

The stereochemical behavior of a molecule originates in its symmetry

hence

molecular symmetry must be determined unambiguously

Since molecules are elusive objects we must operate on molecular models and the choice and properties of the model are of fundamental importance

Symmetry elements and operations

Elements

- rotation axis C_n ($n = 1, 2, 3, \dots$)
- mirror plane σ
- center of inversion i
- roto-reflection axis S_n ($n = 4, 6, \dots$)

Operations

- rotation around the axis by $360^\circ/n$
- reflection through the plane
- inversion of cartesian coordinates (x, y, z to $-x, -y, -z$)
- rotation around the axis by $360^\circ/n$ followed by reflection through a plane perpendicular to the axis (if $n = 1$, $S_1 = \sigma$; if $n = 2$, $S_2 = i$)

Simple rotational elements C_n and the corresponding operations are of the first order

Reflection elements S_n and the corresponding operations are of the second order

Chirality

The presence or the absence of certain symmetry elements in a molecule allow to make a fundamental distinction among molecules, according to which they are defined **chiral** or **achiral**.

The problem of how to define chirality baffled great philosophers....

"What can be more similar to my hand, and more equal to it in all of its parts, than its image in the mirror? And yet such a hand as is seen in the mirror cannot take the place of the original; for if the original was a right hand, the hand in the mirror is a left one, which could never take the place of the original. Despite their mutual equality and similarity, left and right hands can nevertheless not be encompassed within the same boundaries, they cannot be rendered congruent; the glove of one hand cannot be used on the other. Then, what is the solution ?"

I. Kant, Prolegomena zu einer jeden kunftigen Metaphysik, 1783

...was Investigated by scientists...

"I call any geometric figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself. Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar. These are also called "enantiomorphs". Any chiral object and its image in a plane mirror are heterochirally similar. "

Sir W. Thompson (later Lord Kelvin), 1893

The etymology of the word chirality can be found in the old greek term for hand.

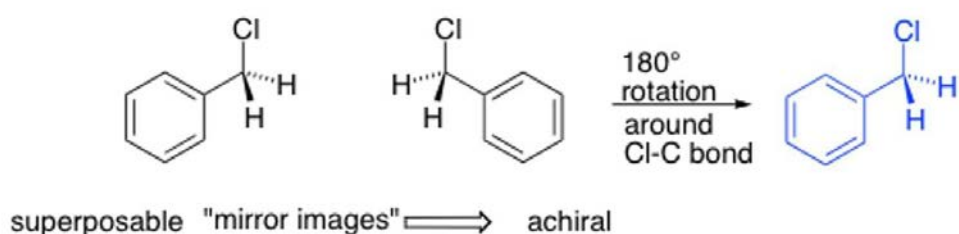
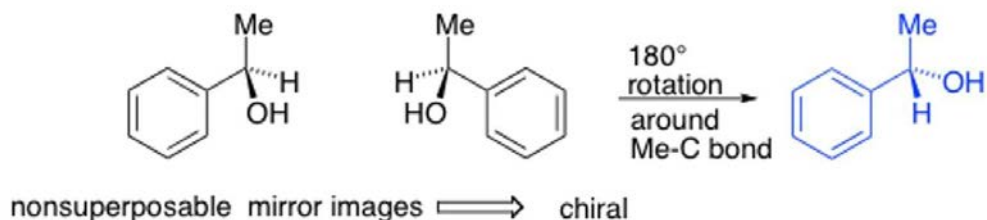
Since the two hands are "identical" and "nonsuperposable", all the objects that share these properties are "hand-like", hence "chiral", and have "handedness", hence "chirality".

...and solved by a (stereo)chemist.

An object is chiral if and only if it is not superposable on its mirror image; otherwise is achiral.

K. Mislow, Top. Stereochem. 1998, 22, 1

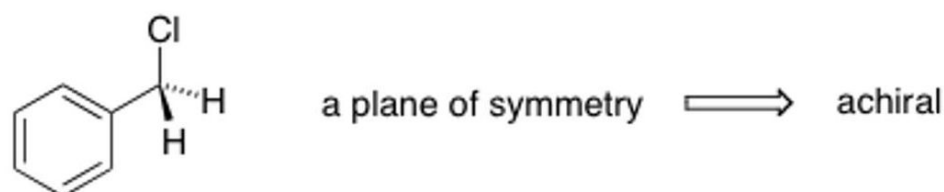
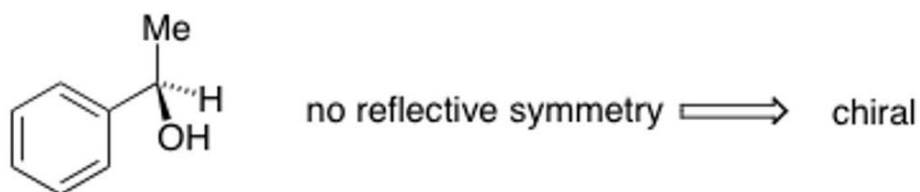
Quindi alla domanda circa la chiralità di un oggetto si risponde affermando che esso è **chirale se non è sovrapponibile alla propria immagine speculare**.



How to recognize chirality at the molecular level?

A molecule is chiral if it does not possess any element of "reflective" symmetry (mirror planes, center of inversion, roto-reflection axes)

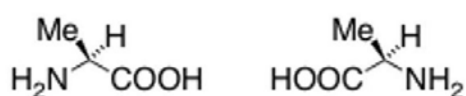
Chirality is rooted in symmetry. Only molecular symmetry considerations provide an unambiguous approach to recognize chirality in a molecule.



Consequences of molecular chirality

The most important consequence of molecular chirality is the existence of a chiral molecule as two distinct entities. These are defined **enantiomers**, or "opposite isomers", that is isomers (molecules made up of the same atoms present in the same number) with opposite spatial arrangement of atoms or groups of atoms around a given structural unit.

Two enantiomers are heterochiral. Two identical chiral molecules (homomers) are homochiral.



enantiomers and heterochiral



homomers and homochiral

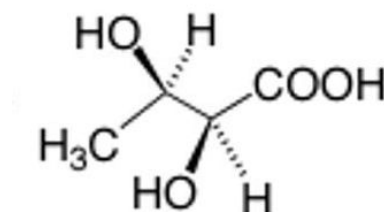
Being made up of the same atoms present in the same number, enantiomers are stereoisomers.

Stereoisomers are isomeric molecules with different spatial disposition of atoms or groups of atoms. If the disposition is opposite, stereoisomers are enantiomers; if the disposition is different, stereoisomers are diastereoisomers.

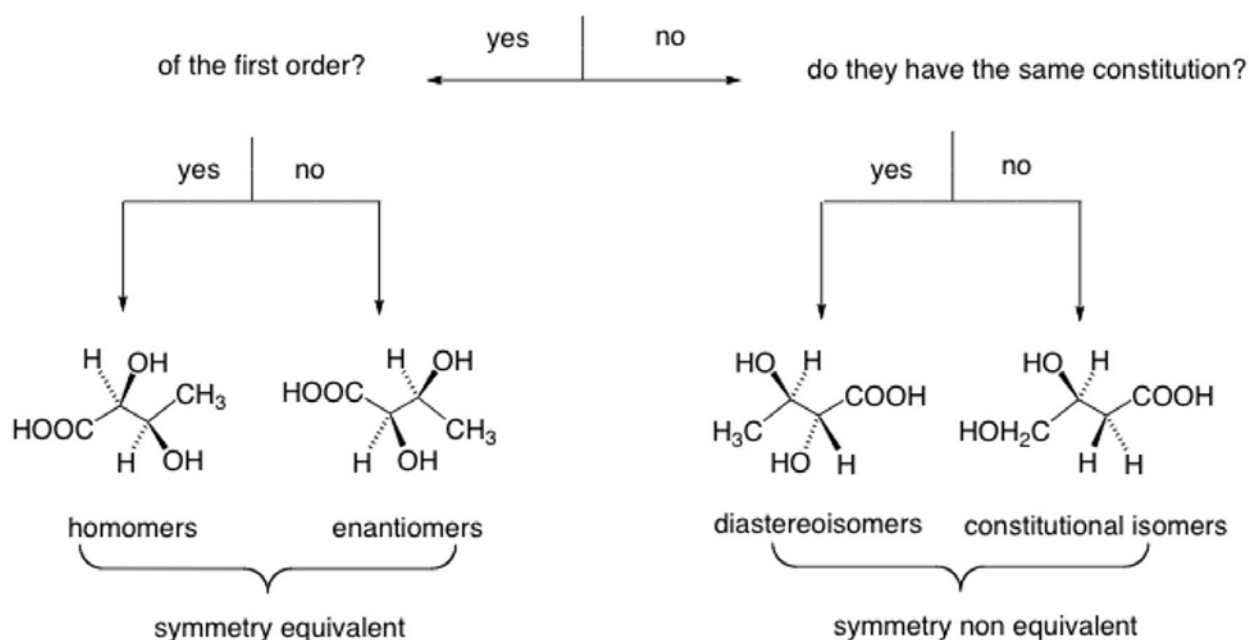
The symmetry relationships between two isomers allows to make their unambiguous pairwise classification.

Pairwise relationships between isomers (*Mislow, Bull. Soc. Chim. Belg. 1977, 86, 595*):

Take as reference the following and any other isomer $C_4H_8O_4$:

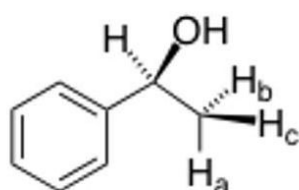


Are the reference molecule and its isomer related by a symmetry operation?



About the power of symmetry arguments

Symmetry arguments warrant the existence of a symmetry-related phenomenon, but not its observability, which depends on the nature of the phenomenon, the method of observation, and the timescale of the observation experiment. Thus, in this molecule:



$H_a/H_b/H_c$ are diastereotopic by definition and hence symmetry non equivalent. Still in a standard 1H -NMR experiment they will appear magnetically equivalent and isochronous because the method of observation does not allow their differentiation.

Chirality is a pervasive property of the molecule

All of the points of a chiral molecule are equally chiral. They are defined chirotopic.

(K. Mislow and J. Siegel, JACS 1984, 106, 3319)

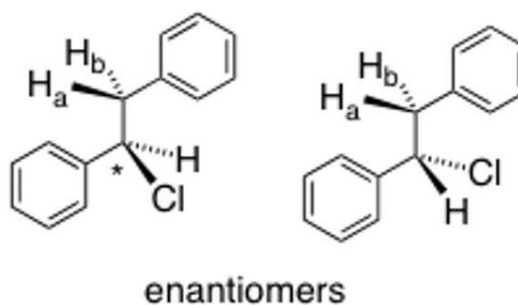
Chirotopicity is the property of a point of a molecule that resides in a chiral environment and is not located on a symmetry element of the second order. Since a chiral molecule does not contain symmetry elements of the second order by definition, all of its points are chiral and chirotopic.

Within a molecule chirality shows itself by making symmetry non equivalent (and hence different) constitutionally equivalent atoms and groups. Therefore, chirality is not localized on an atom, but informs of itself the whole molecule. Accordingly, it is not correct to localize chirality on an atom or on a group of atoms, but chirality must be recognized as a property of the whole molecule.

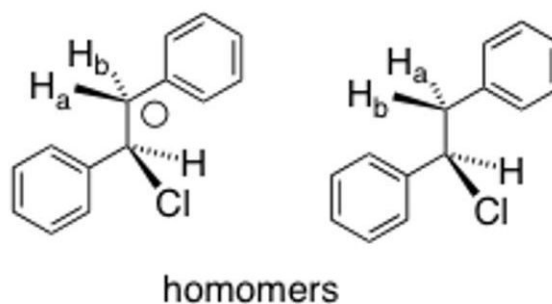
Chirality and stereogenicity are distinct molecular properties

An exchange of ligands at the equally chirotopic tetrahedral carbon atoms in this molecule has different consequences.

Any exchange of ligands at C* generates a stereoisomer (in this case, the enantiomer) of the original structure



Any exchange of ligands at C° does not generate a stereoisomer, even if this carbon carries "different" substituents (H_a and H_b are magnetically different)



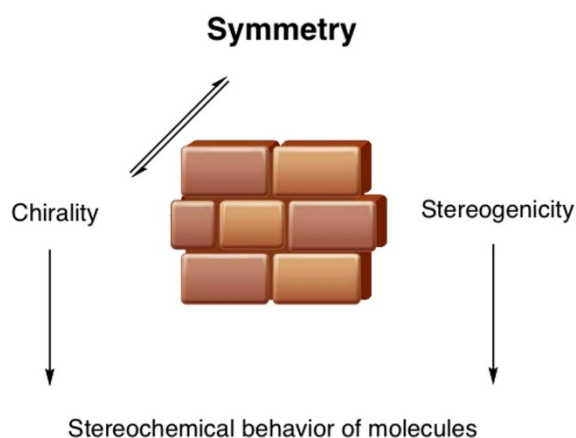
A tetrahedral atom (typically, a C atom) for which an exchange of ligands generates a stereoisomer of the original structure is defined a **stereogenic center** or, in short, a **stereocenter**. Stereogenicity is the property of an atom or group of atoms to generate stereoisomeric structures by an exchange of two ligands. **Hence, differently from chirality, stereogenicity is localized on an atom.**

Chirality and stereogenicity are distinct molecular properties

They have been unruly confused because a tetrahedral atom is the only structural unit for which an exchange of ligands results in the inversion of the sense of chirality of the molecule.

Chemists, and in particular organic chemists, always faced this disconcerting coincidence because of the ubiquitary presence of tetrahedral carbon atoms with four different ligands as a structural unit possessing both chirality and stereogenicity. In this light it is easily realized why expressions like "asymmetric carbon atom" and "chiral center" are so popular.

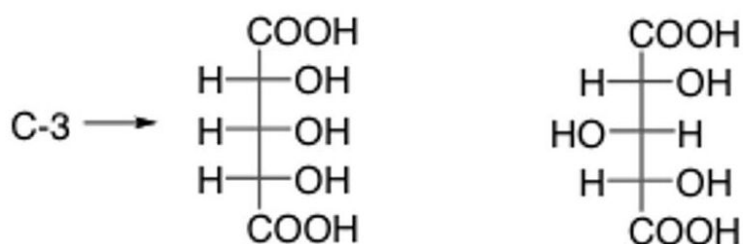
Nevertheless, logic imposes to keep a **clear distinction** between the two concepts of **chirality** and **stereogenicity** while dealing with stereochemical problems. At the same time, expressions in which molecular chirality is localized on a given molecular fragment must be avoided.



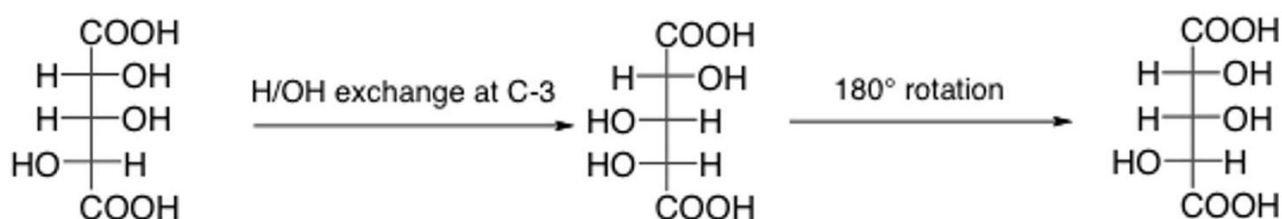
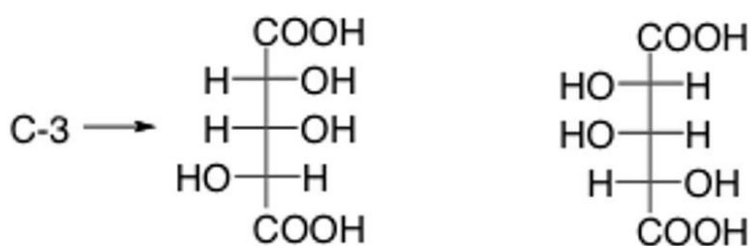
Thus the notions of "chiral center", "chiral axis", "chiral plane" are void of any rational meaning.

Chirality and stereogenicity are distinct molecular properties

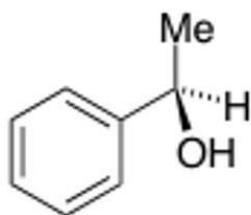
In the two **achiral** forms of trihydroxyglutaric acid C-3 is achirotopic (as it is located on the plane of symmetry) and **stereogenic** (as the H/OH exchange generates the other achiral form). All the atoms outside the plane are chirotopic. **C-2 and C-4 are stereogenic.**



In the two **chiral** forms of trihydroxyglutaric acid C-3 is chirotopic (like all the other atoms of these molecules), **but not stereogenic**: indeed the H/OH exchange generates the same molecule (the homomer). As before, **C-2 and C-4 are stereogenic.**

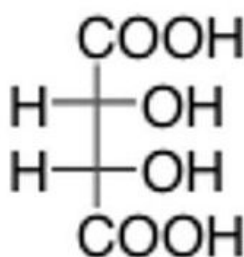


Chirality and stereogenicity are distinct molecular properties



This molecule is chiral not because it contains a carbon atom carrying four different substituents, but only because it does not feature symmetry elements of the second order.

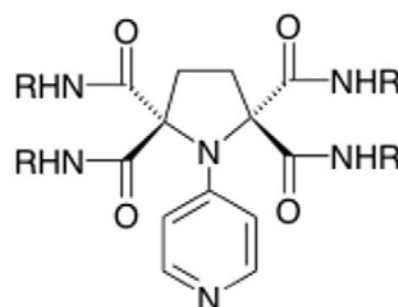
Indeed, achiral molecules do exist that contains carbon atoms with four different ligands, as does this isomer of tartaric acid:

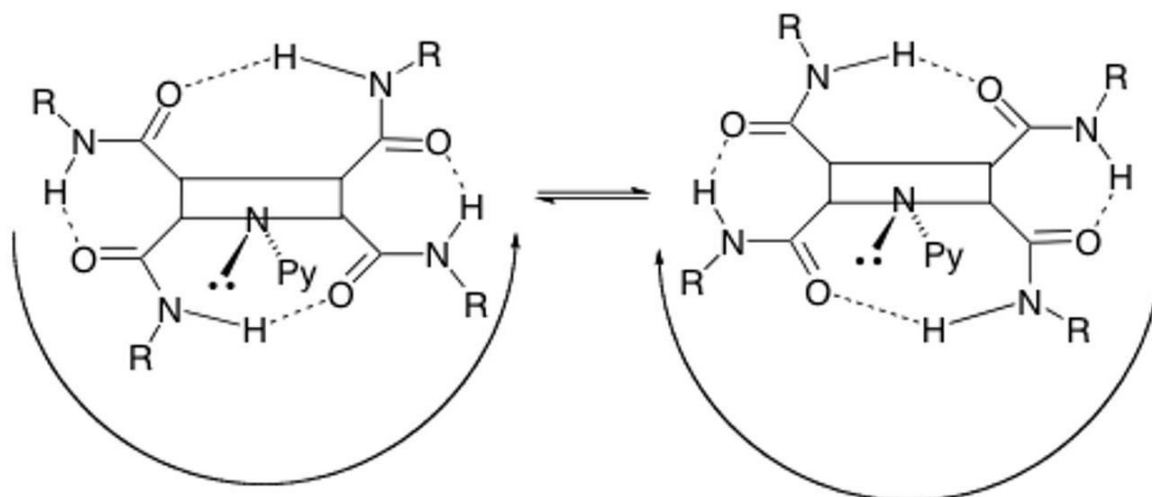


On the other hand, chiral molecules do exist that contain carbon atoms carrying four identical substituents!

The absence of reflective symmetry is a necessary and sufficient condition for chirality

This molecule does not contain any stereogenic center. Still, formation of four intramolecular H-bonds blocks the amido groups in a chiral, spiral-type disposition lacking any reflective symmetry.



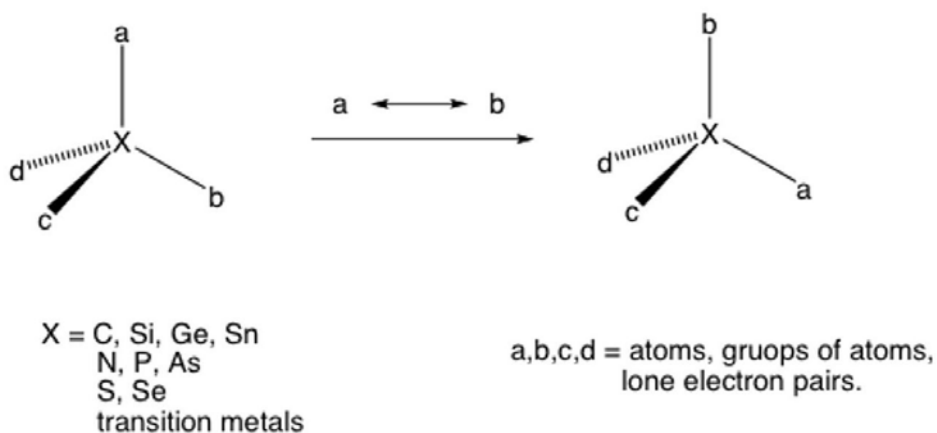


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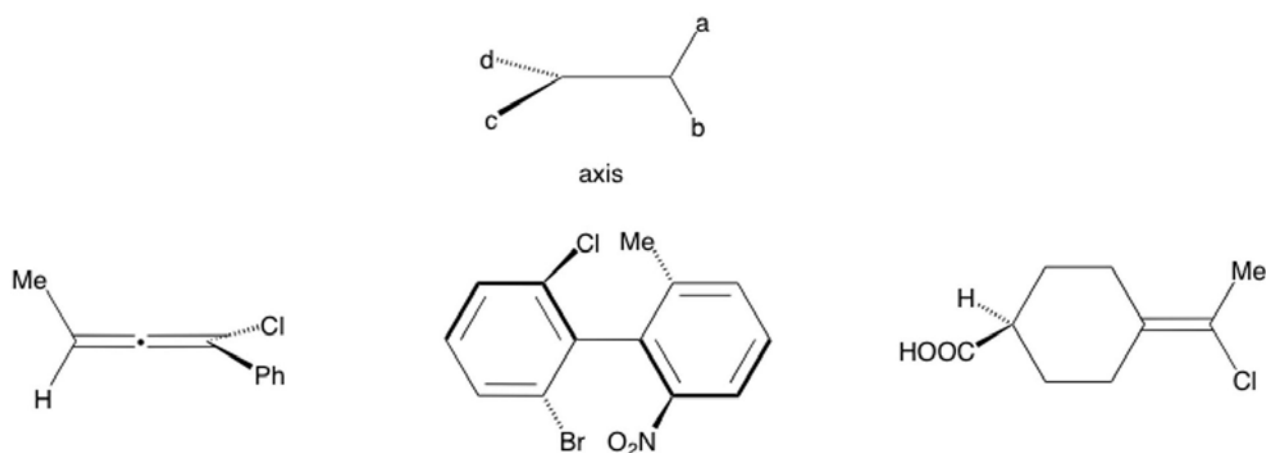
Stereogenic units: stereogenic centers

Structural units for which an exchange of ligands generates a stereoisomer of the original structure are defined stereogenic units.

In particular, a tetrahedral atom bearing four different ligands is defined a stereogenic center (shortly, a stereocenter). Generally, in this case a single exchange of ligands generates the enantiomer of the original structure (exceptions are found when the ligands in their turn contains stereocenters)



Example: Other stereogenic units: stereogenic axes



Because of tetrahedron desymmetrization by deformation, stereogenicity is maintained also in the presence of pairs of identical ligands. Enantiomers are generated by exchange of ligands at one end of the axis:



Do not mess with chirality!

In general, every attempt to deal with chirality using considerations other than those of symmetry is dangerous and can generate serious mistakes.

Thus beware of trying to "localize", "transfer", "measure", "quantify", or "amplify" chirality: chirality is a "yes or no" property that depends exclusively on the geometry and symmetry features of a molecule.

Take-home message

When dealing with stereochemical problems, symmetry leads the way.

Symmetry is an unambiguous property of the whole molecule.

Molecular symmetry has a powerful predictive ability for every chemical phenomena, including, most notably, reactivity and spectroscopy.

Chirality is a pervasive property of the whole molecule, rooted in symmetry and geometry

Stereogenicity is a property of structural units, rooted in bond connectivity.

Chirality and stereogenicity are different properties, each to be used in its own domain and never to be confused.