Stereo-Isomers in Pesticides

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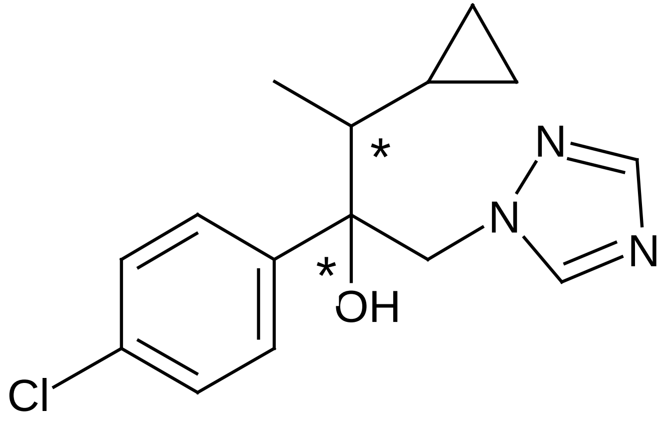
Outline

- Relevance of Stereo-Isomers for Pesticides
- Regulatory Evaluation of Pesticides
- Introduction to Stereo-Isomerism
  - Enantiomers
  - Diastereomers
- Relevance for Evaluation of Pesticides

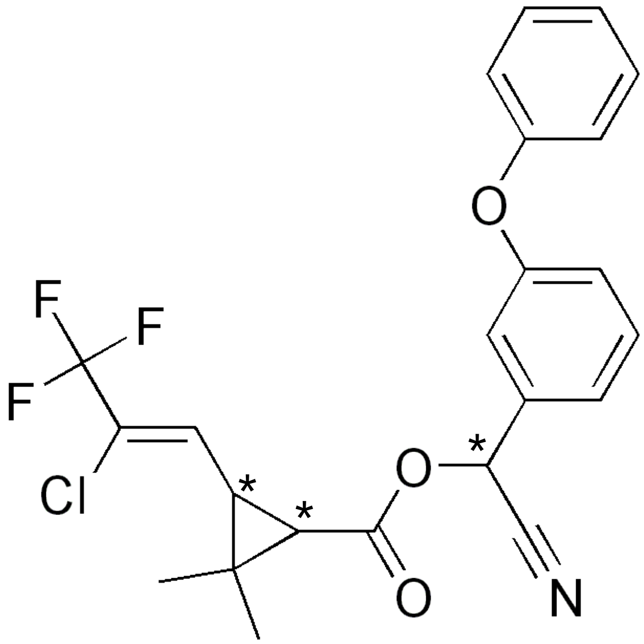
Relevance of Stereo-Isomers for Pesticides

Many CP Chemicals show stereo-isomerism:

Cyproconazole (fungicide)



Cyhalothrin (insecticide)



* Chiral centers

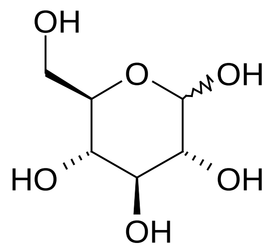
Relevance of Stereo-Isomers for Pesticides

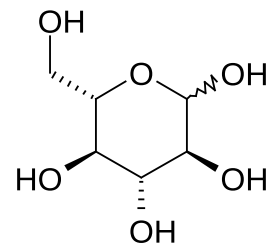
- Approximately 32% of the pesticides registered in the UK contain one or more chiral centers - DEFRA project PS2501
- Large majority of them are produced via achiral synthesis => 1:1 ratio of the enantiomers
- Only minority is produced enantio-selectively. Examples of enantio-enriched pesticides:
    - Metalaxyl–M
    - S-Metalachlor
    - Fluazifop-p–butyl
    - S-Methoprene

Stereo-Isomerism Makes a Big Difference

- Glucose

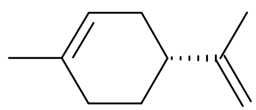
D = diabetes

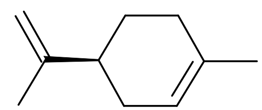




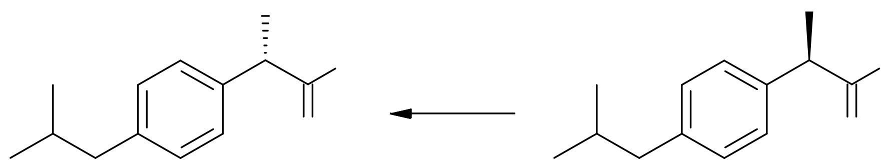
L = laxative

- Limonene





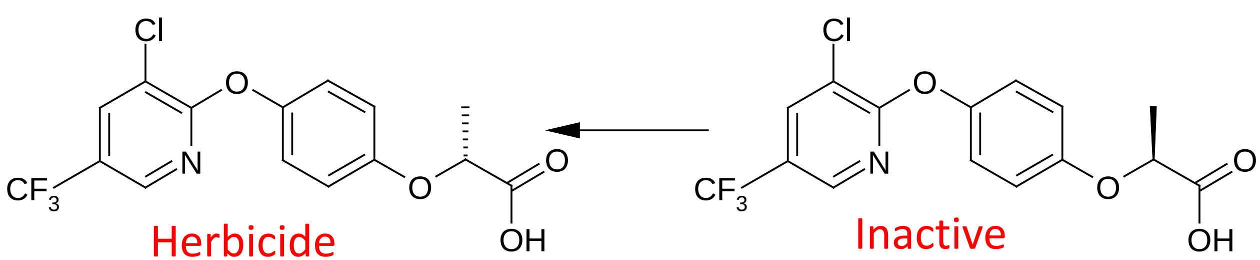
- Ibuprofen



Analgesic

Inactive

- Haloxyfop



Herbicide

Inactive

Regulatory Evaluation of Pesticides

Aspects to be considered when evaluating such chemicals:

- Product Chemistry (physical and chemical properties)
- Toxicology
- Eco-toxicology
- Animal Metabolism
- Plant Metabolism
- Residues
- Environmental Fate
  - Biological degradation
  - Chemical and photochemical degradation

Interaction of pesticides with biological systems

Interaction of pesticides in abiotic systems

Message to Take Home for Product Chemistry

- Abiotic world does not discriminate between molecules that are mirror-images! This is in contrast to biological systems.
  => No discrimination of molecules that are mirror-images of each other.
- If the pesticide is synthesised in a way that does not discriminate between mirror-images, they are formed in equal amounts (1:1 ratio).
  => No scientific justification to ask to experimentally demonstrate the ratio being 1:1.
  => No scientific justification to ask for an analytical method that separates these mirror-images or for experimentally demonstrating that the storage stability is the same for both mirror-images!

Outline

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  - Enantiomers
  - Diastereomers
- Relevance for Evaluation of Pesticides

Constitutional Isomers

Isomers with a different connectivity (which atom is bonded to which atom)

e.g. C_4H_{10}

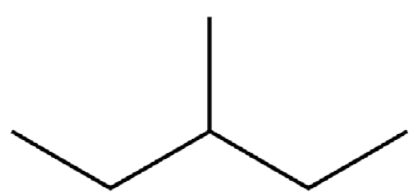
$CH_3CH_2CH_2CH_3$

n-butane

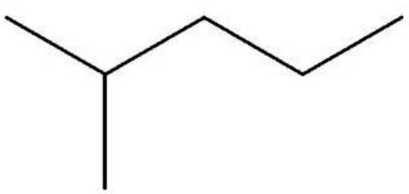
$$\begin{array}{c} \quad CH_3 \\ \quad | \\ CH_3CHCH_3 \end{array}$$

isobutane

e.g. C_6H_{14}



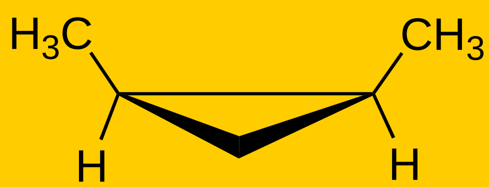
3-methylpentane



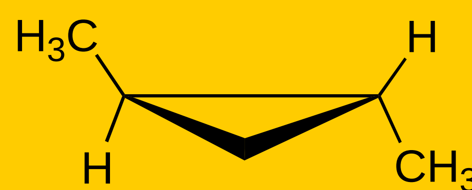
2-methylpentane

Stereo-Isomers

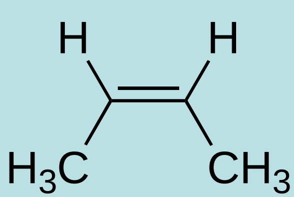
Isomers with the same connectivity but a different orientation of their atoms in space



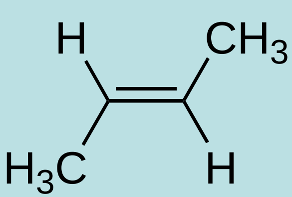
cis-1,2-dimethylcyclopropane



trans-1,2-dimethylcyclopropane

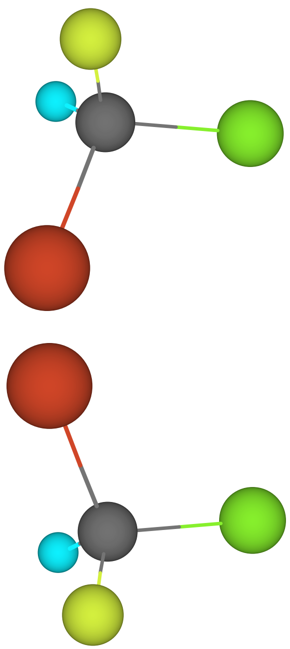


cis-2-butene



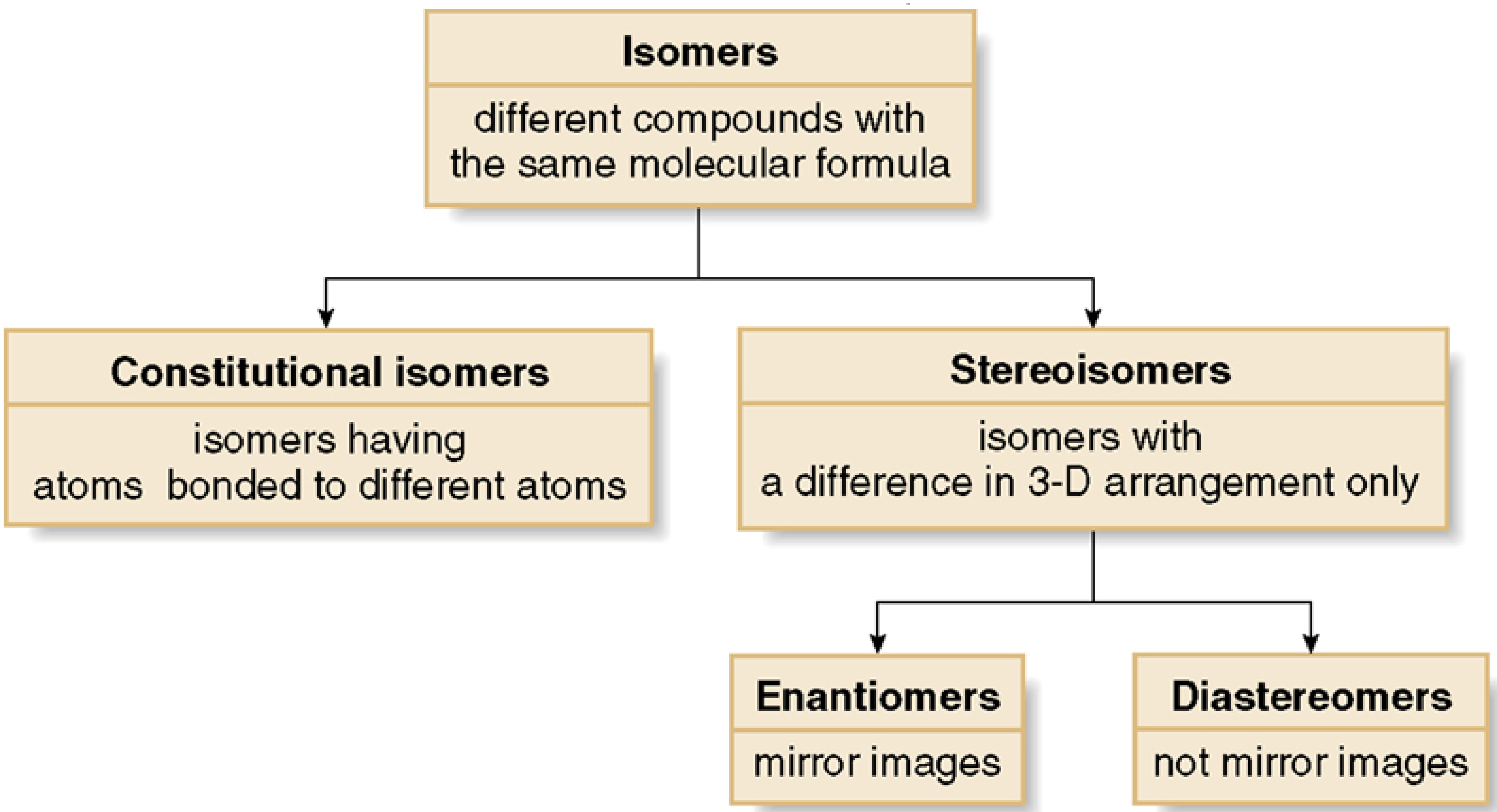
trans-2-butene

Some atom to atom distances differ when considering distances among **all** atoms!



All distances the same!

Isomers and Stereo-Isomers



Chirality

- Chiral: from the Greek, *cheir*, hand
  - an object that is not superposable on its mirror image
- Achiral: an object that is superposable on its mirror image
  - an achiral object has at least one element of symmetry:
  - plane of symmetry: an imaginary plane passing through an object dividing it so that one half is the mirror image of the other half
  - center of symmetry: a point so situated that identical components are located on opposite sides and equidistant from that point along the axis passing through it

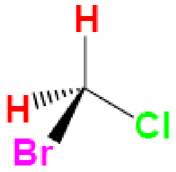
Chiral Center

- The most common (but not the only) cause of chirality in organic molecules is a tetrahedral atom, most commonly carbon, bonded to four different groups.
- A carbon with four different groups bonded to it is called a chiral center. All chiral centers are stereo-centers.
- Enantiomers: Stereo-isomers that are non-superposable mirror images.
  - This is a relationship between <u>pairs</u> of objects

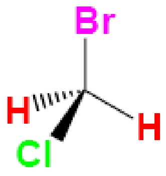
Enantiomers

Let's consider some molecules……

First pair



A

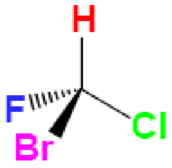


B

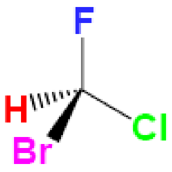
- same molecular formula (CH_2BrCl)
- same atom connectivity
- superposable

➡ **identical (same compound)**

Second pair



C



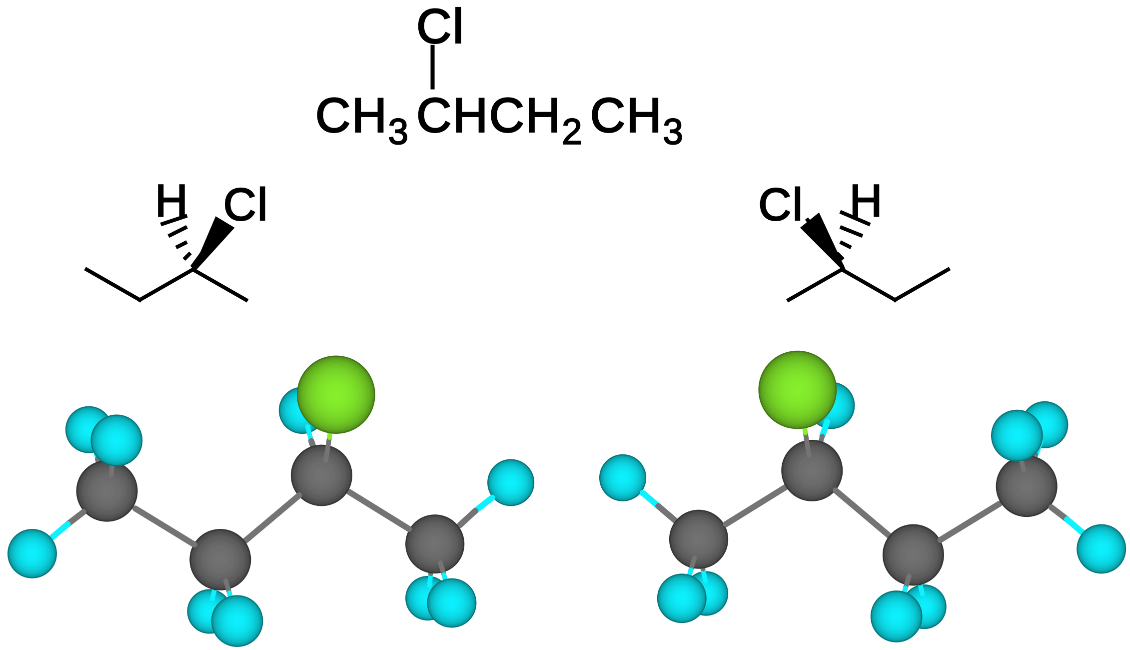
D

- same molecular formula (CHFBrCl)
- same atom connectivity
- nonsuperposable

➡ **stereoisomers (two different compounds)**

Enantiomers

2-Chlorobutane



Enantiomers

- The physical properties of enantiomers in an **achiral environment** are identical: Melting point, boiling point, solubility in water or organic solvent, vapour pressure, chromato-graphic behaviour (e.g. retention time) in conventional (achiral) chromatography.
- The chemical properties of enantiomers in an **achiral environment** are identical: E.g. reaction kinetics and thermodynamics. If enantiomers are formed, the ratio will be 1:1.

Achiral Environment: Environment that only contains achiral substances and, if present, equal amounts of enantiomers (1:1 ratio).

Enantiomers

- An equal amount of two enantiomers is called a racemic mixture or racemate.
- The physical properties of enantiomers in an achiral environment are identical – but not necessarily the same as of the racemate!

Property	**100% A**	**100% B**	**Racemate (50%A + 50%B)**
Melting Point	Same as 100% B	Same as 100% A	May be different to A or B
Boiling Point	Same as 100% B	Same as 100% A	May be different to A or B
Achiral (usual) Chromatography	Same as A or B or racemate	Same as A or B or racemate	Same as A or B or racemate
Chiral Chromatography	1 peak, different retention time than B, but same peak area	1 peak, different retention time than A, but same peak area	2 peaks (one for A and one for B), peak area 50% each

Insertion - Symmetry for Physicists

- Parity is conserved in gravity, electromagnetism, and strong interaction.
- But parity is violated in weak interaction (e.g. beta decay in cobalt-60).
- Quantum electrodynamics allows an excellent qualitative and quantitative description of chemistry (physics of the electron shell).
- The impact of the weak interaction is very minimal
- Parity-violating energy differences are estimated to be $<< 10^{-11}$ J mol^{-1} ($<< 10^{-16}$ eV) in enantiomers of chiral molecules.

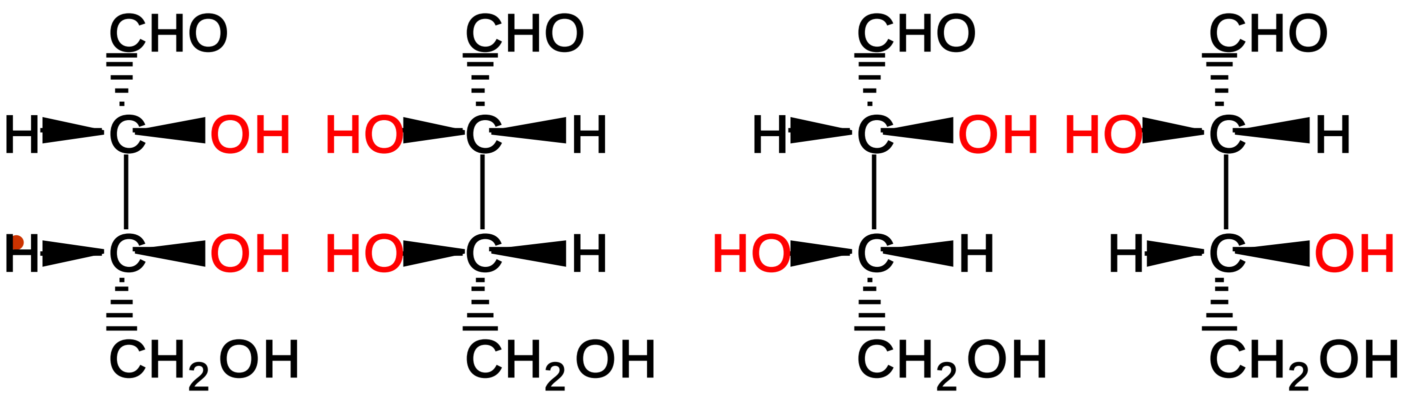
=> Completely negligible for any practical purposes!

Enantiomers & Diastereomers

- For a molecule with 1 chiral center, $2^1 = 2$ stereo-isomers are possible
- For a molecule with 2 chiral centers, a maximum of $2^2 = 4$ stereo-isomers are possible
- For a molecule with *n* chiral centers, a maximum of 2^n stereo-isomers are possible

Enantiomers & Diastereomers

- Example: 2,3,4-Trihydroxybutanal
  - two chiral centers
  - 2^2 = 4 stereo-isomers exist; two pairs of enantiomers

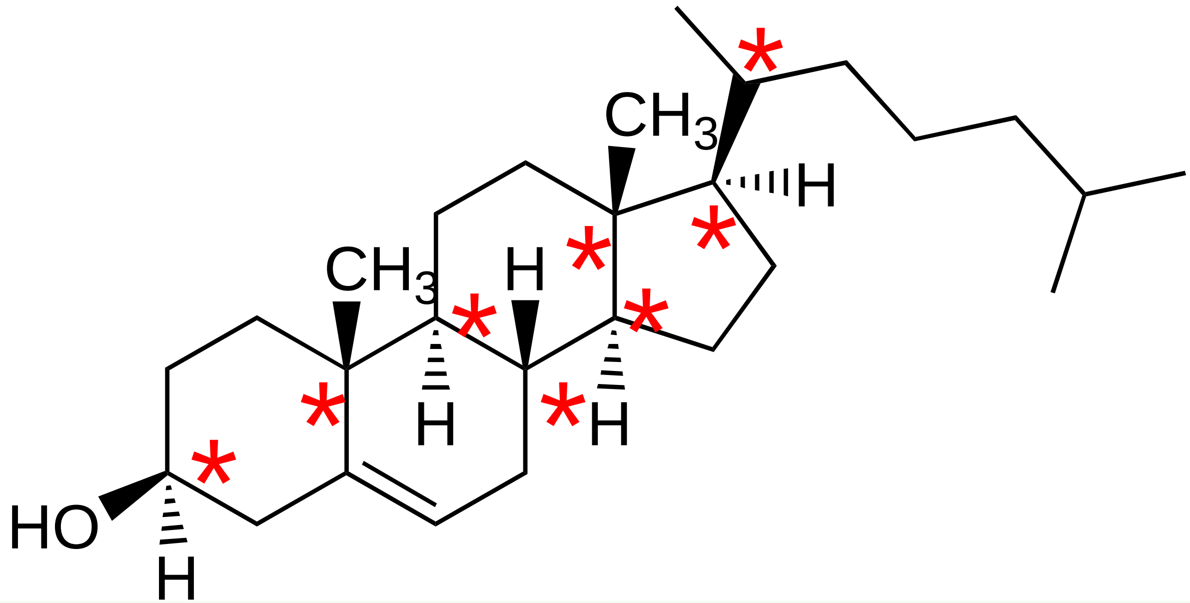


A pair of enantiomers (Erythreose) A pair of enantiomers (Threose)

- Diastereomers:
  - Stereo-isomers that are not mirror images
  - refers to the relationship among two or more objects

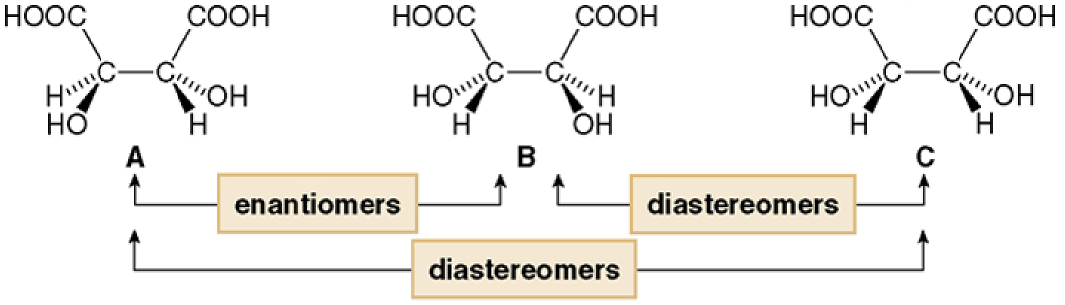
Enantiomers & Diastereomers

- For a molecule with *n* chiral centers, a maximum of 2^n stereo-isomers are possible: E.g. Cholesterol: eight chiral centers, $2^8 = 256$ possible stereo-isomers (only one of which is naturally occurring; this is typical of substances occurring in biology)



Enantiomers & Diastereomers

- Enantiomers have identical physical and chemical properties in achiral environments (see examples above)
- Diastereomers have different physical and chemical properties and can be separated by common physical techniques. In high resolution chromatography, they usually elute at different times.



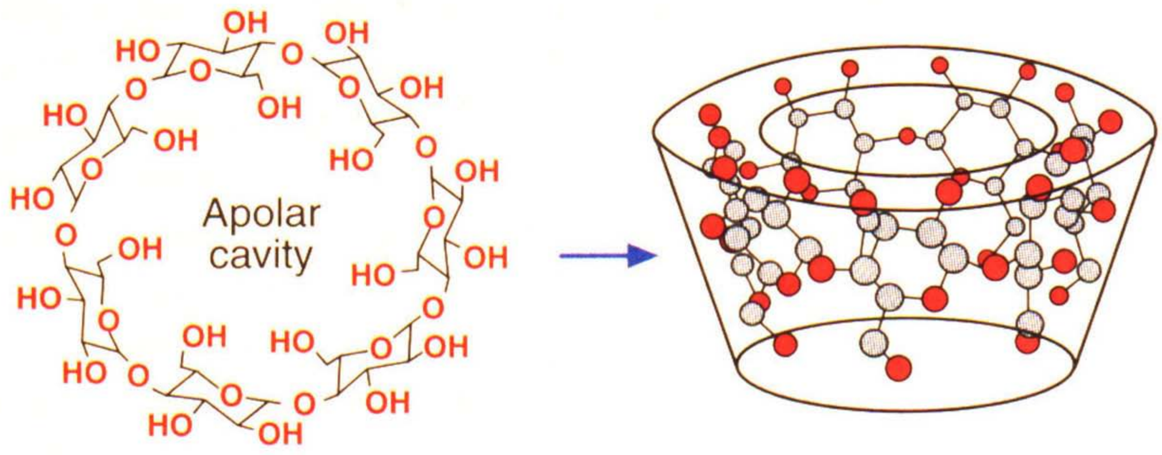
Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139

Separation of Enantiomers (part 1)

- In an achiral environment enantiomers have identical physical and chemical properties.
- Thus, enantiomers cannot be separated by common physical techniques like distillation.
- If separation is wanted, a chiral element must be introduced. Two approaches are common:
  - Chromatography where the stationary or mobile phase is chiral or
  - Conversion of the enantiomers by a chemical reaction with a single enantiomer into diastereomers. Diastereomers have different physical properties and therefore can be separated by conventional techniques (e.g. distillation, crystallization)

Separation of Enantiomers (part 1)

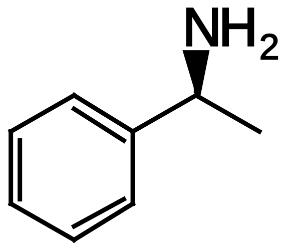
- Chromatographic separation (usually very expensive):
  - Chiral component in the mobile or stationary phase (e.g. cyclodextrines = cyclic sugars)



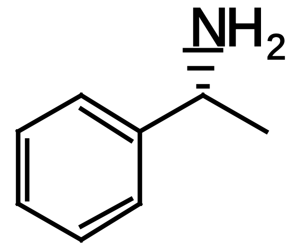
Enantiomers spend a different amount of time in the chiral cavity. Thus, they will elute at different times from the column!

Separation of Enantiomers (part 2)

- Chemical conversion of the enantiomers into diastereomers:
  - racemic acids can be separated using commercially available enantio-pure chiral bases such as

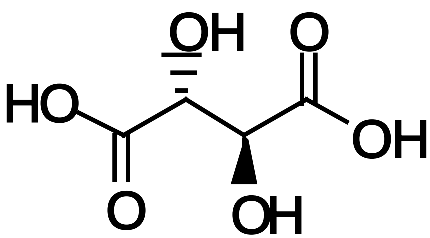


(*S*)-1-Phenylethanamine

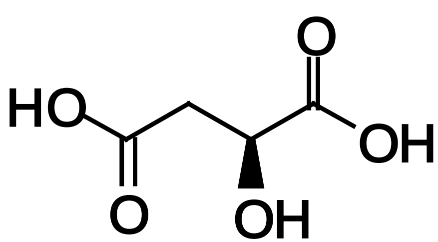


(*R*)-1-Phenylethanamine

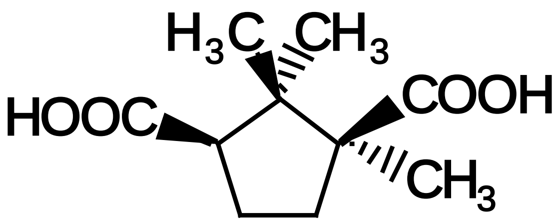
  - racemic bases can be separated using commercially available enantio-pure chiral acids such as



(2*R*,3*R*)-(+)-Tartaric acid



(S)-(-)-Malic acid



(1S,3R)-(+)-Camphoric acid

Chirality in Our World

- The abiotic world is essentially achiral. Most common abiotic (and achiral) molecules are, e.g. H_2O, O_2, N_2, and inorganic salts like NaCl, carbonates, phosphates, sulphates.

- The biological world is always chiral: Peptides, proteins, sugars, nucleotides are all chiral molecules where only one of the two enantiomers exists! They never exist as racemates!

Chirality in the Biological World

- Consider chymotrypsin, a protein-digesting enzyme in the digestive system of animals
  - Chymotrypsin contains 251 chiral centers
  - The maximum number of stereo-isomers possible is 2^{251}
  - There are “only” 2^{38} stars in our galaxy!
  - Only one stereo-isomer exists in animals!

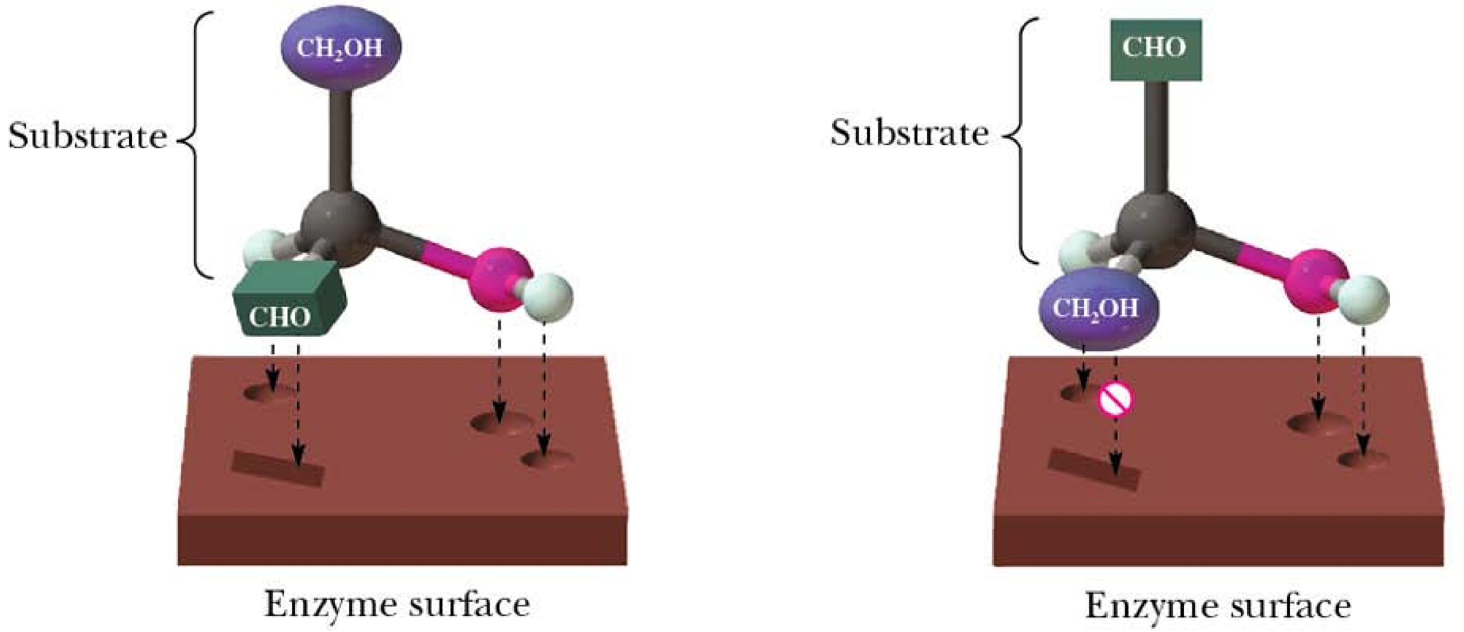
Chirality in the Biological World

Enzymes are like hands in a handshake

- the substrate fits into a binding site on the enzyme surface
- a left-handed molecule will only fit into a left-handed binding site and
- a right-handed molecule will only fit into a right-handed binding site
- enantiomers have different physiological properties because of the handedness of their interactions with other chiral molecules in living systems

Chirality in the Biological World

A schematic diagram of an enzyme surface capable of binding with one enantiomer but not with the other



This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface.

This enantiomer of glyceraldehyde does not fit the same binding sites.

So What?

- In the abiotic world there is no discrimination of enantiomers.
  => If they are formed, they are formed in equal amounts. If they decompose, they do it at the same speed (the 1:1 ratio remains) and producing the same decomposition products (also 1:1, if chiral).
- In the biological world there is usually a discrimination between enantiomers.
  => If they are formed, they are not formed in equal amounts. If they decompose, they often do not decompose at the same rate.

Recall Markus Müller‘s presentations in the past!

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    - Enantiomers
    - Diastereomers
- Relevance for Evaluation of Pesticides

Relevance for Evaluation of Pesticides

- Achiral syntheses are usually cheaper.
  Two approaches to get enantio-enriched substances:
  - Chiral separation (see above). This additional purification step makes enantio-enriched substances more expensive
  - Use of enantio-pure chemicals from biological origin. Up to now only in rare cases (e.g. use of lactic acid) they are cheaper than the chemically synthesised racemates.
- Thus, the majority of pesticides are still synthesised in an achiral way, leading to racemates.
- If there is more than one chiral center, the technical active substance will normally also contain a number of diastereomers, with varying relative amounts.

In evaluating pesticides all stereo-isomers present in significant amounts ought to be taken into consideration!

Relevance for Evaluation of Pesticides

- Pesticides are supposed to interact with biological systems (plants and animals). Thus, it can be expected that enantiomers (and also diastereomers) behave differently.
  => This needs to be considered when evaluating pesticides with respect to toxicology, eco-toxicology, plant and animal metabolism and environmental fate in biological systems.

Regulatory Evaluation of Pesticides

Aspects to be considered when evaluating such chemicals:

- Product Chemistry (physical and chemical properties)
- Toxicology
- Eco-toxicology
- Animal Metabolism
- Plant Metabolism
- Residues
- Environmental Fate
  - Biological degradation
  - Chemical and photochemical degradation

Interaction of pesticides with biological systems

Interaction of pesticides in abiotic systems

Implication for Product Chemistry?

- Abiotic world is achiral
  => No discrimination of molecules that are mirror-images of each other.
  => If the pesticide is synthesised in a achiral environment, the enantiomers are formed in equal amounts (1:1 ratio, racemate).
  => No scientific justification to ask to experimentally demonstrate the ratio being 1:1.
  => No scientific justification to ask for an analytical method that separates enantiomers or for experimentally demonstrating that the storage stability is the same for both enantiomers!
- But asking such data for diastereomers is scientifically justifiable!

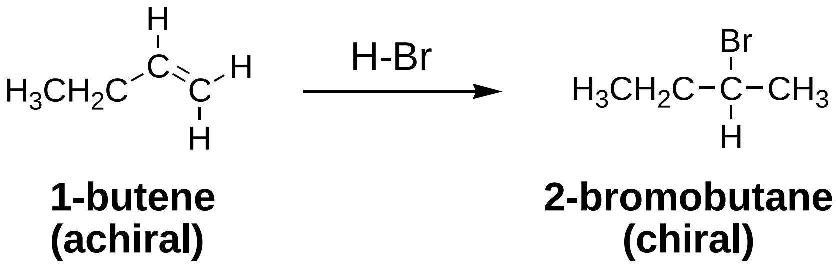
Thanks for your patience!

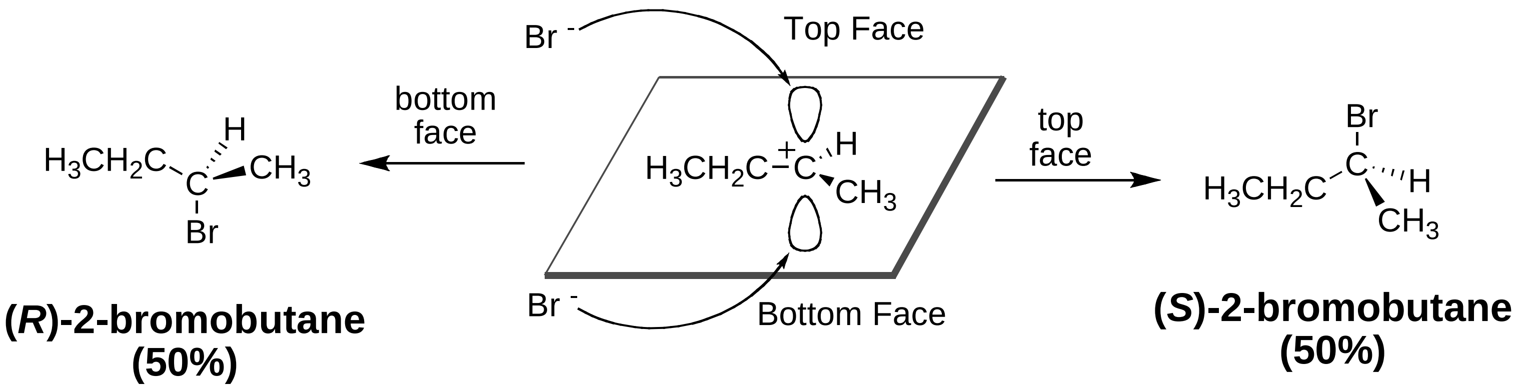
Any questions or comments?

Back-Up

Enantiomers – Chemical Reactions that Create a Chiral Center

Achiral reactants may generate products with chiral centers:





There is an equal chance for Br^- to add from the top face or the bottom face resulting in a 50:50 mixture (racemate).