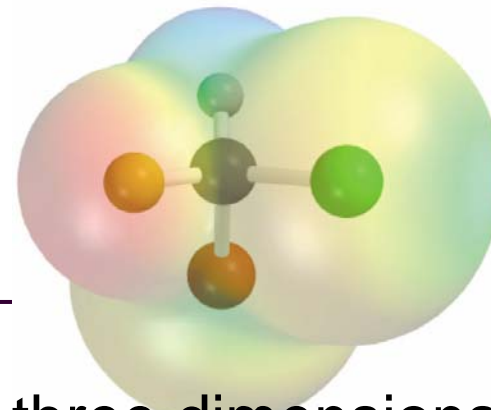




Chapter 7. Stereochemistry

Based on
McGraw Hill's *Organic Chemistry*, 5th edition, Chapter 7

What is Stereochemistry?



- Stereochemistry refers to chemistry in three dimensions.
- Its foundations were laid by Jacobus van't Hoff and Joseph Achille Le Bel in 1874: the four bonds to carbon were directed toward the corners of a tetrahedron.
- **Our major objectives** in this chapter are to develop a feeling for molecules as three dimensional objects and become familiar with stereochemical principles, terms, and notation.

A Brief Review of Isomerism

Constitutional isomer

(同分子式, 原子结合次序不同)

C骨架异构
位置异构
功能基异构
互变异构

Stereoisomer

(同分子式/同原子连接次序,
不同的空间排列方式)

Configuration
构型

Conformation
构象

Enantiomers
(mirror-image)
对映异构 (光学异构)

Diastereomers
(non mirror-image)
非对映异构
(如: cis, trans)

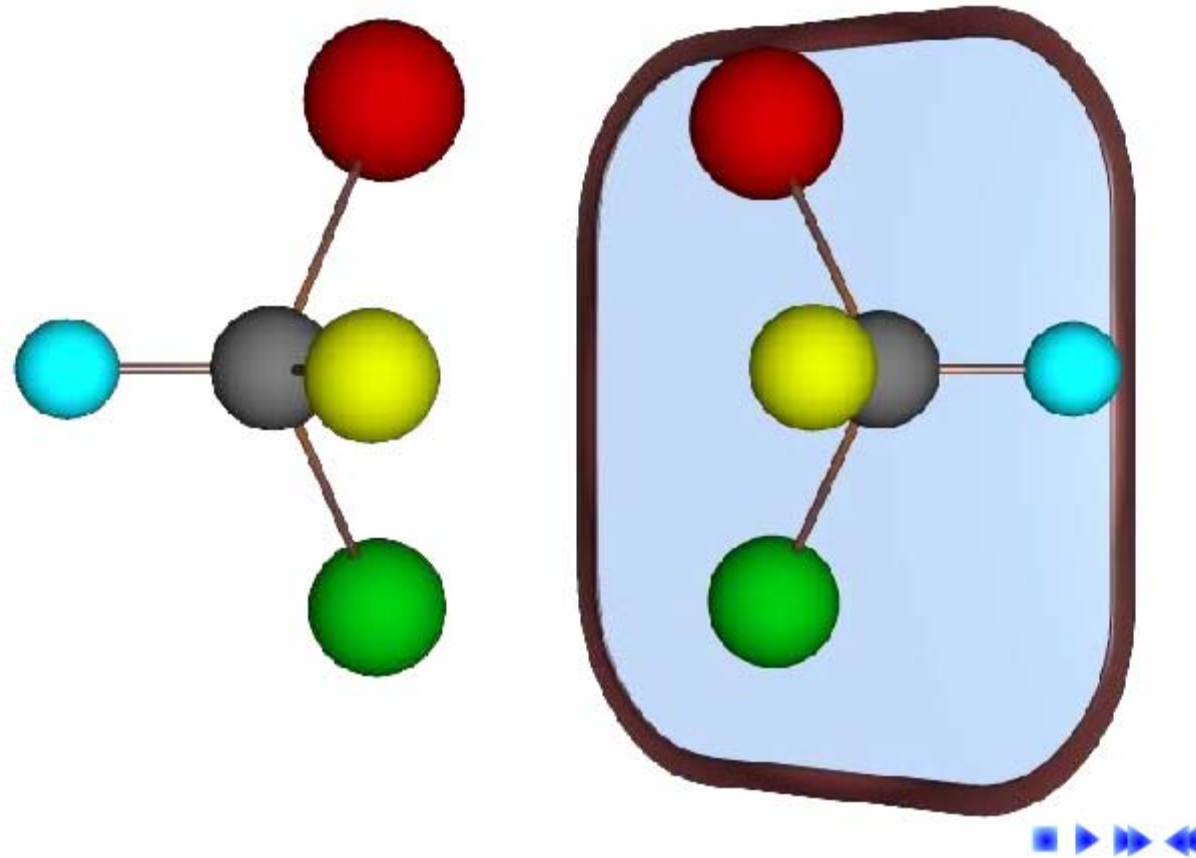
Isomers that have the same constitution but differ in the spatial arrangement of their atoms are called **stereoisomers**.

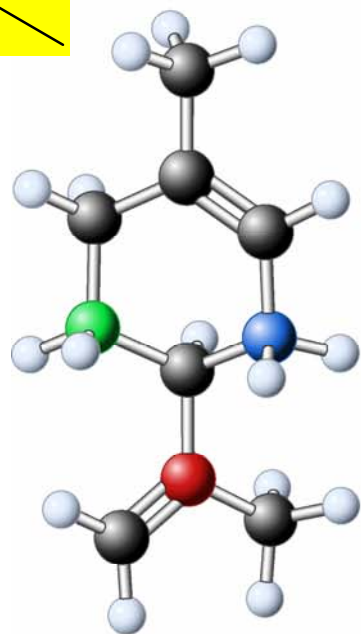
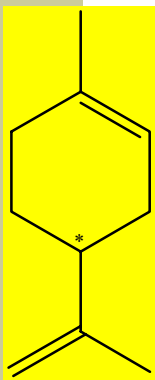
Mirror-image Superimposability



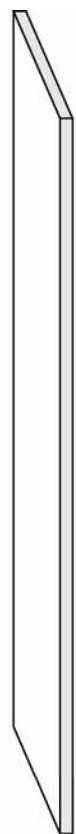
- Everything has a mirror image, but not all things are superimposable (重疊) on their mirror image.
- Everyone is not superimposable on her/his mirror image—and this is the more interesting case.

Not Superimposable

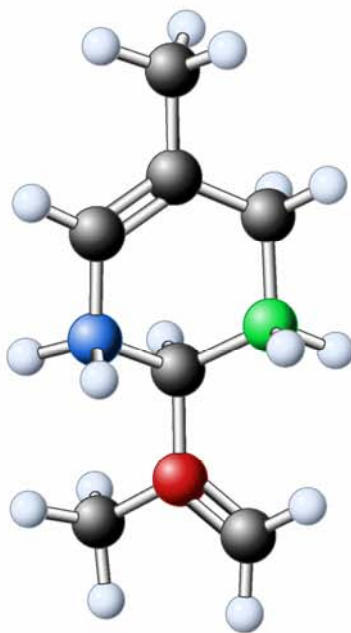




S-(-)-柠檬烯



镜子



R-(+)-柠檬烯

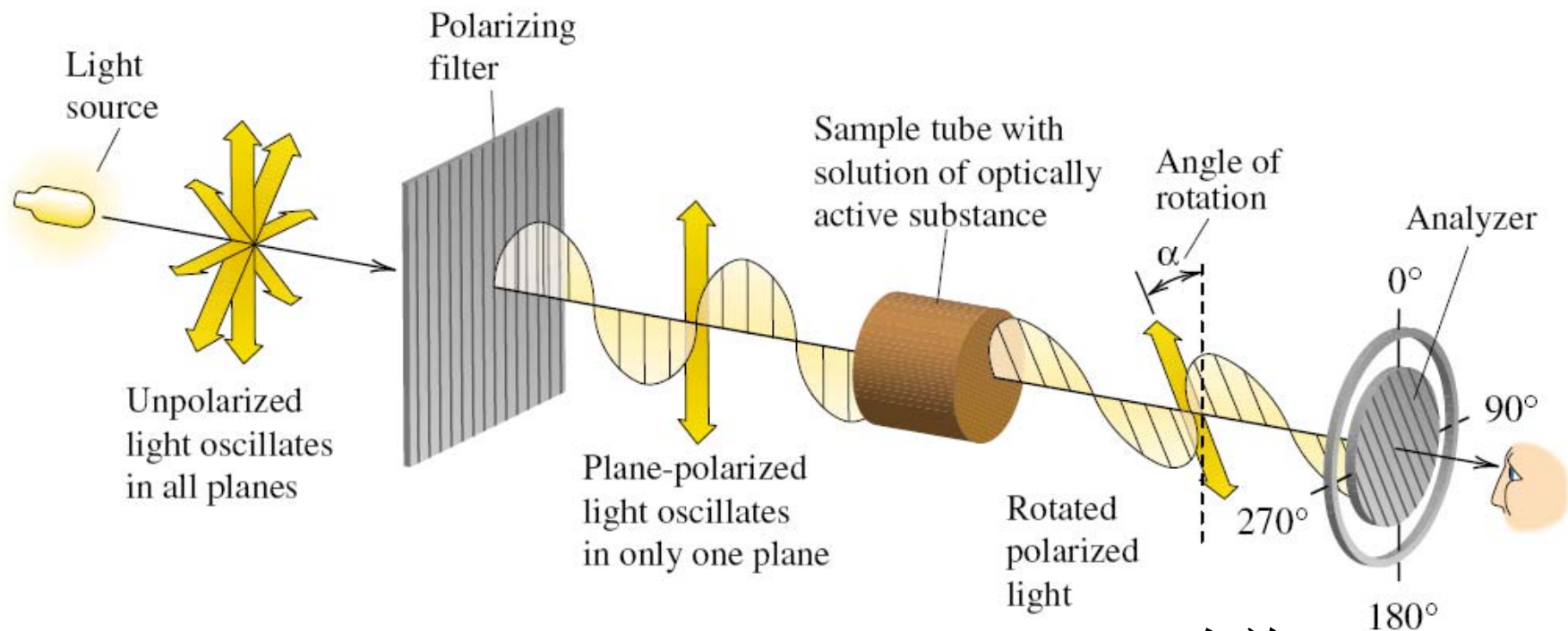


气味：松节油

橙子特有的芳香气味

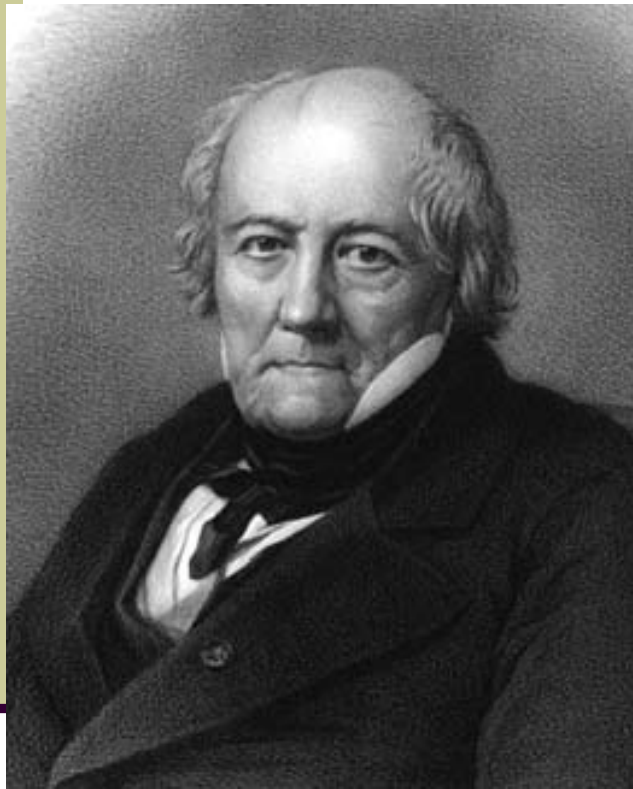
7.1.1 Optical Rotation

- The angle between the entrance plane and exit planes is the optical rotation (α : 表观旋光).

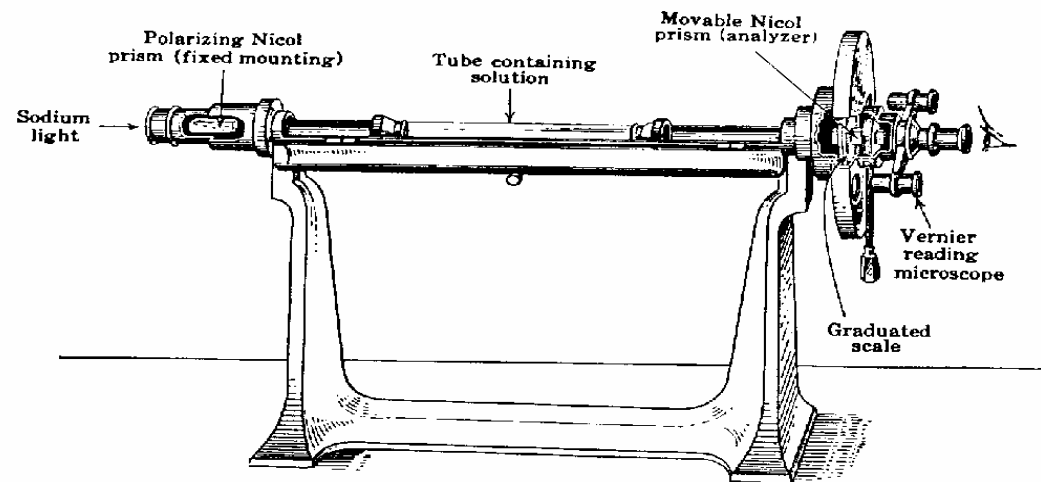


- Clockwise rotation is called **dextrorotation** (右旋)
- Anti-clockwise is **levorotatory** (左旋)

A Simple Polarimeter



Jean Baptiste Biot



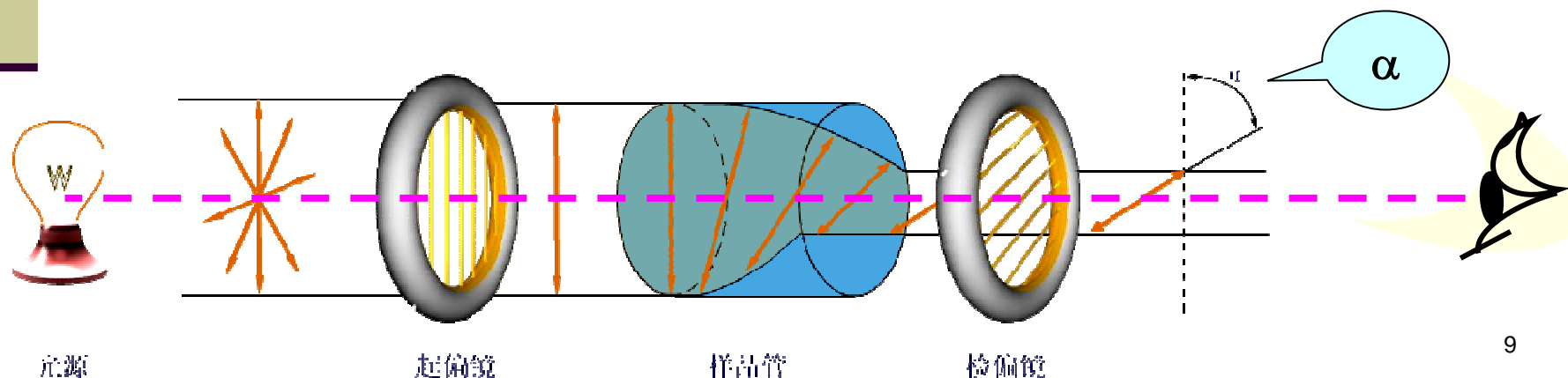
His work on determining the optical rotation of naturally occurring molecules included an experiment on turpentine (松节油) (discovered in 1815).

7.1.2 Specific Rotation

- To have a basis for comparison, define **specific rotation**, $[\alpha]_D$ (比旋光度) for an optically active compound.

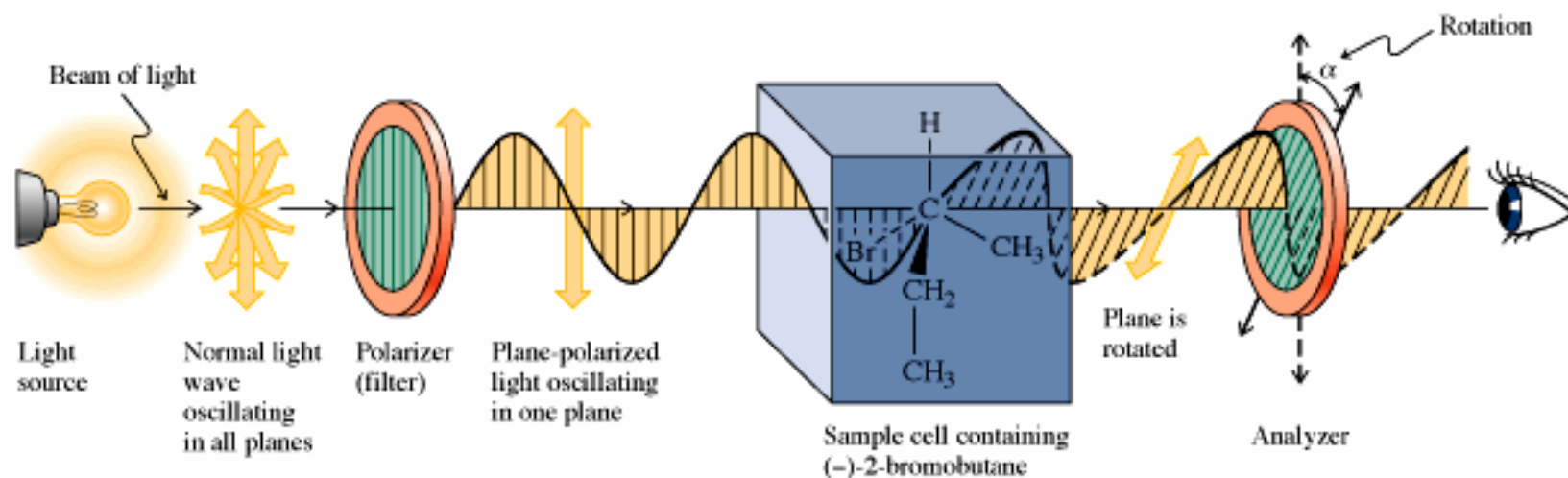
$$[\alpha]_D = \frac{\alpha}{cl}$$

α : The observed rotation,
 c : The concentration of the sample (g/mL)
 l : The length of the sample tube(dm)
 D : wavelength(589nm), Na



7.1.3 Optical Activity

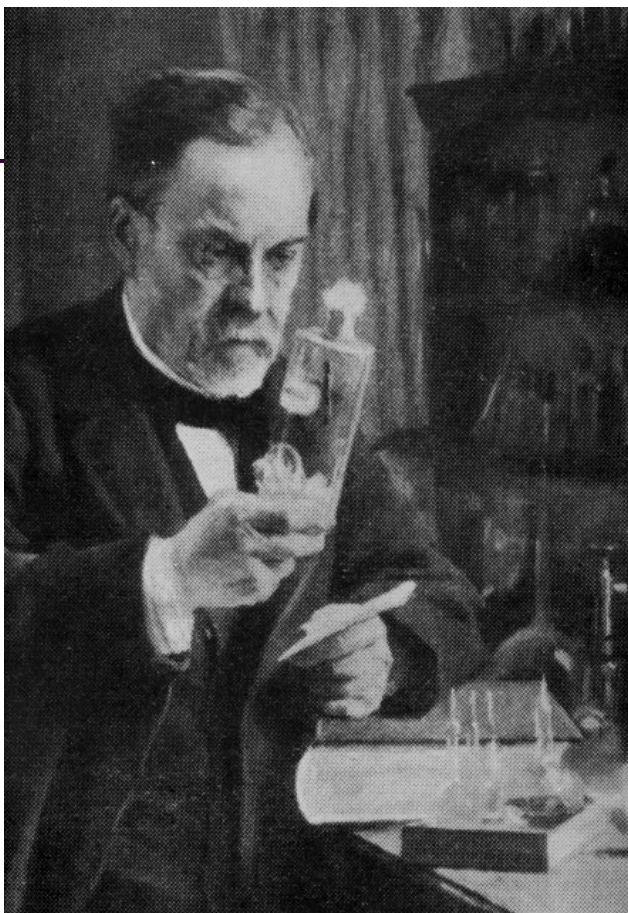
- Light restricted to pass through a plane is *plane-polarized*.
- Plane-polarized light (平面偏振光) that passes through solutions of **achiral** compounds remains in that plane.
- Solutions of **chiral compounds** rotate plane-polarized light and the molecules are said to be **optically active**



7.1.4 Specific Rotation of Molecules

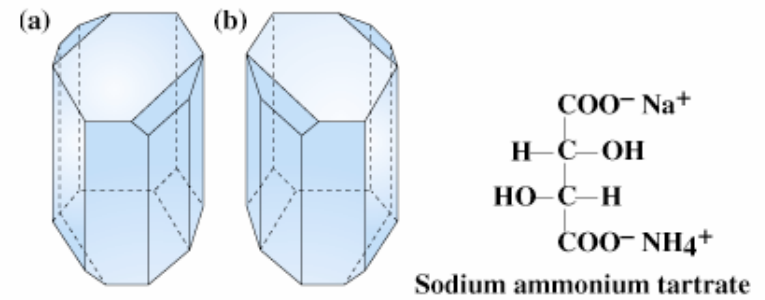
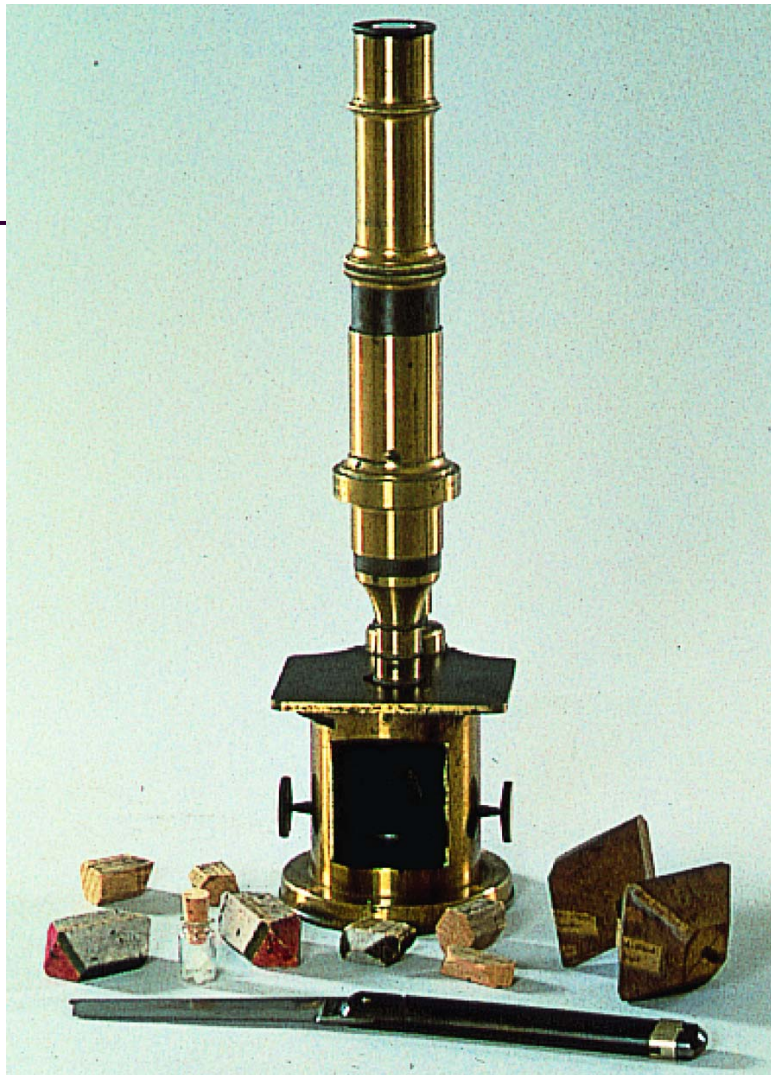
Specific Rotation of Some Organic Molecules

Compound	$[\alpha]_D$ (degrees)	Compound	$[\alpha]_D$ (degrees)
Penicillin V	-233	Cholesterol	-31.5
Sucrose	-66.47	Morphine	-132
Camphor	-44.26	Acetic acid	0
Monosodium glutamate	+25.5	Benzene	0



Louis Pasteur
(1822-1895)

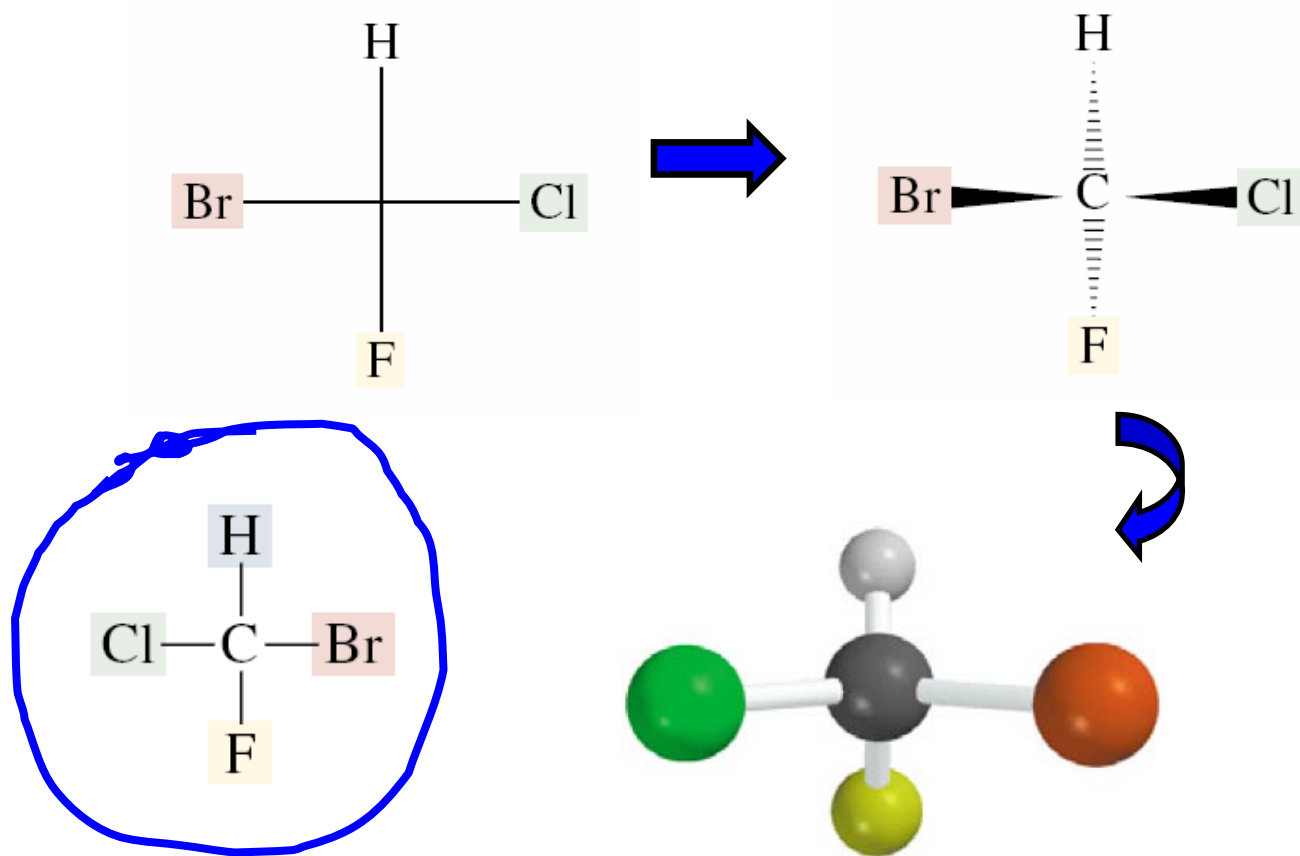
Best known to chemists for his work on the tartaric acids, **he recognized the structural relationships (now called chirality) responsible for optical isomerism**, and that microorganisms can distinguish between enantiomers. Pasteur also showed that micro-organisms cause fermentation and various diseases, and he developed methods for "pasteurization" and for vaccination against anthrax and rabies. His work saved the wine, beer, and silkworm industries for France.



Pasteur 旋光仪及 (+) - 和 (-) - 酒石酸晶体

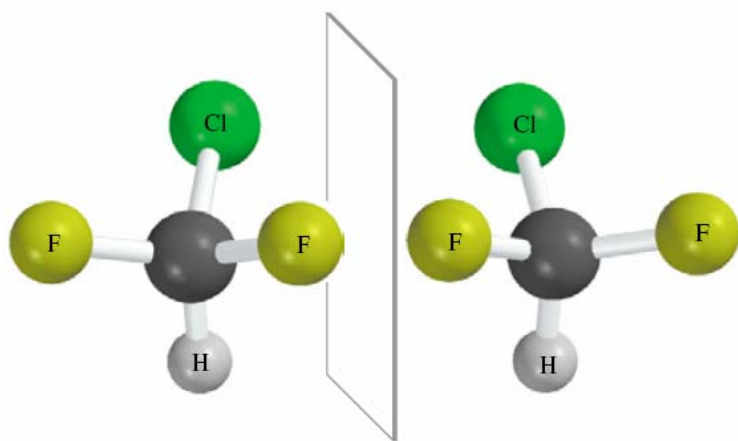
7.2 Enantiomers–Mirror Images

- Molecules exist as three-dimensional objects.

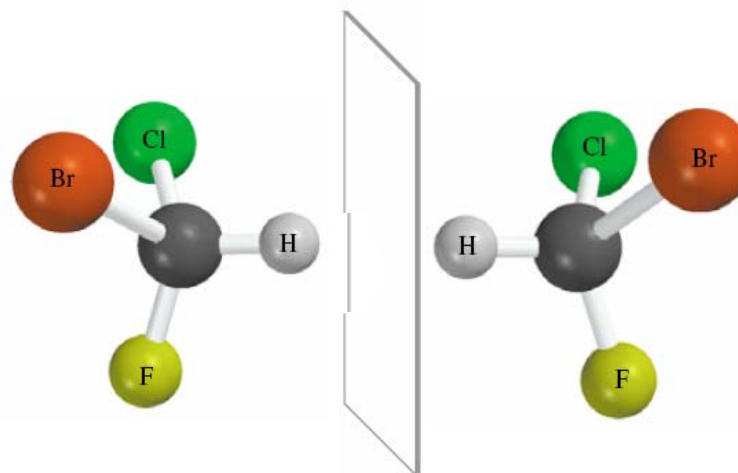


Enantiomers–Mirror Images

- Some molecules are the same as their mirror image.
- Some molecules are different than their mirror image
 - These are stereoisomers called enantiomers.



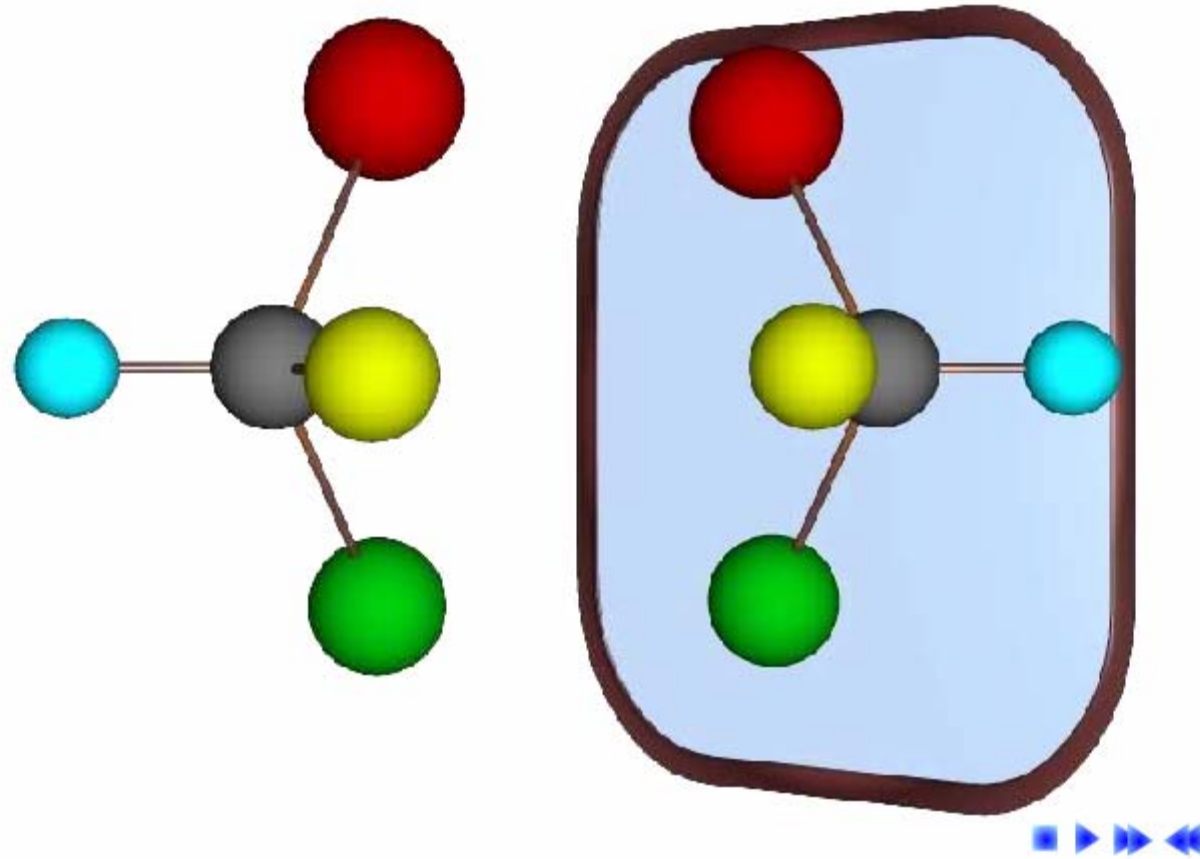
the same



the different

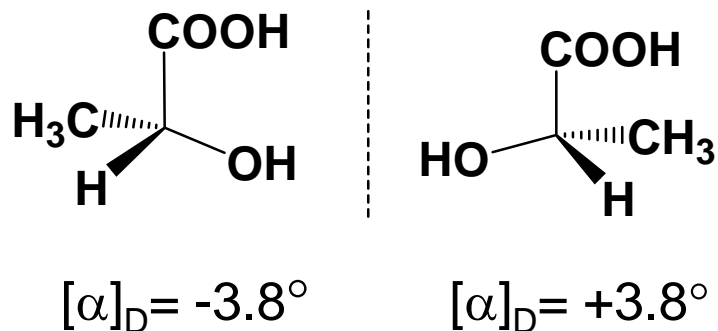
What is this difference?

Not Superimposable



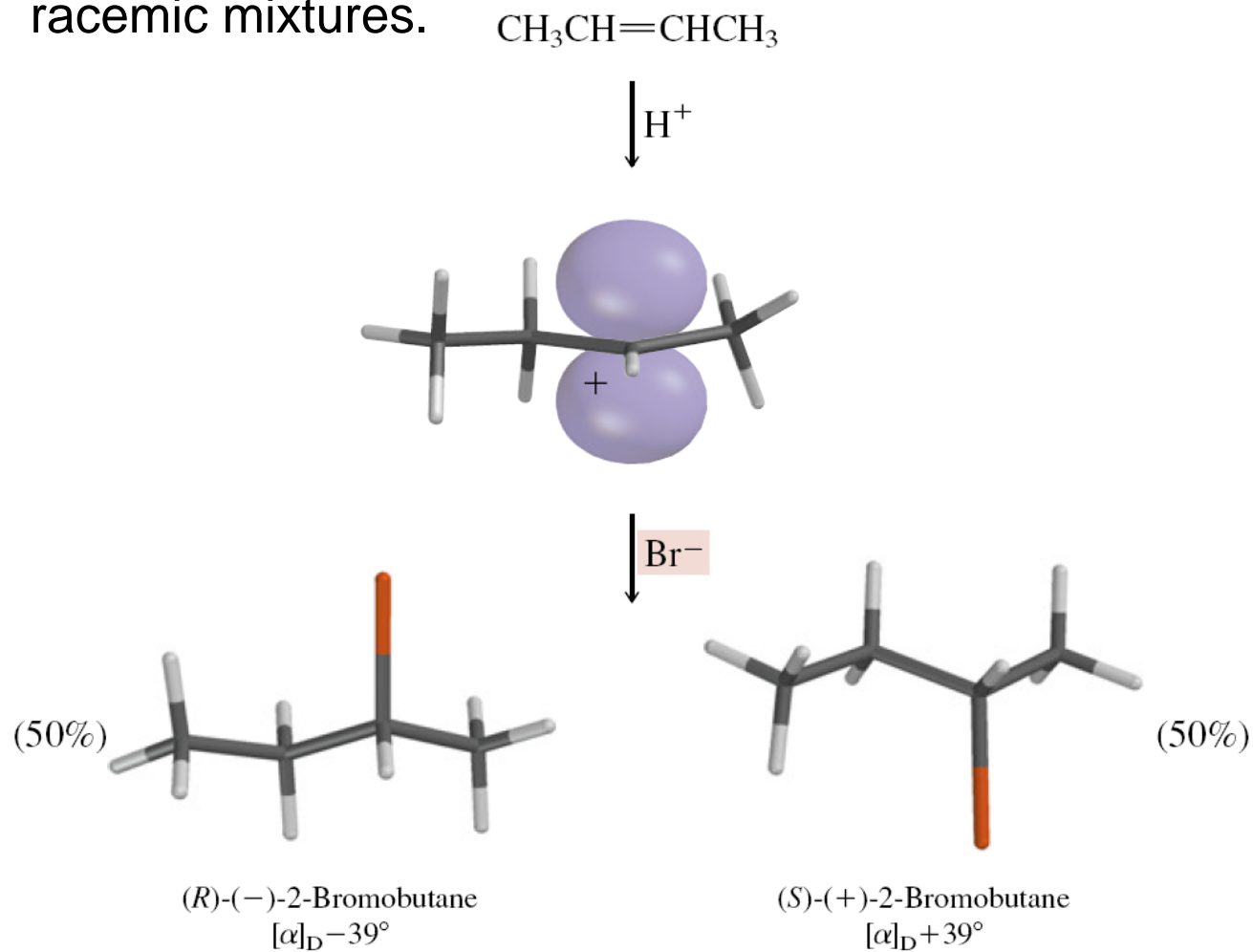
7.2.1 Characteristic of Enantiomer

- The molecular constitution of the enantiomer is the same.
- The specific rotation of the enantiomer is equal in magnitude but opposite in sign.



7.2.2 Racemic Mixtures (外消旋体)

- Mixtures containing equal quantities of enantiomers are called racemic mixtures.

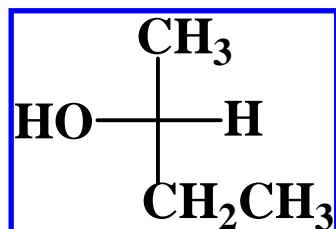


7.2.3 Percent Enantiomeric Excess

Percent enantiomeric excess (ee, 对映体过量百分数)

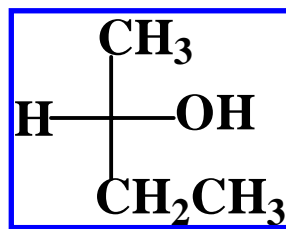
$$ee = \frac{\text{Moles of one enantiomer} - \text{moles of other enantiomer}}{\text{Moles of both enantiomers}} \times 100$$

$$= \frac{\text{Observed specific rotation}}{\text{Specific rotation of pure enantiomer}}$$



(-)-2-Butanol

$$[\alpha]_D = -13.25^\circ$$



(+)-2-Butanol

$$[\alpha]_D = +13.25^\circ$$

$$ee = \frac{+6.76^\circ}{+13.5^\circ} \times 100 = 50\%$$

7.3 Molecular Chirality

- Molecules that are not superimposable with their mirror images are chiral.
- *Characteristic property of a compound that is optically active – the compound must be chiral.*



chiral

not superimposable

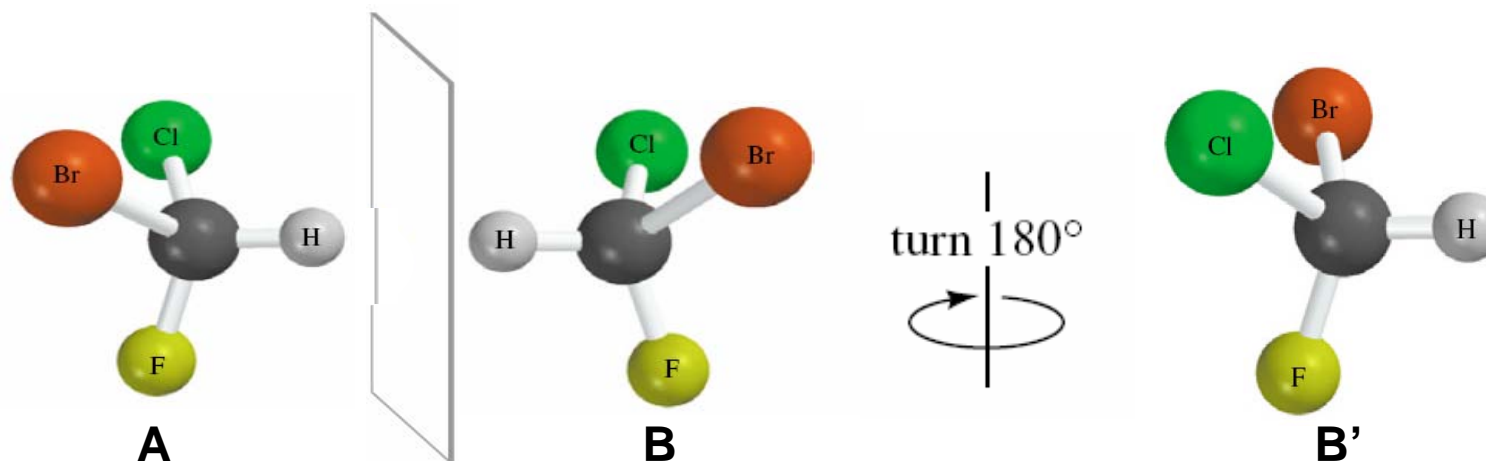


achiral

superimposable

7.3.1 Chirality

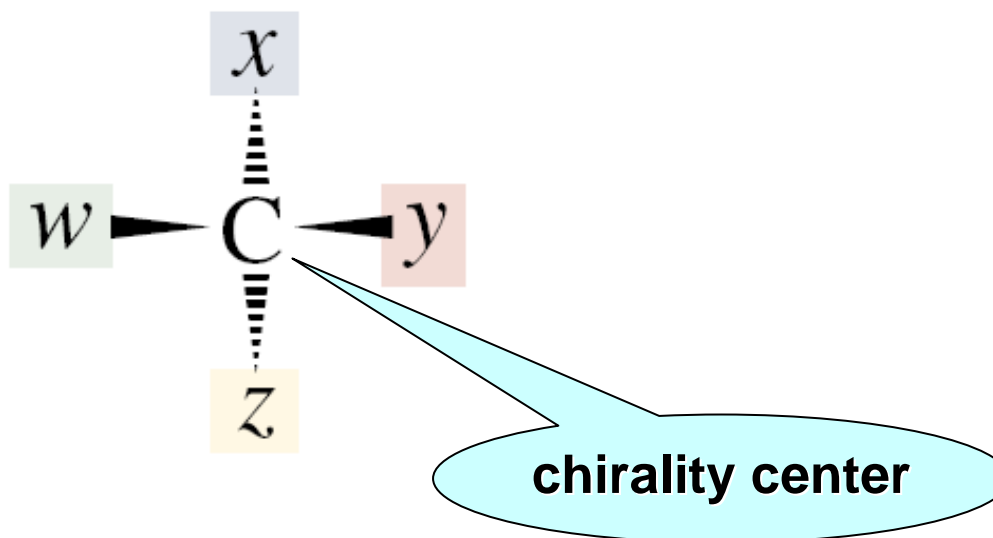
- **Chirality: A molecule isn't superimposable with their mirror image**
(一个分子与其镜像不可重合，我们称之为手性)



- A and B cannot be superimposed on each other (to test for superimposability, reorient B by turning it 180° , then compare A and B' and found the two do not match).
- Bromochlorofluoromethane is therefore **a chiral molecule**.

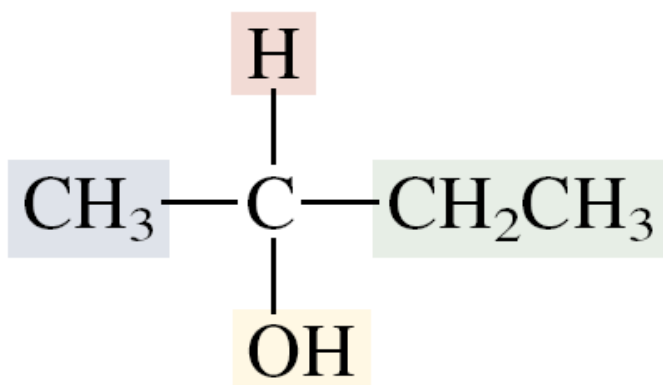
7.3.2 Chirality Centers

- A tetrahedral carbon atom that bears four different atoms or groups is called a **chirality center**.



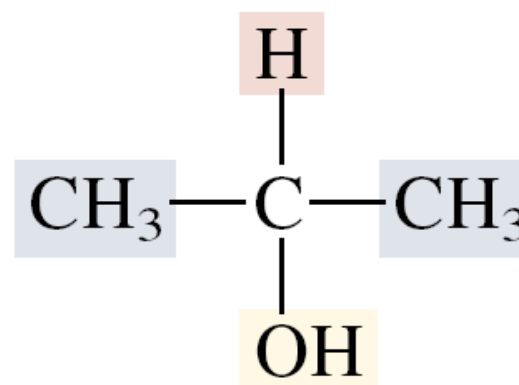
7.3.3 Whether a Molecule is Chiral or Achiral?

- A molecules with one chirality center should be chiral.



2-Butanol

Chiral; four different substituents at C-2

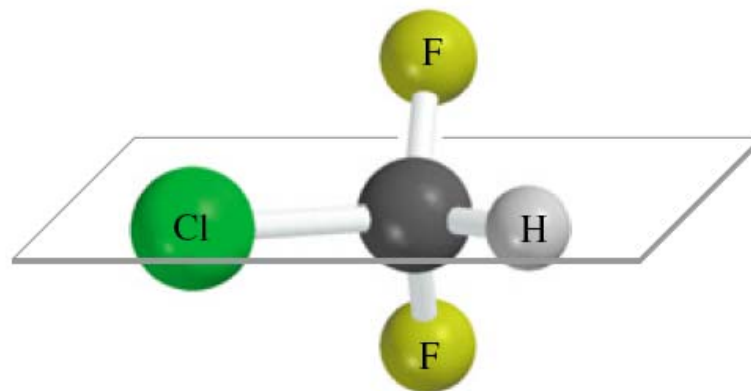
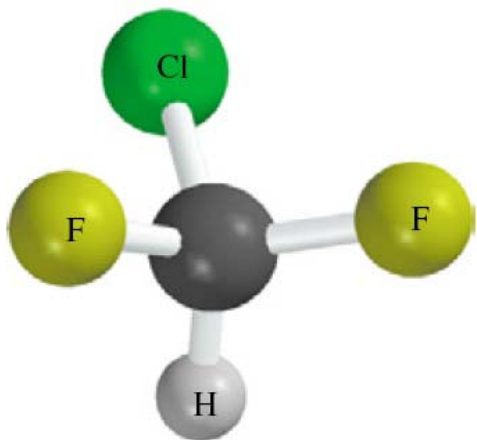


2-Propanol

Achiral; two of the substituents at C-2 are the same

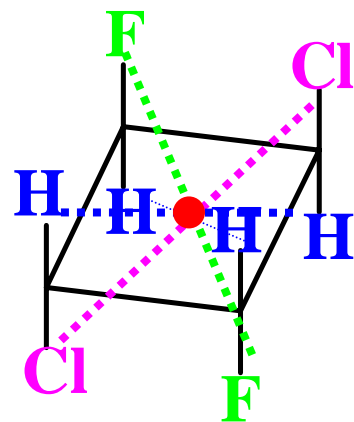
Whether a Molecule is Chiral or Achiral?

- molecules with more than one chirality center may or may not be chiral.
- a molecule that has a plane of symmetry or a center of symmetry is superposable on its mirror image and is achiral.



achiral: a plane of symmetry

Examples



achiral: a center of symmetry

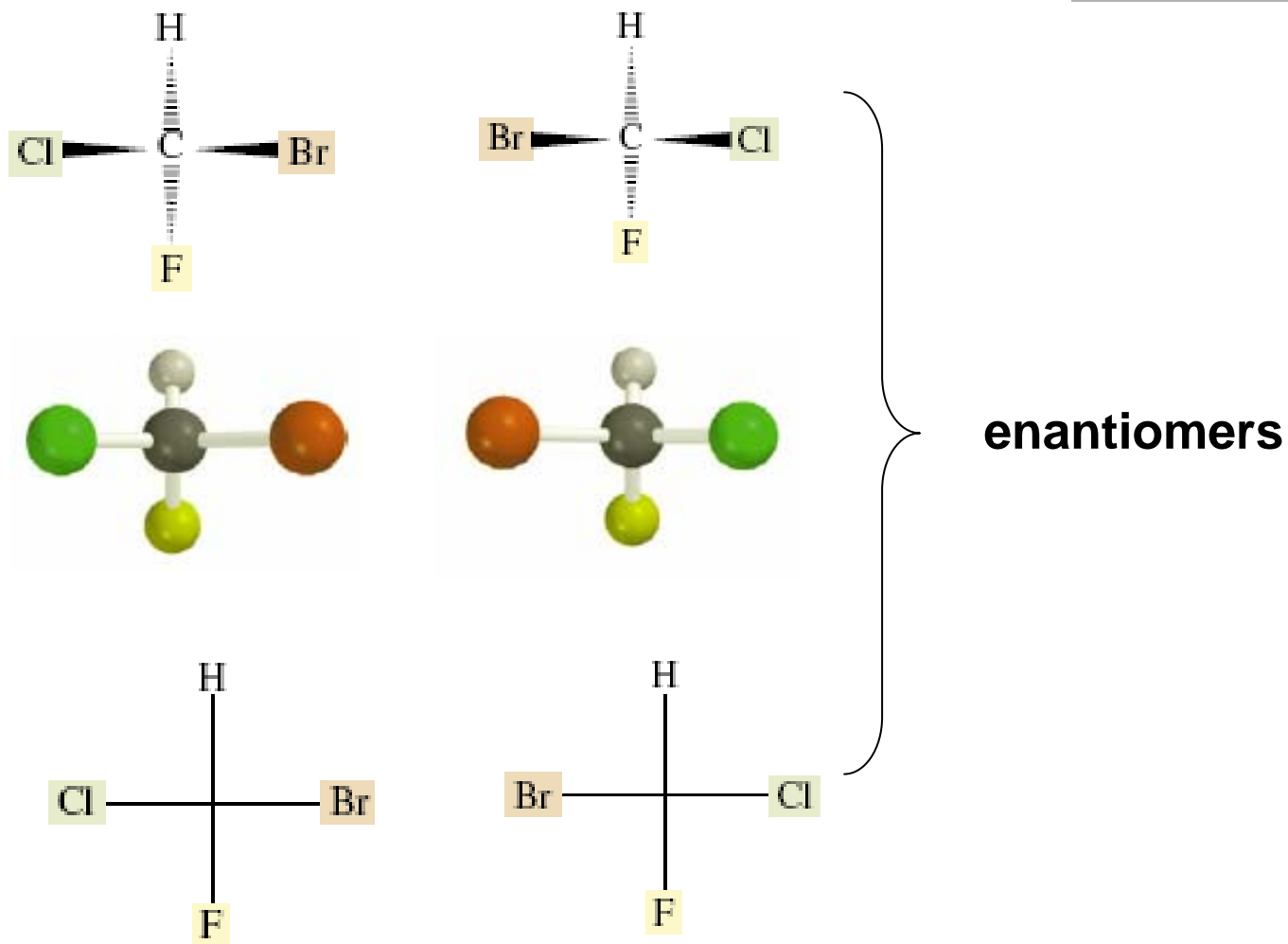


Hermann Emil Fischer

(1852-1919)

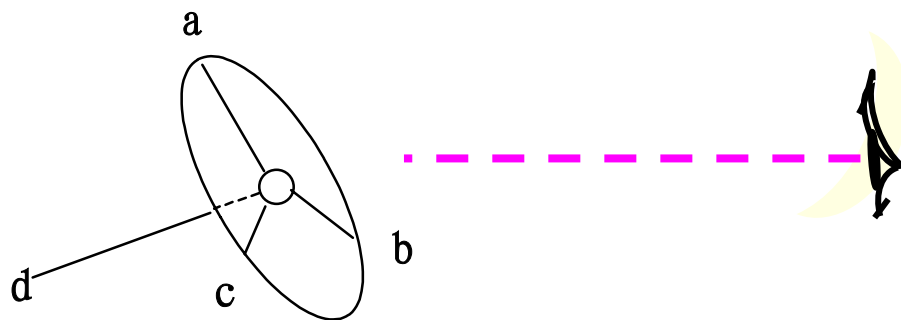
Generally considered the greatest organic chemist of his time, Fischer received the 1902 Nobel Prize in Chemistry for his work on carbohydrates and purines. His discovery that phenylhydrazine reacts with carbohydrates to form osazones enabled him to elucidate the stereochemistry of sugars. First to synthesize adenine and guanine, he made the first synthetic nucleotides. Among many other contributions was his work on protein structure and synthesis, the "lock-and-key" model for enzyme reactions, structure of triarylmethane dyes, and the design of laboratory hoods and safety equipment.

7.4 Fischer Projections



7.4.1 Sequence Rules (IUPAC)

- The spatial arrangement of substituents at a stereogenic center is its **absolute configuration**
- **Sequence rules**, is used to specify the absolute configuration at the chirality center

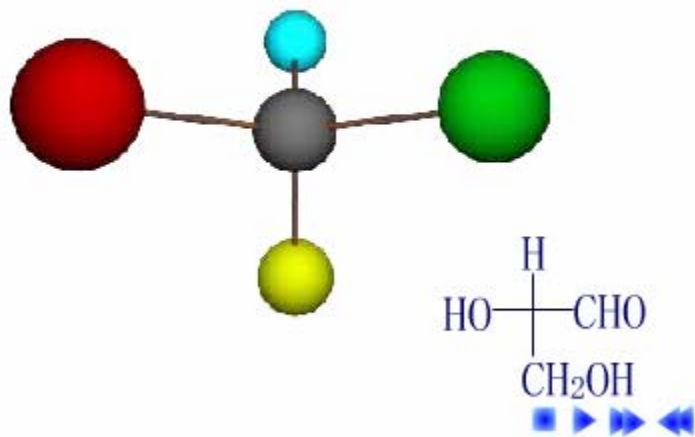


$\mathbf{a > b > c > d}$ (Clockwise) — **R**

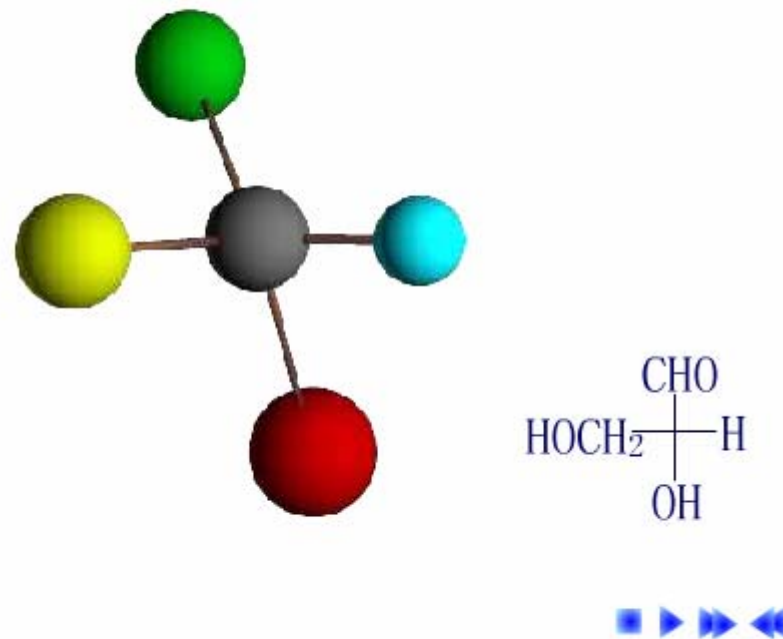
$\mathbf{a > c > b > d}$ (Counterclockwise) — **S**

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Naming by R-S Notational System

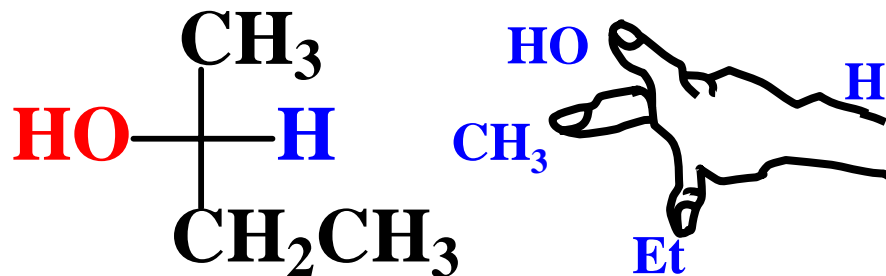


(R)-甘油醛

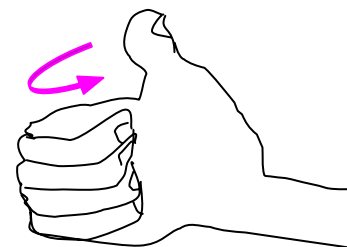
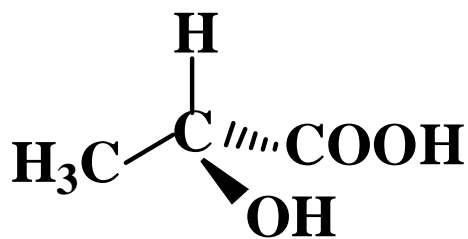


(S)-甘油醛

Applications: Sequence Rules

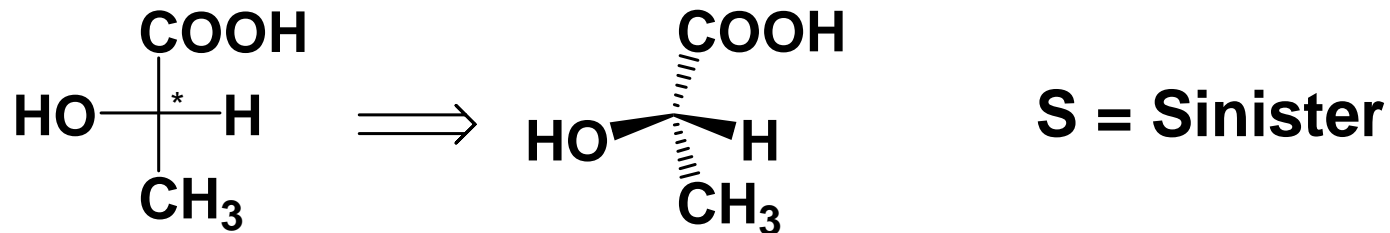
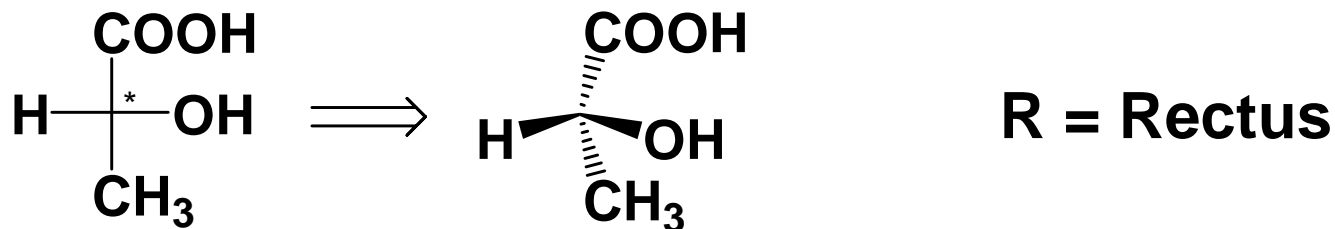


(R)-2-Butanol



(R)-Lactic acid

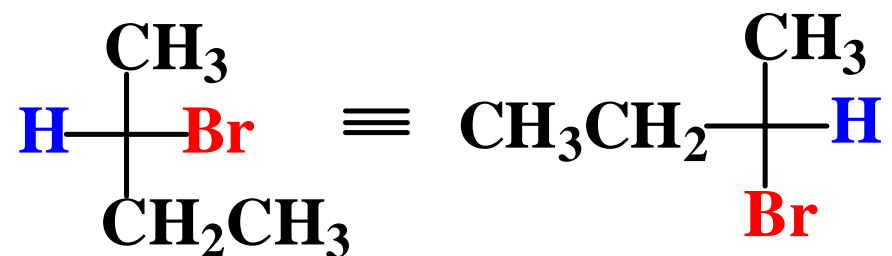
Examples

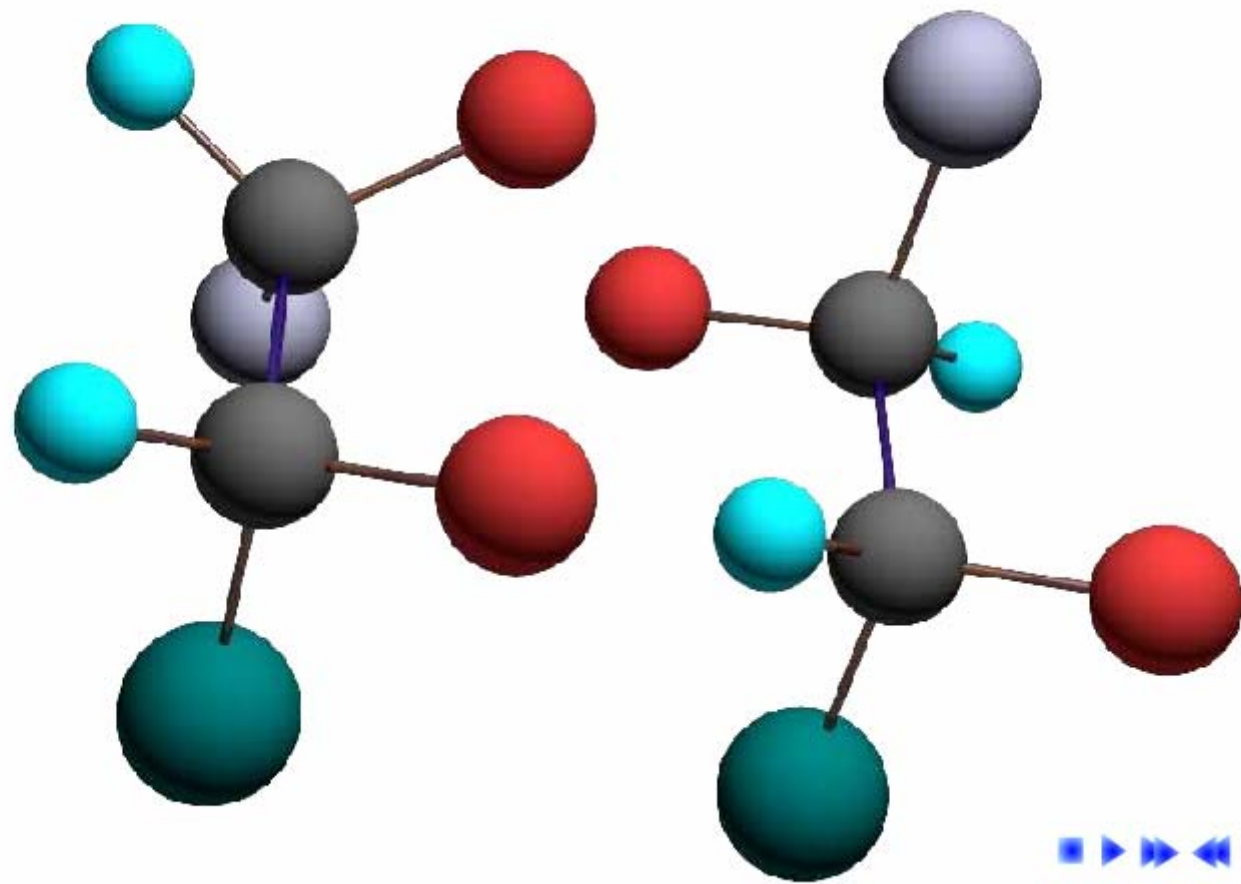


♣ the *R* or *S* configuration and the sign of rotation are incorporated into the name of the compound, as in (***R***)-(-)-Lactic acid and (***S***)-(+)-Lactic acid.

7.4.2 Characteristics of Fischer Projection

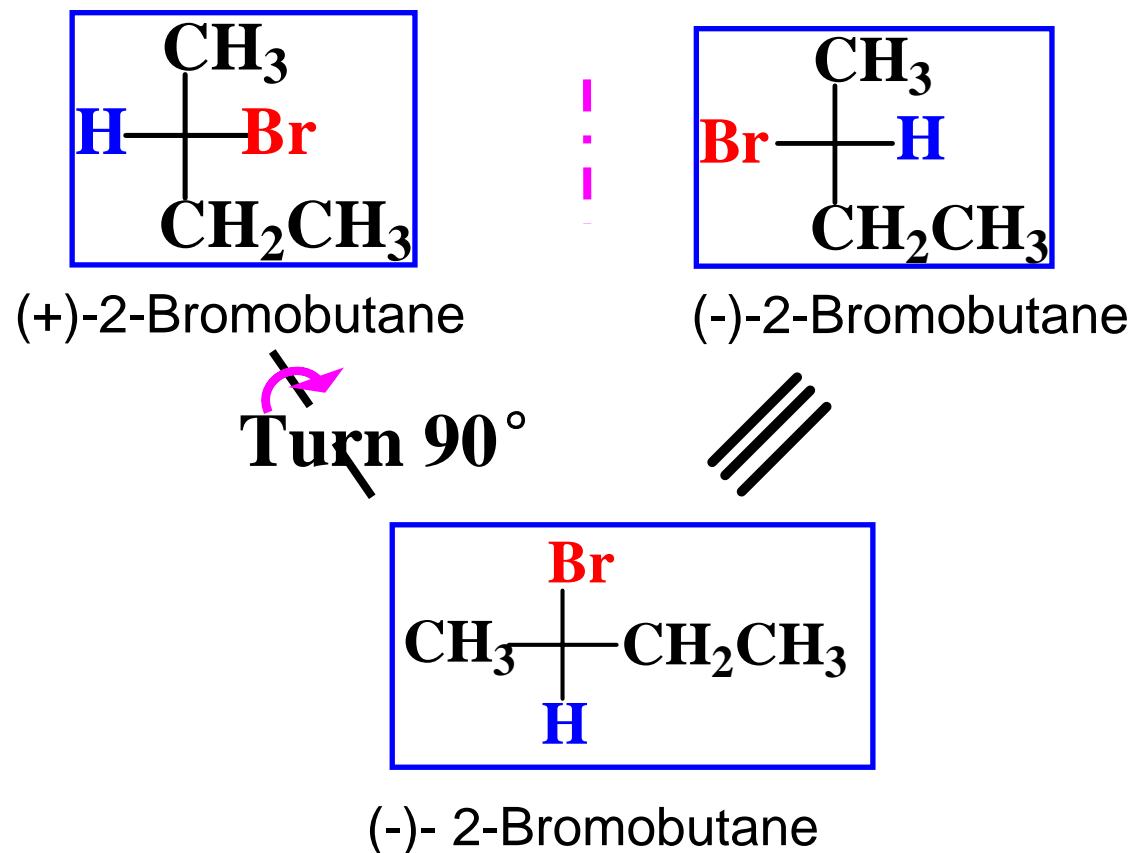
- One group is fixed, the other three groups are rotated **in turn**, the configuration is not changed.



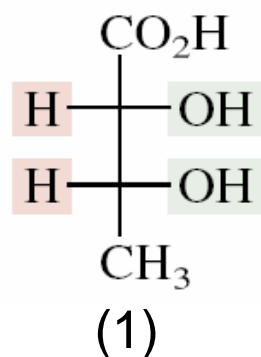


Characteristics of Fischer Projection

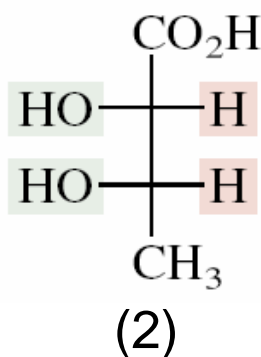
- To rotate the projection to 90°, on the plane of the paper, the other enantiomer was got.



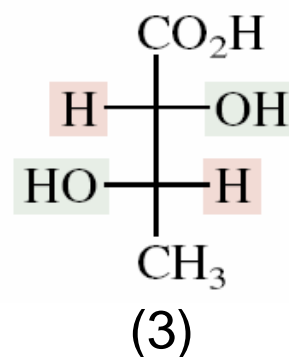
7.5 Chiral Molecules With Two Stereocenter



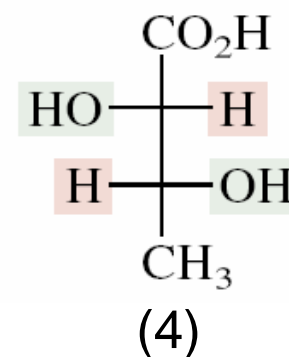
(2R,3R)-



(2S,3S)-



(2R,3S)-

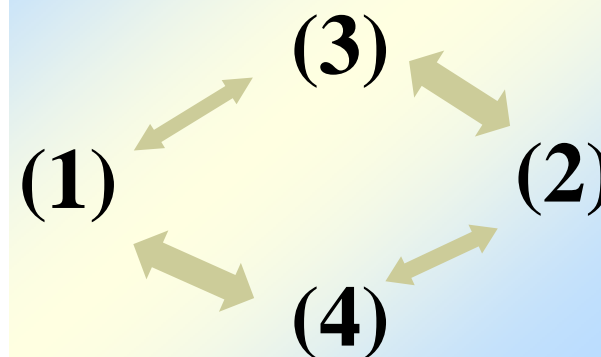


(2S,3R)-

2,3-Dihydroxybutanoic acid
(2, 3-二羟基丁酸)

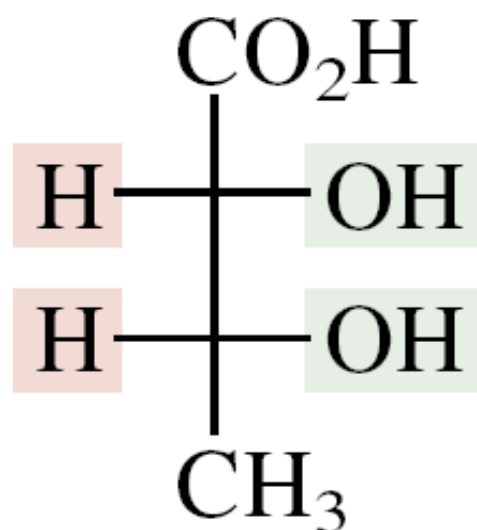
Enantiomers: (1) ↔ (2)
(3) ↔ (4)

Diastereomers:



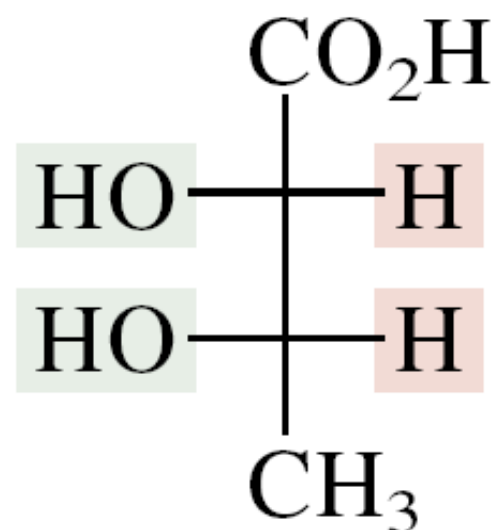
7.6 Racemic Mixtures

Racemic forms (\pm): 1:1 mixture of (R)- and (S)-enantiomers



I

(2R,3R)-2,3-Dihydroxybutanoic acid

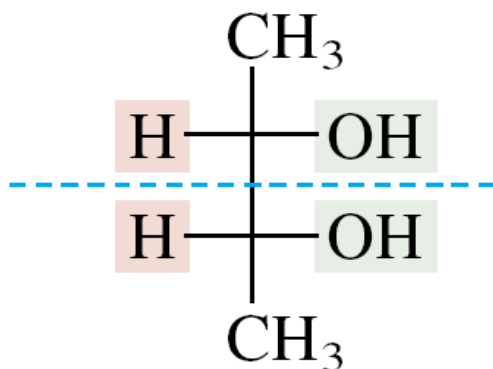


II

(2S,3S)-2,3-Dihydroxybutanoic acid

7.7 Meso Compounds

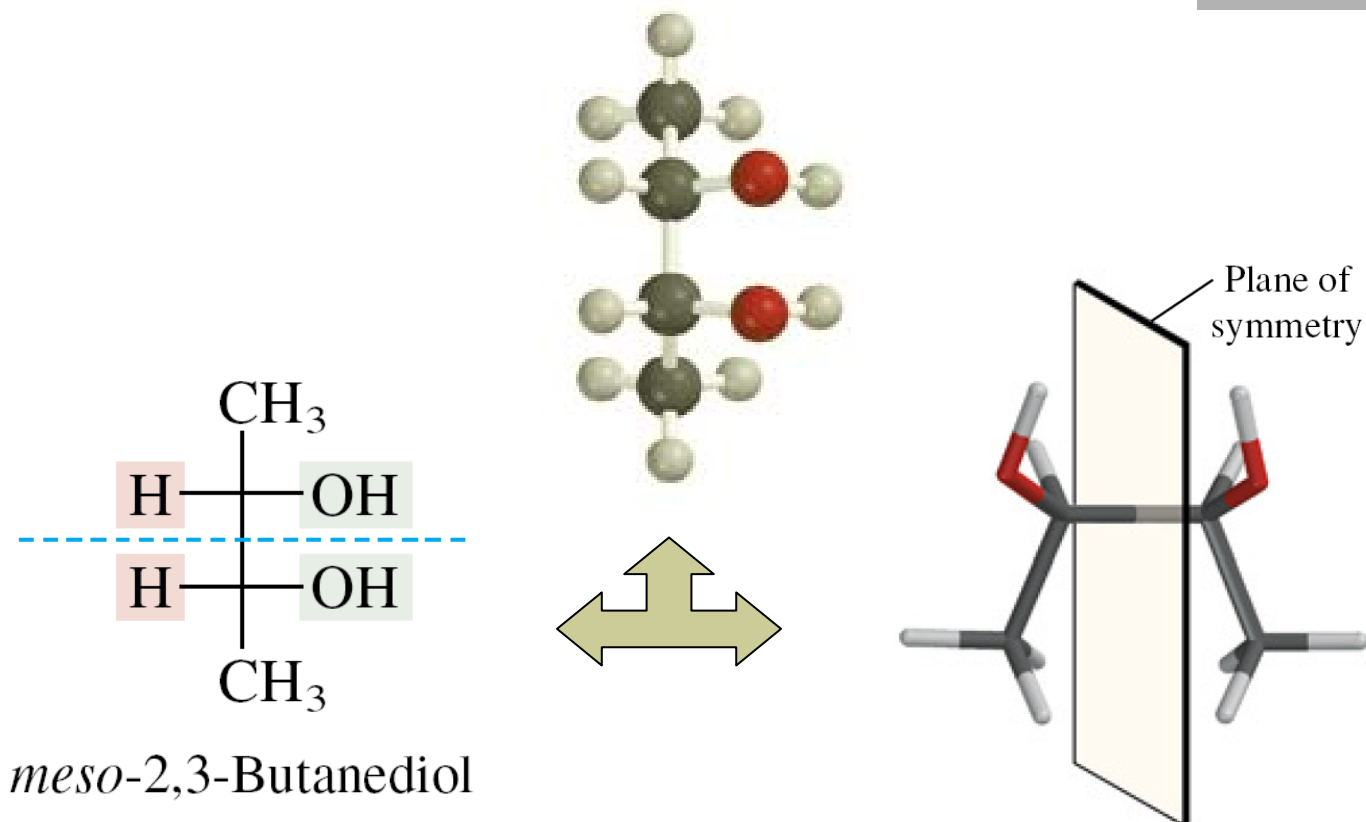
- Tartaric acid has two chirality centers and two diastereomeric forms
- One form is chiral and the other is achiral, but both have two chirality centers
- An achiral compound with chirality centers is called a **meso compound** – it has a plane of symmetry



(2R,3R)-2,3-Butanediol



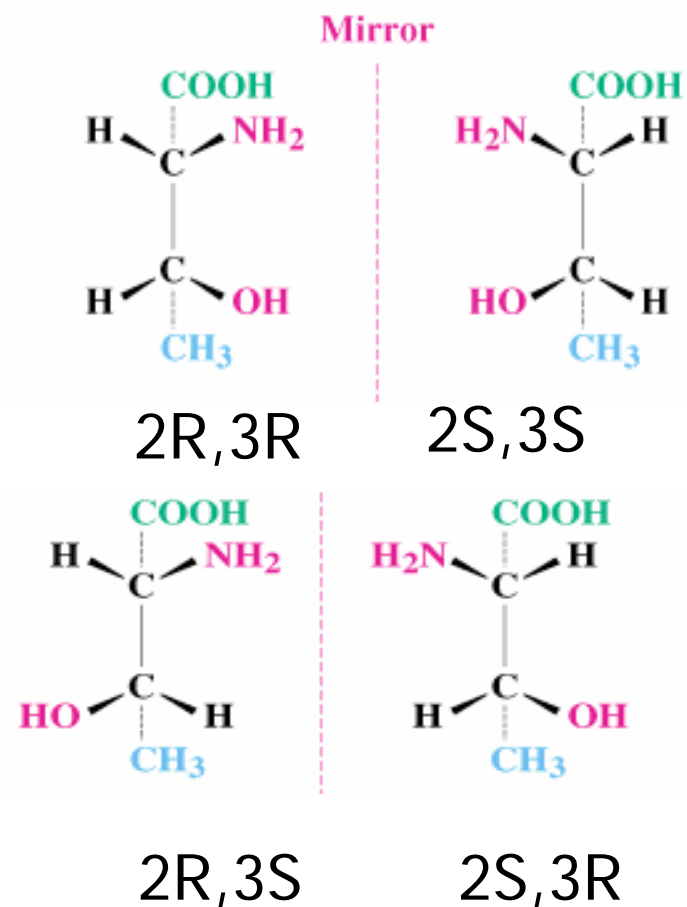
meso-2,3-Butanediol is Achiral

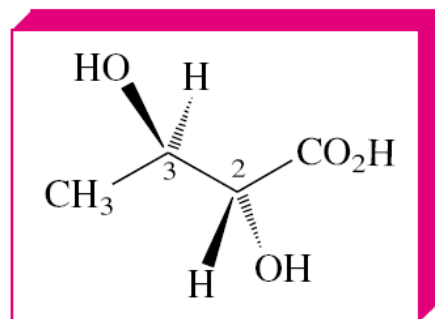


Achiral molecules with two same stereogenic centers

7.8 Diastereomers

- Molecules with more than one chirality center have mirror image stereoisomers that are enantiomers
- In addition they can have stereoisomeric forms that are not mirror images, called **diastereomers**

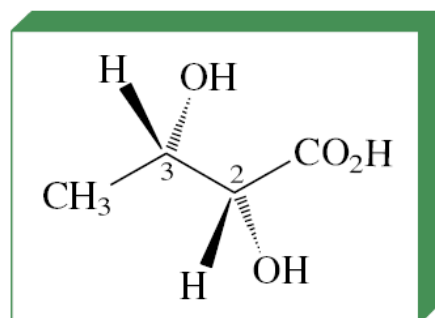




I

$(2R,3R) : [\alpha]_D -9.5^\circ$

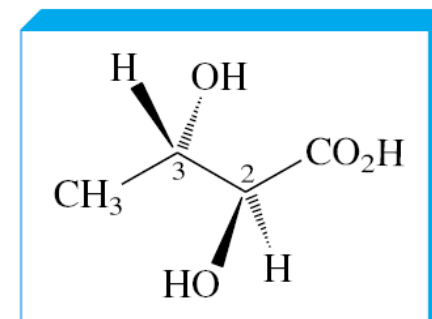
Diastereomers



III

$(2R,3S) : [\alpha]_D +17.8^\circ$

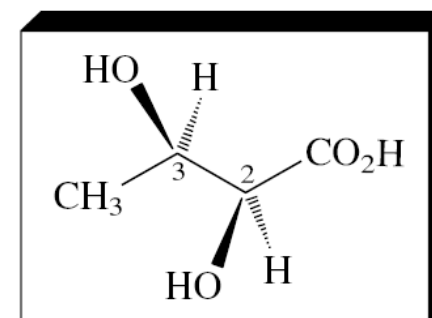
Enantiomers



II

$(2S,3S) : [\alpha]_D +9.5^\circ$

Diastereomers



IV

$(2S,3R) : [\alpha]_D -17.8^\circ$

Enantiomers

Diastereomers

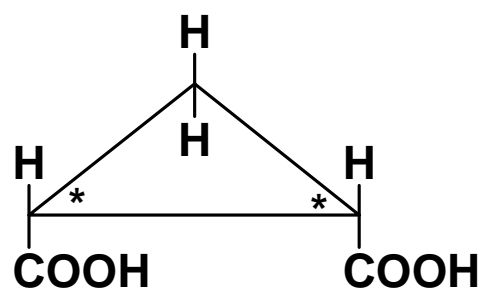
A chiral molecules with two defferent stereogenic centers

7.9 Molecules with More Than Two Chirality Centers

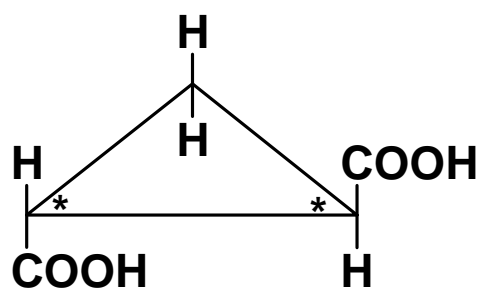
- Molecules can have very many chirality centers.
- Each point has two possible permanent arrangements (*R* or *S*), generating two possible stereoisomers.
- So the number of possible stereoisomers with *n* chirality centers is 2^n .

See Page 128

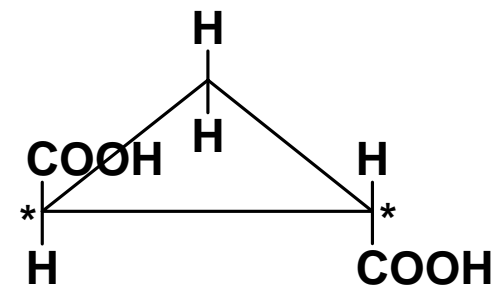
7.10 Stereochemistry of Cyclic Compounds



(Z)-configuration



(E)-configuration

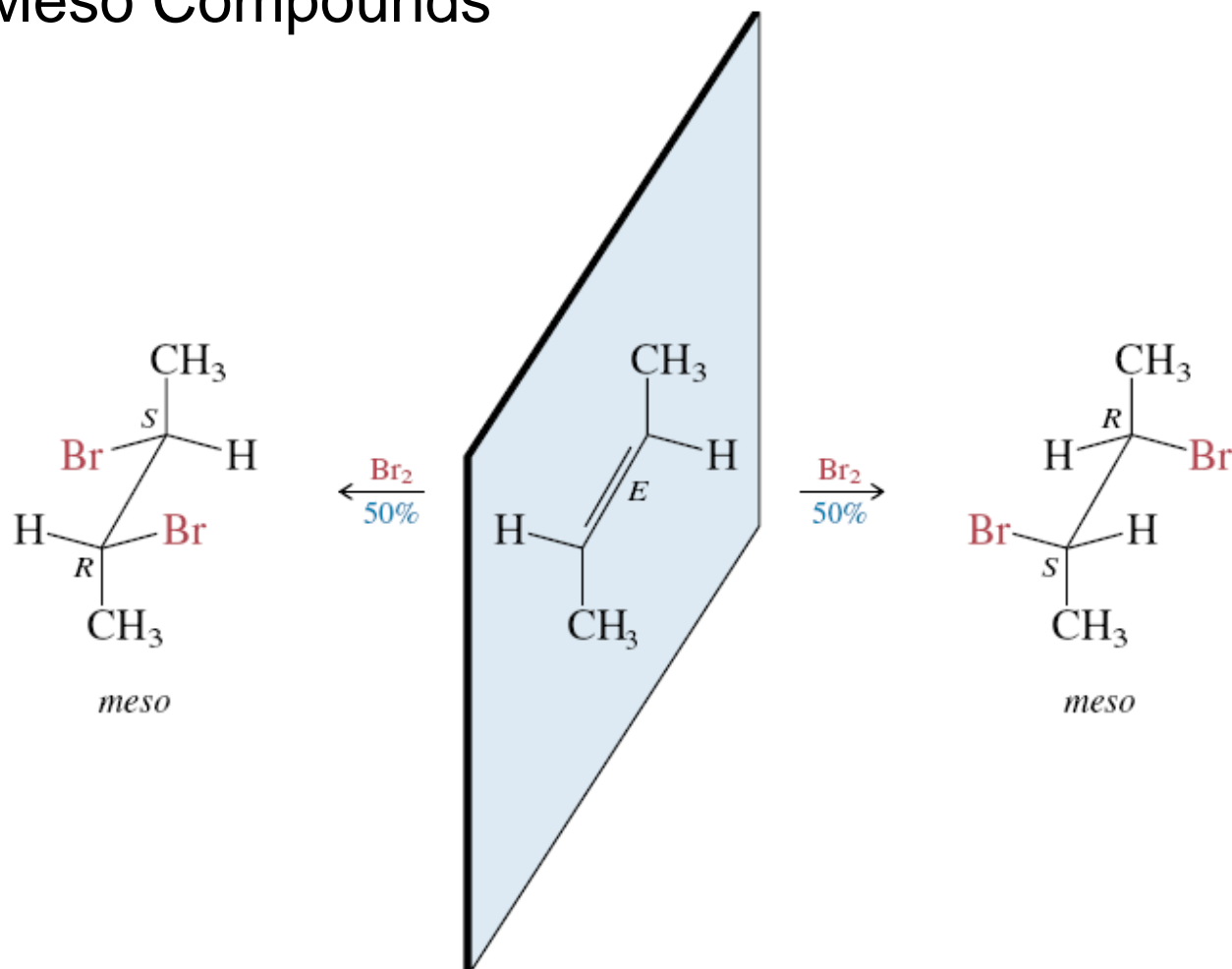


Enantiomers

- cyclic compound — might be Z/E configurations
- Compound containing chiral center — might be enantiomers

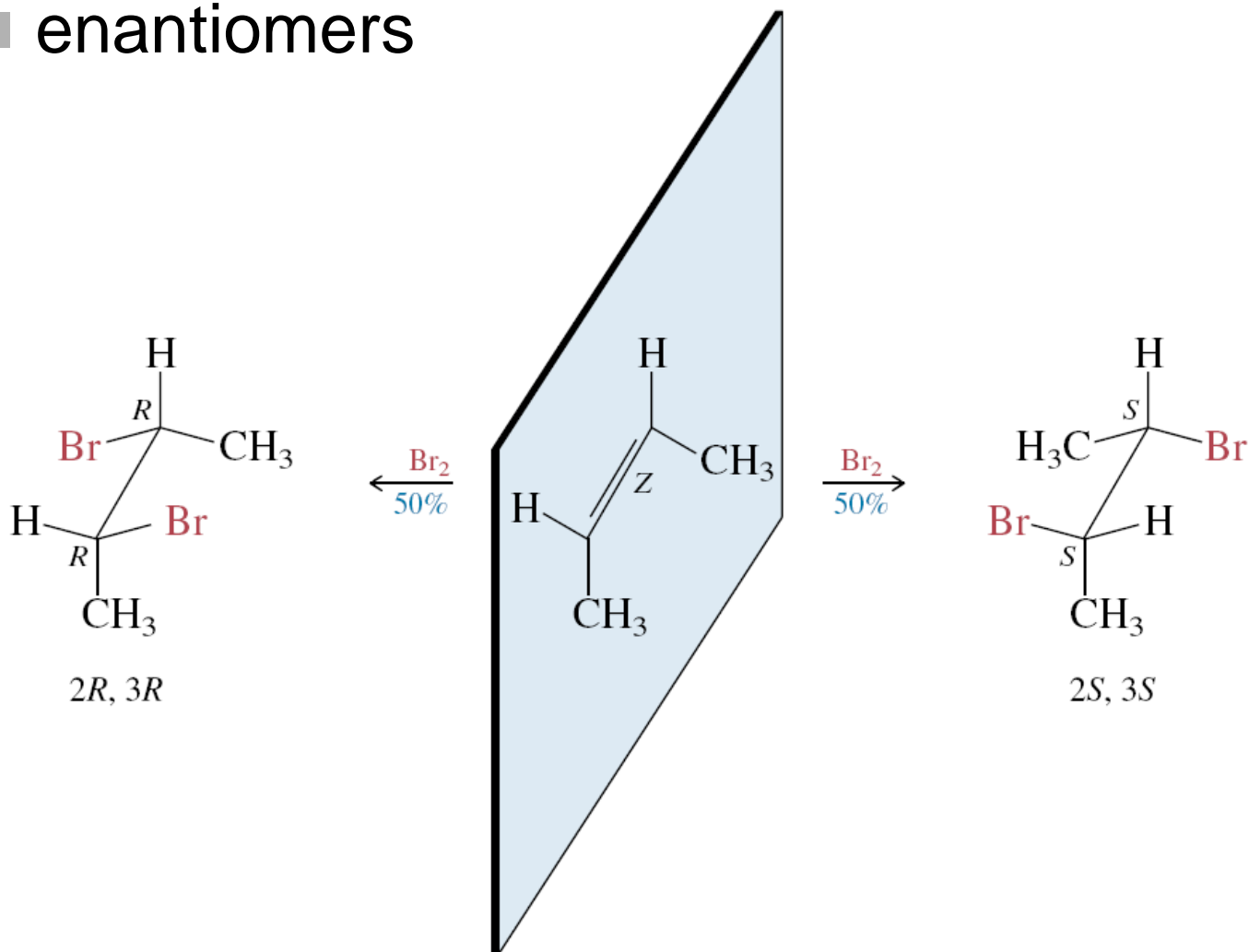
7.11 Reactions That Produce Stereoisomers

■ Meso Compounds

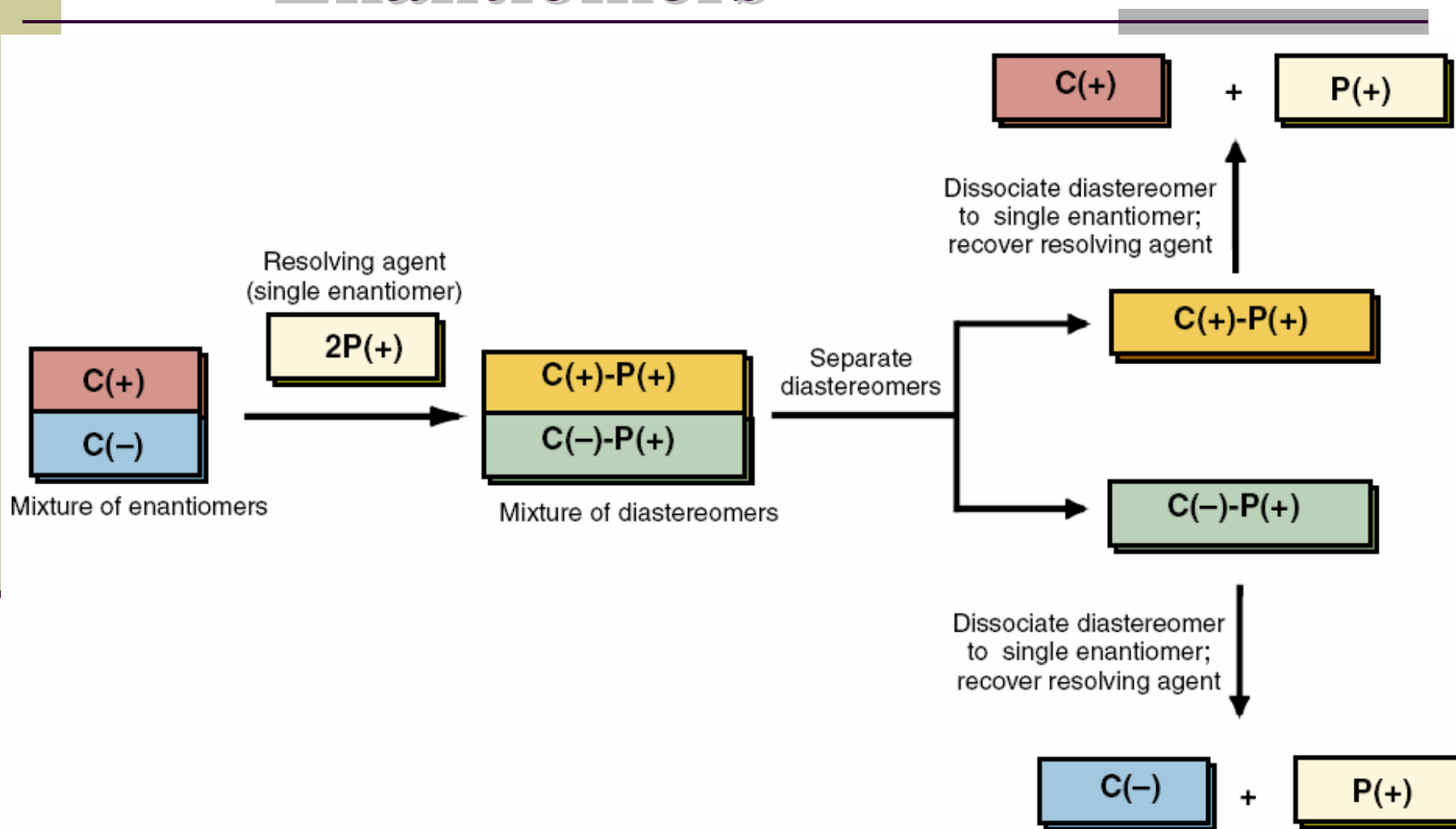


Reactions That Produce Stereoisomers

- enantiomers



7.12 Resolving a Mixture of Enantiomers



7.13 Physical Properties of Stereoisomers

- Enantiomeric molecules differ in the direction in which they rotate plane polarized but their other common physical properties are the same
- Diastereomers have a complete set of different common **physical properties**

TABLE 9.3 Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$ (degrees)	Density (g/cm ³)	Solubility at 20°C (g/100 mL H ₂ O)
(+)	168–170	+12	1.7598	139.0
(-)	168–170	-12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

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7.14 Stereoregular Polymer



(a) Isotactic polypropylene

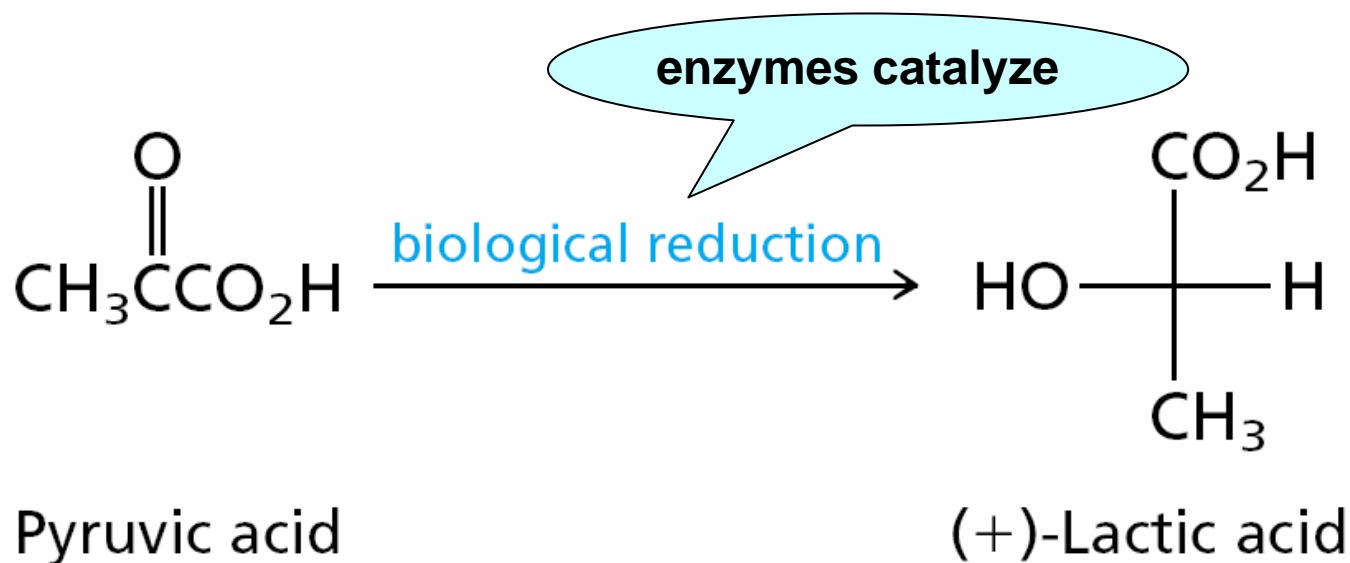


(b) Syndiotactic polypropylene

7.15 Chirality in Nature



- Stereoisomers are readily distinguished by chiral receptors in nature
- Properties of drugs depend on stereochemistry
- Think of biological recognition as equivalent to 3-point interaction



Where did Chirality Come From?

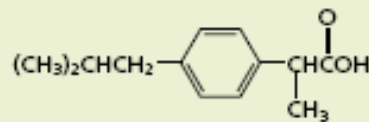


美国亚利桑那州东北部Winslow附近的陨石坑的鸟瞰。也被称为Barringer陨石坑

CHIRAL DRUGS

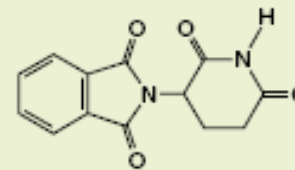
A recent estimate places the number of prescription and over-the-counter drugs marketed throughout the world at about 2000. Approximately one-third of these are either naturally occurring substances themselves or are prepared by chemical modification of natural products. Most of the drugs derived from natural sources are chiral and are almost always obtained as a single enantiomer rather than as a racemic mixture. Not so with the over 500 chiral substances represented among the more than 1300 drugs that are the products of synthetic organic chemistry. Until recently, such substances were, with few exceptions, prepared, sold, and administered as racemic mixtures even though the desired therapeutic activity resided in only one of the enantiomers. Spurred by a number of factors ranging from safety and efficacy to synthetic methodology and economics, this practice is undergoing rapid change as more and more chiral synthetic drugs become available in enantiomerically pure form.

Because of the high degree of chiral recognition inherent in most biological processes (Section 7.8), it is unlikely that both enantiomers of a chiral drug will exhibit the same level, or even the same kind, of effect. At one extreme, one enantiomer has the desired effect, and the other exhibits no biological activity at all. In this case, which is relatively rare, the racemic form is simply a drug that is 50% pure and contains 50% "Inert Ingredients." Real cases are more complicated. For example, it is the *S* enantiomer that is responsible for the pain-relieving properties of ibuprofen, normally sold as a racemic mixture. The 50% of racemic ibuprofen that is the *R* enantiomer is not completely wasted, however, because enzyme-catalyzed reactions in our body convert much of it to active (*S*)-ibuprofen.



Ibuprofen

A much more serious drawback to using chiral drugs as racemic mixtures is illustrated by thalidomide, briefly employed as a sedative and anti-nausea drug in Europe and Great Britain during the period 1959–1962. The desired properties are those of (*R*)-thalidomide. (*S*)-Thalidomide, however, has a very different spectrum of biological activity and was shown to be responsible for over 2000 cases of serious birth defects in children born to women who took it while pregnant.



Thalidomide

Basic research directed toward understanding the factors that control the stereochemistry of chemical reactions has led to new synthetic methods that make it practical to prepare chiral molecules in enantiomerically pure form. Recognizing this, most major pharmaceutical companies are examining their existing drugs to see which ones are the best candidates for synthesis as single enantiomers and, when preparing a new drug, design its synthesis so as to provide only the desired enantiomer. In 1992, the United States Food and Drug Administration (FDA) issued guidelines that encouraged such an approach, but left open the door for approval of new drugs as racemic mixtures when special circumstances warrant. One incentive to developing enantiomerically pure versions of existing drugs is that the novel production methods they require may make them eligible for patent protection separate from that of the original drugs. Thus the temporary monopoly position that patent law views as essential to fostering innovation can be extended by transforming a successful chiral, but racemic, drug into an enantiomerically pure version.