



CHEMISTRY 2500

Topic #3: Stereochemistry

Fall 2014

Dr. Susan Findlay



Stereoisomers

- We have established that molecules which have the same molecular formula but different connectivity are referred to as **constitutional isomers**. It is also possible to have molecules which have the same molecular formula and the same connectivity but which are still not superimposable. These are **stereoisomers** (literally, “isomers by shape”).
- You have seen examples of stereoisomers in both CHEM 1000 and CHEM 2000:

cis- and *trans*-diamminedichloroplatinum(II)
(cisplatin is an anti-cancer; drug transplatin is toxic)



Stereoisomers: Geometric Isomers

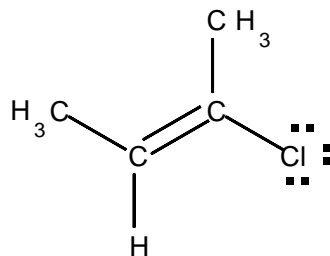
cis-1,2-dichlorocyclopentane and *trans*-1,2-dichlorocyclopentane

- These are examples of **geometric isomers**, isomers which can be distinguished by whether the two most important* groups are on the same side of a ring/double bond (*Z* for zusammen = 'together', or *cis*) or on opposite sides of a ring/double bond (*E* for entgegen = 'across', or *trans*).

* The importance of a group in this context is determined by the mass of the first atom. So, Cl is more important than CH₃ which is, in turn, more important than H. We will look at rules for distinguishing between groups beginning with the same atom shortly.

Stereoisomers: Geometric Isomers

- Why use *E*- or *Z*- when we could just use *cis*- or *trans*-?
Consider the following molecule:



Does it look like it should be *cis*- or *trans*-?

Use the rules in the box on the previous page to assign which is the more important group attached to each carbon of the double bond then name the molecule including either the *E* or *Z* designation at the beginning of the name.

- As you can see, using the *E/Z* designation causes less confusion in situations like these. The *cis/trans* designation is usually reserved for molecules in which each atom has one group and one hydrogen atom so that there is no ambiguity.

Stereoisomers: Cahn-Ingold-Prelog Convention

- The complete set of rules for assigning priority are referred to as the **Cahn-Ingold-Prelog convention**. For geometric isomers you are considering the groups attached to each atom of the double bond (or ring) separately.

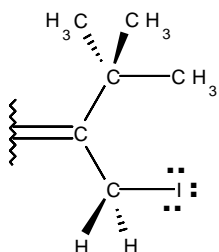
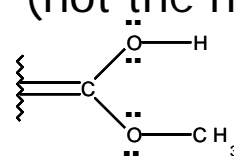
- Compare the atomic numbers of the atoms immediately attached. The one with a higher atomic number (Z) is of higher priority. Lone pairs are considered to have $Z = 0$:



- If the atoms are isotopes of the same element (same Z), the heavier isotope is of higher priority:



- If the atoms attached are the same, look at the next "shell" of atoms one bond farther and compare those. Look for the highest individual atomic number (not the highest average atomic number):

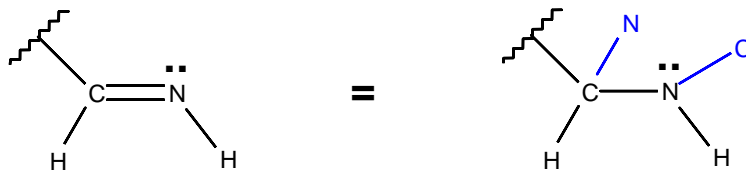


- If a group contains π bonds, treat each as an additional bond to an atom of the same element. (see next page for "phantom atoms")

Stereoisomers: Cahn-Ingold-Prelog Convention

- When dealing with π bonds, use “phantom atoms”. Redraw each double (or triple) bond as a set of single bonds so that every atom has the same number of bonds to atoms of each element as it does in the “real” structure.

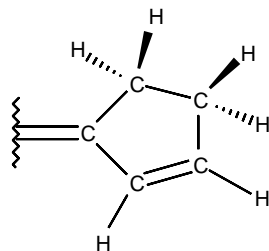
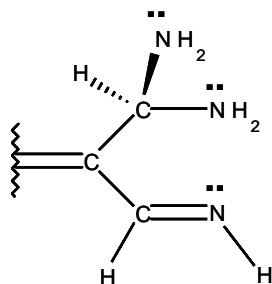
e.g.



Here, the phantom atoms are shown in blue (with blue bonds). Note that you do not add extra “phantom atoms” attached to the blue phantom atoms. It is only necessary that all the atoms from the “real” structure have the correct number of bonds.

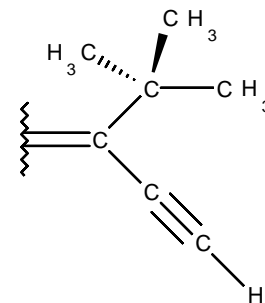
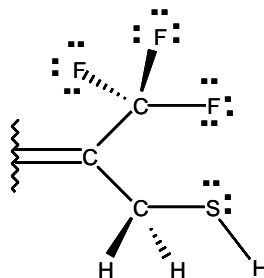
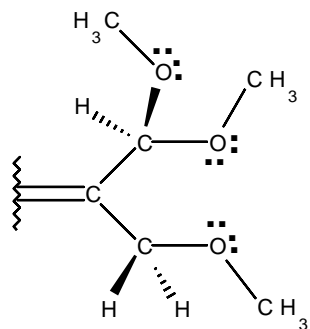
Stereoisomers: Cahn-Ingold-Prelog Convention

- In each partial molecule below, circle the group which gets higher priority. To do so, you should first redraw the groups containing π bonds using the "phantom atom" method.



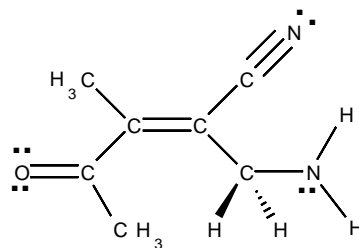
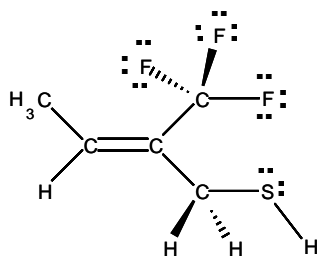
Stereoisomers: Cahn-Ingold-Prelog Convention

- Determine which group gets higher priority for each of the following double bond "halves":



Stereoisomers: Cahn-Ingold-Prelog Convention

- Assign the following compounds as having *E*- or *Z*- configuration:





Stereoisomers: Enantiomers and Chirality

- Geometric isomers can often be distinguished by looking at their structures on paper; however, this is not true for all kinds of stereoisomers. The easiest way to tell whether two molecules with the same connectivity are stereoisomers or just the same molecule (possibly rotated or twisted) is to build a model of each then determine whether or not the two models can be superimposed. When doing so, you are allowed to rotate bonds or flip rings but you are not allowed to break or form bonds.
- Consider, for example, the two geometric isomers of 1,2-dichlorocyclopentane:

Build two different *trans*-1,2-dichlorocyclopentane molecules which are **mirror images**. They are **not superimposable** (no matter how much you rotate them).



Stereoisomers: Enantiomers and Chirality

- Build two mirror images of *cis*-1,2-dichlorocyclopentane:

- These two mirror images *can* be superimposed. As such, *cis*-1,2-dichlorocyclopentane can be described as **achiral** (literally “not chiral”) even though it has chirality centers. Find the chirality center(s) in *cis*-1,2-dichlorocyclopentane and mark it/them on your drawing above.

- Achiral compounds that have chirality center(s) are referred to as **meso** compounds. They can be recognized by the plane of symmetry through the molecule. Find the plane of symmetry in *cis*-1,2-dichlorocyclopentane.

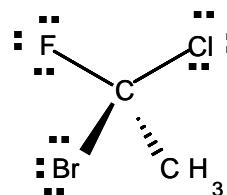
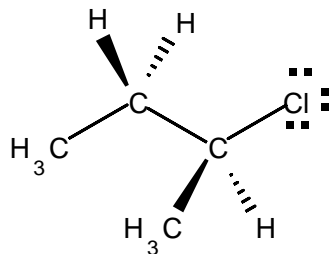


Stereoisomers: Enantiomers and Chirality

- What if you wanted to indicate one particular enantiomer of *trans*-1,2-dichlorocyclopentane without having to draw it out? There is a naming convention similar to the *E/Z* naming convention that allows us to distinguish between enantiomers. According to this convention, the configuration of each chirality center is either *R* or *S*. For two molecules to be enantiomers, every chirality center must have the opposite configuration:
 - *R*-2-chlorobutane is the enantiomer of *S*-2-chlorobutane
 - *(1R,2S,5R)*-menthol is the enantiomer of *(1S,2R,5S)*-menthol but would *not* be the enantiomer of *(1R,2R,5R)*-menthol.
 - *(1R,2S,5R)*-menthol and *(1R,2R,5R)*-menthol would be classified as **diastereomers** (stereoisomers that are not enantiomers).
- In order to assign *R* or *S* to a chirality center, it is *essential* that you draw the molecule's geometry properly using wedge-and-dash notation. It will also be helpful to remember that switching any two groups around the chirality center switches the configuration (from *R* to *S* or from *S* to *R*). Switching a second time gets you back to the original configuration.

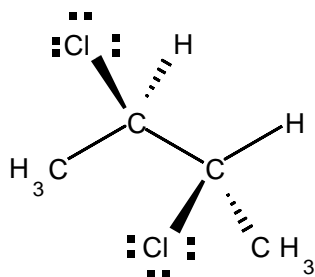
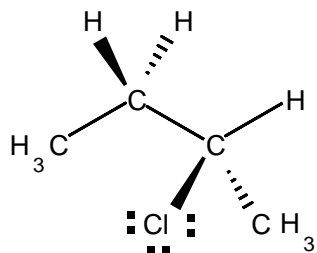
Stereoisomers: Enantiomers and Chirality

- To assign the configuration of a chirality center:
 - First, assign priority to each of the four groups attached following the Cahn-Ingold-Prelog convention (same as for *E/Z*),
 - Second, draw the molecule such that the lowest priority group attached to the chirality center is pointing away from you (i.e. on the dashed line).
 - Third, draw a circular arrow from the top priority group to the second priority group to the third priority group.
 - If the arrow is going clockwise, the chirality center is *R*.
 - If the arrow is going counterclockwise, the chirality center is *S*.
- Assign the configuration of each chirality center in the molecules below:



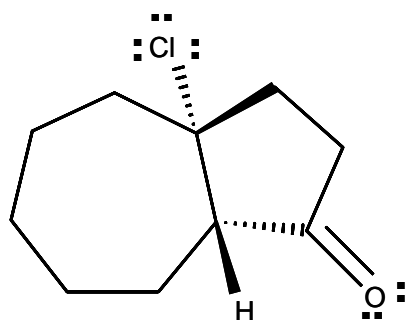
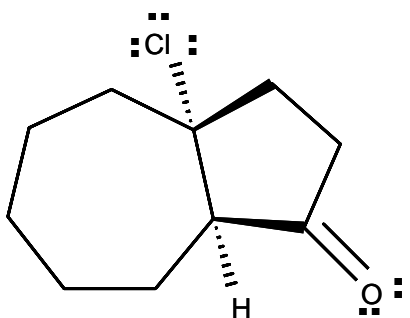
Stereoisomers: Enantiomers and Chirality

- Assign the configuration of each chirality center in the molecules below:



Stereoisomers: Enantiomers and Chirality

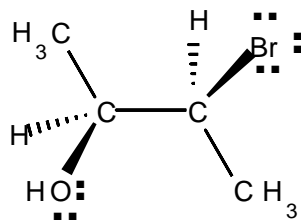
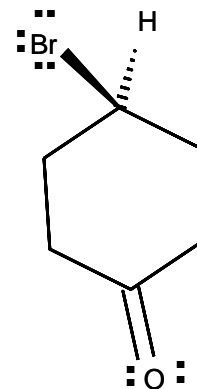
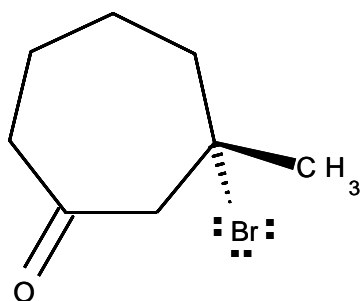
- Note that, when switching groups, there is no need to redraw the whole group...



- Note that the two molecules above *are* stereoisomers but they are *not* enantiomers. They are therefore diastereomers.

Stereoisomers: Enantiomers and Chirality

- More practice assigning *R* and *S*...



If you ever have a hard time assigning configuration from structures drawn on paper, build a model.

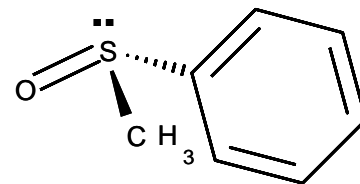
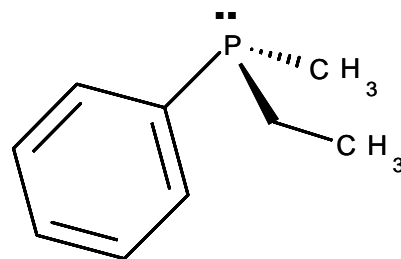
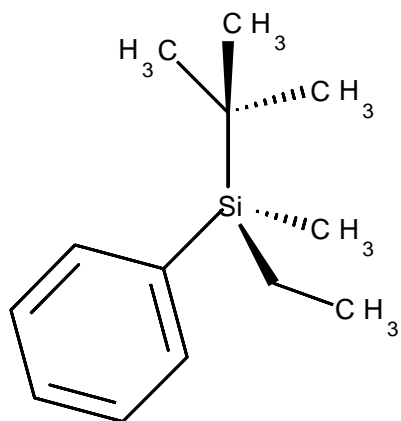


Stereoisomers: Enantiomers and Chirality

- How can you tell the difference between two samples which are enantiomers?
 - They behave identically in any achiral environment and react identically with achiral reagents/systems.
 - They will rotate plane-polarized light in opposite directions. This led to the term “optically active” which was originally used to describe chiral compounds.
 - They interact differently with chiral environments (e.g. biological systems), sometimes with tragic consequences. This is because one enantiomer may “fit” better into the chiral environment – just as your right hand fits better into a righthanded baseball glove.
- What if a sample consists of a mixture of enantiomers?
 - If a chiral material is made in the lab from achiral starting materials, a 50-50 mixture of each enantiomer results. This is referred to as a **racemic mixture**. Racemic mixtures do not rotate plane-polarized light (half of the molecules rotate it clockwise but the other half rotate it counterclockwise); however, their properties in biological systems do **not** “average out”. If either enantiomer is toxic, the racemic mixture will also be toxic.

Stereoisomers: Enantiomers and Chirality

- A chirality center does not have to be a carbon atom. Any atom with tetrahedral or trigonal pyramidal geometry will do:

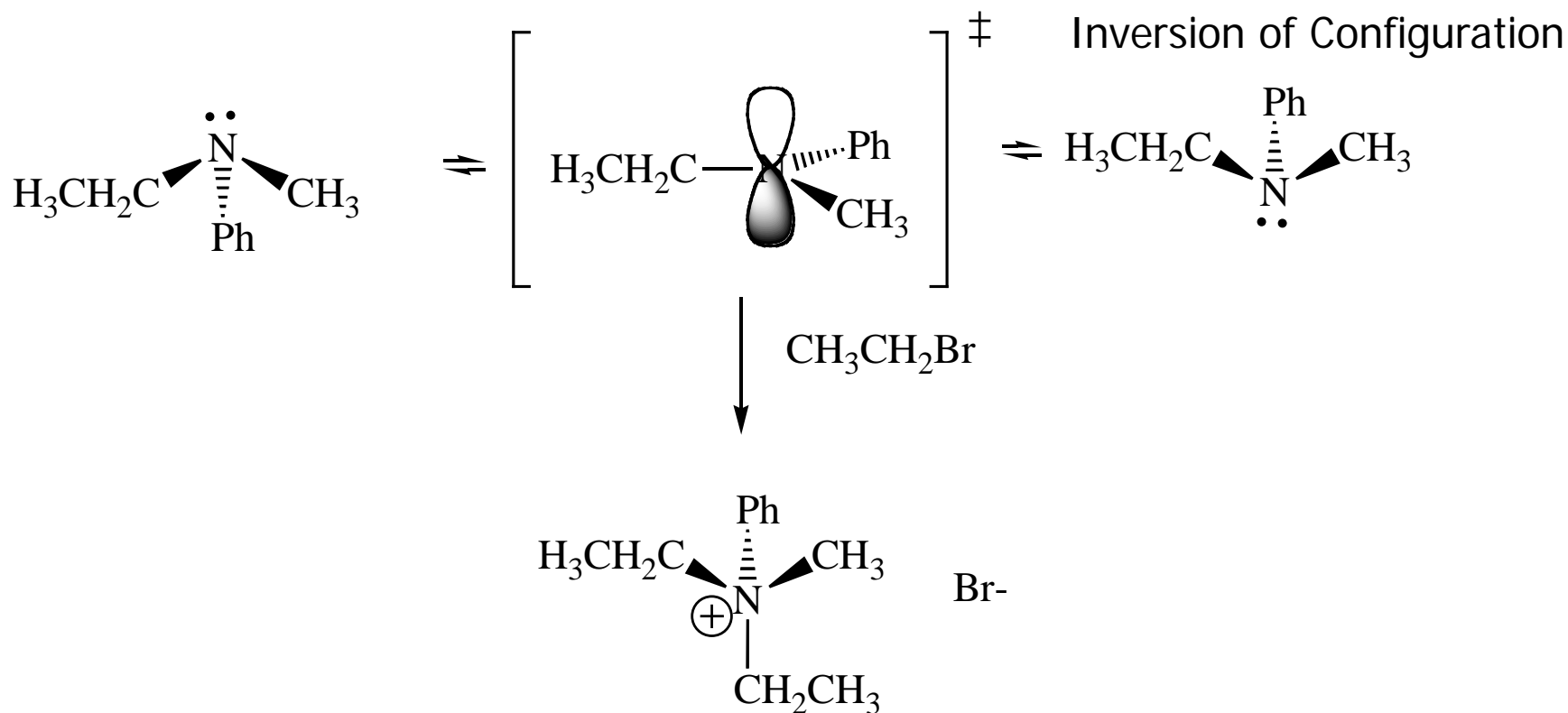


- While a trigonal pyramidal nitrogen atom can serve as a chirality center at extremely low temperatures, at room temperature, it inverts rapidly (flipping between *R* and *S* configuration) so molecules whose only "chirality center" would be a trigonal pyramidal nitrogen atom are not considered to be chiral. If protonated (making the nitrogen atom tetrahedral), the nitrogen becomes a more stable chirality center.

Stereoisomers: Enantiomers and Chirality

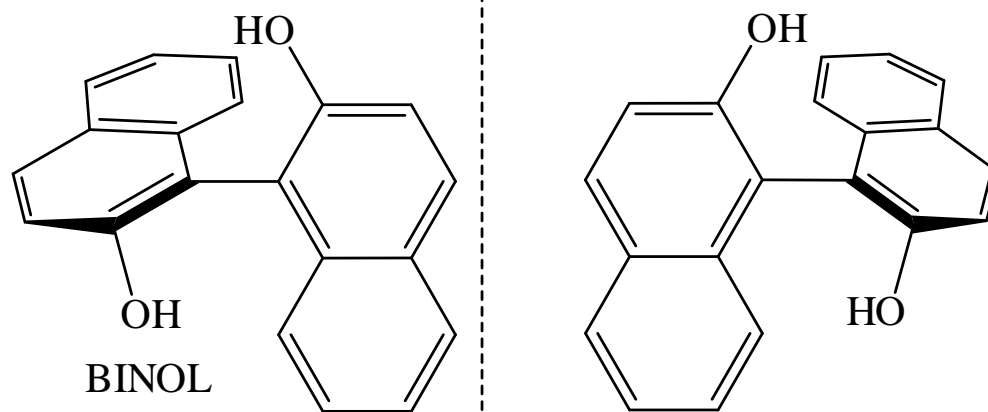
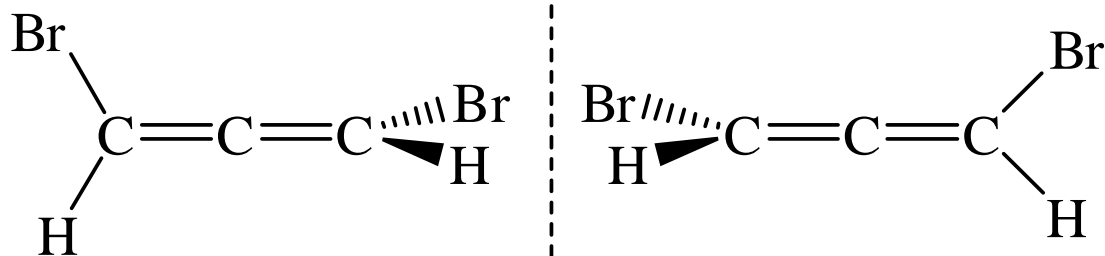
- Nitrogen inverts configuration (unless tetrahedral cation):

Atoms other than carbon?



Stereoisomers: Enantiomers and Chirality

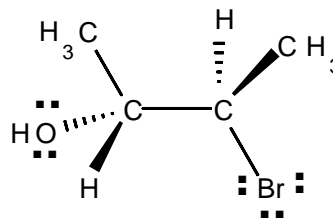
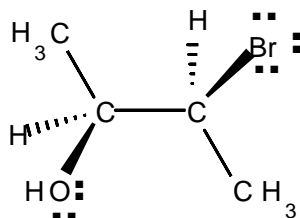
- There are even chiral molecules whose chirality center(s) are not the traditional tetrahedral atoms:



We will not focus on these molecules in this course.

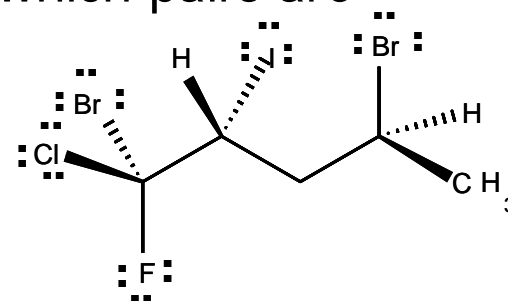
Stereoisomers: Diastereomers

- We saw earlier than stereoisomers which are not enantiomers are referred to as **diastereomers**. Diastereomers have different physical and chemical properties and are therefore separable (unlike enantiomers which can only be separated in chiral environments). *cis*- and *trans*-1,2-dichlorocyclopentane can also be referred to as diastereomers (which is a more general term than “geometric isomers”).
- A molecule with only one chirality center cannot have a diastereomer. Why not?
- Are the stereoisomers a pair of enantiomers or diastereomers:



Stereoisomers: Diastereomers

- Draw all possible stereoisomers for the molecule below. Indicate which pairs are enantiomers and which pairs are diastereomers.

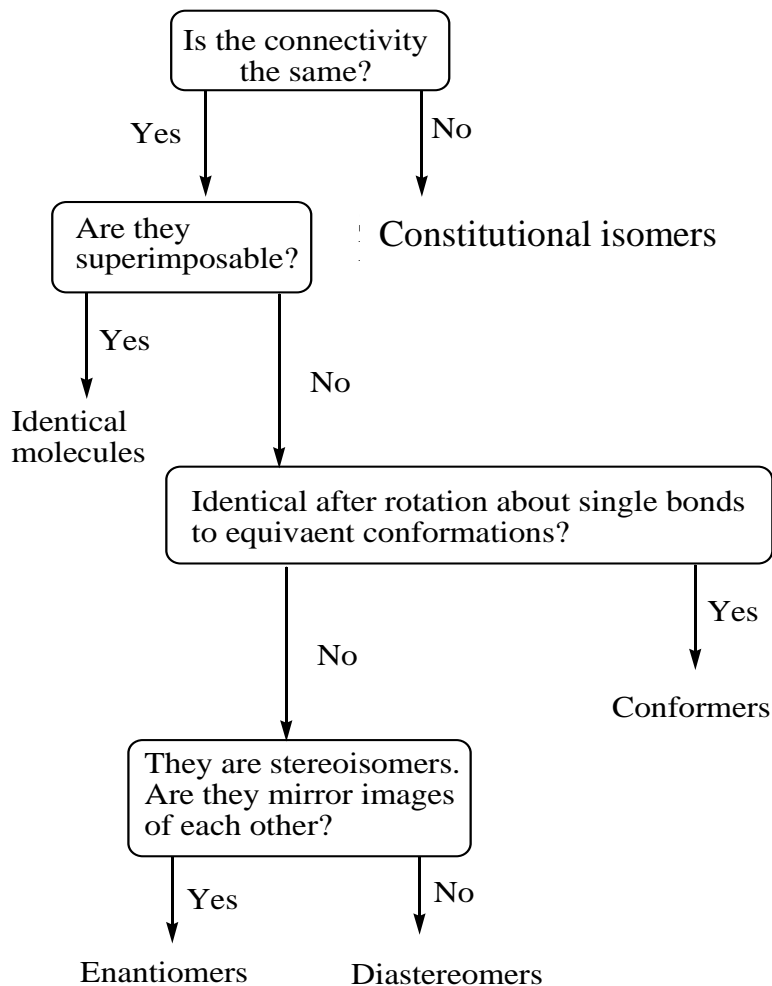


Hint: A molecule can have a maximum of 2^n stereoisomers (including itself).
If there are no meso isomers, there will be exactly 2^n stereoisomers.

Stereoisomers: Summary

Stereochemistree

So, you've got two molecules and you want to know their relationship...



Stereoisomers: Fischer Projections

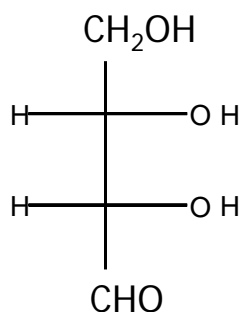
- Most chemists like to draw chiral molecules in 3D (as we have been doing thus far). Biochemists and a few specialist groups of chemists (e.g. carbohydrate chemists) sometimes use a different drawing convention called the **Fischer projection**. A Fischer projection is intended to show three-dimensional structure without actually drawing in 3D.
- The convention is that vertical lines always indicate groups going away from the central atom while horizontal lines always indicate groups coming forward from the central atom:



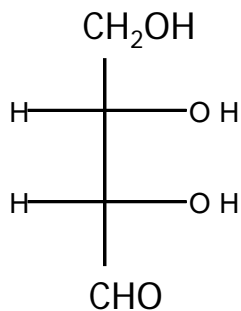
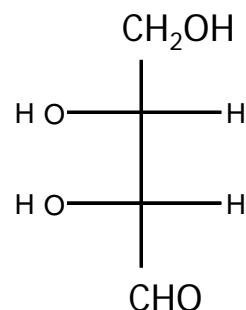
Is the *R*- or the *S*- isomer depicted above?

Stereoisomers: Fischer Projections

- Fischer projections were developed primarily to represent sugars which contain many chirality centers. The idea is that it is easy to tell whether two molecules are diastereomers or enantiomers by looking at the Fischer projections (which will be mirror images of each other if the molecules are enantiomers). Compare:



vs.



vs.

