



Molecular Literacy for All

making sense of the “monstrous and boundless thicket” of everyday chemistry

The covalency model transforms a two-dimensional drawing into a 3D object.

“The Same or Not the Same?”, that is the question

Today's Outline

Molecules have three-dimensional shapes

Stereoisomers of the same molecule

What kind of stereoisomer

Chirality

The stereocenter

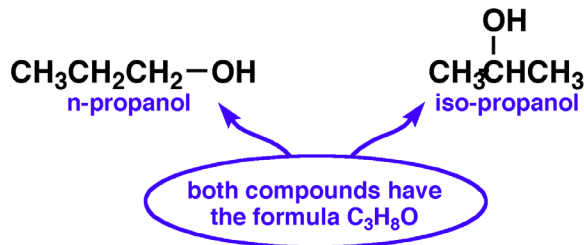
The Fischer projection

Molecules with more than one stereocenter

Drawing conventions

Stereochemistry: There's More to Structure Than Connectivity

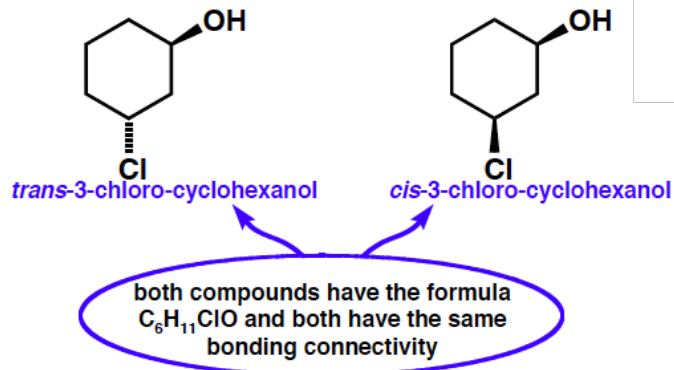
- Stereochemistry has to do with the spatial arrangement of atoms within a molecule. It is an aspect of structure that goes beyond bonding connectivity. At the heart of the matter is a comparison between two structures. There are two questions of prime importance: (1) are the two structures the same or not the same and (2) if they are not the same, then how do they differ?
- Before we talk about stereochemistry, let's first introduce the concept of isomers.
- **Isomers** are two different structures that have the same molecular formula. **Constitutional isomers** are isomers that differ according to the way the atoms are connected. An example of two different structures that are related as constitutional isomers is n-propanol and iso-propanol. Both have the same molecular formula so they are isomers. Yet, they are obviously not the same. They differ in the way the atoms are connected together.



constitutional isomers have the same molecular formula but different bonding connectivity

Stereoisomers

Isomers with the same bonding connectivity but which differ according to how the atoms are arranged in space are called **stereoisomers**. Consider the two cyclohexane structures below. Both have the same molecular formula and both have their atoms connected in the same way. For example, in both structures the bonding pathway from chlorine to oxygen involves four bonds. All other bonding pathways are the same in both structures. The way they differ is in how the atoms are arranged in space. For the structure on the left, the Cl and OH are oriented in opposite directions with respect to the cyclohexane plane of the screen. In the structure on the right, both the Cl and the OH are oriented above the plane of the screen. The different spatial relationship among their atoms is what makes this a pair of stereoisomers.

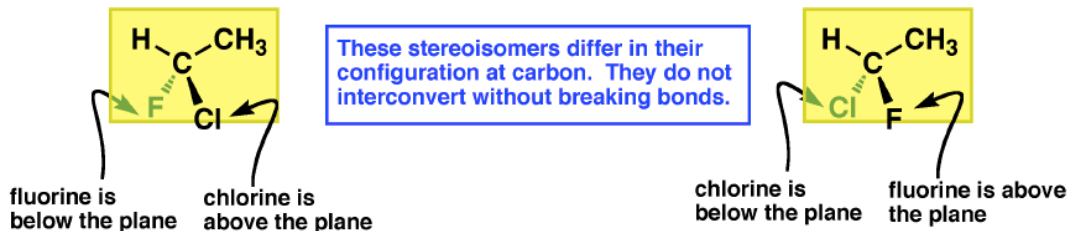
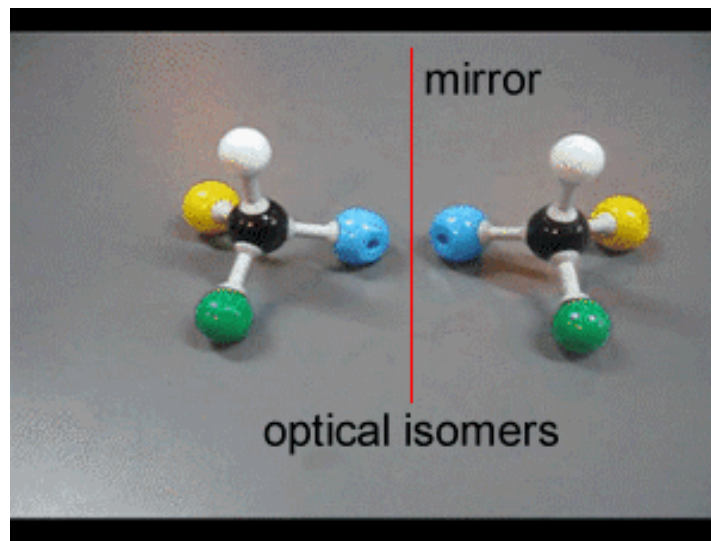


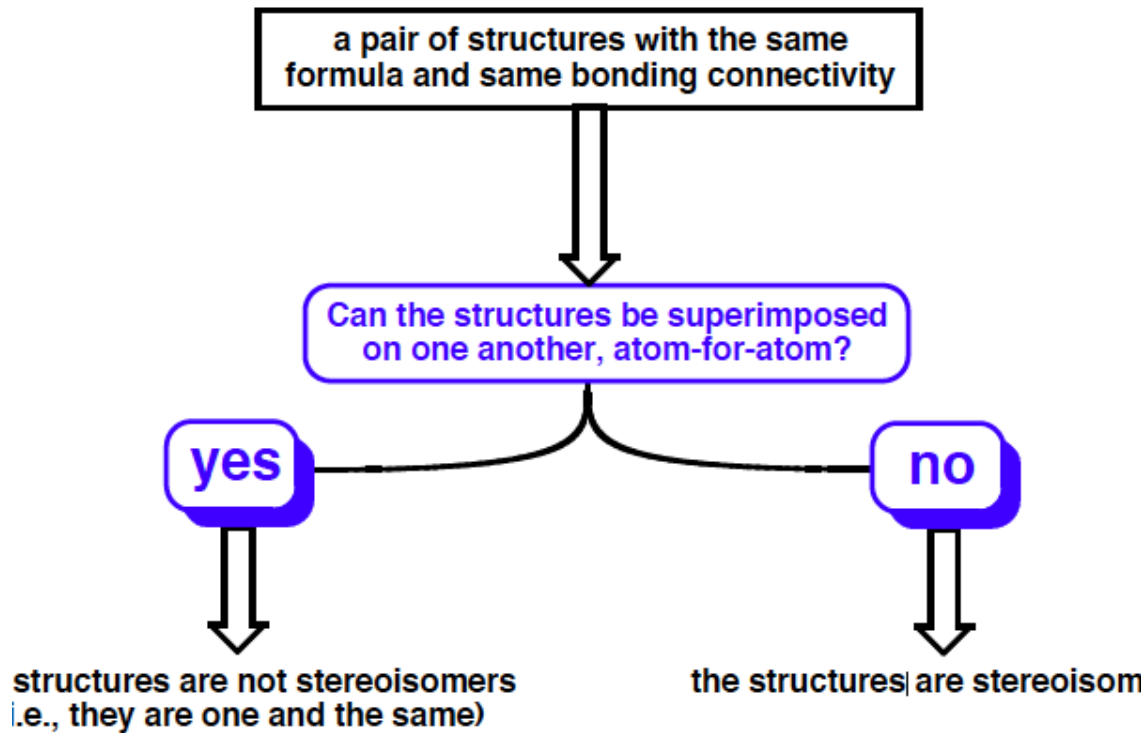
Convention

- Wedge - toward viewer
- Dash - away from viewer
- Wiggly - toward or away

The Same or Not the Same?

At this point it is best to build a physical model of each 1-chloro-1-fluoroethane stereoisomer shown below. Build them exactly as they are shown.

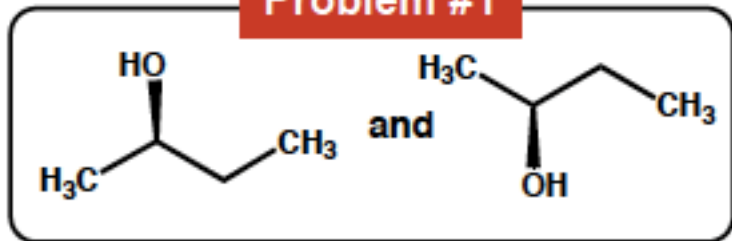




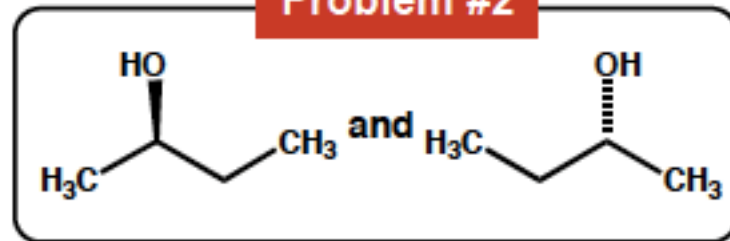
A flowchart to determine if a pair of structures are stereoisomers

Practice: Are these pairs stereoisomers?

Problem #1

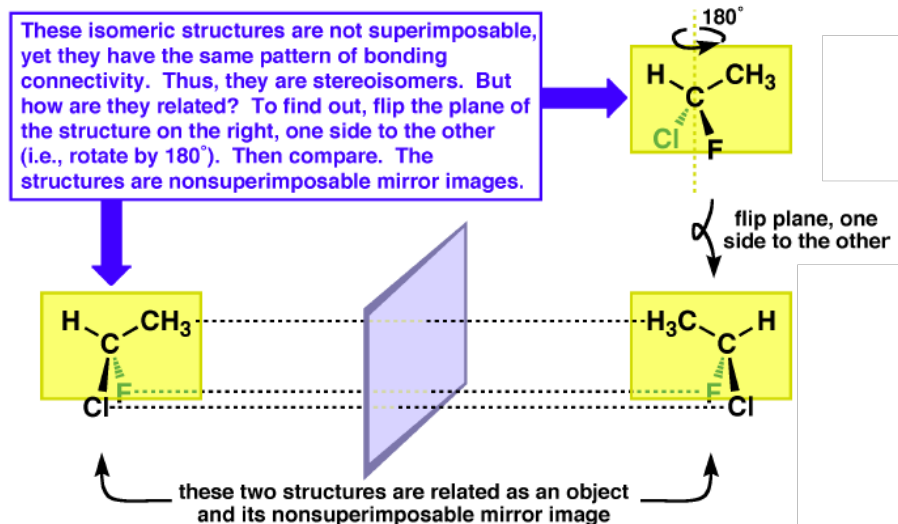


Problem #2



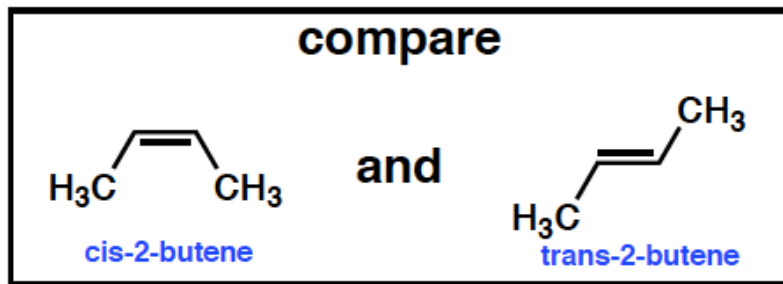
There are two different types of stereoisomers.

- Once we know that a pair of structures is related as stereoisomers, we would then like to know what kind of stereoisomers they are. The two main classes of stereoisomers called **enantiomers** and **diastereomers**. The example below illustrates the case of enantiomers – stereoisomers related as mirror images.
- A **racemic mixture** has equal quantities of both enantiomers.
- Mirror images? By mirror image relationship we mean that each atom projected through a plane will find the equivalent atom on the opposite side and at an equidistant.
- Stereoisomers that do not have a mirror image relationship are **diastereomers**.

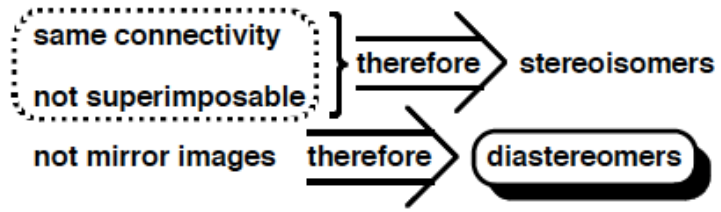


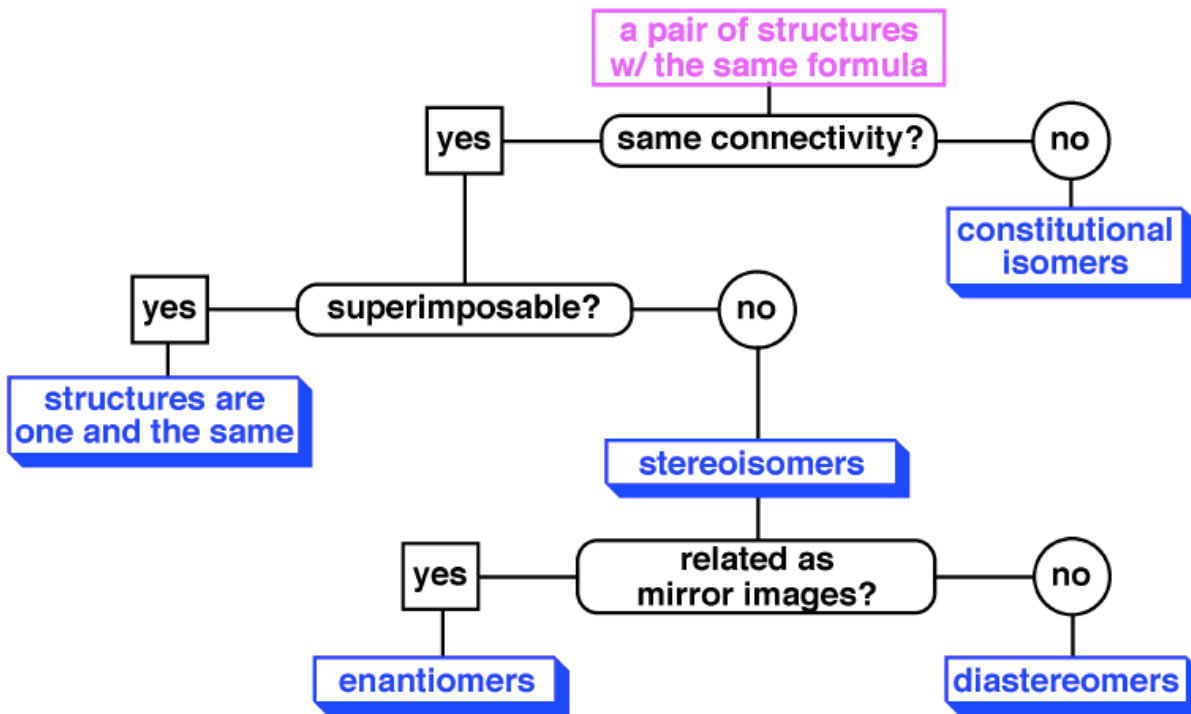
Another example of diastereomers

Compare the cis and trans isomers of 2-butene. How are they related? They have the same connectivity, yet they are not superimposable; therefore, they are stereoisomers. However, they are not related as an object and its mirror image. Therefore, they are diastereomers.



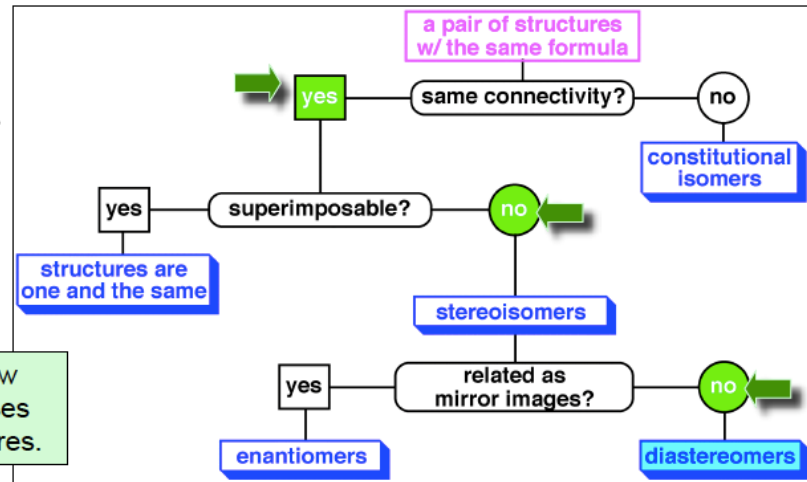
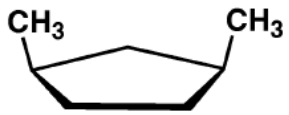
isomer classification tests





A Flowchart to Determine Stereoisomers

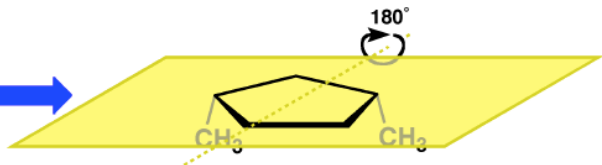
These structures cannot be superimposed and they are not related as mirror images. They are diastereomers.



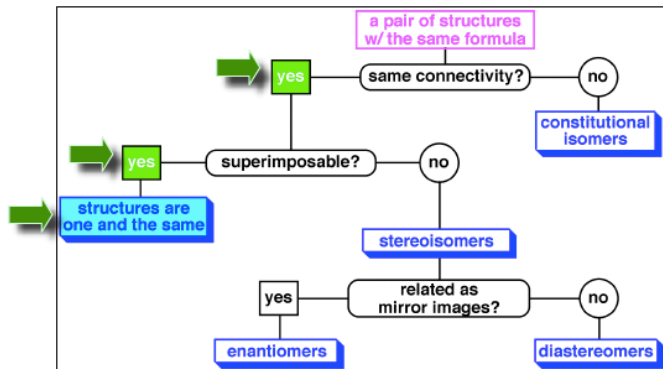
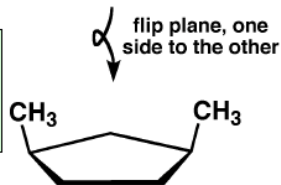
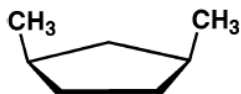
The green boxes show the flowchart responses for this pair of structures.

Examples using the flowchart

These structures can perfectly be superimposed on one another. To see this, flip the plane of the structure on the right, one side to the other (i.e., rotate by 180°). Then compare. The drawings are simply different representations of the same structure.



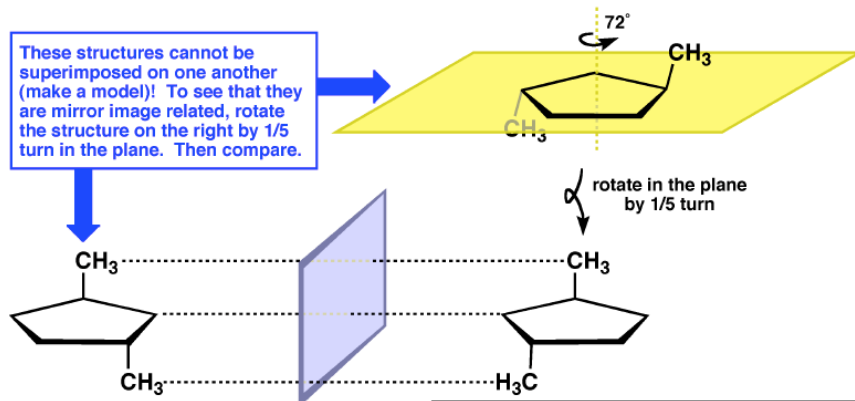
these two structures are related as superimposable objects - they are one and the same



The green boxes show the flowchart responses for this pair of structures.

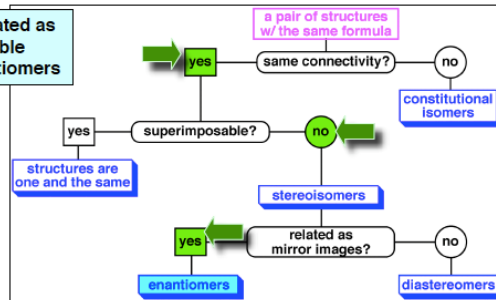
Examples using the flowchart

These structures cannot be superimposed on one another (make a model)! To see that they are mirror image related, rotate the structure on the right by 1/5 turn in the plane. Then compare.



these two structures are related as object and nonsuperimposable mirror image; they are enantiomers

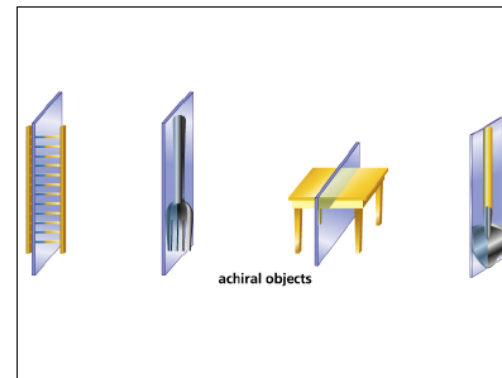
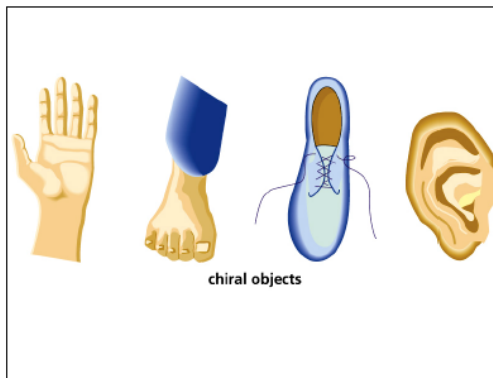
The green boxes show the flowchart responses for this pair of structures.



Examples using the flowchart

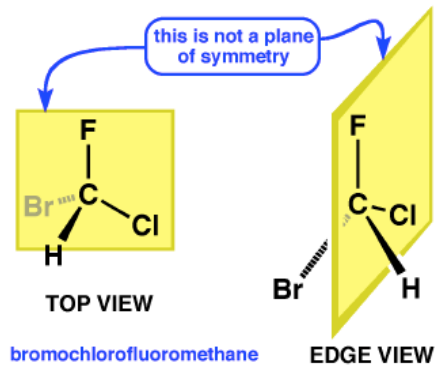
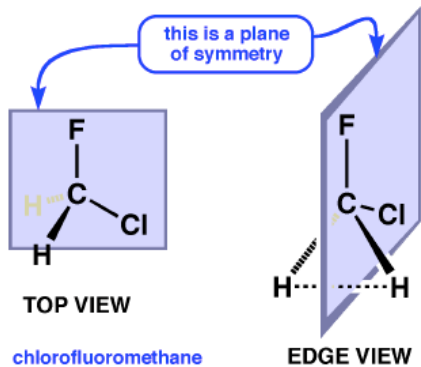
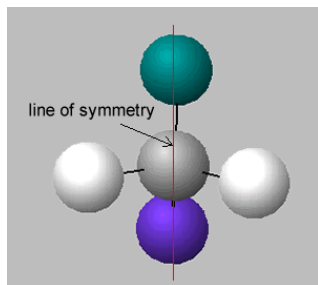
Chirality

Chirality is a geometric property of an object. A chiral object is not superimposable on its mirror image. We have already encountered chiral structures in our discussion above. Specifically, each structure belonging to an enantiomeric pair, by definition, must be chiral. In contrast to enantiomers, the structures corresponding to diastereomeric pairs may or may not be chiral. One way to tell if a structure is chiral is to draw the mirror image form and see if the mirror image is superimposable on the original. If the mirror image is superimposable on the original, the structure is achiral; if it is not, the structure is chiral.

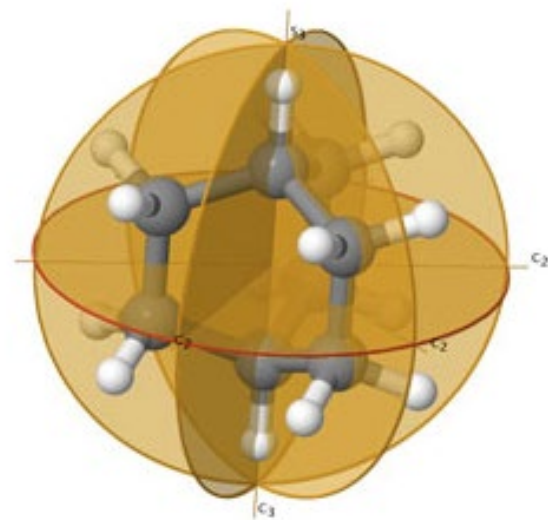


Recognizing chirality by finding symmetry planes

An equally rigorous test for chirality is to check for the absence of either a plane of symmetry or an inversion center. Having a plane of symmetry means that all of the atoms in one half of a molecule reflect through the symmetry plane (traveling along a direction perpendicular to the plane), coinciding exactly with and equidistant to the same atoms in the molecule's other half. Atoms that are in the plane do not have counterparts because they are part of the plane itself. For example, chlorofluoromethane possesses a plane of symmetry. In contrast, bromochlorofluoromethane does not. Chlorofluoromethane is achiral while bromochlorofluoromethane is chiral.



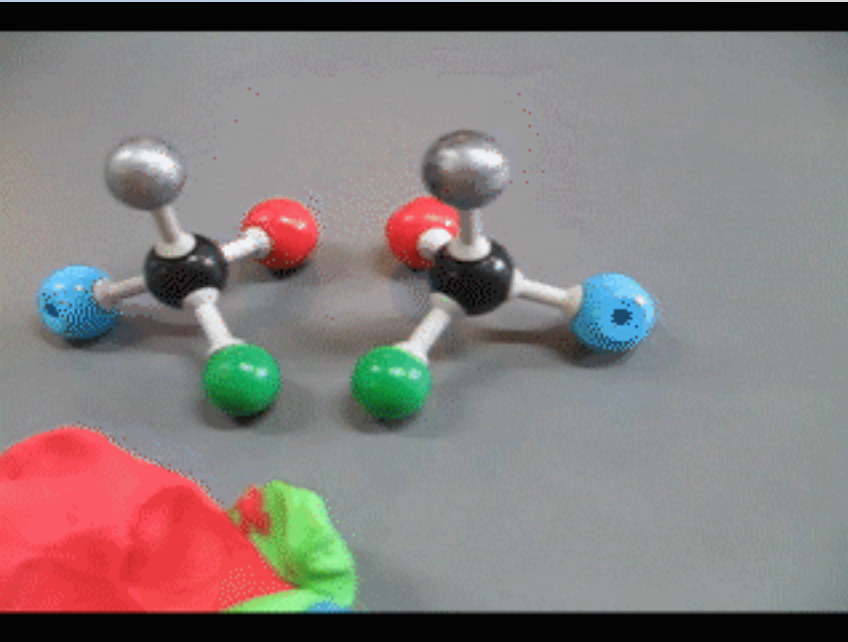
[Symmetry Resources](#)



Point Group = D_{3h}

Chem

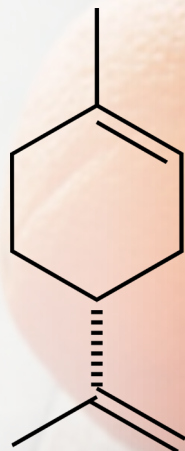
The molecular handshake



- It is hard to imagine that molecules with the same atoms but a different spatial arrangement can have different chemical properties. Let's take the example of biological model of a protein receptor binding to a stimulus molecule.
- Consider the two molecules "A" and "B" shown below. They are structurally similar but differ in the spatial arrangement of atoms around central carbon atoms.
- Molecule "A" fits nicely into the protein, represented by the plasticine, however, molecule "B" does not form a perfect fit no matter how we rotate the molecule around the two central carbon atoms. Molecule "A" will initiate a response as it binds perfectly but molecule "B" will not. This demonstration also shows how enzymes, which are really protein catalysts, can distinguish between optical isomers.

Everyday molecules every day: The Odor of OJ

- *Fresh orange juice is a highly desirable but unstable product. This review examines analytical findings, odor activity, and variations due to cultivar, sampling methods, manner of juicing, plus possible enzymatic and microbial artifacts.*
- *(+)-Limonene is an essential component in orange juice odor although its exact function is still uncertain.*
- *"By themselves some of them stink, but they are necessary to the mix," said Anne Plotto, from the Agriculture Research Service of the U.S. Department of Agriculture.*



D-limonene
also called
(+)-limonene

Stereochemistry in your nose

Chem. Senses 24: 161–170, 1999



Olfactory Discrimination Ability of Human Subjects for Ten Pairs of Enantiomers

Matthias Laska and Peter Teubner

Institut für Medizinische Psychologie, Ludwig-Maximilians-Universität München, Goethestraße 31, D-80336 München, Germany

Correspondence to be sent to: Matthias Laska, Institut für Medizinische Psychologie, Ludwig-Maximilians-Universität, Goethestraße 31, D-80336 München, Germany. e-mail: Laska@imp.med.uni-muenchen.de

Abstract

We tested the ability of human subjects to distinguish between enantiomers, i.e. odorants which are identical except for chirality. In a forced-choice triangular test procedure 20 subjects were repeatedly presented with 10 enantiomeric odor pairs and asked to identify the bottle containing the odd stimulus. We found (i) that as a group, the subjects were only able to significantly discriminate the optical isomers of α -pinene, carvone and limonene, whereas they failed to distinguish between the (+)- and (–)-forms of menthol, fenchone, rose oxide, camphor, α -terpineol, β -citronellol and 2-butanol; (ii) marked individual differences in discrimination performance, ranging from subjects who were able to significantly discriminate between 6 of the 10 odor pairs to subjects who failed to do so with 9 of the 10 tasks; (iii) that with none of the 10 odor pairs were the antipodes reported to differ significantly in subjective intensity when presented at equal concentrations; and (iv) that error rates were quite stable and did not differ significantly between sessions, and thus, we observed a lack of learning or training effects. Additional tests of the degree of trigeminality and threshold measurements of the optical isomers of α -pinene, carvone and limonene suggest that the discriminability of these three enantiomeric odor pairs is indeed due to differences in odor quality. These findings support the assumption that enantioselective molecular odor receptors may only exist for some but not all volatile enantiomers and thus that chiral recognition of odorants may not be a general phenomenon but is restricted to some substances.

Introduction

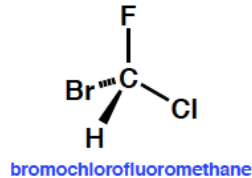
Chiral recognition of substances, i.e. the ability to distinguish a molecular structure from its mirror image, is one of the most important and widespread principles of biological activity (Holmstedt *et al.*, 1990). Discrepant enantiomer effects are well-established, with numerous examples in drug effectiveness (e.g. Caldwell, 1996), taste perception (e.g. Siertsema *et al.*, 1998) and insect chemical communication (e.g. Silverstein, 1979).

The first molecular event in odor perception is the interaction of an odorant with a receptor. As olfactory receptors have been identified as proteins, i.e. chiral molecules (Buck and Axel, 1991; Hildebrand and Shepherd, 1997), this interaction should also be enantioselective, meaning that odor

Chiral recognition

The stereocenter

A tetrahedral carbon with four different substituents is called a **stereocenter** (some texts call this a “chiral carbon” but we will generally use stereocenter). A stereocenter has the property that permuting (i.e., exchanging) any two substituents results in a new stereoisomer. For example, if the hydrogen and bromine of bromochlorofluoromethane are exchanged, is an isomer produced? A stereoisomer? If so, what kind of stereoisomer?

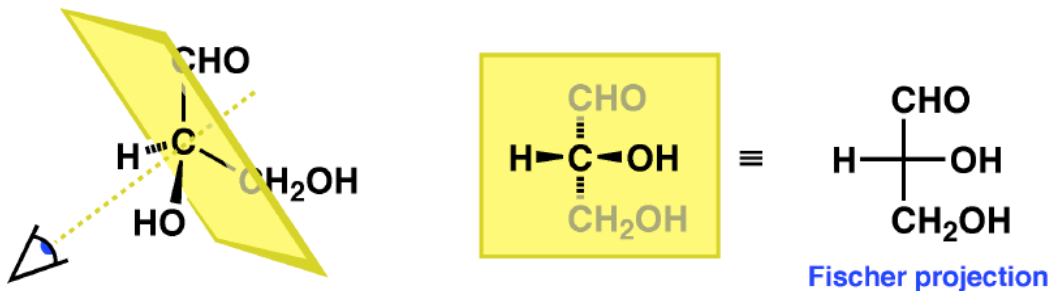


Permute -H and -Br.
What does this generate?



The Fischer projection

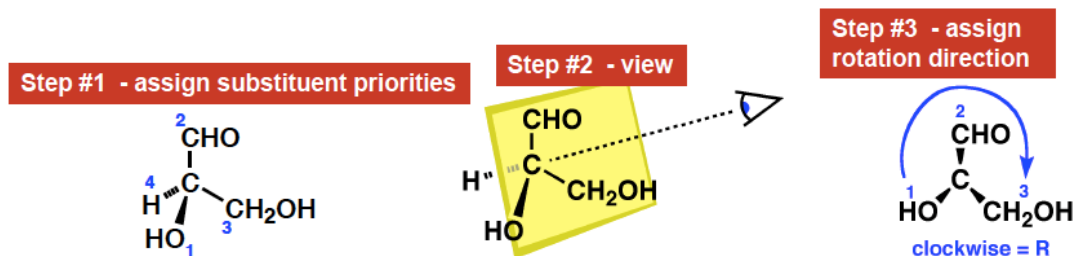
The Fischer projection is a shortcut way to draw structures possessing stereocenters. The Fischer projection represents each stereocenter as a perpendicular pair of crossing lines. In the Fischer projection, the carbon chain is oriented vertically. The stereocenter's substituents are positioned to the left and right projecting above the plane of the page. The drawings below show the relationship between the 3D structure and the 2D drawing that is used for the Fischer projection.



Stereochemical Descriptors

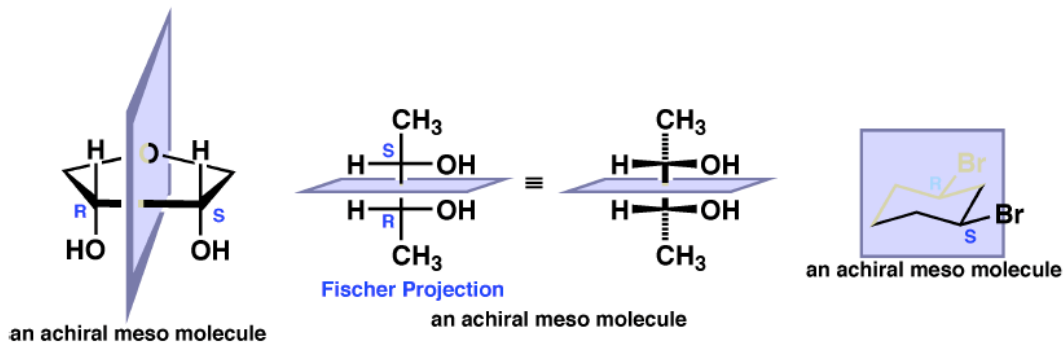
1. The higher the atomic number, the higher the priority. (Different isotopes of the same element are assigned a priority according to their atomic mass.)
2. If two substituents have the same immediate substituent atom, evaluate atoms progressively further away from the stereocenter until a difference is found.
3. If double or triple bonded groups are encountered, they are treated as an equivalent set of single-bonded atom.

The configuration of stereocenters can be assigned a designation known as an R,S-descriptor. To do the assignment manually, you first assign priority to the four different substituents according to the rules below. To complete the process, it is very helpful to make a physical model. Orient the structure about the stereocenter so that the substituent of lowest priority is directed to the back of the plane of the page. You should be staring at three substituents that are oriented toward you. Starting from the highest priority substituent, move to the second highest then the third highest. If the direction you traced was clockwise, the stereocenter is assigned the R-descriptor. If the direction you traced was counterclockwise, the stereocenter is assigned the S-descriptor.



Structures having more than one stereocenter

If a structure contains more than one stereocenter, it may or may not be chiral. Meso molecules are achiral structures that have stereocenters. Finding a plane of symmetry in a structure that possesses stereocenters is one way to identify meso molecules. Any conformation of the molecule in which there is a plane of symmetry renders it an achiral structure. Note that if you assign R,S-descriptors to the stereocenters of a meso molecule, you will find that stereocenters on opposite sides of the plane have opposite configuration. The examples below illustrate this point.

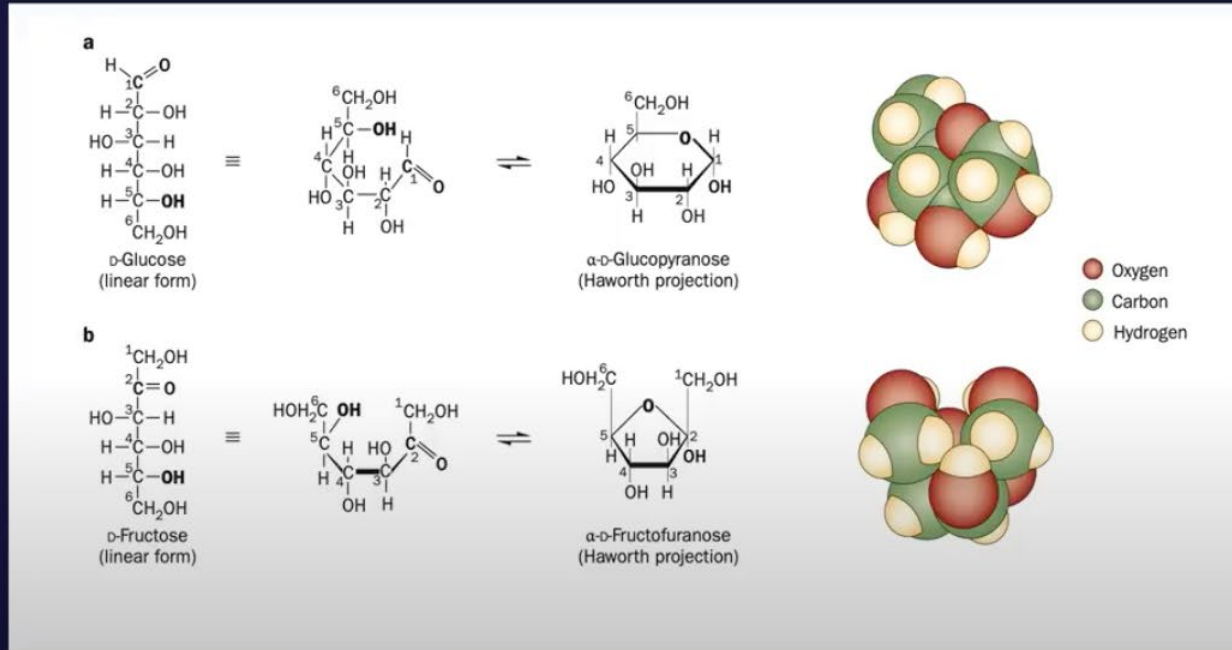


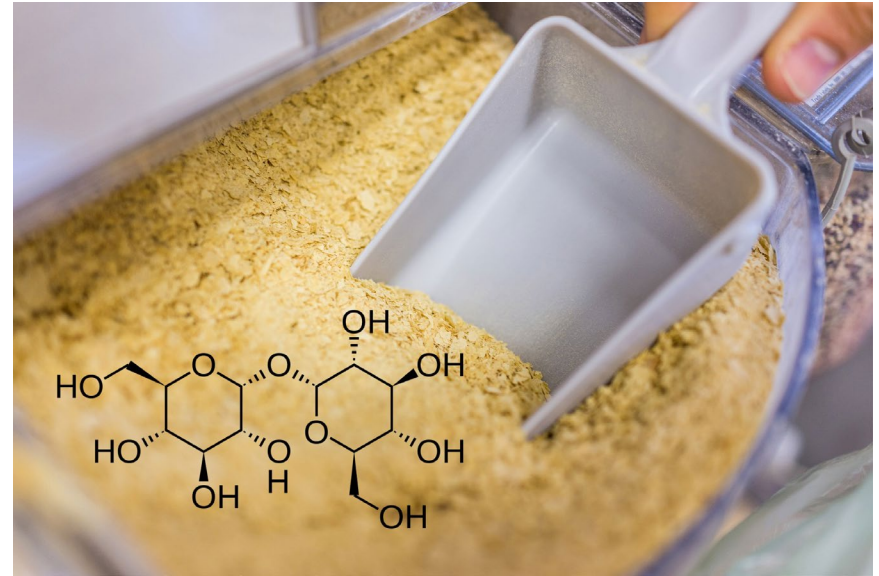
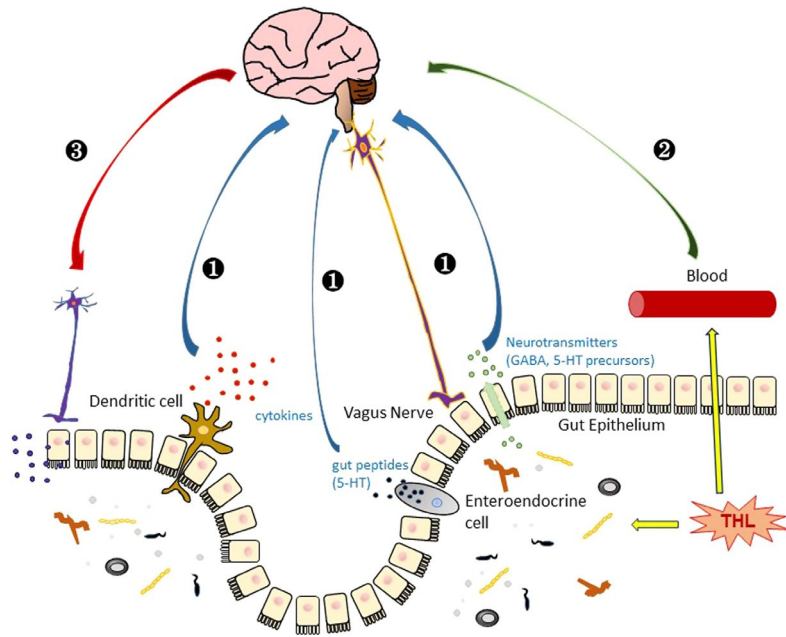
Drawing conventions

1. Molecules have three-dimensional shapes. We need conventions to represent their three-dimensional structures on paper.
2. A heavy or bold bond indicates that the substituent is pointing toward you, out of the plane of the paper. A hashed bond indicates that a substituent is pointing away from you, behind the plane of the paper. Sometimes a dashed line is used for the same purpose as a hashed line, but most chemists use a dashed line to represent a partial bond (e.g., for transition states).
3. A squiggly or wavy line indicates that there is a mixture of both stereochemistries at that stereocenter (i.e., that the substituent is pointing toward you in some fraction of the sample, and away from you in the other fraction).
4. A plain line is used when the stereochemistry at a configuration is irrelevant. If a compound has only one stereocenter, and the compound is racemic, it's better not to indicate stereochemistry.
5. If a compound has two stereocenters, and only a single diastereomer is to be represented, the configuration at both stereocenters must be defined (but either enantiomer can be drawn if this compound is a racemic mixture).



The furan ring of fructose is more unstable, so at equilibrium, fructose exists in the linear form





Neuroprotection by trehalose

Cell Death & Disease 9, 712 (2018)