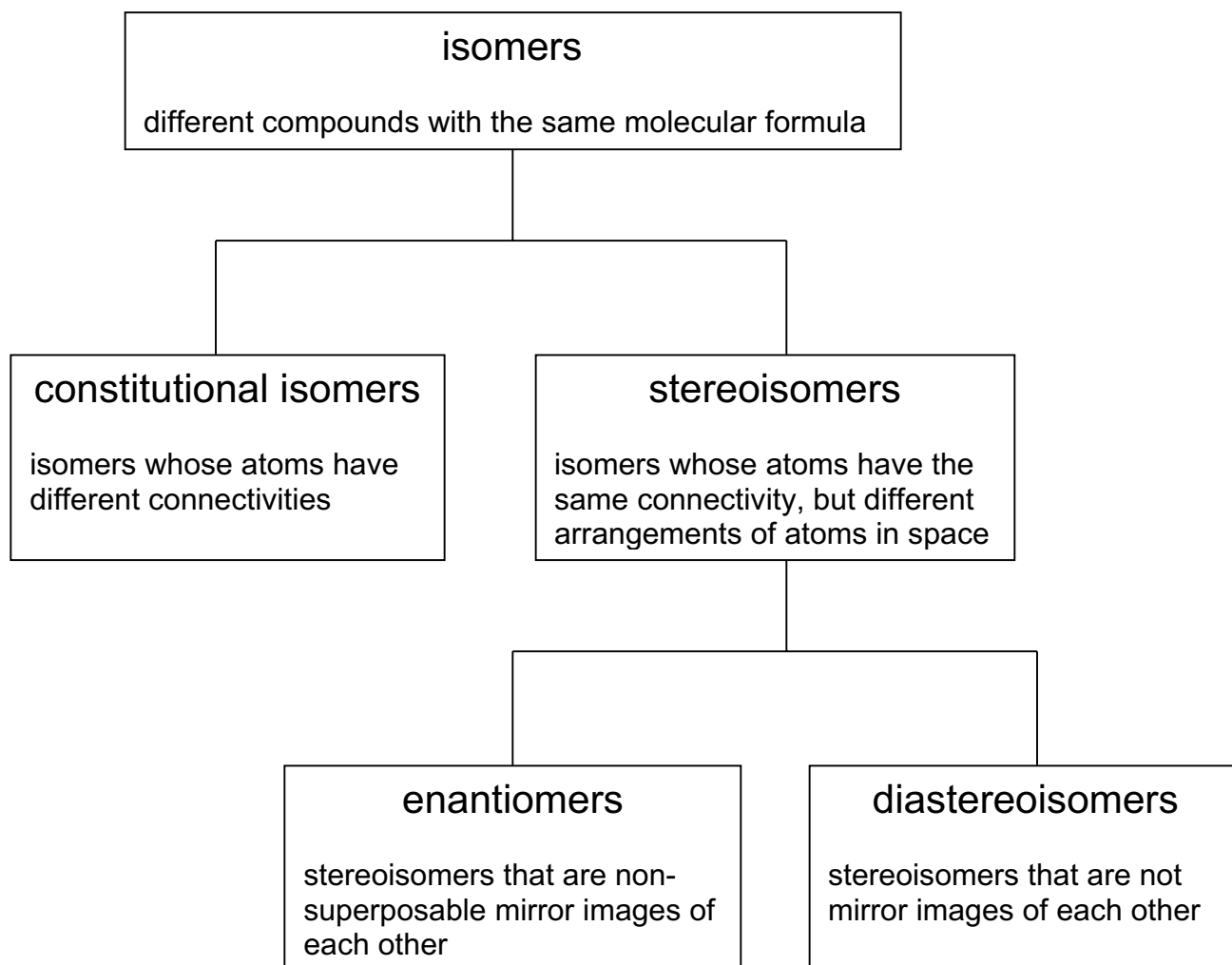


## Stereochemistry: Chiral Molecules

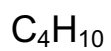
The hierarchy of isomers. The categories become more specific as we go down the branches.



The next pages look more closely at each category.

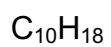
# Constitutional Isomers

Clearly different shapes, different functional groups etc. Constitutional isomers have different physical properties.



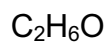
butane

isobutane



*trans*-decalin

bicyclo[5.3.0]decane



ethanol

dimethyl ether

## Stereoisomers: Diastereoisomers

Different physical properties, but likely to be similar. Diastereoisomers are separable without a second chiral component. This statement will make more sense when we look at enantiomers. Diastereoisomers often have more than one chiral center.

*trans*-1,2-dimethylcyclohexane

*cis*-1,2-dimethylcyclohexane

glucose

galactose

But not necessarily...

*trans*-1,2-dichloroethene

*cis*-1,2-dichloroethene

# Enantiomers

A **chiral** molecule is not **superposable** on its mirror image. A chiral molecule and its non-superposable mirror image constitute a pair of **enantiomers**. The dichloroethene diastereoisomers above are not chiral – they are superposable on their mirror images.

Glucose and galactose are both chiral molecules, but they are not enantiomers. The enantiomer of D-glucose is its mirror image, L-glucose.

D-glucose

L-glucose

The same holds for galactose. Don't worry about the D and L for now. They're just an old way of describing the chirality of sugars.

D-galactose

L-galactose

2-chlorobutane

mirror

non-superposable mirror images  
enantiomers

We can't rotate any bond in the molecule on the left, or rotate the molecule on the left as a whole, or any combination of bond/molecular rotations, and make the molecule on the right.

In contrast, consider 2-methylbutane

Mirror

Rotation about the marked bond gives the structure on the right. The mirror images are superposable, and 2-methylbutane is **achiral** and does **not** exist as a pair of enantiomers.

Enantiomers have identical physical properties. They can only be distinguished by using another chiral entity. For example enantiomeric amines can be separated by forming a diastereomeric salt from a single enantiomer of a carboxylic acid (more about this later).

## Using Symmetry to Determine Chirality

Inorganic chemistry has many examples of highly symmetric molecules, such as the octahedral complex  $[\text{Fe}(\text{NH}_3)_6]^{2+}$ . Here's a quick reminder of some of the symmetry elements of an octahedron.

Fortunately, organic chemistry doesn't need to get much more complicated than a tetrahedron:

In fact, usually we only need to identify a **plane of symmetry**. All molecules that have a plane of symmetry are **achiral**. Molecules with a plane of symmetry usually have two or more of the same group (or atom) attached to the **stereogenic carbon** center. So another way to interpret the mirror plane argument is to say that *molecules with four different groups (or atoms) attached to the stereogenic center are chiral*. For such a molecule a pair of enantiomers is always possible.

## Stereochemistry: R, S Nomenclature

The 2 enantiomers of 2-chlorobutane are chemically indistinguishable. But they are different. This difference becomes apparent when they interact differently with other chiral entities. Before we explore this difference further, we need some way to distinguish between enantiomers.

We do this by ranking the substituents on the stereogenic carbon according to their position in the periodic table.

Rule 1. The higher the atomic number, the higher the priority.

The substituents are- H, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, and -Cl. How do we rank them? H is clearly lowest priority (N = 1), and Cl is highest (N = 17). The middle two are both C (N = 6). How do we distinguish them?

Rule 2. Move down the chain away from the stereogenic center and assign priority at the first point of difference.

So now we have an increasing order of priority: H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl. How do we use this to identify a chiral center?

Rule 3a. Rotate the molecule so that the lowest priority group points away from you.

Rule 3b. Draw a circle, highest priority to lowest (excluding the lowest priority group). If this circle is drawn clockwise, the chiral center has (R) stereochemistry (from the latin rectus, meaning right). If this circle is drawn counterclockwise, the chiral center has (S) stereochemistry (from the latin sinister, meaning left).

So this is ( )-2-chlorobutane. This is the Cahn-Ingold-Prelog system (named after its inventors) and as described it will allow (R) or (S) assignments to be made for most chiral centers. There's one more rule for dealing with multiple bonds.

Rule 4. Double and triple bonds are assigned priority as if the atoms on either end of the multiple bond were duplicated (double bond) or triplicated (triple bond).

## Optical Activity

I've hedged about the different physical properties of (R) and (S) enantiomers by saying that they interact differently with "chiral entities". One such chiral entity is polarized light.

Unpolarized light:

Plane polarized light

A solution of molecules of a single enantiomer will interact with plane polarized light in such a way that the plane of polarization is rotated by the solution.

The amount of rotation at a particular wavelength is called the **optical rotation**, and has a specific value for given  $\lambda$ , T, c.

If the rotation is clockwise, the molecule is said to be **dextrorotatory** *d*

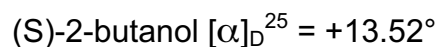
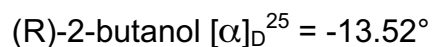
If the rotation is counterclockwise, the molecule is said to be **levorotatory** *l*

Usually the wavelength is 589.6 nm, the orange light from the sodium D line

Concentration is reported in g/mL

Temperature is 25°C.

A pair of enantiomers will have equal and opposite **specific rotations**.



There is no obvious correlation between (R) and (S), and *d* and *l*.

## Enantiomeric Excess (ee)

$$ee = \frac{\text{moles of one enantiomer} - \text{moles of the other enantiomer}}{\text{moles of one enantiomer} + \text{moles of the other enantiomer}}$$

$$ee = \frac{\text{observed specific rotation}}{\text{specific rotation of pure enantiomer}}$$

The ee's can be converted to percent ee's by multiplying by 100. A 1:1 mixture of enantiomers is called a **racemic** mixture.

## Stereochemistry: Multiple Stereogenic Centers

What is and what isn't allowed when we're trying to superpose two molecules.

### **We can**

Rotate  $360^\circ$  about any single bond or any combination of single bonds

Rotate the entire molecule about any arbitrary axis

Combine the above operations in any way

### **We can't**

Rotate about any double or triple bonds

Reflect the molecule in any plane

Transform the molecule through a center of inversion

Consider the stereoisomers of 2,3-dichloropentane. Starting with a cis arrangement, we can generate two **enantiomers**. These are **non-superposable mirror images** of each other.

We can do the same for the trans arrangement. Again, this results in a pair of enantiomers.

If 3 and 4 are enantiomers, what are 1 and 4?

What are 2 and 3?

Do you expect 1 and 3 to have the same physical properties?

What happens if we shorten the carbon chain to make 2,3-dichlorobutane? Here's the trans configuration and its enantiomer

And here's the cis arrangement

They're not enantiomers! In fact, they're the same molecule. If you put this molecule in a polarimeter, you would measure  $[\alpha] = 0$ . No optical activity. Even though this molecule has tetrahedral centers with 4 different substituents, it is **achiral** because it has an **internal plane of symmetry**. Such molecules are called **meso** compounds.

Of course, we can assign all the stereogenic centers, including the stereogenic centers of meso compounds, as (R) or (S).

# The Fischer Projection

So far we've been using wedges and dashes to indicate stereochemistry. When we want to draw multiple chiral centers, the **Fischer projection** makes it easier to see planes of symmetry.

**Vertical** lines go **away** from the viewer, or lie in the plane of the paper.

**Horizontal** lines come **towards** the viewer.

The Fischer projection for (2S,3S)-2,3-dichlorobutane goes as follows

When we want to know whether two Fischer projections are the same, there's a new rule.

**We can't**

Rotate the molecule 180° out of the horizontal plane (that's end over end, or sideways).

**We can**

Rotate the molecule anywhere from 0 to 360° in the plane.

# Stereoisomerism of Cyclic Compounds

## 1,2-dimethylcyclohexanes

*trans*-1,2-dimethylcyclohexane

**Chiral**, because there is no internal mirror plane. Mirror images are non-identical. A pair of enantiomers.

*cis*-1,2-dimethylcyclohexane

No internal plane of symmetry. Mirror images are non-identical. A pair of enantiomers. **But** the stereoisomers are interconvertible by a ring-flip. The two conformers interconvert rapidly at room temperature because they have the same energy ( $a_e = e_a$ ) and the energy barrier is low. The two enantiomers are really **different conformations of the same molecule**.

So there are 4 stereoisomers of 1,2-dimethylcyclohexane, but only 3 are distinguishable at room temperature.

## 1,3-dimethylcyclohexanes

*trans*-1,3-dimethylcyclohexane

No internal plane of symmetry. Non-superposable mirror images. A pair of enantiomers. Flipping the ring does not interconvert the two enantiomers.

*cis*-1,3-dimethylcyclohexane

Has an internal plane of symmetry, and is **achiral**.

So there are 3 stereoisomers of 1,3-dimethylcyclohexane.

## **1,4-dimethylcyclohexanes**

Both cis- and trans-1,4-dimethylcyclohexane have an internal mirror plane. Neither is chiral, and there are only 2 stereoisomers of 1,4-dimethylcyclohexane.