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Files, Medicine and Life

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Exciting Science

24th March 2013



nd its basic elements

What is life?

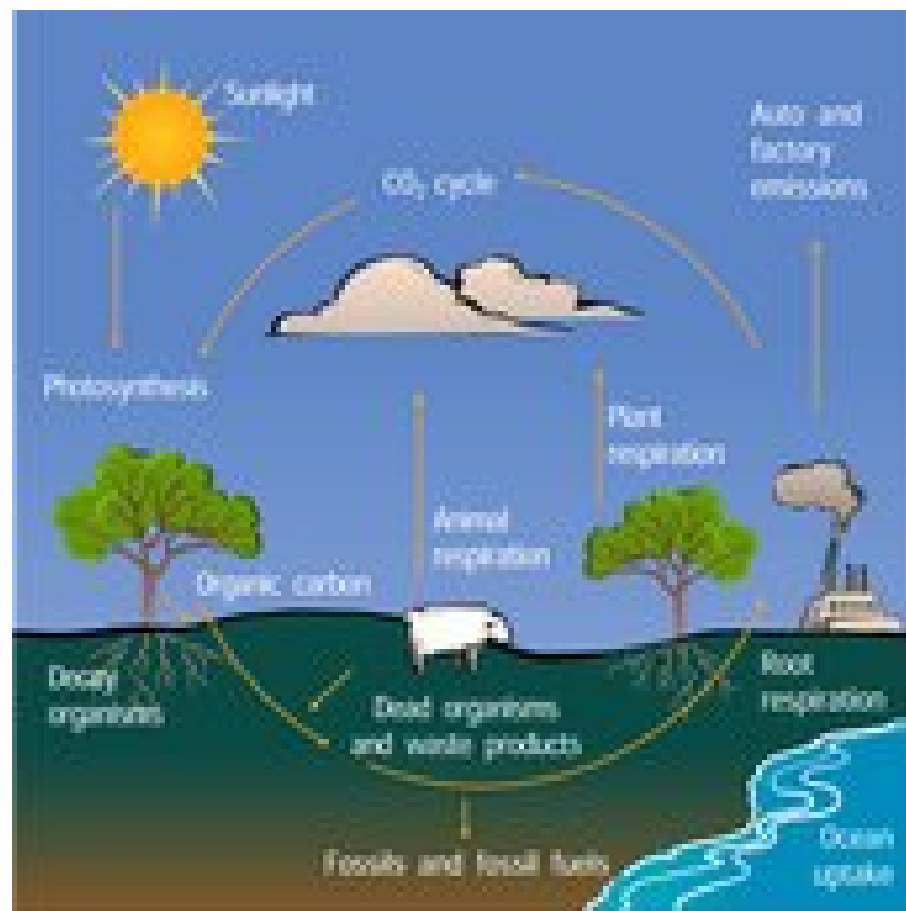
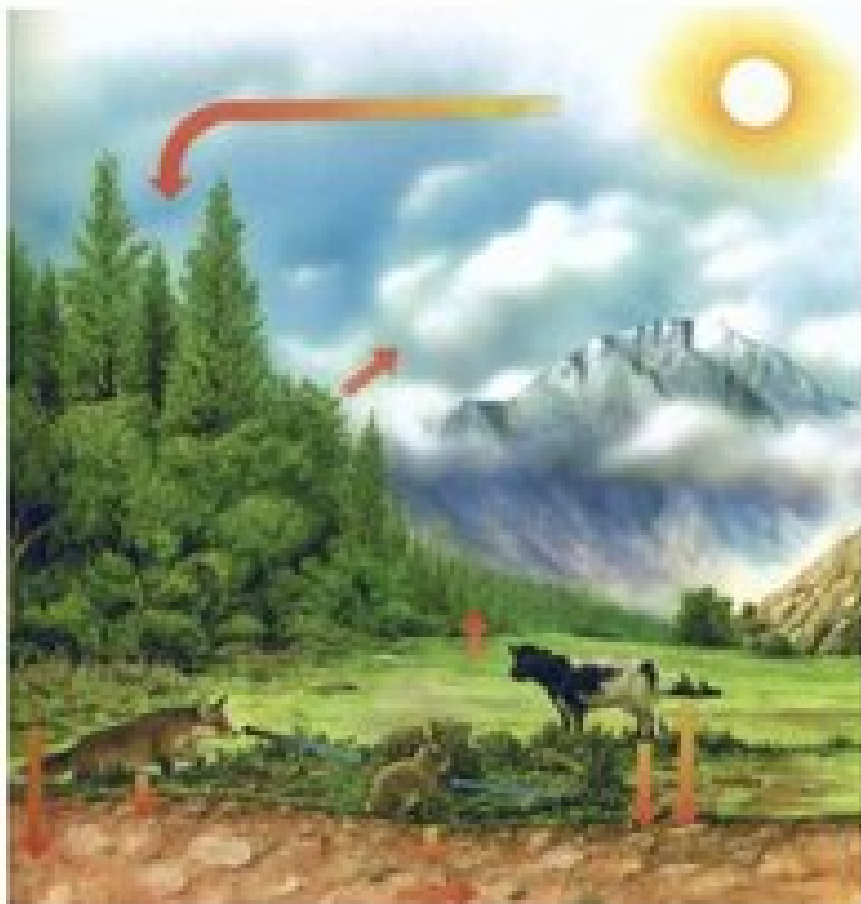
What are we made of? What is our surrounding made of?

Atoms....Molecules....most interestingly, molecules with
carbon.



Molecules: The Backbone of Life

Carbon is preserved in nature via the carbon cycle



The idea that organic compounds arise only in organisms, was disproved when chemists synthesized these compounds

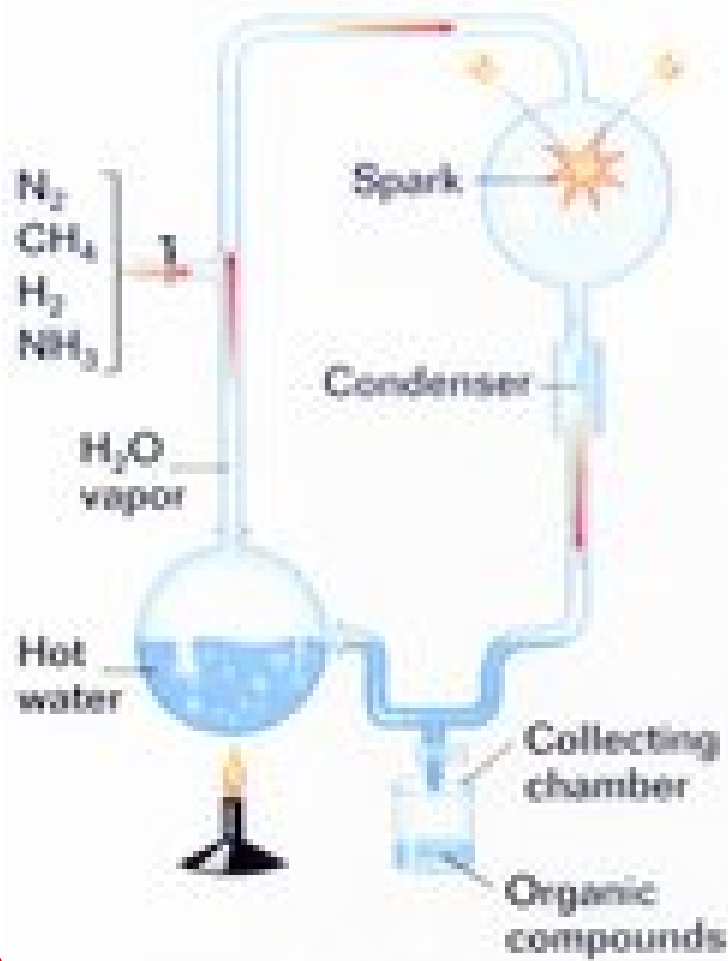
Miller Experiments: Clues to Origin of Life on Earth



Dr. Stanley L. Miller as a 20-year-old graduate student in 1951.

Stanley Miller, 1953

Chemistry graduate student at University of Chicago



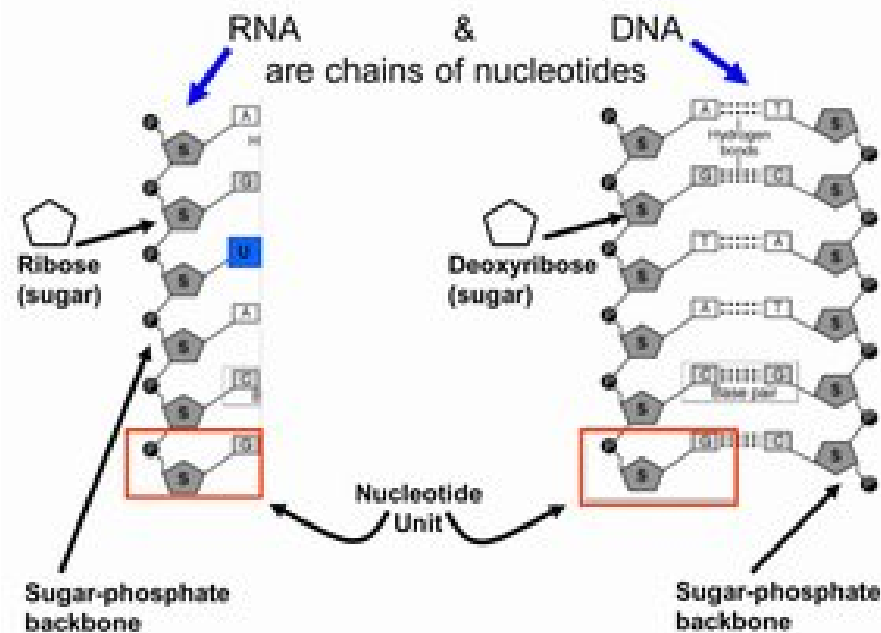
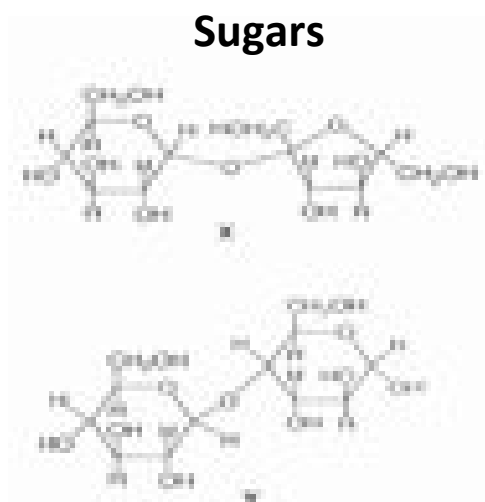
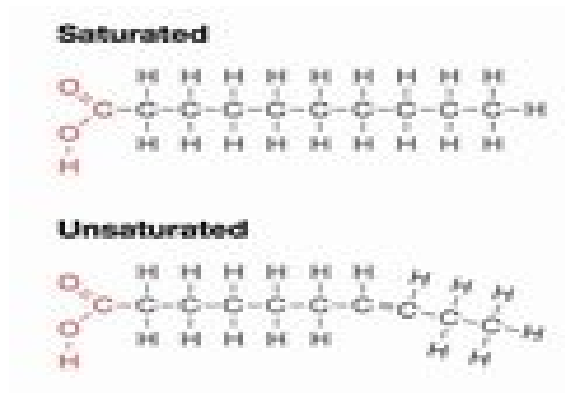
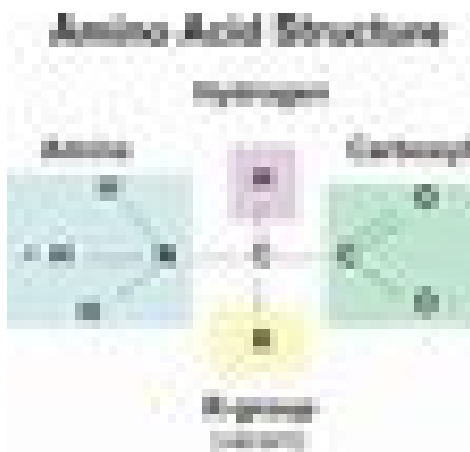
Miller's classic experiment demonstrated the abiotic synthesis of organic compounds

Experiments support the idea that abiotic synthesis of organic compounds, perhaps near volcanoes, could have been a stage in the origin of life

Adapted from "A Production of Amino Acids under Possible Primitive Earth Conditions," Stanley L. Miller, *Science*, Vol. 117, (May 15, 1953), pp. 528-529.

Miller Found....

Biological Molecules Involved In the Origin of Life





What was common among themThese were all composed of



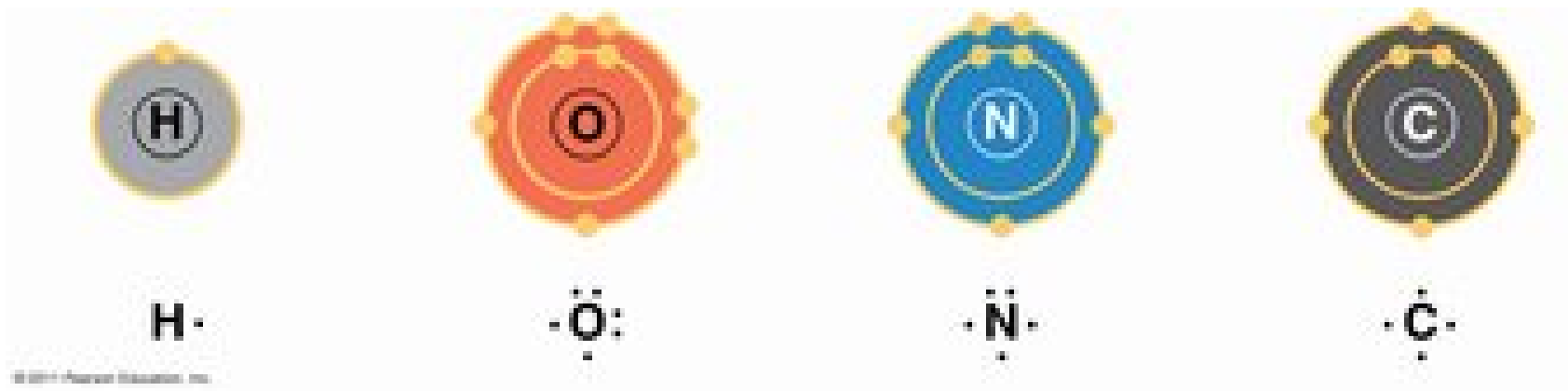
Protein, DNA, carbohydrates, and other molecules that distinguish living matter are all composed of carbon compounds

Basically all natural or organic molecules are just arrangement of elements around Carbon!



Carbon's Ability to Form Bonds

- “ With four valence electrons, carbon can form four covalent bonds with a variety of atoms: This ability makes large, complex molecules possible
- “ In molecules with multiple carbons, each carbon bonded to four other atoms has a tetrahedral shape
- “ However, when two carbon atoms are joined by a double bond, the atoms joined to the carbons are in the same plane as the carbons
- “ The electron configuration of carbon gives it covalent compatibility with many different elements
- “ The valences of carbon and its most frequent partners (hydrogen, oxygen, and nitrogen) are the “building code” that governs the architecture of living molecules

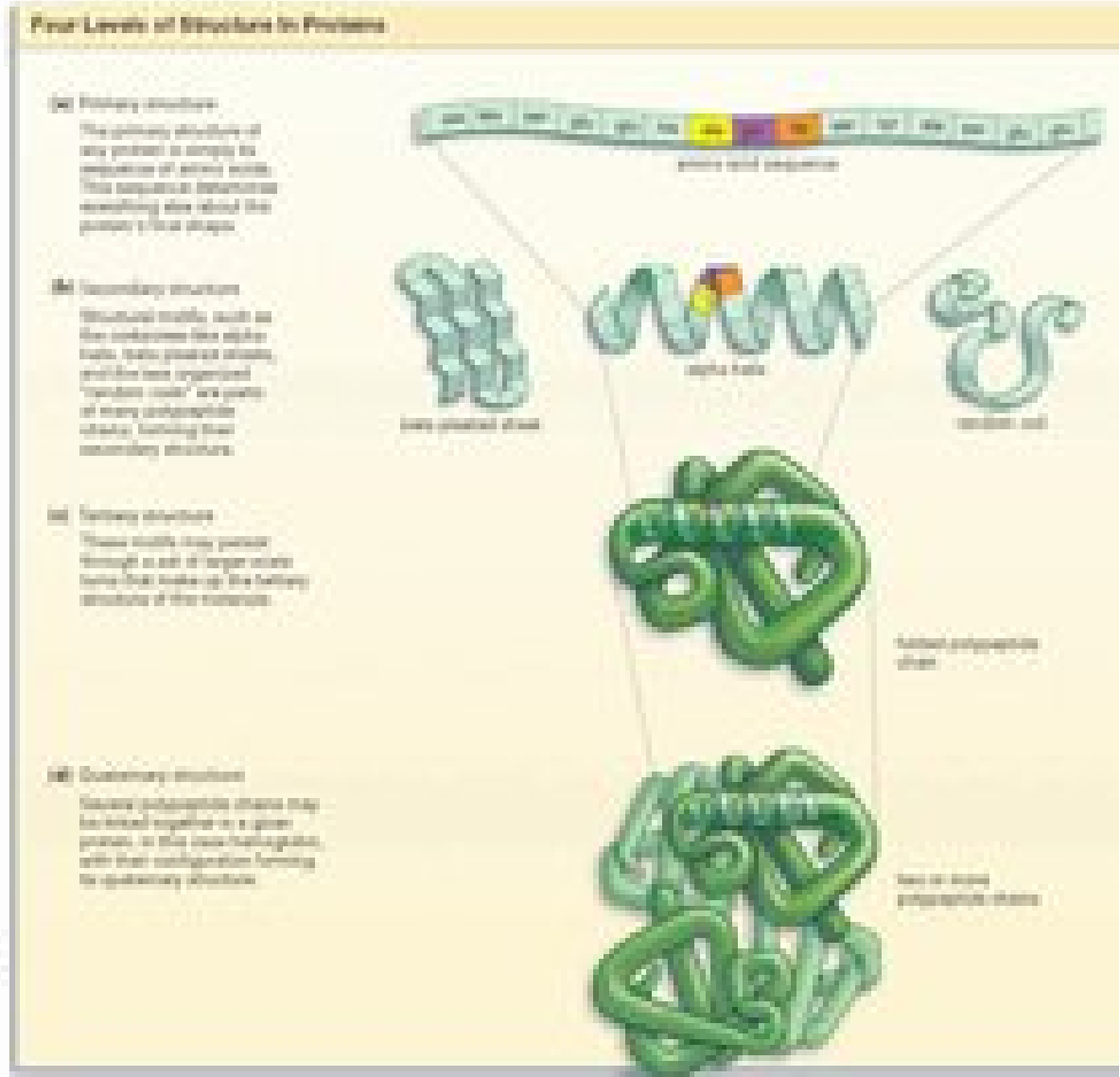
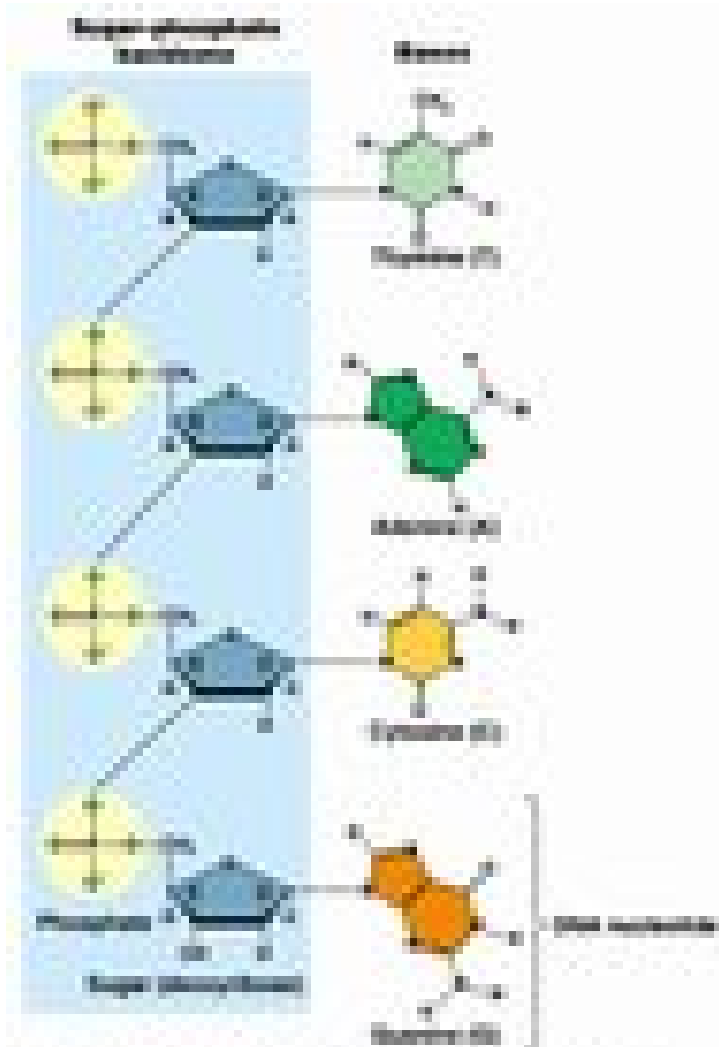




But...with these carbon based molecules,
how does nature perform complex
processes and that too with specificity?
(Remember Enzymes and its specificity?)

Don't we need many molecules then to
perform all the processes?

Small Molecules: Possesses Specificity



Source: Campbell Biology, 11th Edition, © 2012 Pearson Education, Inc. All rights reserved.

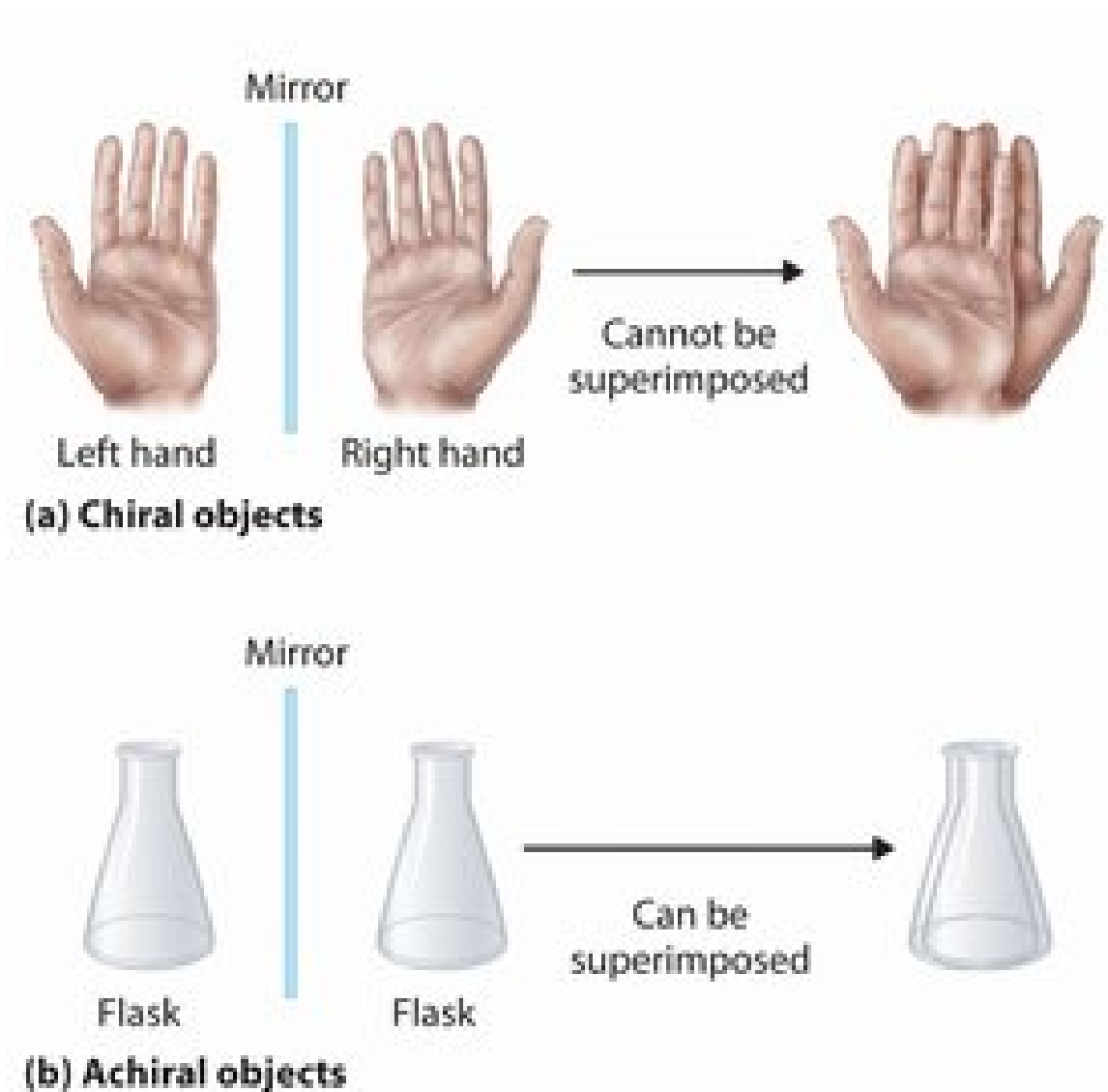
Strategy for Reducing the Number of Molecules



Make them in pairs!

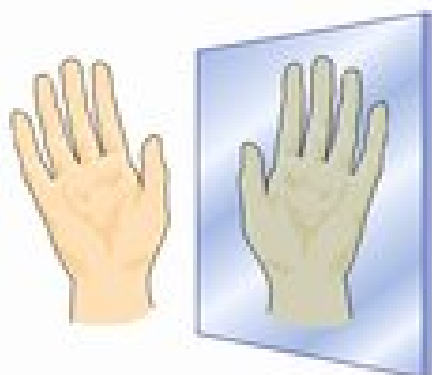
They are not the same...they are mirror images

Images : Chirality or Handedness

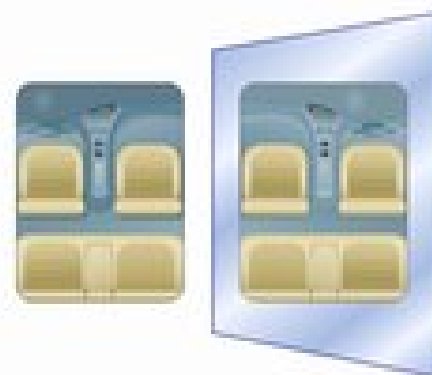
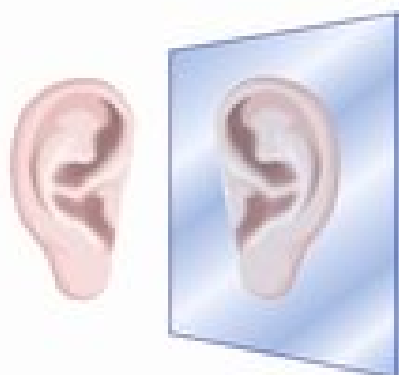


Some More Examples.....

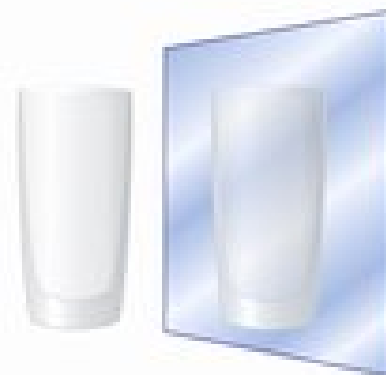
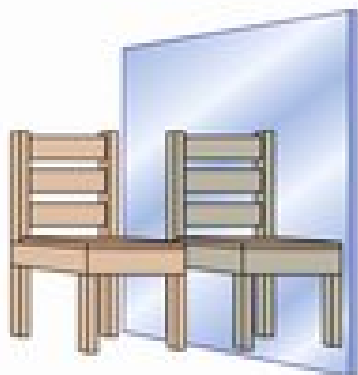
chiral objects



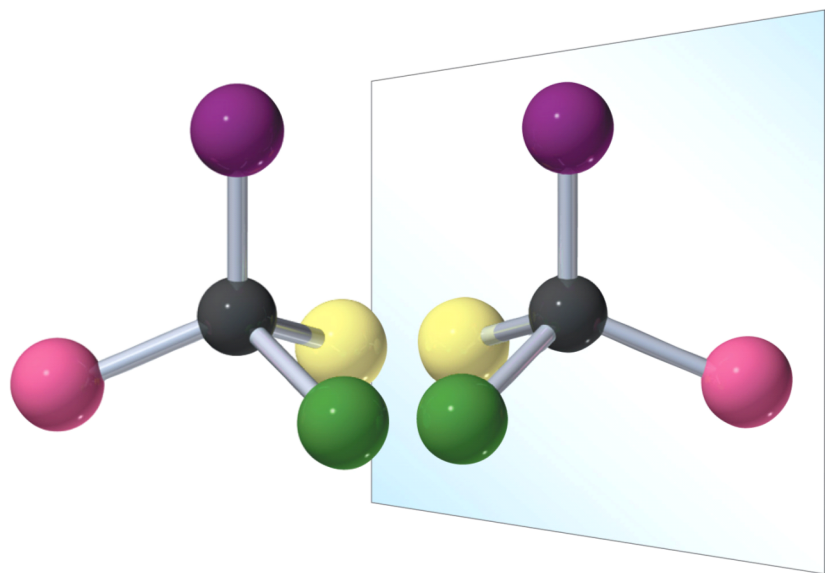
right hand left hand



achiral objects



Chirality In Organic Molecules



nonsuperimposable mirror images



The geometric property of a molecule being **non-superimposable** on its mirror image; **non-superimposable** is **not** being able to place over or something.

Enantioselectivity in Biological Molecules Derives from Chirality



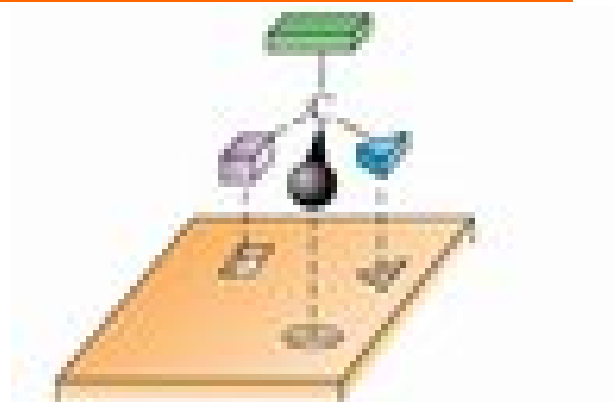
y in Nature Due to Chirality



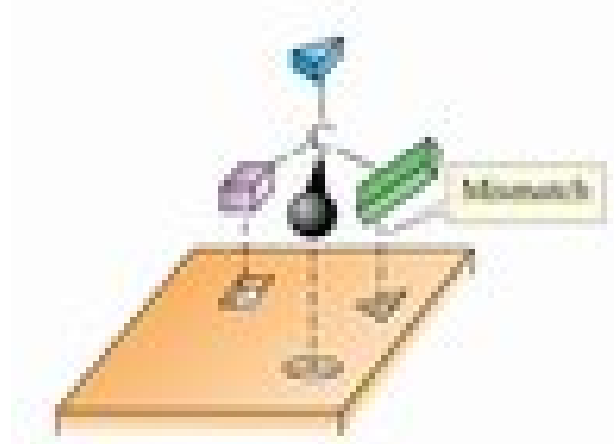
Just Like Hands and Gloves!

Molecules can Distinguish Between Enantiomers: Enzymes

On the above model, a chiral reactant binding to a chiral reactant site where everything fits into place.



On the next model however, the enantiomer of the reactant below will not bind to the enzyme, so it will not react.



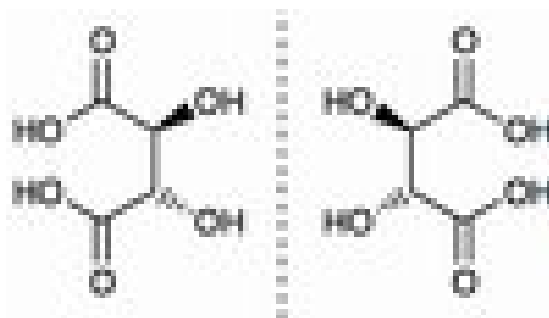
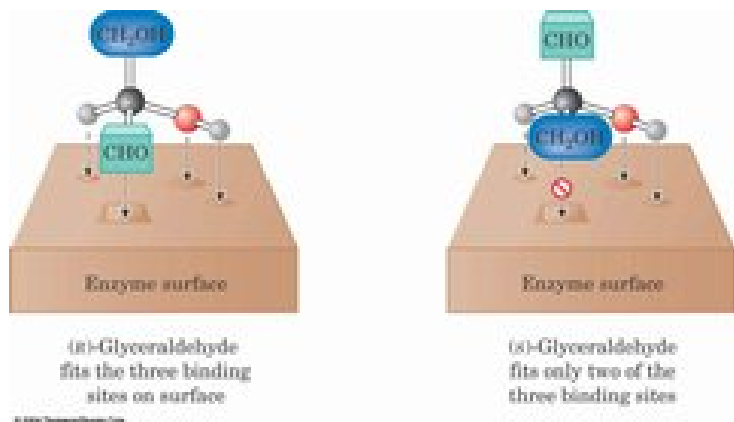
This leads to substrate specificity

Enzymes: Enzyme catalyses only one reaction type (reaction specificity) and operates on only one type of **substrate**.

Natural Requirement For Chirality

A molecule that has a non-identical mirror image, which does not contain a plane of symmetry, is said to be **chiral**. The pair of molecules are called **enantiomers**.

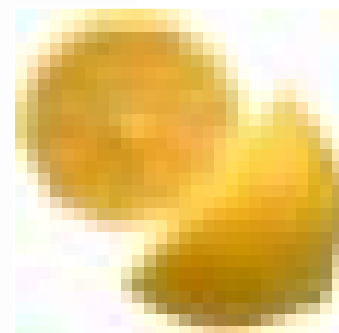
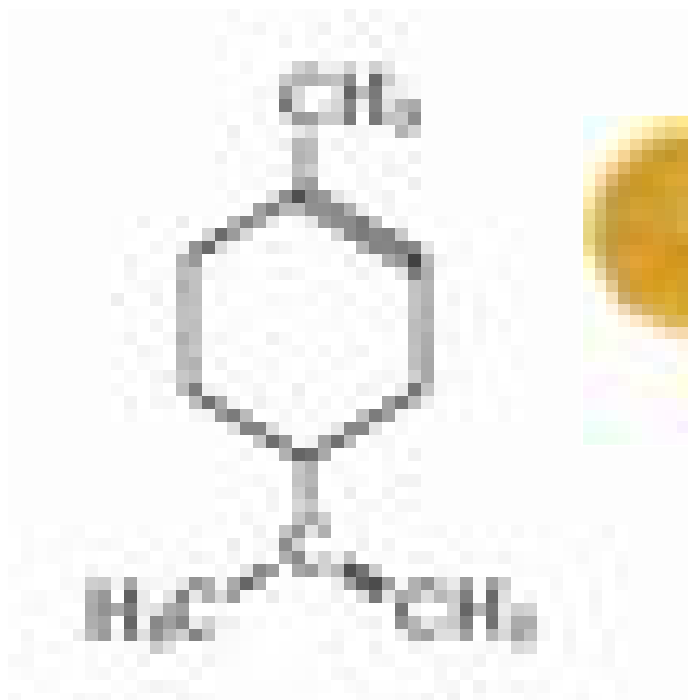
When an atom has four non-equivalent atoms or groups attached to it, this is termed as the **chirality center**.



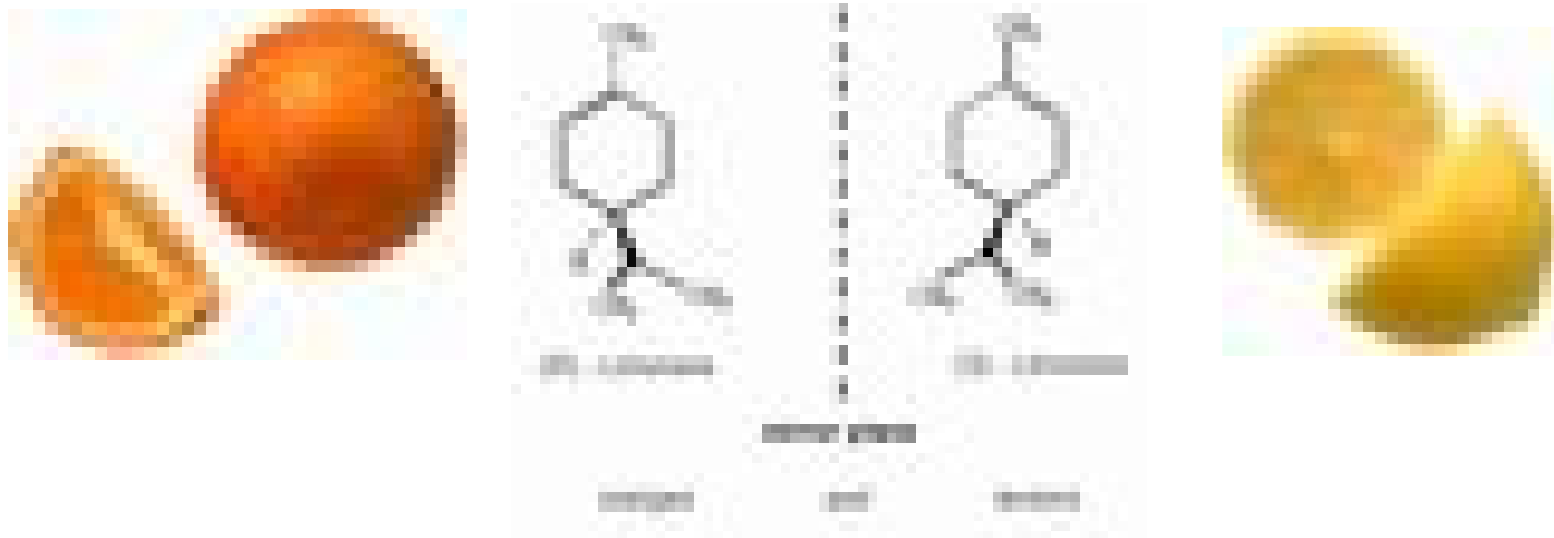
Louis Pasteur



Are Lemon and Oranges the same?



Isomers of Limonenes Behave Differently



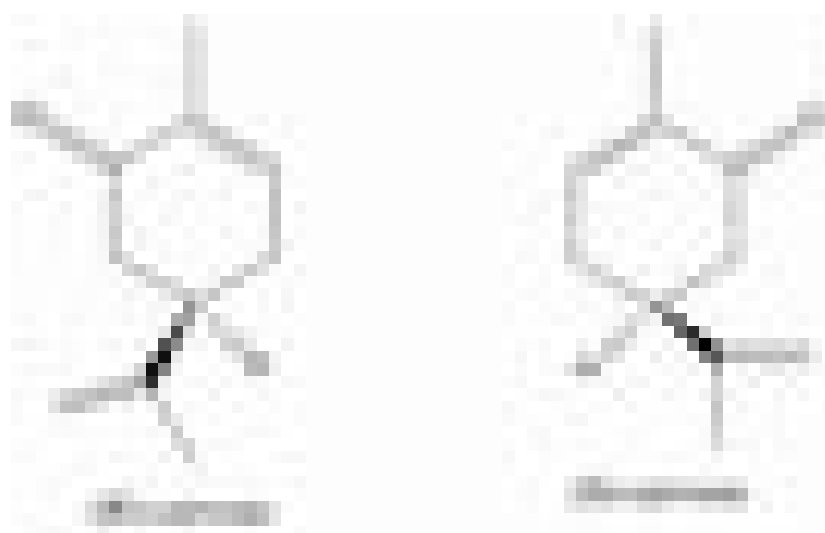
- Oranges contain the left-handed molecule, and lemons, the right-handed.
- The same way your left foot fits only your left shoe, these molecules fit only into the appropriate left or right-handed receptors in your nose.
- This is how the same molecule can cause the orange and the lemon to have different smells.

Effects on Odors: Why Do Lemons and Oranges Smell Differently?

- The affect of chirality on bioactivity★ results in a variation in odor.
 - Each enantiomer has a different 3-D fit on odor receptors in the nose.
 - This phenomenon of specificity is not unlike that of enzyme- substrate relations.
 - The influence of this characteristic not only effects the specific odor, but also intensity of odor.
- ★Note: Bioactivity is defined as: The effect of a given agent, such as a vaccine, upon a living organism or on living tissue.



Enantiomers give different response



Spearmint

Caraway seed

Carvone is a ketone that can be found in caraway dill and spearmint oils.

These oils are used for flavoring liqueurs and in perfumes and soaps.

(S)-carvone is a molecule with a caraway-like odor, while its mirror image molecule, (R)-carvone has a spearmint odor.

Response of Biochemical Reaction

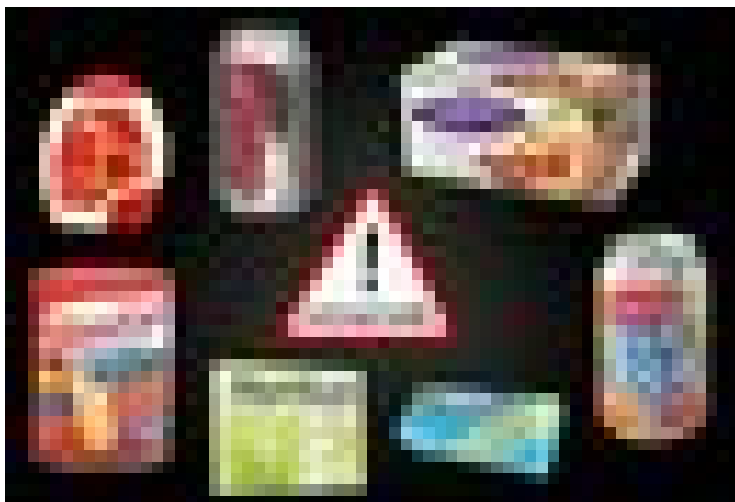
The major components of the food we eat have amino acids, proteins, carbohydrates, triacylglycerols and some vitamins, are all chiral.

This has a major impact on the perceived taste.

Chiral compounds can even be used to determine a products age and whether or not the food is of natural or synthetic origin.



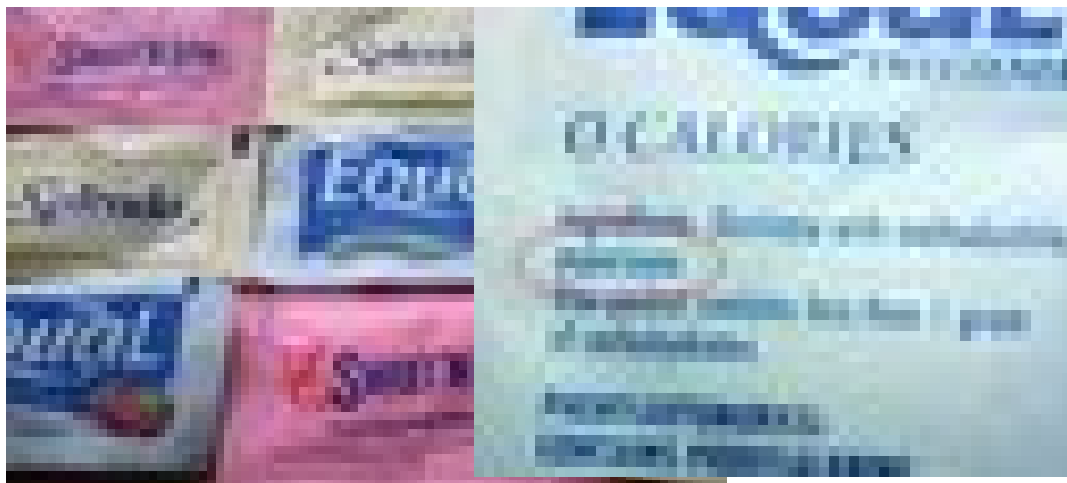
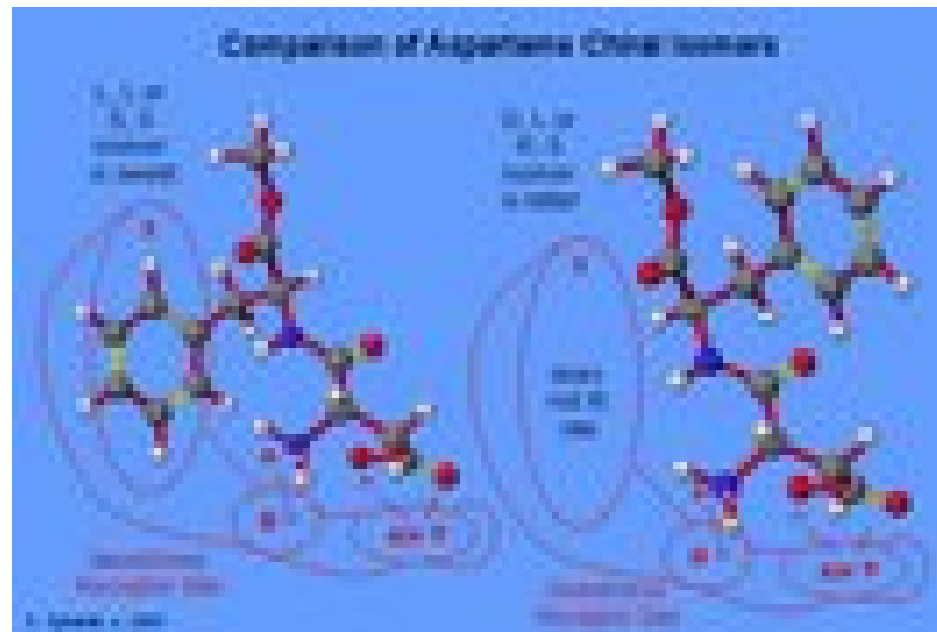
Aspartame: A low Calorie Sweetener



Aspartame is a sugar substitute composed of aspartic acid and phenylalanine.

Found in [Equal](#) and Nutrasweet, aspartame is very low in calories compared to sucrose (table sugar).

Although it is 100-200x sweeter than sugar, its stereoisomer is bitter.





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Chirality and Pharmaceutical Drugs

Most drugs derived from natural sources are chiral and are almost always obtained as a single enantiomer whereas approximately 80% of synthesized drugs are composed of a 50:50 racemic mixture.

Receptors and enzymes in the body are very stereo selective and only react with one of the enantiomers of a chiral molecule in a process called chiral recognition

As a result, one enantiomer has the desired effect on the body, while the other may have no effect or an adverse effect.



Effect of Enantiomers: Pharmaceutical

Both enantiomers exhibit similar therapeutic properties (e.g. Promethazine, Flecainide)

Only one isomer shows pharmacological activity (S-propranolol is a beta blocker for **hypertension**) while the other one is inactive (R-propranolol)

One type of isomer may show one type of pharmacological activity (S-penicillamine, **Antiarthritic**) and the other one shows toxicity (R-penicillamine, **Mutagen**)

One type of isomer may show one type of pharmacological activity (R-methylphenylpropyl barbituric acid – anesthetic) and the other type shows a convulsant effect

Thalidomide Case : A Tragedy



Thalidomide

Drug that was used in Europe during the period 1959 – 1962 to combat morning sickness in pregnant women.

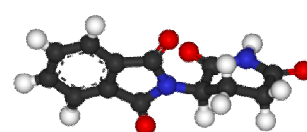
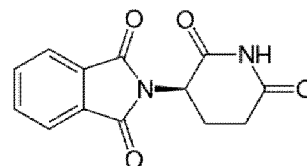
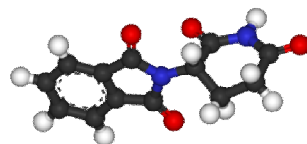
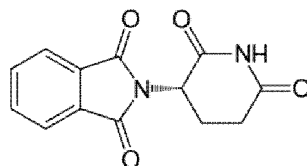
(R) – thalidomide contained the properties that made it useful as a sedative and antinausea drug.

(S) – thalidomide was responsible for many birth defects such as phocomelia.

Even if thalidomide were purified to only the 'R'- isomer, the pH of blood would cause rapid racemization into roughly equal amounts of both isomers.

Thalidomide : After all How Bad It Can Be

S-Thalidomide



R-Thalidomide



Thalidomide Sparked Major Changes for the FDA

Linked to Thalidomide Scandal

'Heroine' of FDA Keeps Bad Drug Off of Market

By [Name]

She is the hero of most of the stories about the thalidomide scandal. She is a woman who has spent her life fighting to keep the drug off the market. She is the heroine of the story.



[Name]

She is the heroine of the story. She is a woman who has spent her life fighting to keep the drug off the market.

The thalidomide scandal was a major event in the history of the FDA. It led to major changes in the way drugs are tested and approved. The FDA now requires more rigorous testing of drugs, especially those that are used during pregnancy.



Chiral Purity is Important

Thalidomide



R-enantiomer
Analgesic (Good)



S-enantiomer
Teratogen (Bad)

Frances Got Prize

“the drug approval process was under considerable criticism, particularly the quality of the scientific data submitted in New Drug Applications and the lack of an efficacy requirement,” according to Kelsey, writing in the 1996 annual report of FDA's Office of Compliance. “The nature and magnitude of the thalidomide disaster,” she wrote, spurred the swift passage of legislation addressing the shortcomings of the 1938 law that had been sitting in Congress before the disaster. Known as Kefauver-Harris Drug Amendments, they were signed into law by President John F. Kennedy in October 1962.”



Recent Chiral Methods

SEPARATION

- “Preparative chiral chromatography
Cheaper despite waste
- “Applicable to most small chiral molecules
- “Crystallization of diastereomeric salts

SELECTIVITY

- “ Chiral pool
- “ A lot of catalysis
- “ Enantioselective processes
- “ Conversion of enantiomers



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