



**Al-Mustaqbal University**  
**College of Science**



# **Drug Stereochemistry**

**Third Year Students / 2<sup>nd</sup> Semester**

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## **Stereoisomerism**

*By*

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# Stereochemistry

## (Stereoisomerism)

Stereochemistry refers to the 3-dimensional properties and reactions of molecules. It has its own language and terms that need to be learned in order to fully communicate and understand the concepts.

# Isomerism

Isomerism : Compounds with the same molecular formula but different structures

There are three major types of isomerism:

- constitutional isomerism
  - geometrical isomerism
  - optical isomerism
- } stereoisomerism

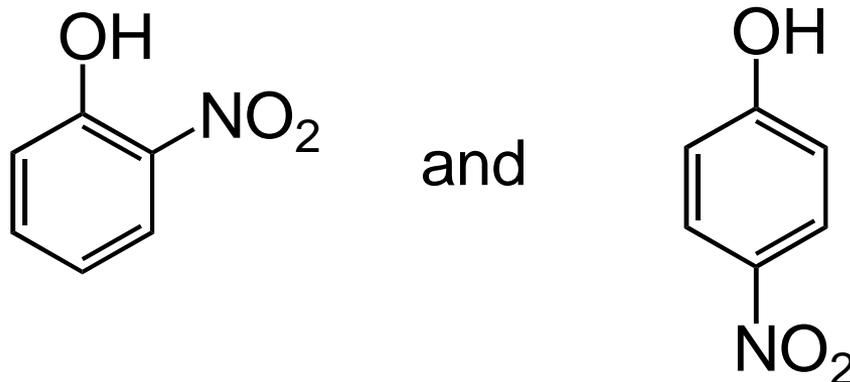
# Constitutional isomers

Constitutional isomers (also known as structural isomers) have the same molecular formula but differ in the sequence in which the individual atoms are bonded (connectivity).

- skeletal isomerism



- positional isomerism



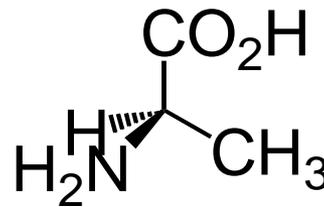
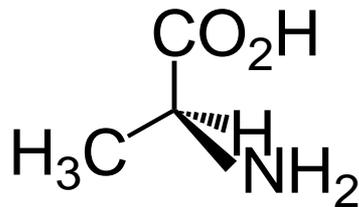
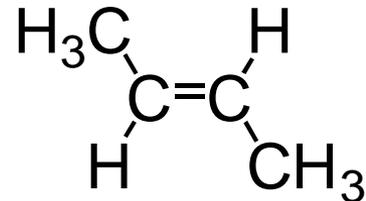
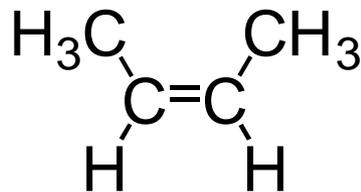
# Constitutional isomers

- Functional isomers: - compounds of identical molecular formula but which have different functional groups.

e.g.  $\text{C}_2\text{H}_5\text{OH}$  and  $\text{CH}_3\text{OCH}_3$

# Stereoisomerism

Stereoisomers have the same atomic connectivity but differ in the spatial arrangement of the constituent atoms.

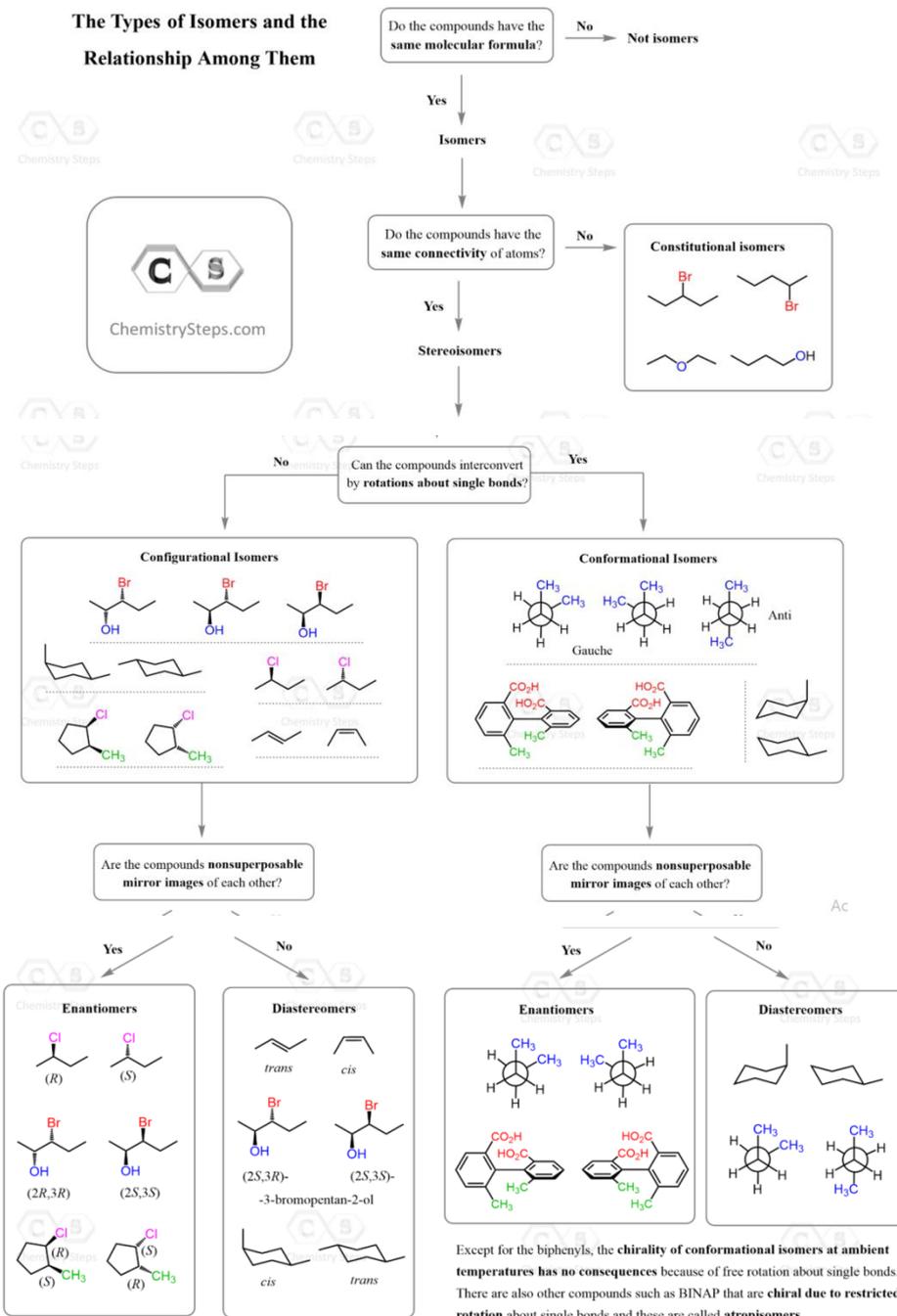


alanine

# Isomerism

- The two major classes of isomers are **constitutional** isomers and **stereoisomers**.
  - **Constitutional/structural isomers** have different IUPAC names, different physical and chemical properties, and may have different functional groups.
  - **Stereoisomers** differ only in the way the atoms are oriented in space. They have identical IUPAC names (except for a prefix like *cis* or *trans*). They always have the same functional group(s).
- A particular three-dimensional arrangement is called a **configuration**. **Stereoisomers differ in configuration.**

# The Types of Isomers and the Relationship Among Them

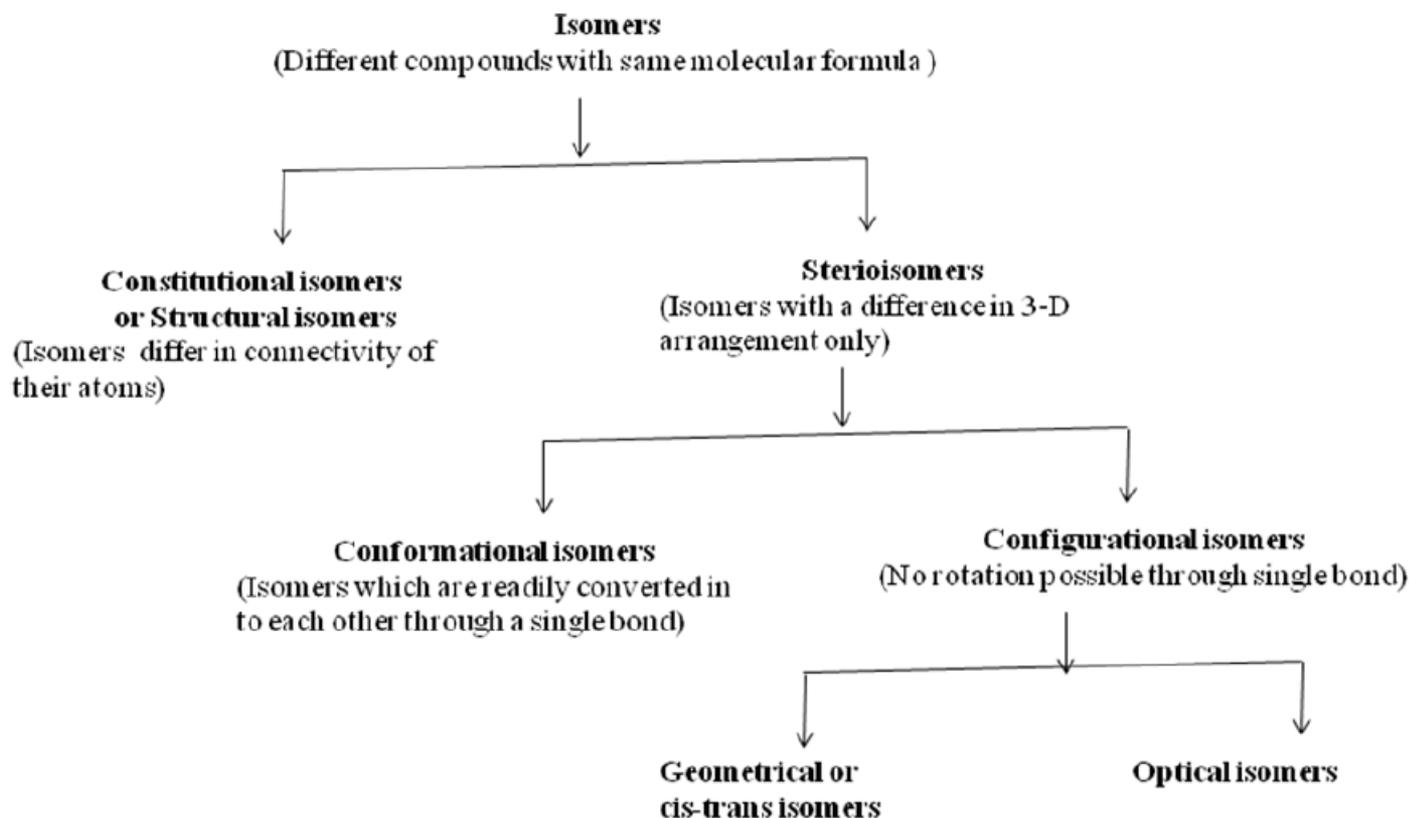


## 1.4. TERMINOLOGY USED IN STEREOCHEMISTRY

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### A. ISOMERS AND THEIR CLASSIFICATION

You are already familiar with the concept of isomers: different compounds which have the same molecular formula. Here we will learn to make distinction between various kinds of isomers, especially the stereoisomers.



**Isomers** are compounds with the same molecular formulae but that are structurally different in some way. It is important to be able to recognise isomers because they can have different chemical, physical properties and biological properties.

**Constitutional** isomers differ in the order in which the atoms are connected so they can contain different functional groups and / or bonding patterns (*e.g.* branching)

- *example*: 1-propanol, 2-propanol and ethyl methyl ether (C<sub>3</sub>H<sub>8</sub>O)

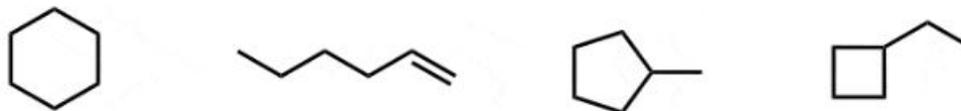
**Stereoisomers** have the same functional groups and connectivities, they differ only in the arrangement of atoms and bonds in space.

**Conformational** isomers (or **conformers** or **rotational isomers** or **rotamers**) are stereoisomers produced by rotation about  $\sigma$  bonds, and are often rapidly interconverting at room temperature

- *example 1*: butane : anti (*left*) and syn (*center*). The C2-C3  $\sigma$  bond rotation is animated (*right*). Try rotating the model to look along the C-C to see the two forms.
  
- *example 2*: cyclohexane : chair (*left*) and boat (*right*). These two forms can be interconverted by twisting the ring structure.

## Types of Isomers - Constitutional Isomers, Stereoisomers, Diastereomers

- Isomers are molecules that share the same **molecular formula**, e.g.  $C_6H_{12}$
- **Constitutional isomers** have the same molecular formula but different connectivity



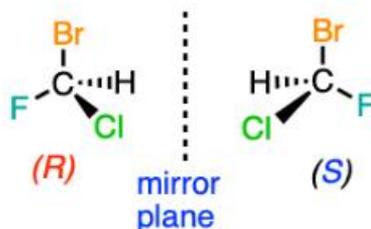
some isomers of  $C_6H_{12}$

an important clue for different connectivity is that the molecules have different IUPAC names (without having to use *R/S* or *E/Z* descriptors)

- **Stereoisomers** have the same connectivity but differ in the arrangement of their atoms in space

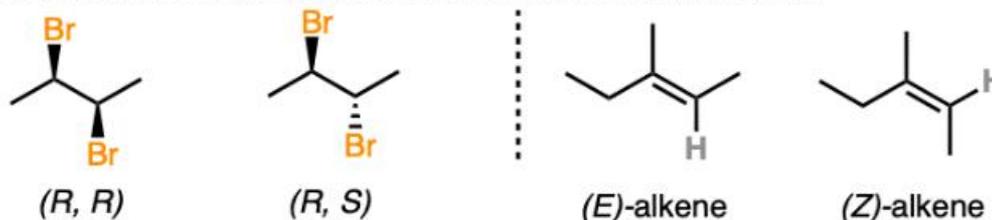
an important clue that molecules are stereoisomers are that they have the same IUPAC name but differ in their *R/S* and/or *E/Z* descriptors

- **Enantiomers** are stereoisomers that are non-superimposable mirror images. (Molecules that are superimposable mirror images are considered to be identical).



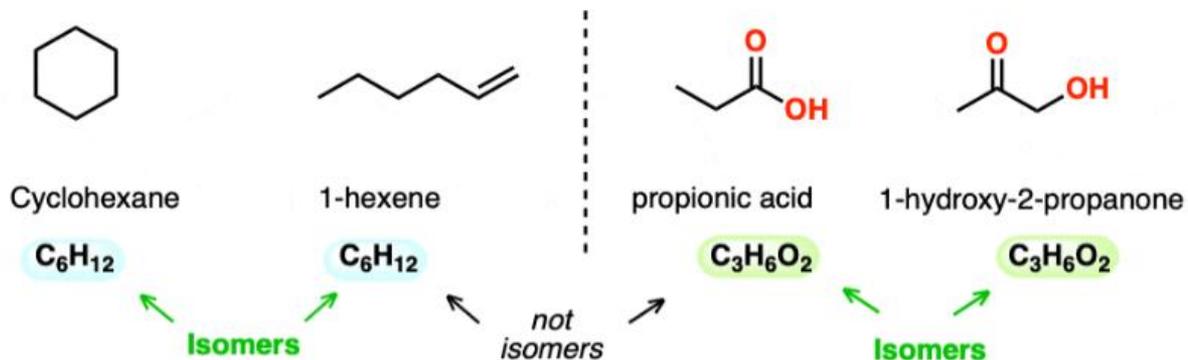
Enantiomers always have opposite *R,S* descriptors

- **Diastereomers** are stereoisomers that are **not** enantiomers.



Share at least one (but not all) *R,S* descriptors, or differ in at least one *E,Z* descriptor

**Isomers** are two (or more) molecules that share the same molecular formula



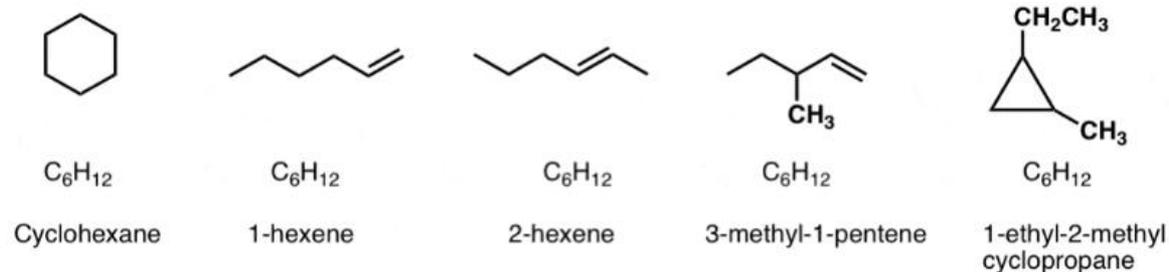
The word "isomer", like "brother" or "cousin" describes a *relationship between two or more entities*.

•cyclohexane and 1-hexene are isomers; cyclohexane and propionic acid are not.

•propionic acid and 1-hydroxy-2-propanone are isomers;  
 propionic acid and 1-hexene are not.

Likewise, propionic acid and 1-hydroxy-2-propanone share the same molecular formula,  $C_3H_6O_2$ , making them isomers of each other (but *not* isomers of cyclohexane or 1-hexene, of course!).

**Constitutional isomers: Same molecular formula, different connectivity**



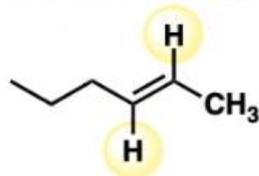
**Hint:** If the molecular formulae are the same, but the IUPAC names and/or numbering are different\*, they are **constitutional isomers**.

\* not counting (R)/(S), (E)/(Z), *cis/trans*

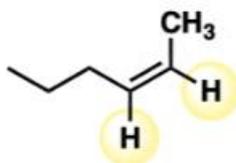
**Stereoisomers: Same connectivity, different arrangement in space**

- Since rotation is not possible about double bonds, there are two 2-hexenes!

This is an example of "same connectivity, different arrangement in space".



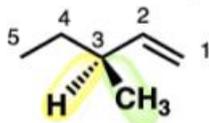
(*E*)-2-hexene



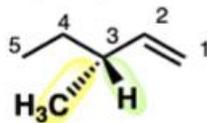
(*Z*)-2-hexene

*same root IUPAC name (2-hexene) but the terms (E) and (Z) distinguish the stereochemistry about the double bond*

- 3-methyl-1-pentene has 4 different substituents on C-3, which can be arranged in two different (non-superimposable) ways



(*S*)-3-methyl-1-pentene



(*R*)-3-methyl-1-pentene

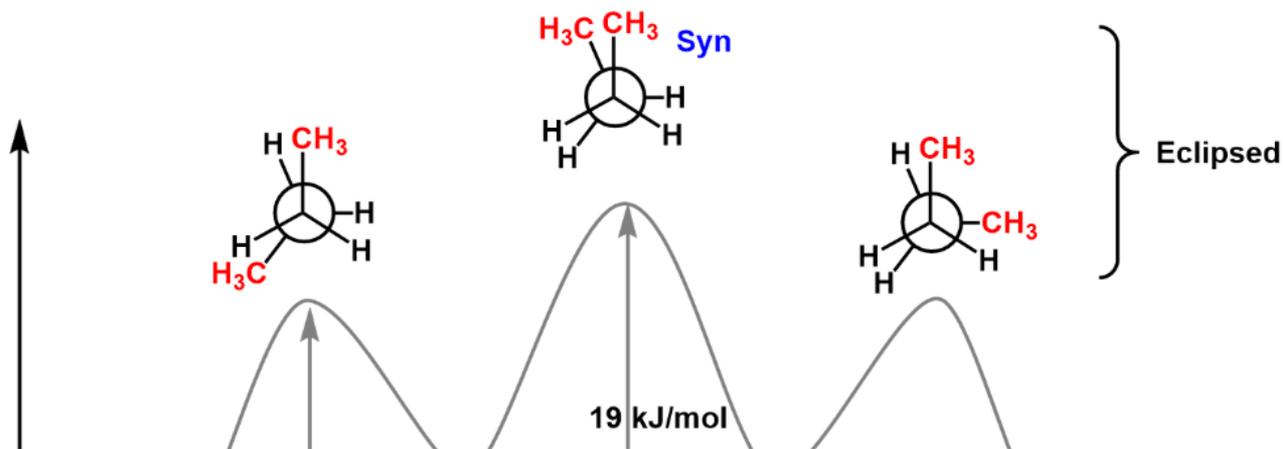
*same root IUPAC name but (S) and (R) describe arrangement of atoms around C-3*

	Molecular Formula	Connectivity	Physical Properties (mp, bp, etc)	Specific rotation (if chiral and non-racemic)
Non-isomers	Different			
Isomers	Same			
<ul style="list-style-type: none"> <li>constitutional isomers</li> </ul>		Different		
<ul style="list-style-type: none"> <li>stereoisomers</li> </ul>		Same		

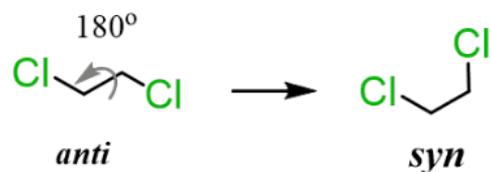
# Configurational Isomers

To understand what configurational isomers are, let's define/describe the terms "configuration" and "conformation". **Configuration** is the orientation/direction of the atoms that we **cannot** change, whereas **conformation** is the orientation of the atoms which we **can change via rotation** about a single bond(s).

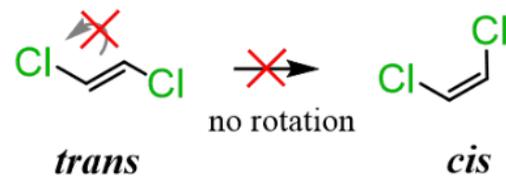
The best way to bring up some examples of conformations is what we saw in [Newman projections of butane](#). There were *syn*, *anti*, and *gauche* conformations, and they were all interchangeable because of the free rotation about single bonds at ambient temperatures:



**Conformers and Stereoisomers are described by Conformations and Configurations**

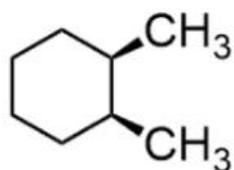
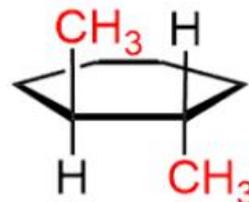
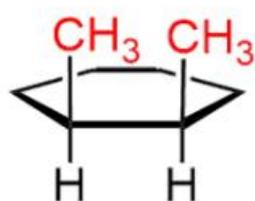


**Conformers**-same compound



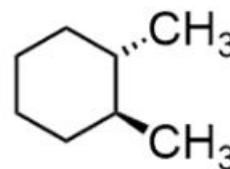
**Stereoisomers**-different compounds

**Cis and Trans Isomerism can also be used in Cycloalkanes**



***cis***-

1,2-dimethylcyclohexane

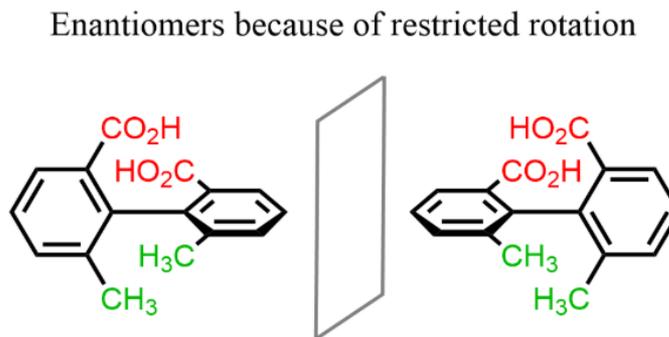


***trans***-

1,2-dimethylcyclohexane

### Atropisomers – Restricted Rotation About Single Bonds

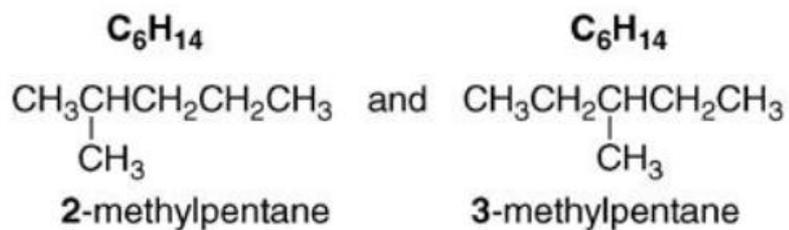
Because of steric hindrance, the rotation about single bonds is restricted in some molecules and they are chiral despite lacking a chiral center. For example, *ortho*-substituted biphenyls may be chiral because the groups are on each other way and there is no free rotation about the single bond connecting the two phenyl groups:



The two conformation of biphenyl shown above are **enantiomers** called **atropisomers**. These are stereoisomers that that lack a chiral center but are nonsuperimposable mirror images because of hindered rotation.

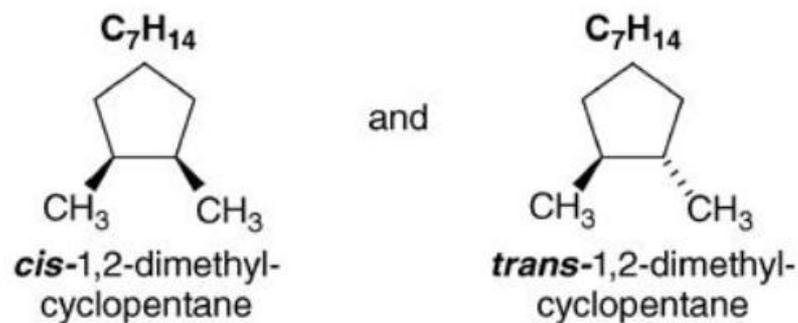
Notice that if we could rotate about the single bond, the two structures would represent the same compound which confirms that they are not constitutional isomers as it may seem like:

# Stereoisomers



same molecular formula  
different names

**constitutional isomers**

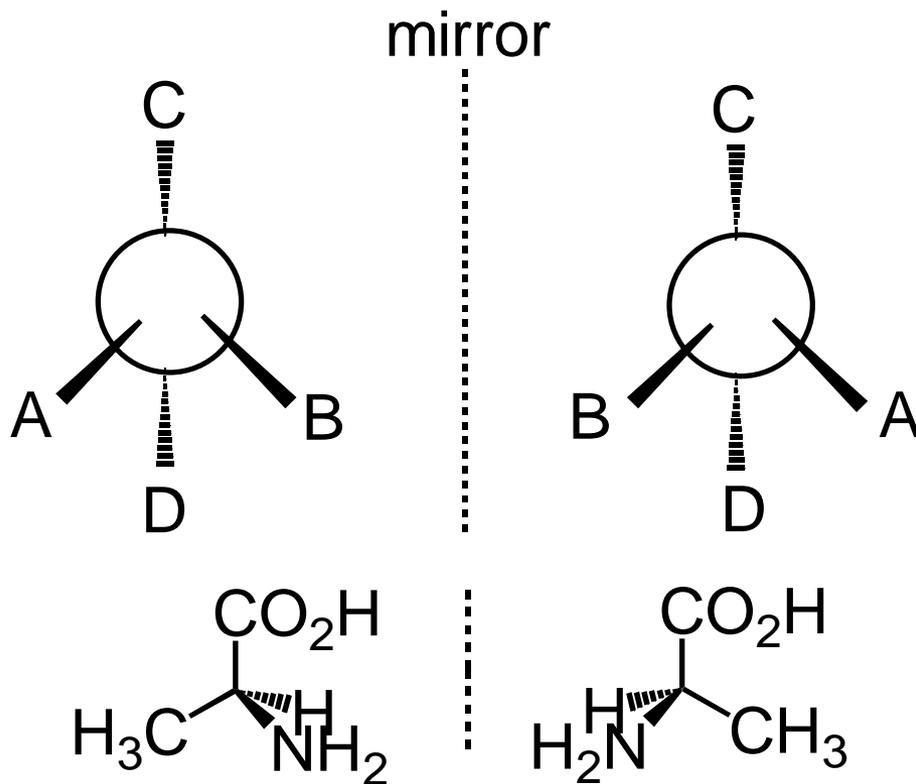


same molecular formula  
same name except for the **prefix**

**stereoisomers**

# Enantiomers

Enantiomers are stereoisomers that are non-superimposable on their mirror images.



# Diastereomers

Diastereomers are stereoisomers that are not mirror images of each other – they are stereoisomers that are not enantiomers.

