclohexanes?

iii. 1,4-disubstituted cyclohexanes have two geometric isomers; both are optically inactive (achiral) because of a plane of symmetry that bisects C-1 and C-4 and their substituents.

This feature is generally found for even-numbered cycloalkanes substituted in opposite positions, for example, 1,3-disubstituted cyclobutanes or 1,5-disubstituted cyclooctanes.
When considering the chirality of structures represented by a Newman projection, you need only consider the most symmetric conformation. Don’t be misled by the unsymmetric conformations and consider the compound chiral – the symmetrical conformation tells the true story. Of course you know that this compound isn’t chiral, because both carbons bear two hydrogens.

12. Chirality without a chiral carbon

There are several compounds that are chiral without having a carbon stereocenter. We mention briefly three classes of compounds in this category: trans-fused cycloalkenes; allenes; and conformationally locked biphenyls. Cylooctene has a strained trans-isomer that exists as a pair of enantiomers as shown.

Allenes have two adjacent (cumulated) C=C double bonds. The pi systems of the two double bonds are mutually perpendicular as are the substituents attached to the terminal carbons. 1,3-disubstituted allenes exist as enantiomeric pairs. A Newman projection of the stereoisomers of 2,3-pentadiene along the C2-C4 axis (below, right) shows this nicely. More about allenes in chapter 9.
Finally some biphenyl derivatives with bulky substituents in the ortho positions also exist as enantiomers. More about this type of compounds in chapters 16/17.

13. Resolutions of Racemic Compounds

When chiral molecules are synthesized from achiral reagents, they are obtained as racemates. The pure enantiomers can be separated (resolved) by different methods. For example, tartaric acid crystallizes in mirror image crystals of pure enantiomers. Louis Pasteur was able to separate them with a pair of tweezers under a microscope. That was in 1848!
Some racemates can be resolved by chromatography over a column filled with a chiral material. One enantiomer will interact with the chiral column filling and proceed more slowly through the column than its non-interacting enantiomer.

In special cases, racemic mixtures can be resolved by reaction with a chiral reagent. For example, racemic 2-butanol can be reacted with \((2R,3R)\)-tartaric acid. The resulting compound, an ester (see Chapter 21), is a pair of diastereomers, which can be resolved by crystallization. The pure 2-butanol enantiomers can be obtained from the resolved esters.

\[
\begin{align*}
\text{(S)-2-butanol} & \quad \text{H OH} \\
\text{(R)-2-butanol} & \quad \text{H OH} \\
\text{diastereomers - can be resolved} & \quad \text{H O(2R,3R)-tartrate} \quad \text{H O(2R,3R)-tartrate}
\end{align*}
\]

14. Reactions of Compounds with Asymmetric Carbons (finally some chemistry)

We need to consider two cases:

A. No bonds of the C* are broken in the reaction; the relative configuration of the four substituents at the stereocenter is maintained, but the absolute configuration (the R,S designation) may change because the priority of the substituents may change.

B. One or more bonds at the asymmetric carbon are broken and new bonds are formed. The stereochemical outcome depends on the mechanism of the reaction; it may either be specific or unspecific (random).

a) Some reactions, such as a free radical halogenation, proceed through a planar intermediate. Even if the product has a stereocenter, it will be a racemic mixture. Such reactions are said to be **stereorandom**.
b) Other reactions have **stereospecific** mechanisms, meaning a given stereoisomer forms another given stereoisomer; the spatial relations of all the participants in the reaction are specified (and predictable) without options. We will see examples of such a reaction in Chapter 6. Stereospecific reactions can occur in two ways: i) in the same position as the bond being broken; ii) the new bond is formed from the opposite side.

![Diagram showing stereospecific mechanisms](image)

C) Examples

We illustrate both cases with a free-radical chlorination, a reaction you have already studied; first we consider chlorination of an achiral substrate, butane; then, to make things more interesting 😊, we look at a chiral substrate, S-2-bromobutane. Since chlorine atoms are not very selective, we expect chlorination to occur at all four centers.

**Chlorination of butane**

The reaction of butane with Cl• generates a primary and a secondary free radical; abstraction of Cl by the primary free radical forms 1-chlorobutane, an achiral product. Simple.

![Chlorination of butane](image)

The case of the secondary free radical is more interesting because its reaction generates a new stereocenter. The intermediate is planar; both sides are equally
accessible; both sides abstract Cl with the same probability: we obtain 2-chlorobutane as a racemic mixture.

Chlorination of S-2-bromobutane

- Chlorination at C-4 leaves the chiral center unaffected (case A, above); the priority of the substituents remains unchanged; we have formed S-3-bromo-1-chlorobutane.

- Reaction at C-1 also leaves the chiral center unchanged (case A), but the priority of the groups is changed: in the starting material CH\textsubscript{3} is the third-ranking substituent, in the product CH\textsubscript{3}Cl ranks second. We have generated R-2-bromo-1-chloro-butane.

- Reaction at C-3 also leaves the chiral center unchanged (case A), but we are facing two problems. First, substituting an H at C-3 will create a new stereocenter, resulting in a pair of diastereomers. Because we start with the S-enantiomer the product is a mixture of (2-S,3-S) and (2-S,3-R)-2bromo-3-chlorobutane. We call a pair of hydrogens that give rise to diastereomers upon replacement of one or the other diastereotopic. Please, verify the assignment.

Second, the free radical generated by hydrogen abstraction has two different faces with different steric hindrance. For this reason, the two products will be formed in unequal yields. A reaction giving diastereomers in unequal amounts is called diastereoselective.
• Chlorination at C-2 is an example of case B: hydrogen abstraction from C-2 produces an achiral free radical (C–2 is planar); reaction of the two faces forms two different enantiomers: they are said to be enantiotopic. The planar intermediate (only one conformation is shown below) allows each face to react equally likely with Cl₂. Therefore chlorine abstraction by the intermediate produces a 50:50 mixture of the two enantiomers, a racemate; the product is optically inactive.

The above reaction is an example of a mechanism that is not stereospecific. Even though the product, 2-bromo-2-chlorobutane, has an asymmetric carbon, it is formed as a racemic mixture.