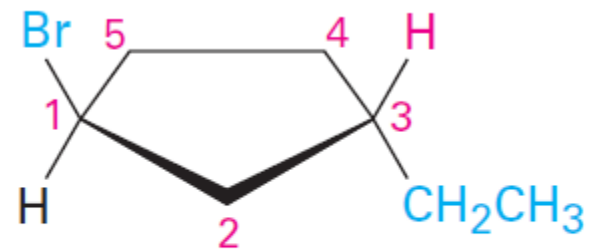
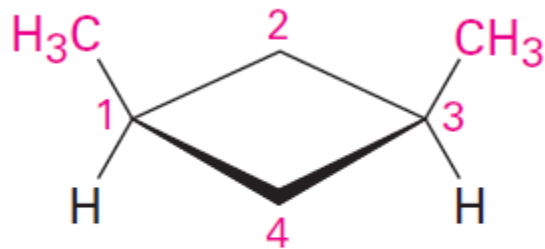


# 1. Stereoisomers

(đồng phân lập thể)

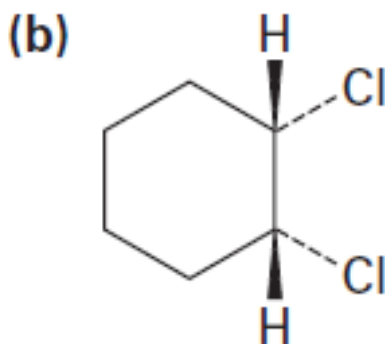
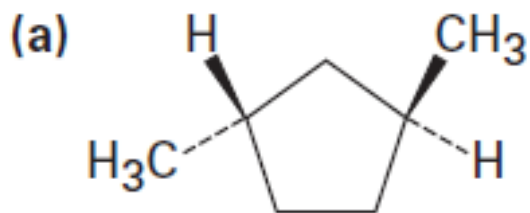
Đọc tên đồng phân với cis, trans cho các chất sau:



## 2. Cis-trans isomers

Đọc tên đồng phân với cis, trans cho các chất sau:

Name the following substances, including the *cis*- or *trans*- prefix:



# 3. Problems

Vẽ công thức cấu tạo cho các chất sau:

## PROBLEM 4-5

Draw the structures of the following molecules:

- (a) *trans*-1-Bromo-3-methylcyclohexane      (b) *cis*-1,2-Dimethylcyclobutane  
(c) *trans*-1-*tert*-Butyl-2-ethylcyclohexane

# Morning sickness (ốm nghén)



Dấu hiệu phổ biến: Buồn nôn và nôn (nausea and vomiting), ở phụ nữ mang thai từ 4 đến 16 tuần. Một phần ít (10%) có thể vẫn mang triệu chứng sau 20 tuần mang thai.

Nguyên nhân: **chưa biết**  
Có thể do tăng hormone trong thời kỳ đầu mang thai.

# Thalidomide disaster

## (thảm họa Thalidomide)

Developed in the 1950s at Chemie Grünenthal GmbH  
Licensed for use 1956 in Germany and Europe (most).  
Marketed 1957 as mild sleeping pill.

Popular for pregnant women: reducing morning sickness

1960s revealed side effects

**10 000 children** were disabilities,  
50% survived



Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

# THE THALIDOMIDE TRAGEDY: LESSONS FOR DRUG SAFETY AND REGULATION

By: Bara Fintel, Athena T. Samaras, Edson Carias

Jul 28, 2009

Bài học về an toàn cho dược phẩm/về quy định liên quan



*Many children in the 1960's, like the kindergartner pictured above, were born with phocomelia as a side effect of the drug thalidomide, resulting in the shortening or absence of limbs. (Photo by Leonard McCombe//Time Life Pictures/Getty Images)*

# WORST DRUG SCANDAL OF ALL TIME

Revelations of their connections with the makers of a deadly drug.

BY **ROGER WILLIAMS** ON 9/10/12 AT 6:00 AM

Sự cố tồi tệ nhất của mọi thời đại



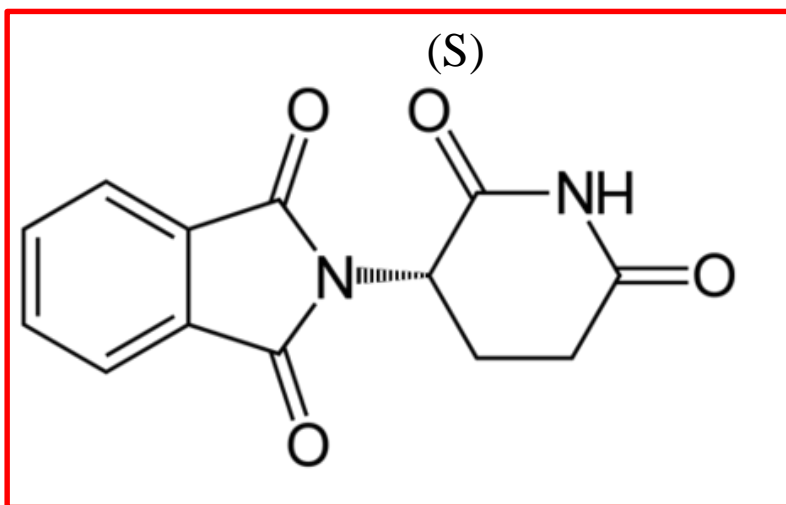
Khoảng 10 000 người sinh ra bị dị tật tay, chân, bàn chân. Bị cấm bán ở nhiều quốc gia từ 1961. **Đồng phân (S) của halidomide gây ra tác hại nghiêm trọng này.**



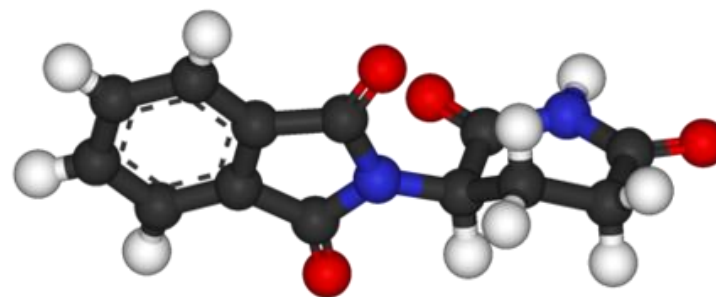
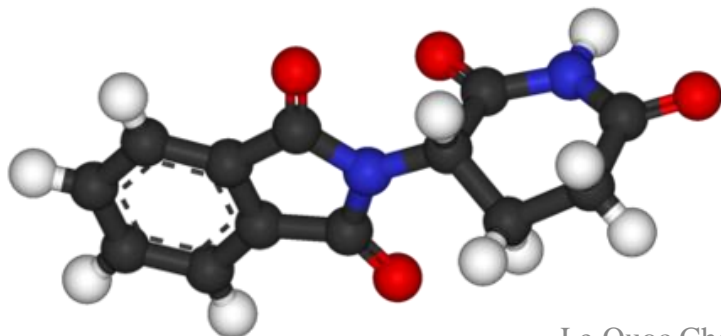
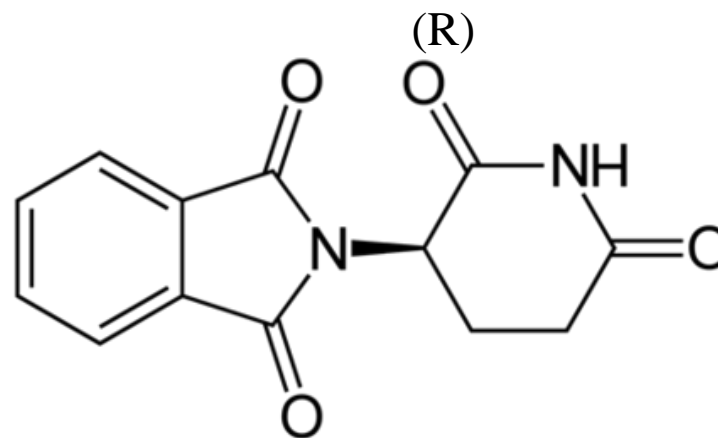
# Causes: the (S) enantiomers

do đồng phân S gây ra

Left: (S)-(-)-thalidomide



Right: (R)-(+)-thalidomide



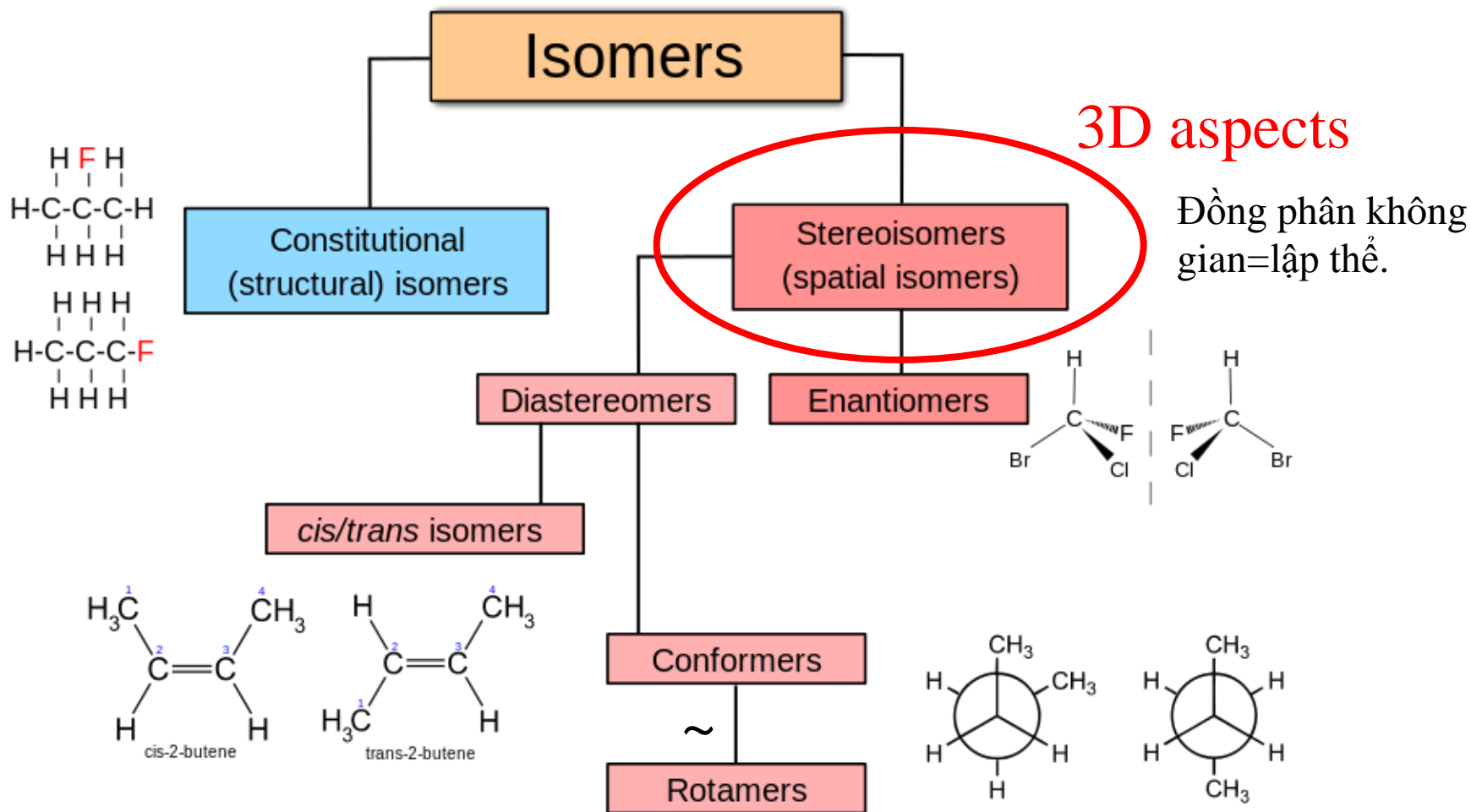
# Organic Chemistry

CHE 203

Lecture 5: Stereochemistry

Le Quoc Chon – Duy Tan University

# Isomerism (đồng phân)



3D aspects

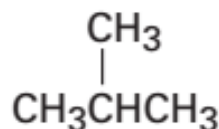
Đồng phân không gian=lập thể.

rotation around single bond

# Constitutional isomers

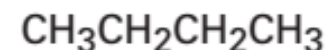
Đồng phân khác nhau do vị trí sắp xếp các nguyên tử

**Different carbon skeletons**



**2-Methylpropane**

and



**Butane**

**Different functional groups**



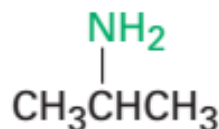
**Ethyl alcohol**

and



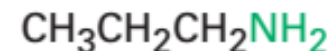
**Dimethyl ether**

**Different position of functional groups**



**Isopropylamine**

and

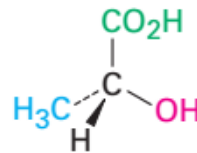


**Propylamine**

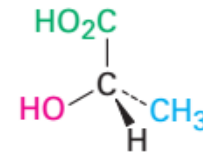
# Stereoisomers

Đồng phân do phân bố trong không gian của các nguyên tử khác nhau

**Enantiomers**  
(nonsuperimposable  
mirror-image  
stereoisomers)

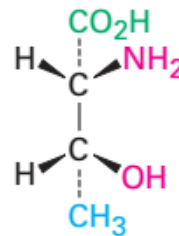


**(R)-Lactic acid**

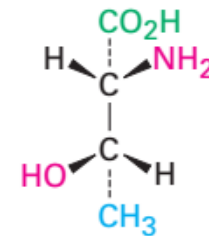


**(S)-Lactic acid**

**Diastereomers**  
(nonsuperimposable  
non-mirror-image  
stereoisomers)



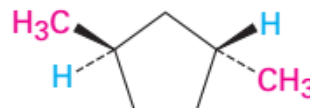
**(2R,3R)-2-Amino-3-hydroxybutanoic acid**



**(2R,3S)-2-Amino-3-hydroxybutanoic acid**

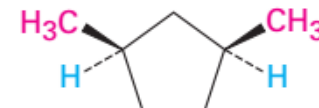
**Configurational  
diastereomers**

**Cis-trans diastereomers**  
(substituents on same  
side or opposite side of  
double bond or ring)



**trans-1,3-Dimethyl-  
cyclopentane**

and



**cis-1,3-Dimethyl-  
cyclopentane**

# Key concepts in Organic Chemistry **you must know**

Tetrahedral carbon (tâm carbon đối xứng)

Stereochemistry (hóa học lập thể)

Enantiomers (đồng phân đối quang)

Diastereomers (đồng phân không đối quang)

Chiral/chirality center (tâm đối xứng)

Meso compounds (hợp chất meso)

Racemic mixture (hỗn hợp racemic)

# Isomerism

**Constitutional isomers:** same molecular formula but different connectedness (giống công thức phân tử nhưng khác nhau vị trí nối mạch)

**Stereoisomers:** same molecular formula, same connectivity of atoms but different arrangement of atoms in space (giống CTPT, giống vị trí nối mạch, nhưng phân bố trong không gian khác nhau)

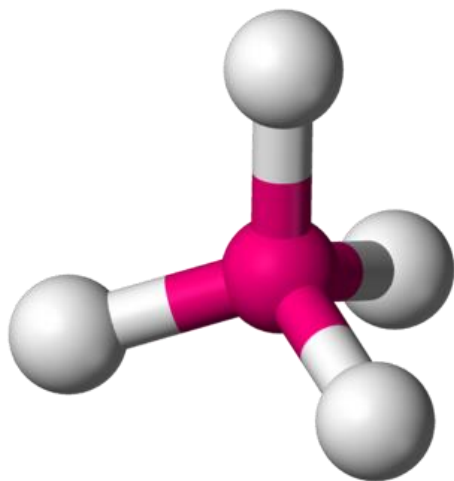
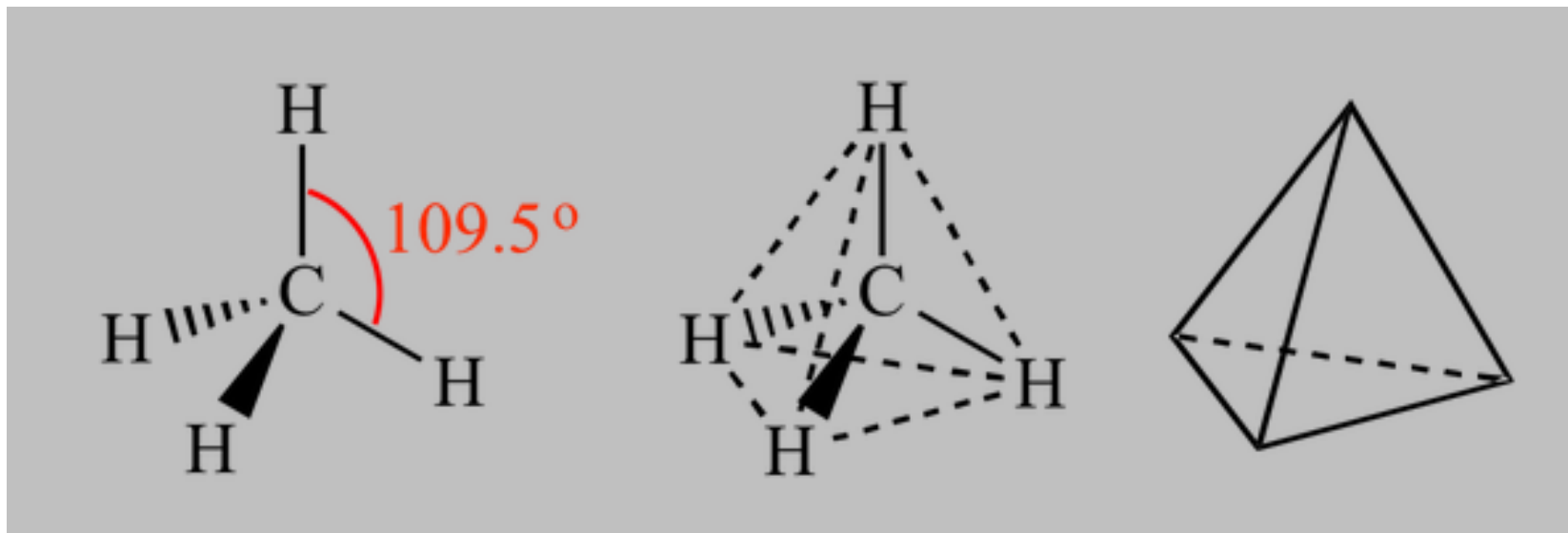
- Enantiomers: stereoisomers whose molecules are nonsuperposable mirror images (đồng phân là hình và ảnh qua gương)
- Diastereomers: stereoisomers whose molecules are not mirror image of each other (không phải hình và ảnh qua gương)

# Isomerism

- **Enantiomers**: stereoisomers whose molecules are nonsuperposable mirror images (đồng phân là hình và ảnh qua gương, không chồng khít lên nhau được)
- **Diastereomers**: stereoisomers whose molecules are not mirror image of each other (không phải hình và ảnh qua gương, không chồng khít lên nhau được)



# Tetrahedral carbon



$sp^3$  hybridization

# Stereochemistry at Tetrahedral center

They are not identical:  
only mirror image

(vật và ảnh qua gương)



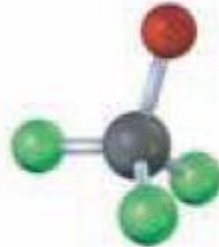
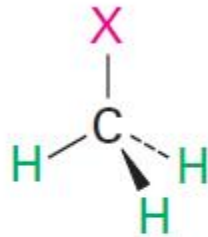
**Left hand**



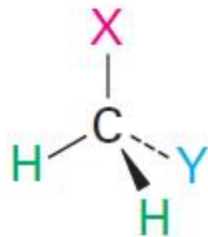
**Right hand**

# Enantiomers (đồng phân quang học)

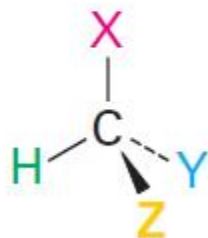
CH<sub>3</sub>X



CH<sub>2</sub>XY



CHXYZ



Superimposable?

Le Qu

(vật ảnh có trùng khít?)

# Enantiomers

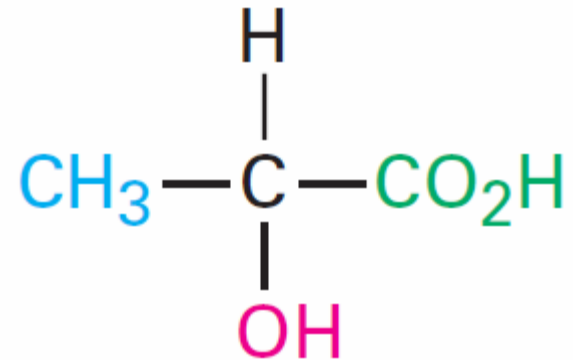
Molecules that are not identical to its mirror images.

(đồng phân quang học: có vật - ảnh không trùng khít nhau)

## Lactic acid

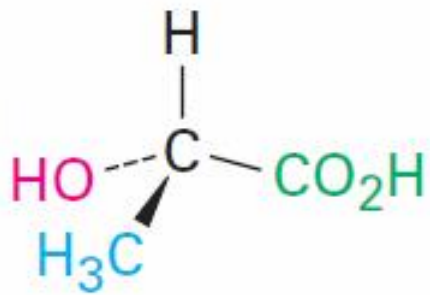
Both (+) and (-) present in sour milk

Only (+) presents in muscle tissue

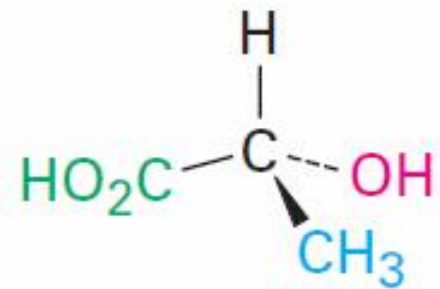
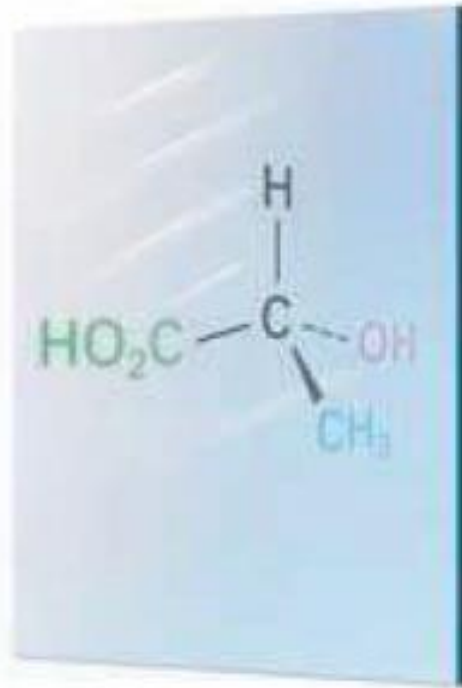


Tetrahedral C ( $sp^3$  – hybridized) bonded to **4 different substituents**. (C bất đối xứng có 4 nhóm thế khác nhau)

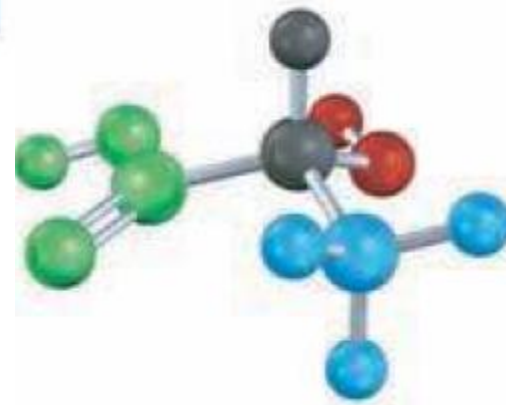
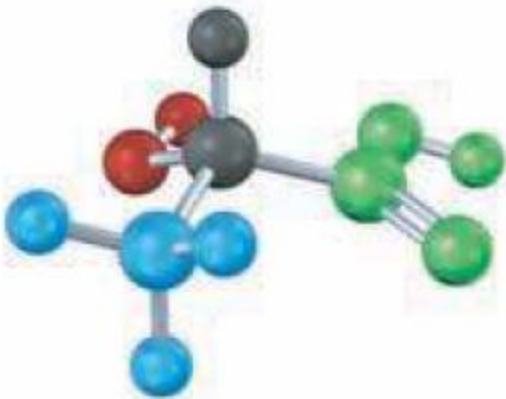
# Enantiomers



**(+)-Lactic acid**



**(-)-Lactic acid**



# Enantiomers & chiral molecules

## Chiral molecule

molecules that are not identical to its mirror image.  
can exist as a pair of enantiomers.

## Pair of enantiomers (cặp đồng phân đối quang)

A chiral molecule and its mirror image

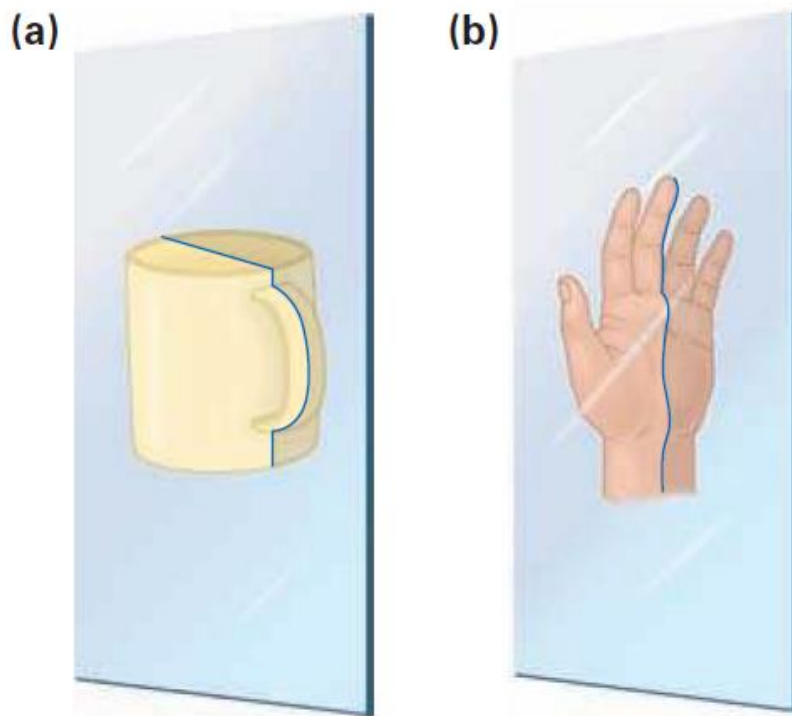
## Achiral molecule

Superposable on its mirror image

# Reason of handedness

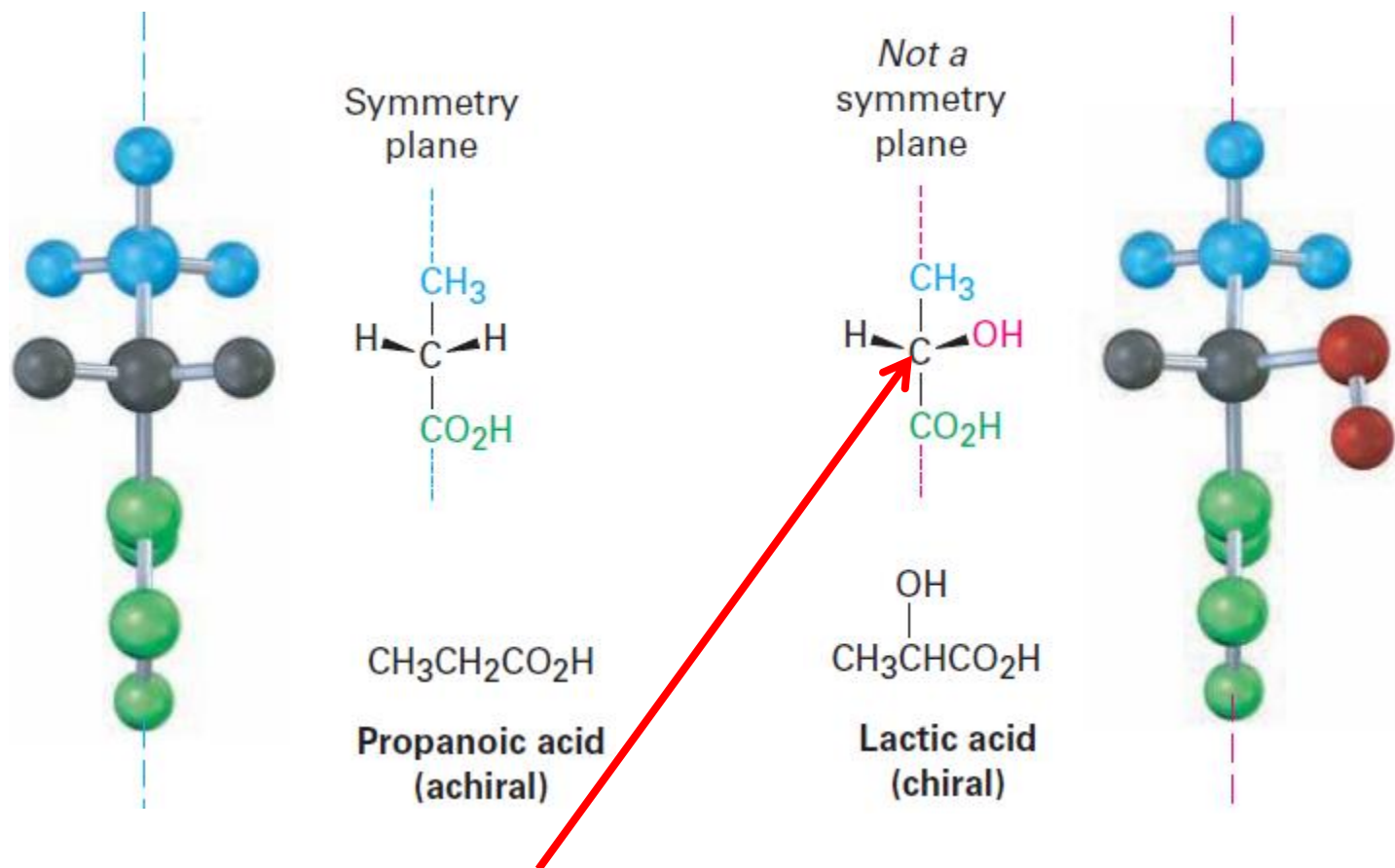
Chiral molecule: a molecule that is not identical to its mirror image and can exist as a pair of enantiomers.

Achiral molecule if it has a plane of symmetry.



# Reason of handedness

(nguyên nhân của đồng phân quang học)

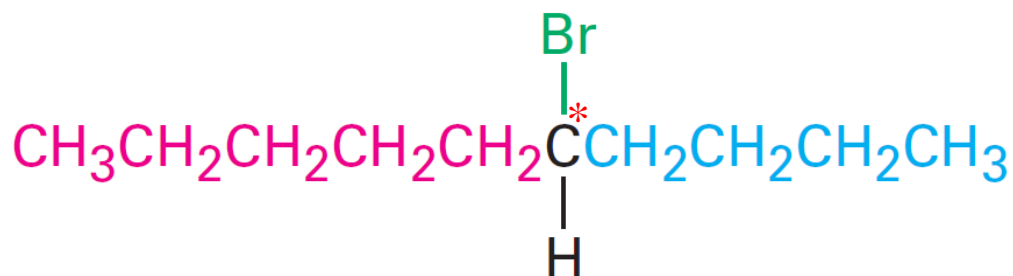


One reason is **the presence of Tetrahedral C bonded to 4 different substituents**: chirality center = asymmetric center = stereocenter



# Chirality center

(C bất đối xứng: có 4 nhóm thế khác nhau)



**5-Bromodecane (chiral)**

Substituents on carbon 5

—H

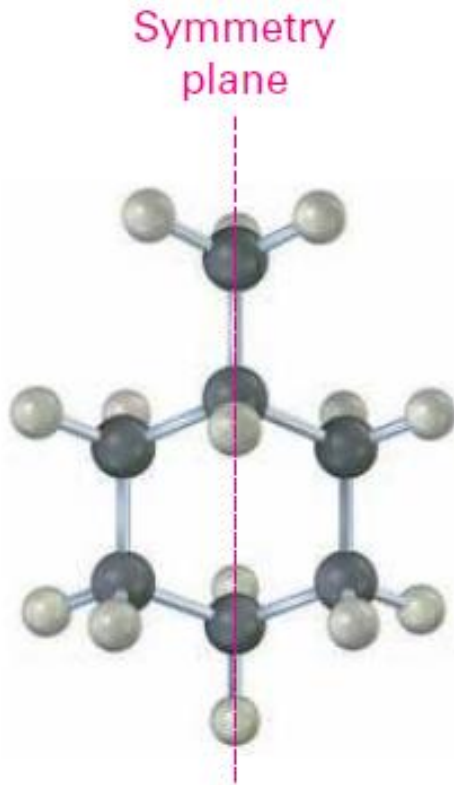
—Br

—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (butyl)

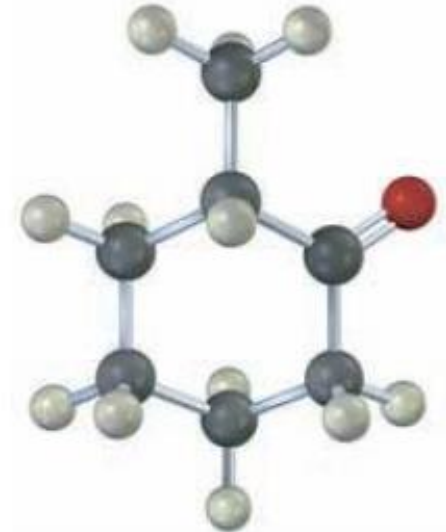
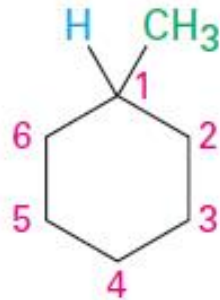
—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (pentyl)

# Chirality center

(C bất đối xứng: có 4 nhóm thế khác nhau)



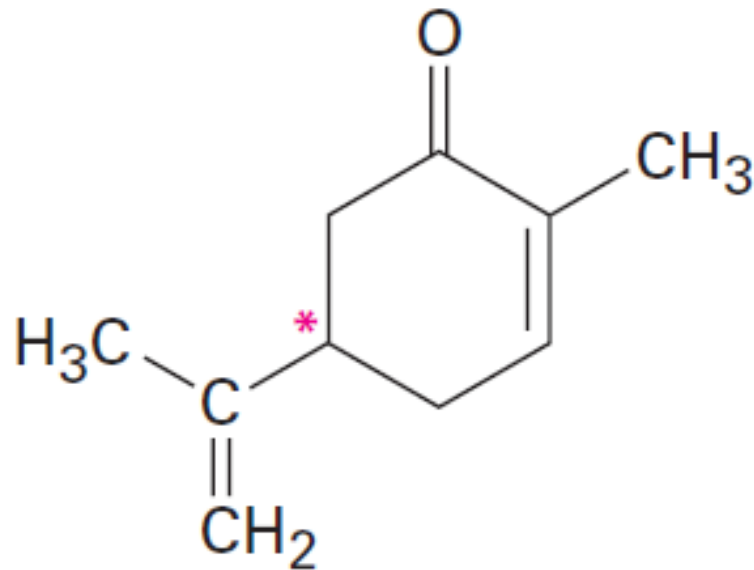
**Methylcyclohexane**  
(achiral)



**2-Methylcyclohexanone**  
(chiral)

# Chirality center

(C bất đối xứng: có 4 nhóm thế khác nhau)



**Carvone (spearmint oil)**

## Odour character differences for enantiomers correlate with molecular flexibility

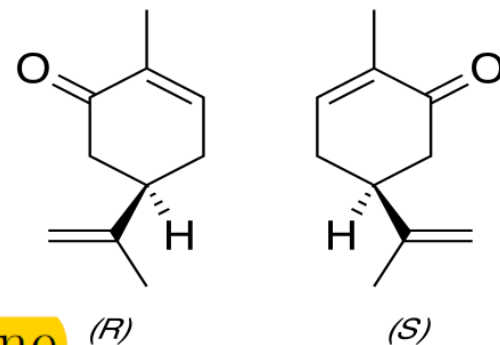
Jennifer C Brookes, A.P Horsfield and A.M Stoneham

*J. R. Soc. Interface* 2009 **6**, 75-86

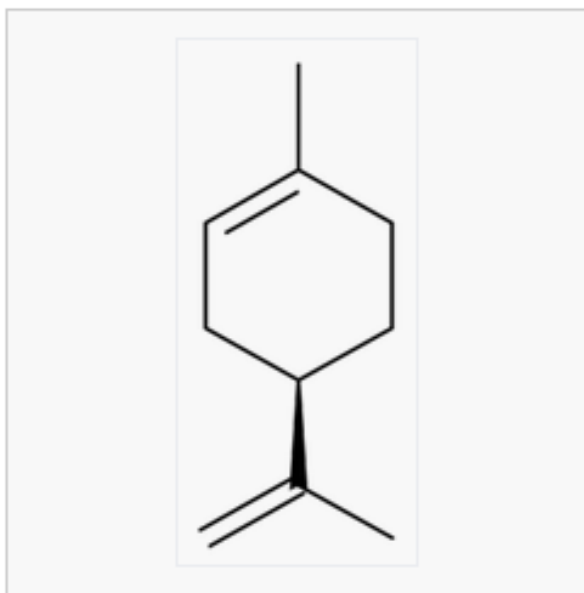
doi: 10.1098/rsif.2008.0165

enantiomers smell different. Thus, (4*R*)-(–)carvone smells minty, whereas (4*S*)-(+)carvone smells like

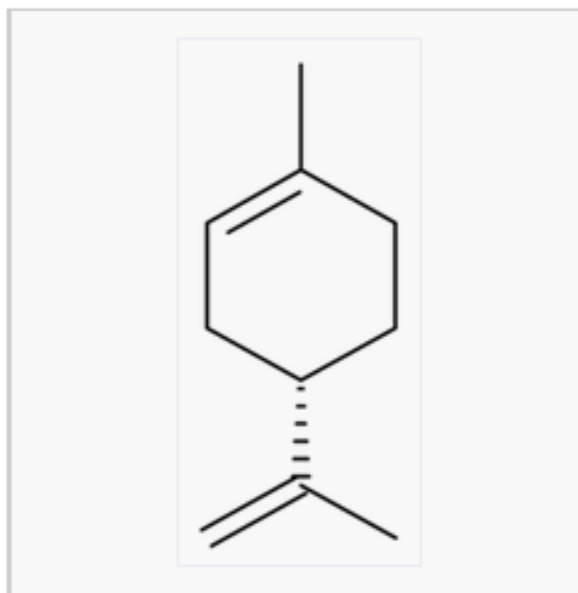
caraway. Non-olfactory examples include the effects of cocaine (1*R*, 2*R*, 3*S*, 5*S* is psychoactive, while 1*S*, 2*S*, 3*S*, 5*R* is inactive), the hormone thyroxine (*R* is inactive, while *S* is active) and the gypsy moth pheromone disparlure (7*R*, 8*S* activates a response, whereas 7*S*, 8*R* inhibits a response). A distinction is also made in taste. In a few cases, D-amino acids have a sweet taste, whereas the enantiomers are tasteless. As



## Limonene from Lemon and Orange.

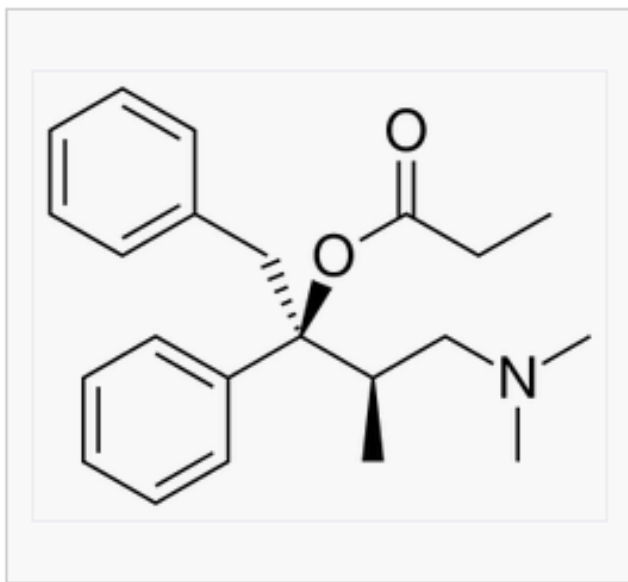


R-(+)-Limonene found in orange

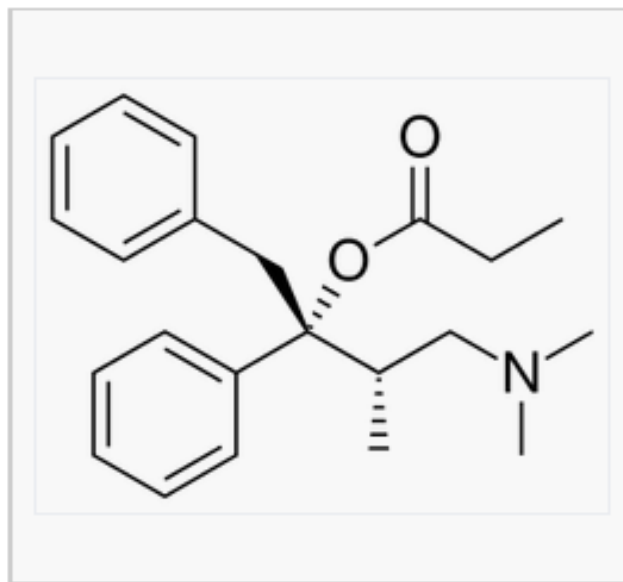


S-(-)-Limonene found in lemon.

## Dextropropoxyphene and Levopropoxyphene



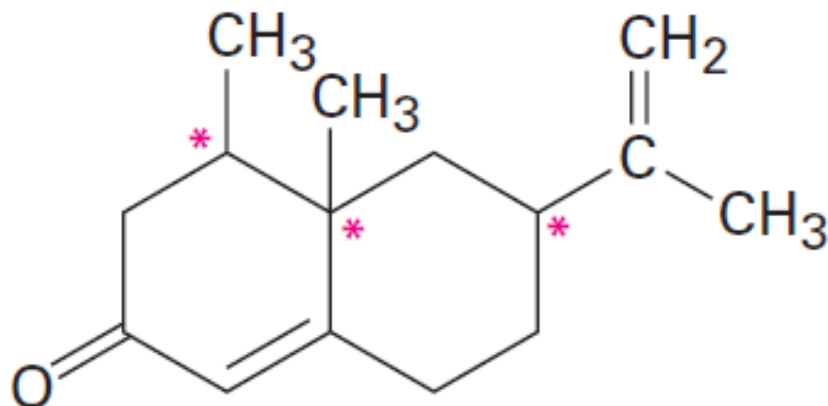
Dextropropoxyphene or Darvon,  
a painkiller.



Levopropoxyphene or Novrad,  
an anticough agent.

# Chirality center

(Tâm C bất đối xứng: có 4 nhóm thế khác nhau)



**Nootkatone (grapefruit oil)**

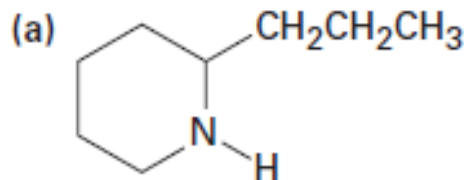
-CH<sub>2</sub>-, -CH<sub>3</sub>, and C in double or triple bond can not be chiral center.

# 5. Problem

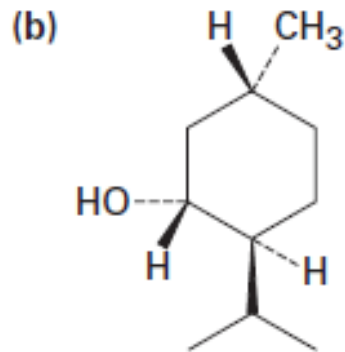
(chất nào sau đây là chiral, chỉ ra chirality centers)

## PROBLEM 5-2

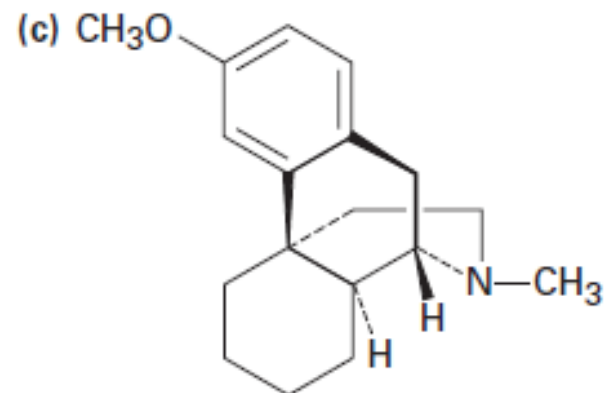
Which of the following molecules are chiral? Identify the chirality center(s) in each.



**Coniine**  
(poison hemlock)  
(sâm độc)



**Menthol**  
(flavoring agent)  
(tạo vị)



**Dextromethorphan**  
(cough suppressant)  
(thuốc giảm ho)

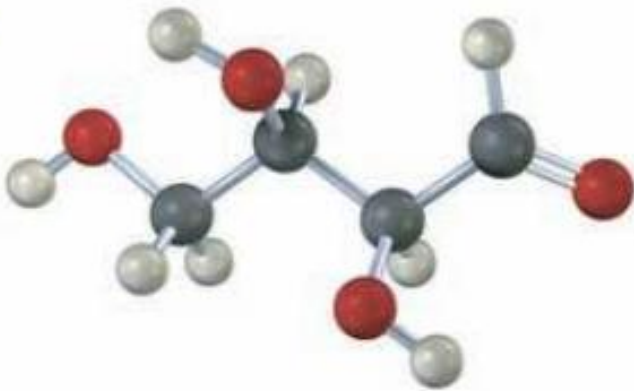


# 6.Problem

**PROBLEM 5-4** (chỉ ra chirality centers trong các chất sau)

Identify the chirality centers in the following molecules (green = Cl, yellow-green = F):

(a)



**Threose**  
(a sugar)

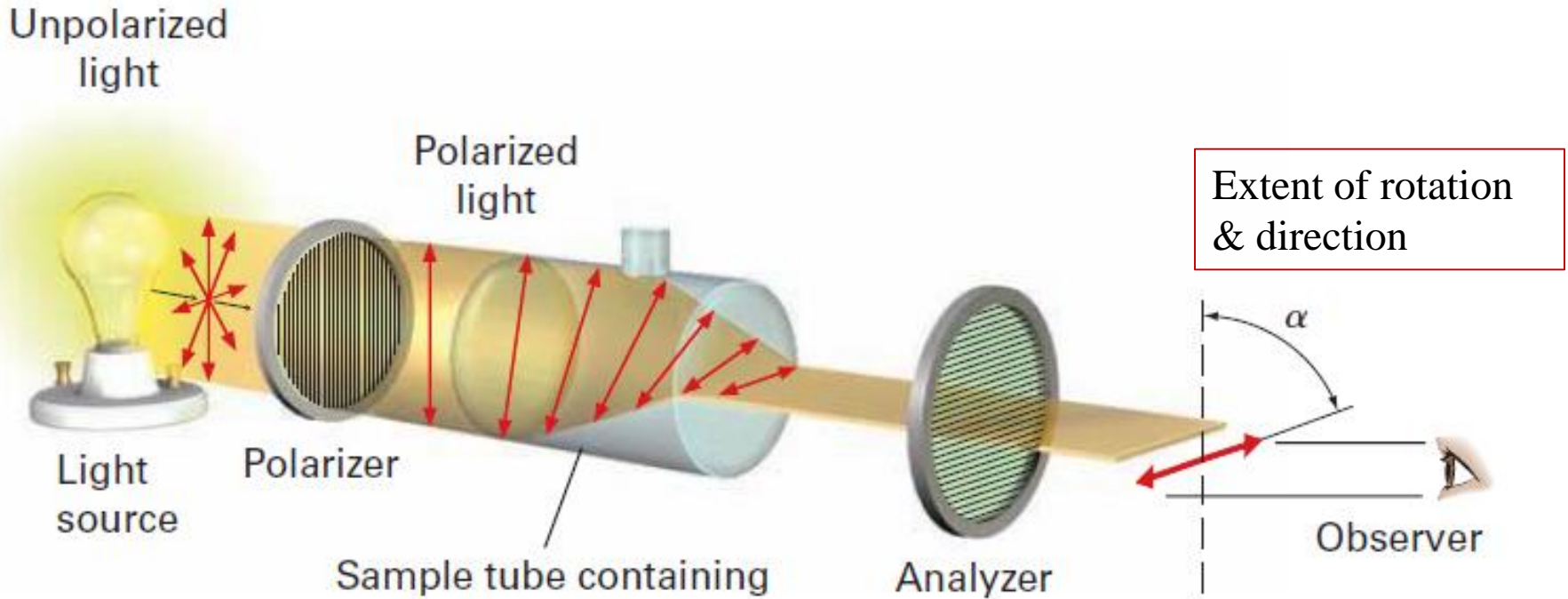
(b)



**Enflurane**  
(an anesthetic)

(thuốc gây mê, nhưng  
hiện nay ít dùng)

# Optical activity (hoạt tính quang học)



**Organic molecules**

Optically active



Clockwise: **dextrorotatory (+)**

Counterclockwise: **levorotatory (-)**

# Extent of rotation

(mức độ quay mặt phẳng ánh sáng phân cực)

$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

TABLE 5-1 Specific Rotation of Some Organic Molecules

Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	+233	Cholesterol	-31.5
Sucrose	+66.47	Morphine	-132
Camphor	+44.26	Cocaine	-16
Chloroform	0	Acetic acid	0

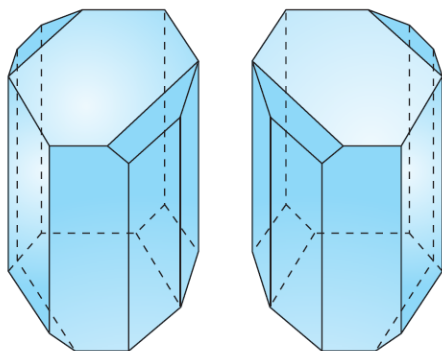
Specific condition:

589.6 nm.

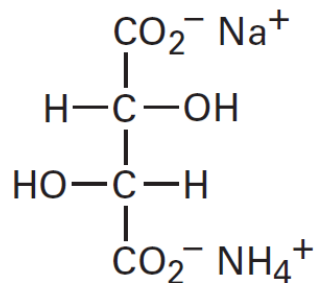
pathlength 1 dm

Sample concentration 1 g/cm<sup>3</sup>

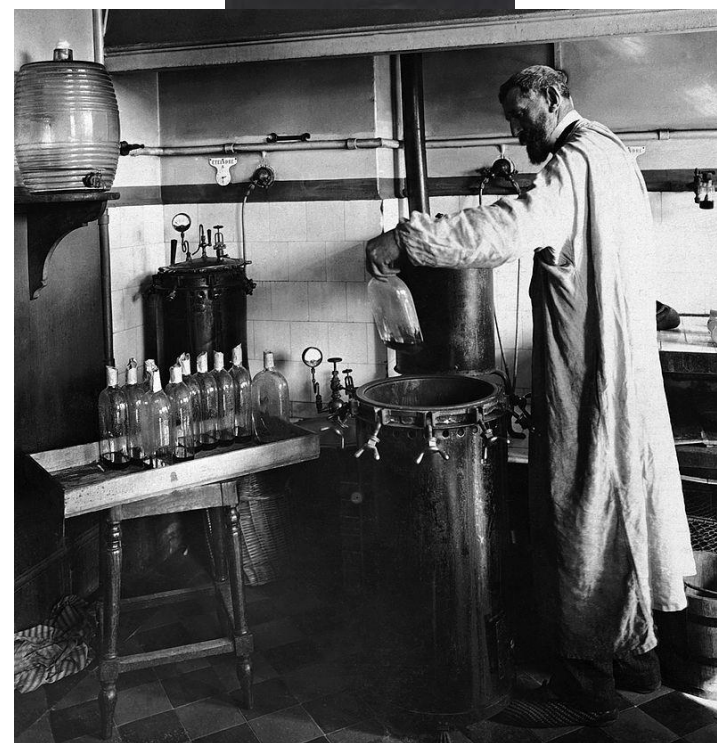
# Pasteur's discovery of Enantiomer



1849



Sodium ammonium tartrate



Two kind of crystals: optical isomers

# REVIEWS

## PUTTING CHIRALITY TO WORK: THE STRATEGY OF CHIRAL SWITCHES

Israel Agranat<sup>\*‡</sup>, Hava Caner<sup>‡</sup> and John Caldwell<sup>\*</sup>

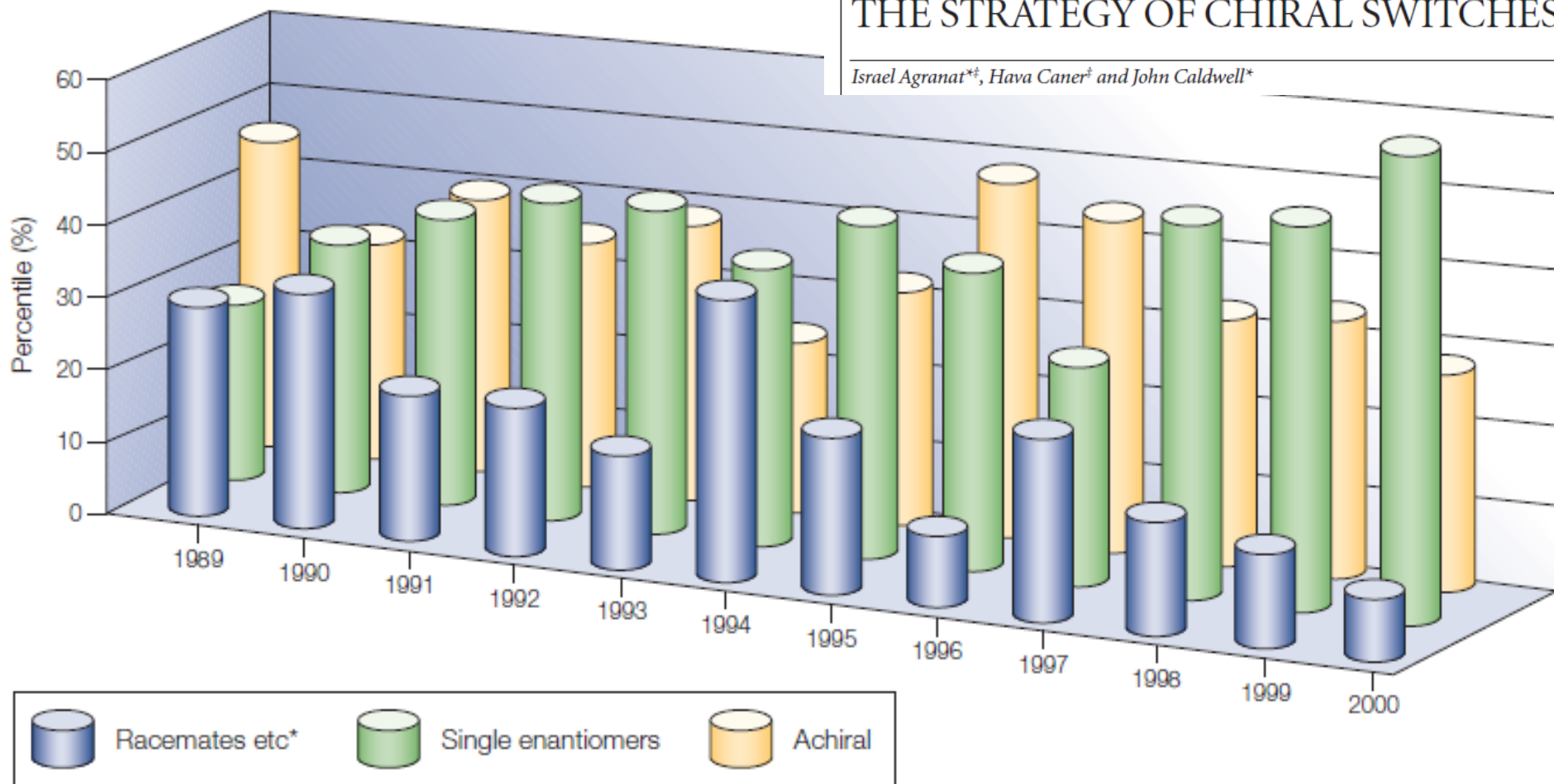
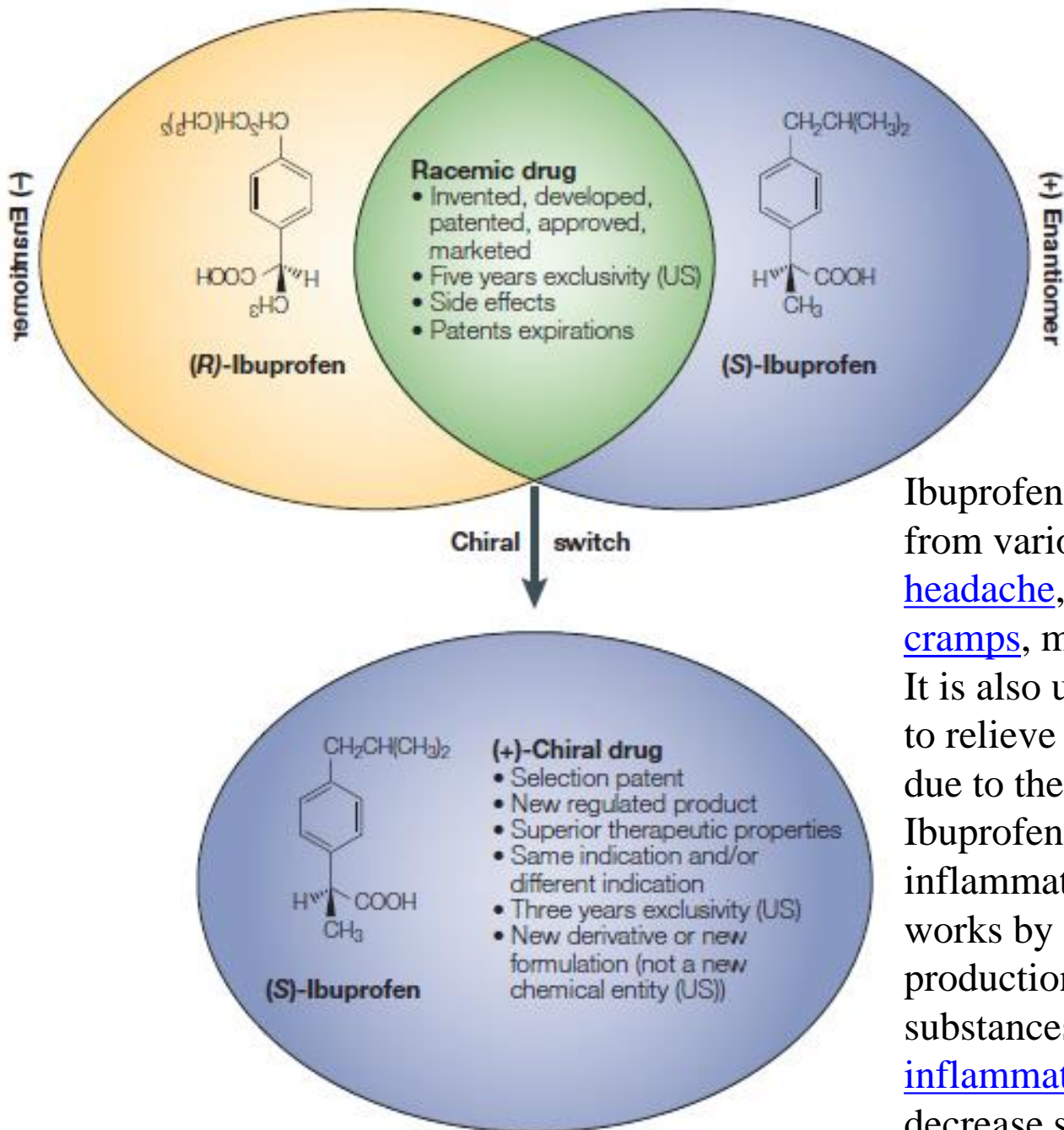


Figure 3 | **Annual distribution of worldwide approved drugs according to chirality character (1989–2000).** Data obtained from REF. 23.\* Including diastereomeric mixtures.

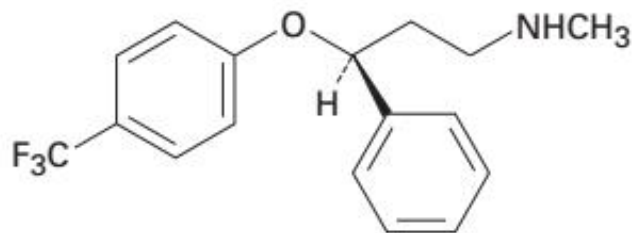
(phân loại thuốc được dùng trên thế giới theo năm)



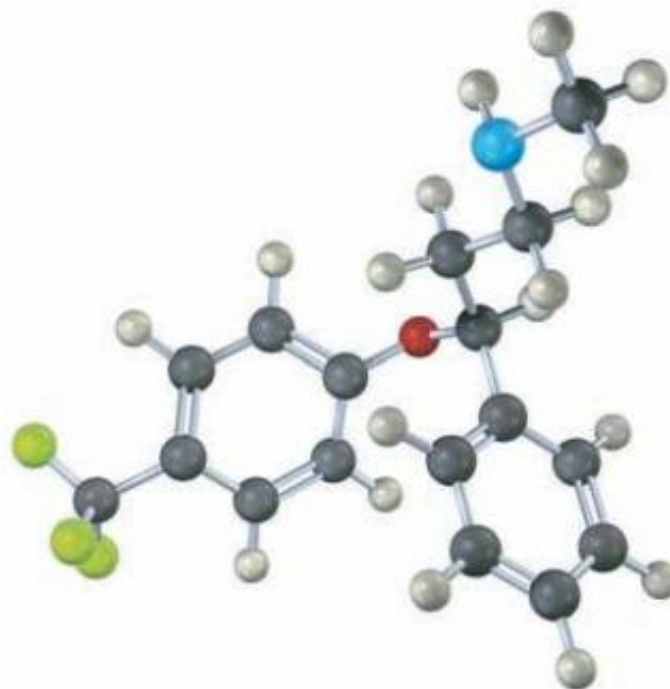
Ibuprofen is used to relieve pain from various conditions such as [headache](#), dental pain, [menstrual cramps](#), muscle aches, or [arthritis](#). It is also used to reduce fever and to relieve minor aches and pain due to the [common cold](#) or [flu](#). Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). It works by blocking your body's production of certain natural substances that cause [inflammation](#). This effect helps to decrease swelling, pain, or fever.

Figure 4 | The chiral-switch concept.

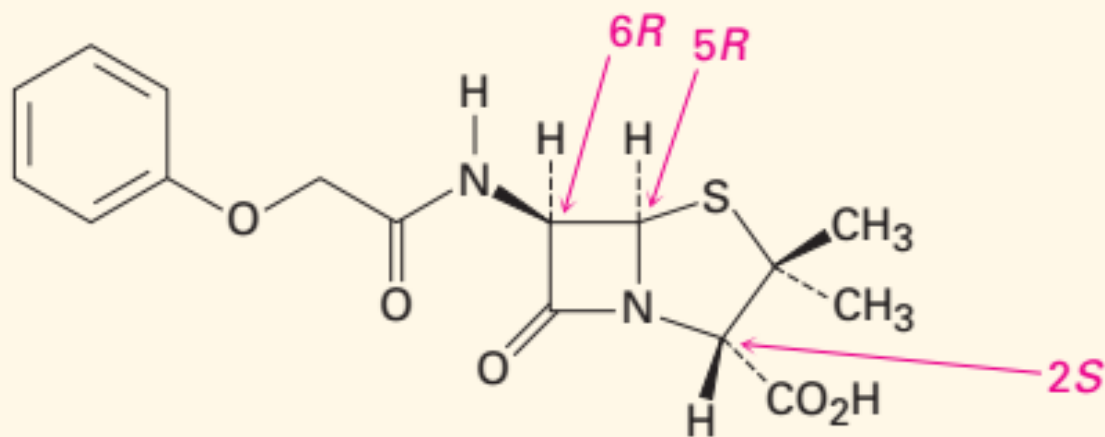
More dramatic examples of how a change in chirality can affect the biological properties of a molecule can be found in many drugs, such as fluoxetine, a heavily prescribed medication sold under the trade name Prozac. Racemic fluoxetine is an extraordinarily effective antidepressant but has no activity against migraine. The pure *S* enantiomer, however, works remarkably well in preventing migraine. Other examples of how chirality affects biological properties are given in *Something Extra* at the end of this chapter.



**(S)-Fluoxetine**  
**(prevents migraine)**



rather than as a racemate. Penicillin V, for example, an antibiotic isolated from the *Penicillium* mold, has the  $2S,5R,6R$  configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.



**Penicillin V ( $2S,5R,6R$  configuration)**



# Configuration of chirality center: R, S (cấu hình R, S)

## **Cahn-Ingold-Prelog** rules:

1. Rank 4 atoms directly attached to chirality center C according to atomic number.
2. If the first atoms are the same, use second, third, fourth atoms.
3. Multiple-bonded atoms are equivalent to the number of single-bonded atoms
4. Orient molecules so that the lowest ranking (4) points directly from us (observer). Connect the others: 1=>2=>3 and determine the direction of this connection. If the connection is Clockwise, chirality center is R configuration, otherwise S.

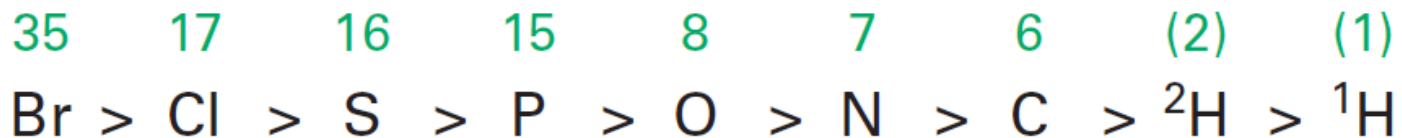
# Configuration of chirality center

**Cahn-Ingold-Prelog** rules:

1. Rank 4 atoms directly attached to chirality center C according to atomic number.

(sắp xếp các nhóm thế gắn với C bất đối xứng theo thứ tự ưu tiên)

**Atomic number**



Higher ranking

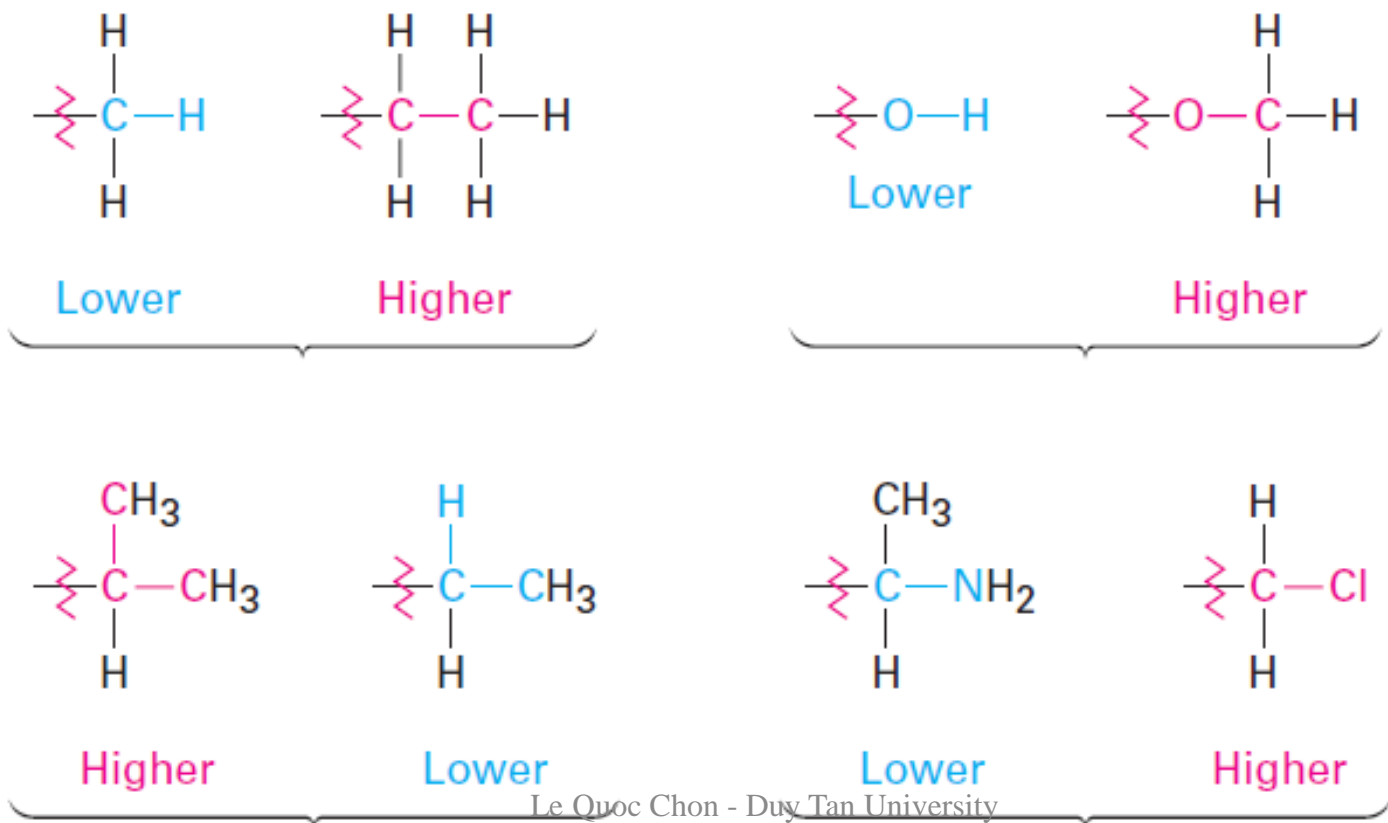
Lower ranking

# Configuration of chirality center

Cahn-Ingold-Prelog rules:

2. If the first atoms are the same, use second, third, fourth atoms.

(nếu nguyên tố đầu tiên giống nhau thì dùng nguyên tố thứ 2, 3,...)

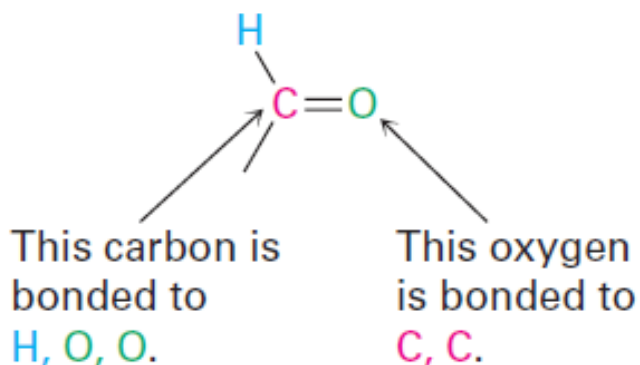


# Configuration of chirality center

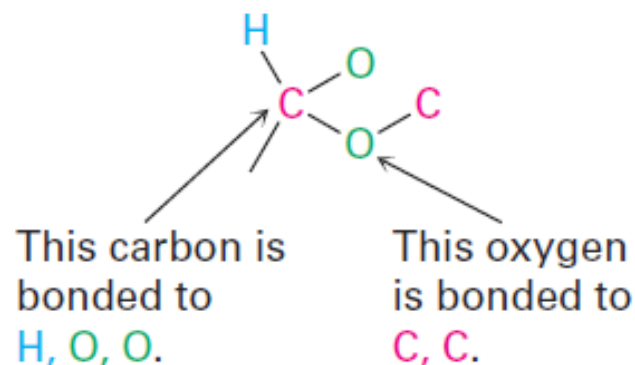
Cahn-Ingold-Prelog rules:

3. Multiple-bonded atoms are equivalent to the number of single-bonded atoms

(liên kết bội (2, 3) tương đương với số nguyên tử (2, 3) có liên kết đơn)



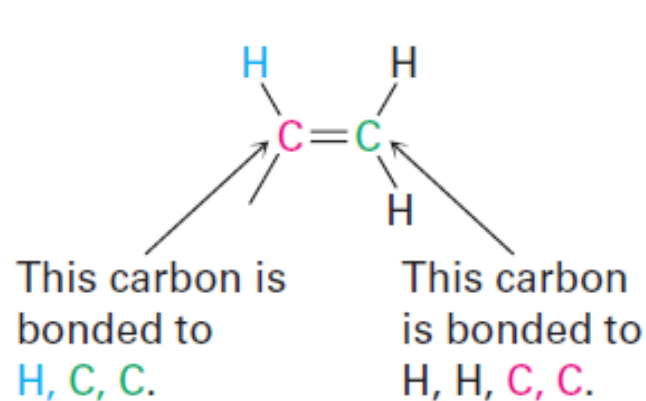
is equivalent to



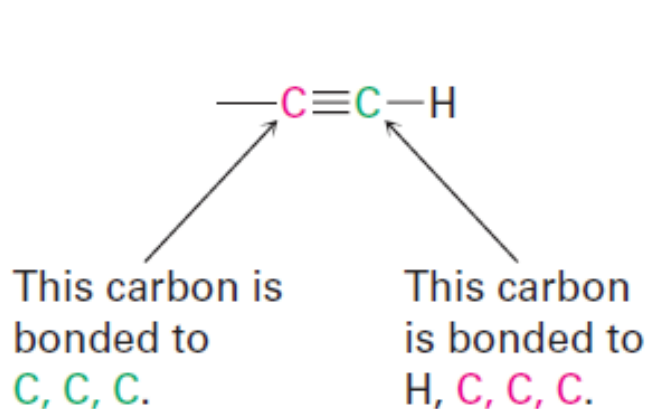
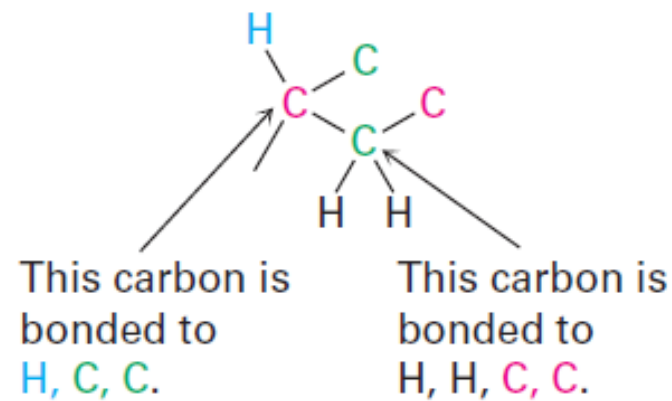
# Rule 3

Cahn-Ingold-Prelog rules:

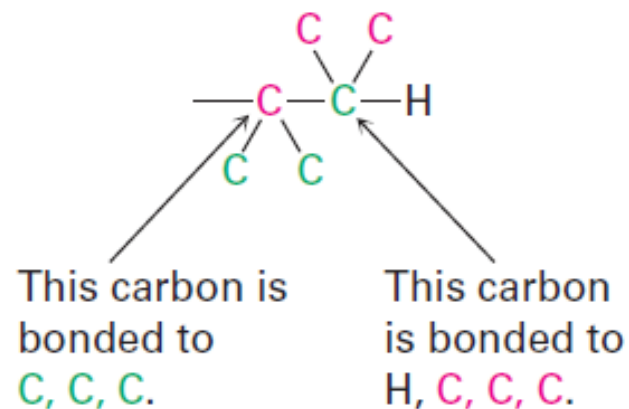
3. Multiple-bonded atoms are equivalent to the number of single-bonded atoms (liên kết bội (2, 3) tương đương với số nguyên tử (2, 3) có liên kết đơn)



is equivalent to

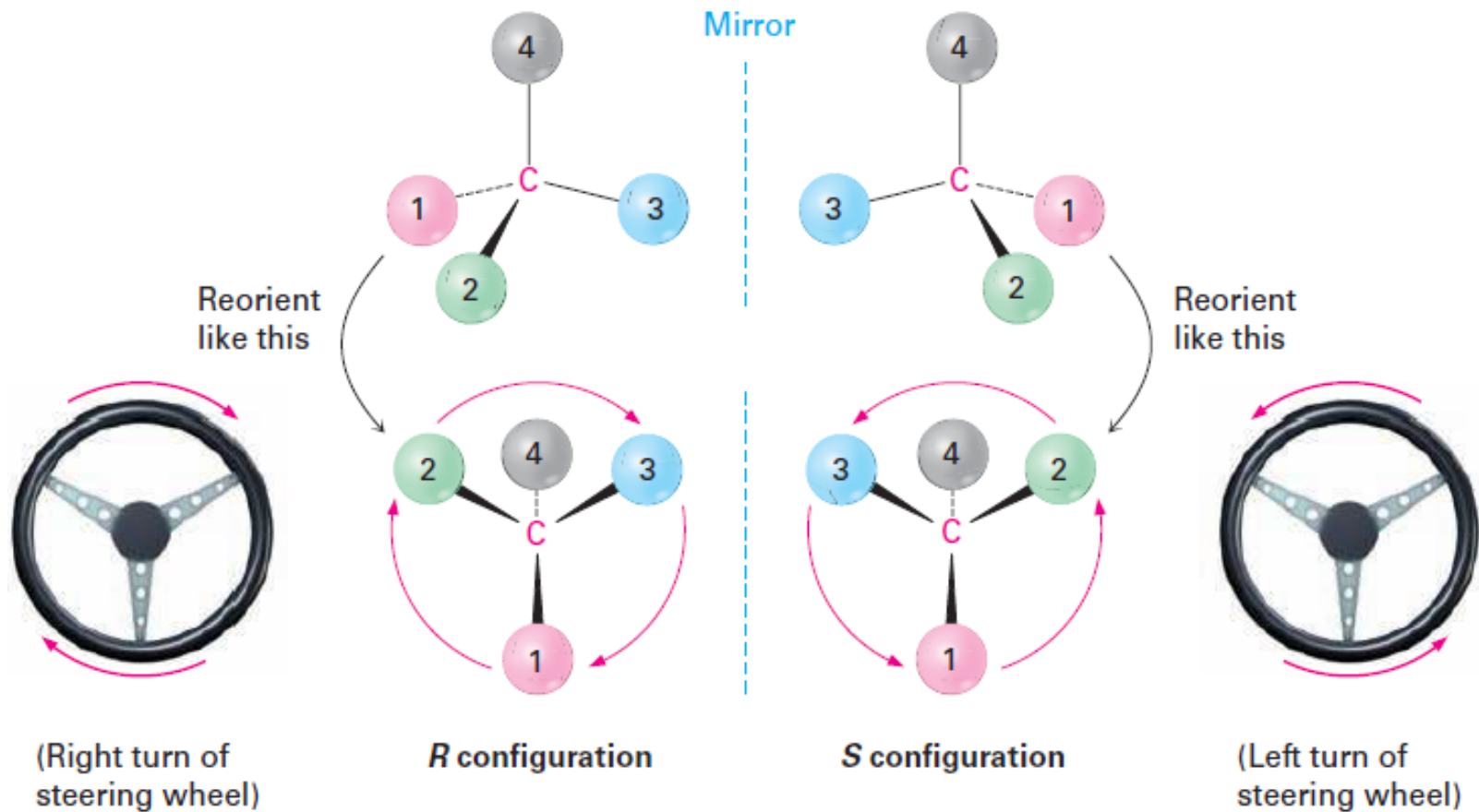


is equivalent to

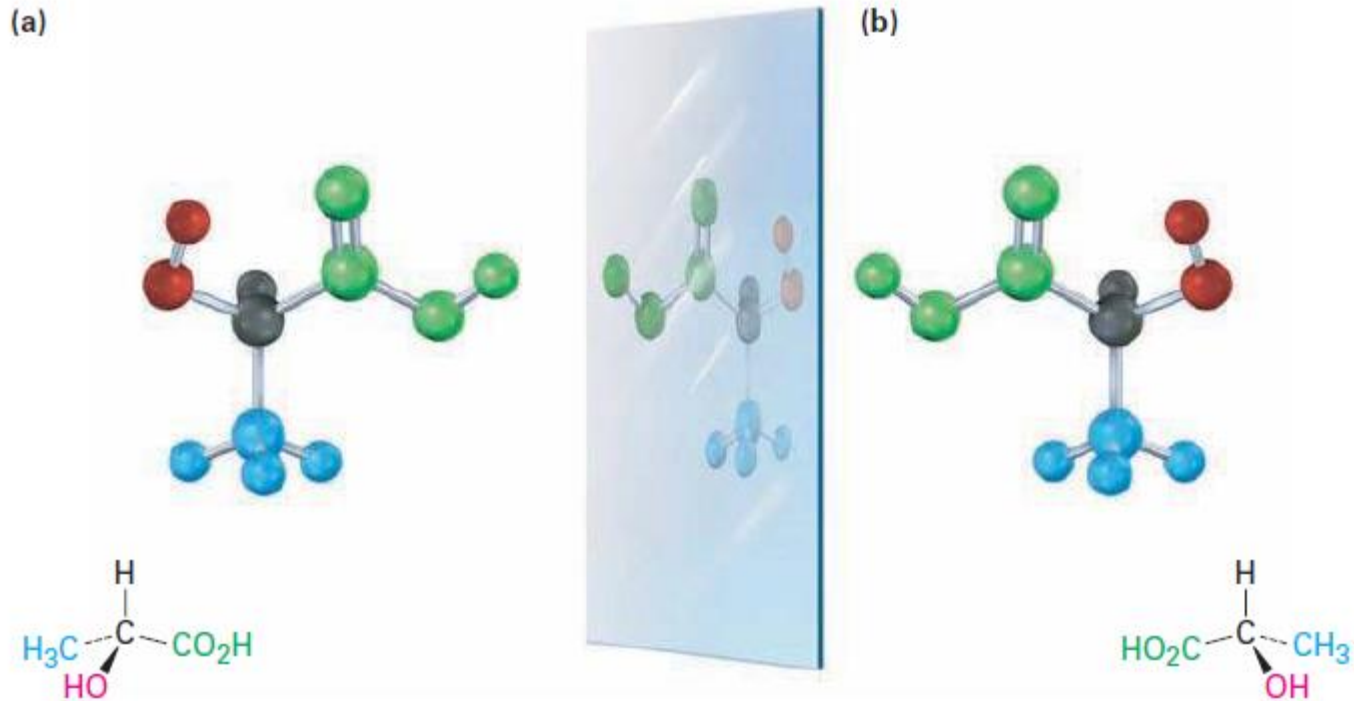


# Rule 4

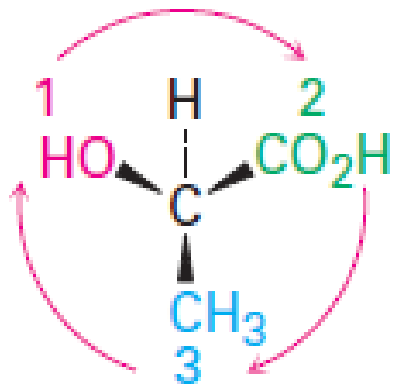
Sắp xếp các nhóm thế xung quanh C\*, sao cho nhóm 4 đứng xa người quan sát nhất. Nối vòng mũi tên các nhóm theo chiều  $1 \Rightarrow 2 \Rightarrow 3$ . Nếu vòng mũi tên xoay theo hướng đồng hồ thì chất có cấu hình R, ngược lại là S.



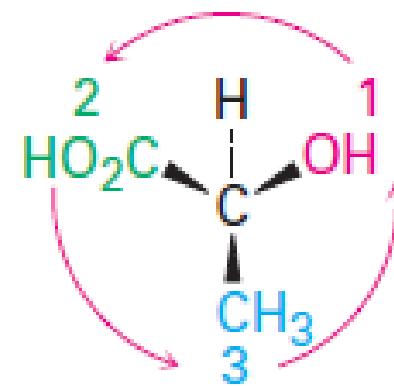
# Example



Xác định cấu hình R, S của Lactic acid.



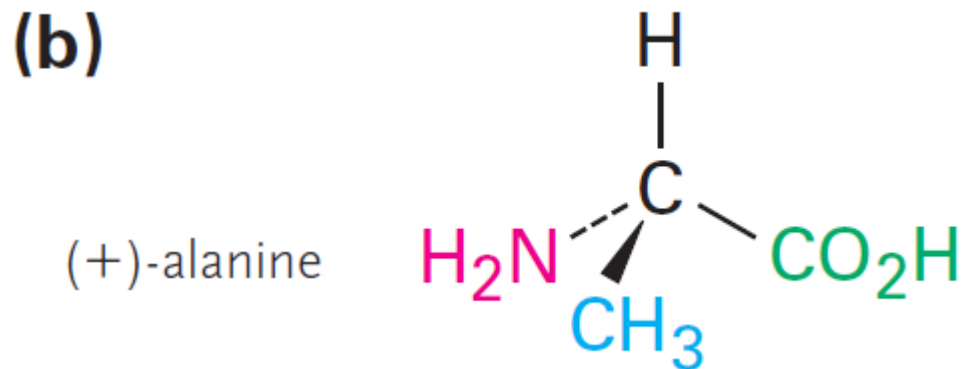
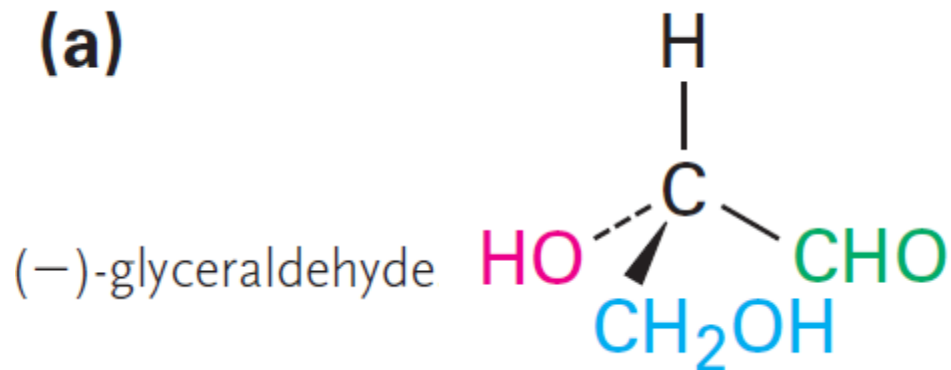
**R configuration**  
**(-)-Lactic acid**



**S configuration**  
**(+)-Lactic acid**

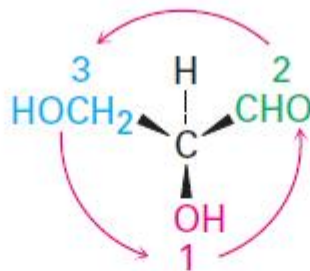
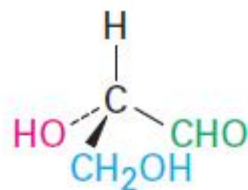


# Example: determine configuration R or S



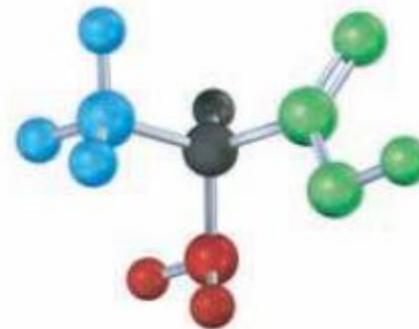
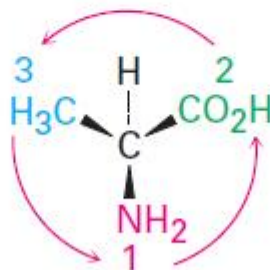
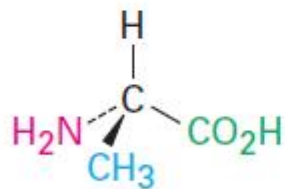
# Example: determine configuration R or S

(a)



**(S)-Glyceraldehyde**  
**[(S)-(-)-2,3-Dihydroxypropanal]**  
 $[\alpha]_D = -8.7$

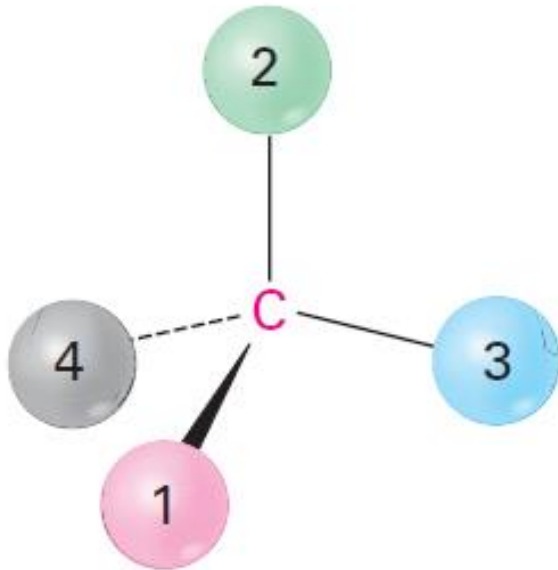
(b)



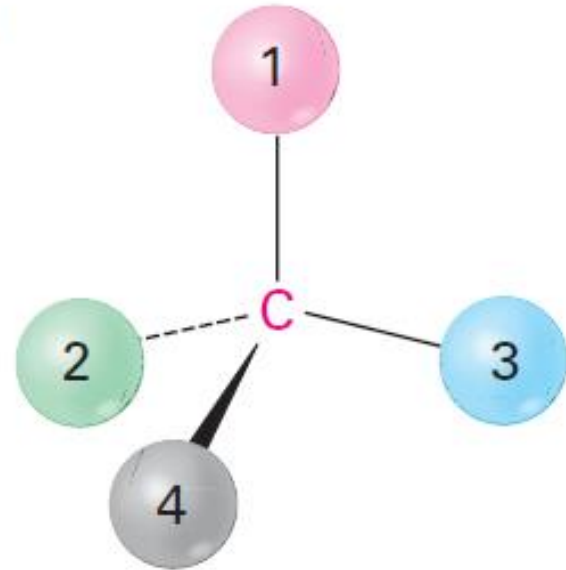
**(S)-Alanine**  
**[(S)-(+)-2-Aminopropanoic acid]**  
 $[\alpha]_D = +8.5$

# Example: determine configuration R or S

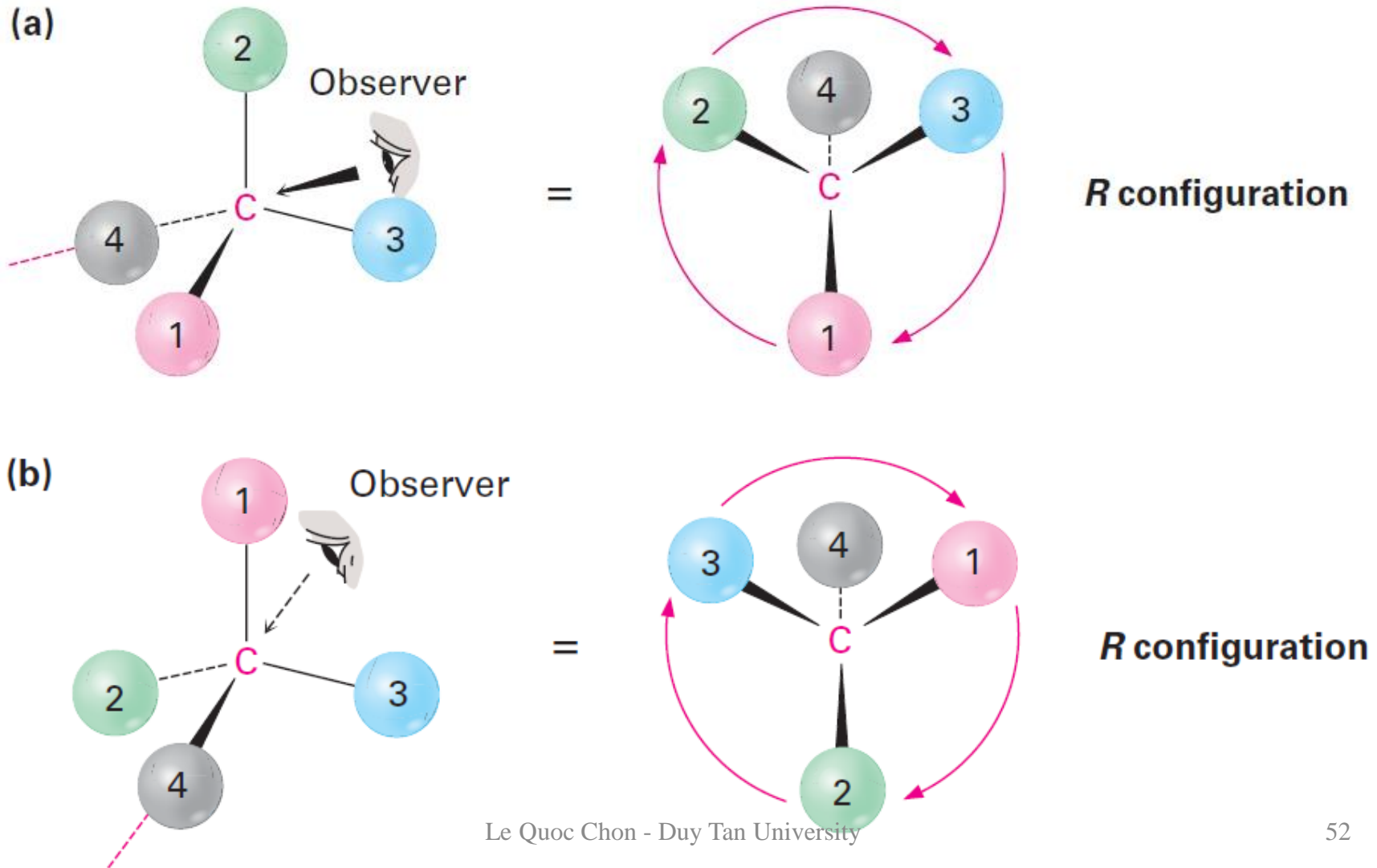
(a)



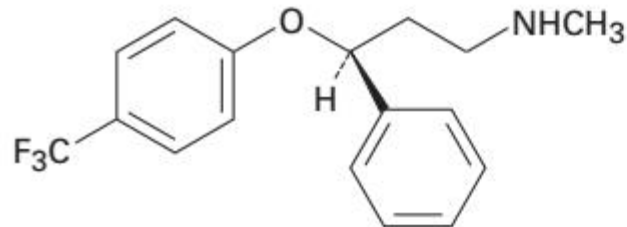
(b)



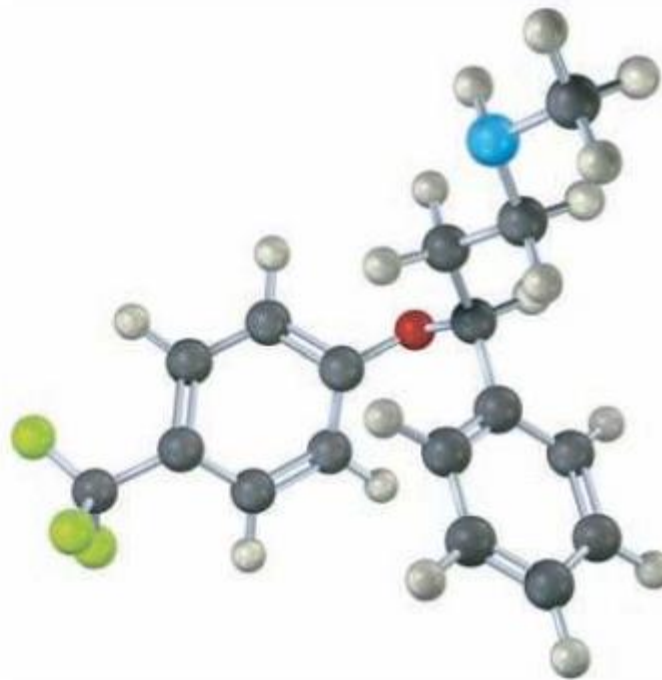
# Example: determine configuration R or S



# R,S configuration vs drug's activity



**(S)-Fluoxetine**  
(prevents migraine)



**Racemic fluoxetine:** antidepressant (but no activity against migraine)

**(S)-Fluoxetine:** prevent migraine

# Problem

(sắp xếp theo thứ tự ưu tiên các nhóm thế)

## PROBLEM 5-7

Which member in each of the following sets ranks higher?

(a)  $-H$  or  $-Br$

(b)  $-Cl$  or  $-Br$

(c)  $-CH_3$  or  $-CH_2CH_3$

(d)  $-NH_2$  or  $-OH$

(e)  $-CH_2OH$  or  $-CH_3$

(f)  $-CH_2OH$  or  $-CH=O$

# Problem

(sắp xếp theo thứ tự ưu tiên các nhóm thế)

## PROBLEM 5-8

Rank the following sets of substituents:

(a)  $-\text{H}$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$

(b)  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{OH}$

(c)  $-\text{CN}$ ,  $-\text{CH}_2\text{NH}_2$ ,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{NH}_2$

(d)  $-\text{SH}$ ,  $-\text{CH}_2\text{SCH}_3$ ,  $-\text{CH}_3$ ,  $-\text{SSCH}_3$

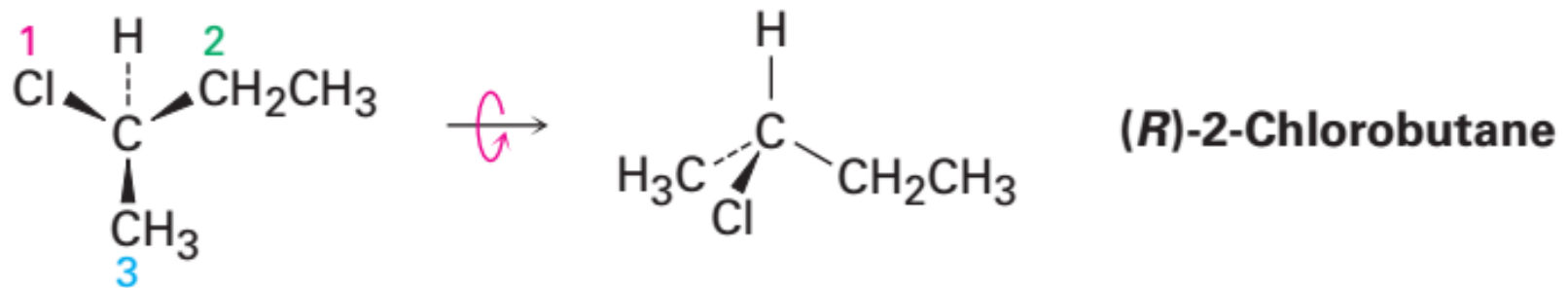
# Problem

Hãy vẽ (R)-2-chlorobutane

Draw a tetrahedral representation of (*R*)-2-chlorobutane.

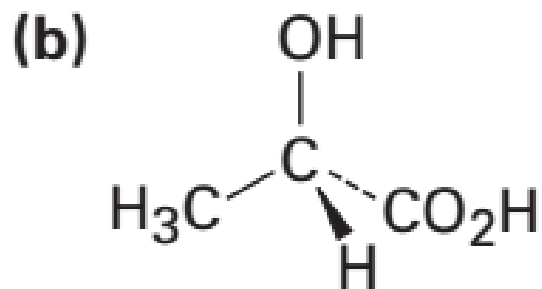
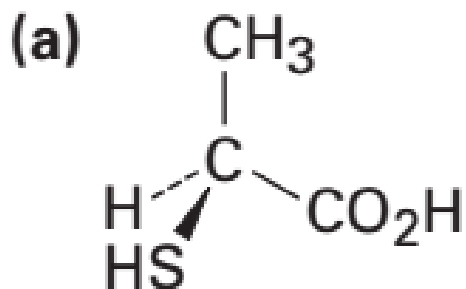


# Solution (kết quả)



# Problem

Xác định cấu hình R, S của tâm bất đối xứng trong các chất sau:

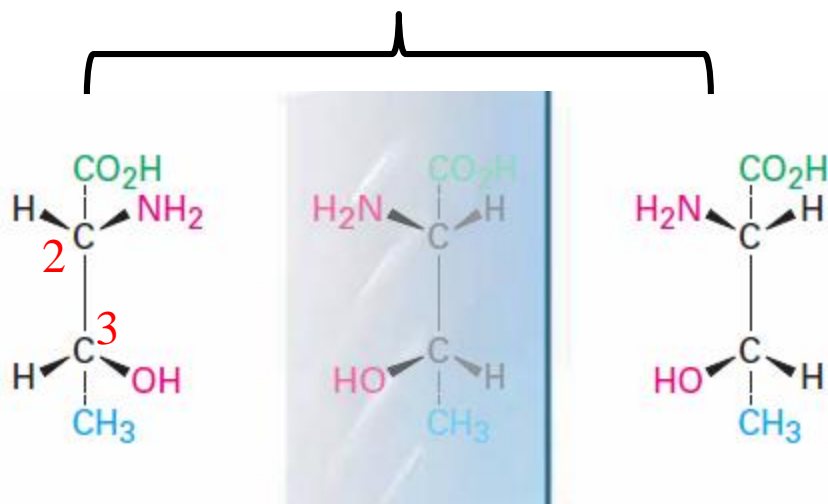


# Diastereomers

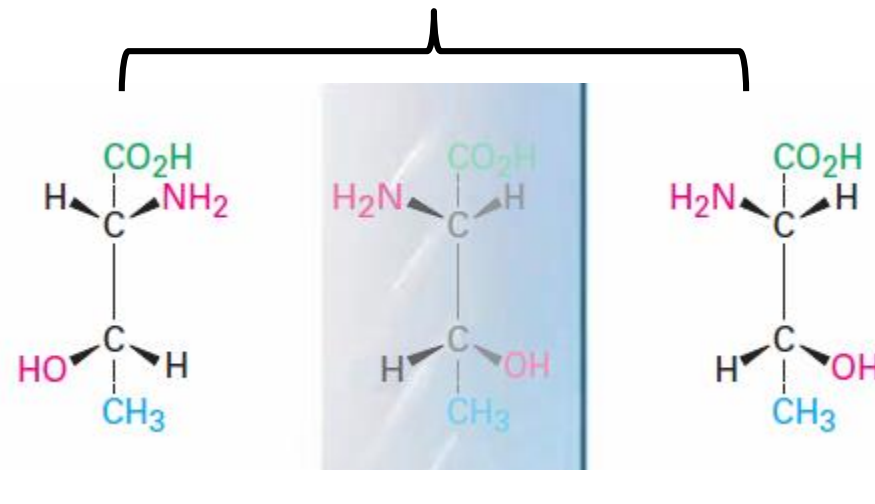
n chirality centers =>  $2^n$  stereoisomers

Diastereomer: stereoisomers that are not mirror images

enantiomers



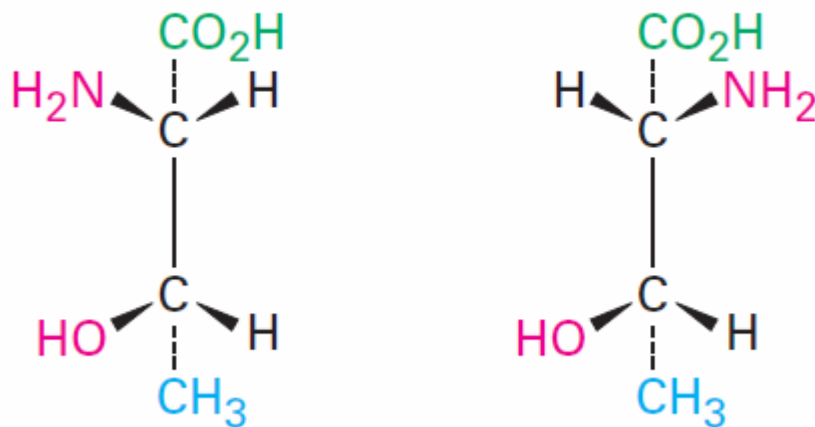
enantiomers



Four stereoisomers of 2-amino-3-hydroxybutanoic acid  
(amino acid threonine)

# Diastereomers

Diastereomers are stereoisomers that are not mirror images.



2S, 3S

2R, 3S

# Diastereomers

**TABLE 5-2 Relationships among the Four Stereoisomers of Threonine**

Stereoisomer	Enantiomer	Diastereomer
$2R,3R$	$2S,3S$	$2R,3S$ and $2S,3R$
$2S,3S$	$2R,3R$	$2R,3S$ and $2S,3R$
$2R,3S$	$2S,3R$	$2R,3R$ and $2S,3S$
$2S,3R$	$2R,3S$	$2R,3R$ and $2S,3S$

Threonine là  $\alpha$  amino acid dùng trong tổng hợp protein bằng phương pháp sinh học.

# Diastereomers

They are similar, but are not identical and are not mirror images.

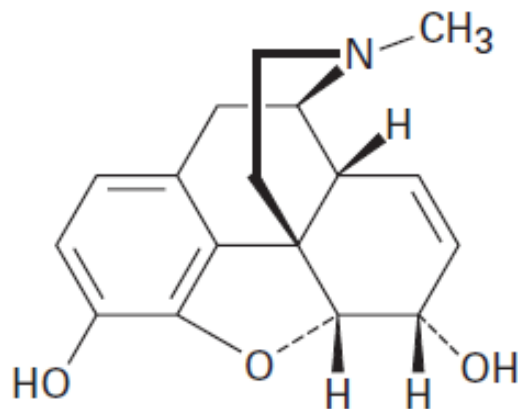
(tương tự nhau, nhưng không phải là ảnh và vật của nhau qua gương)

# Problem

## PROBLEM 5-14

(Chỉ ra các C bất đối xứng trong phân tử Morphine)

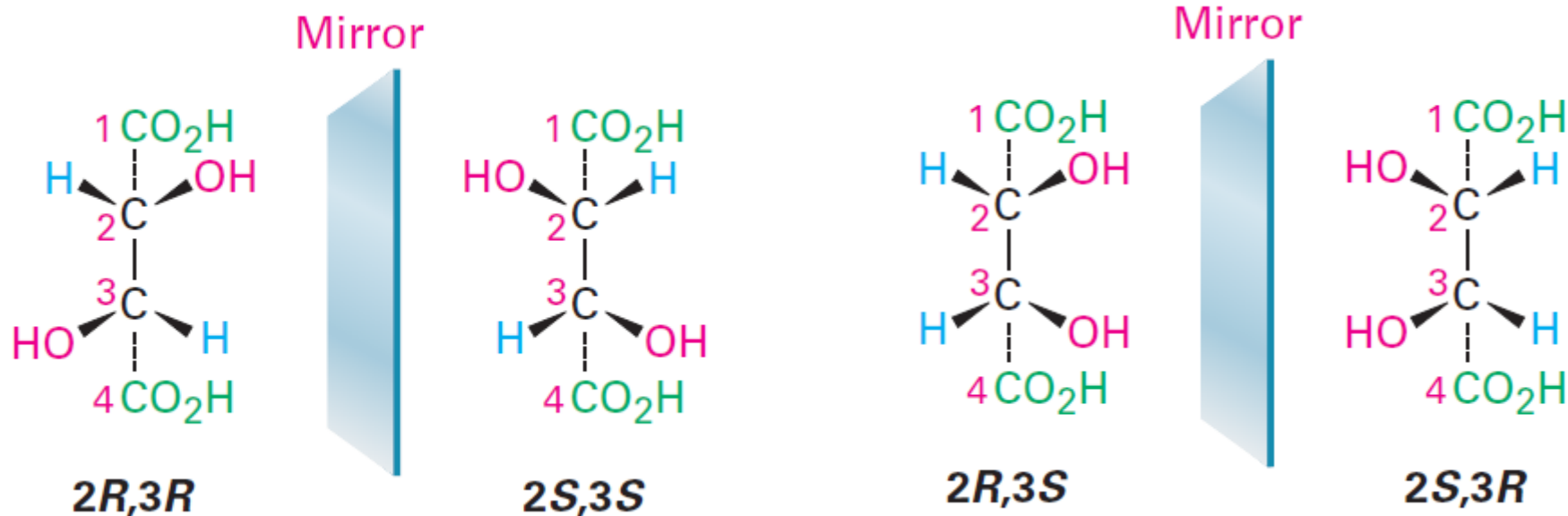
How many chirality centers does morphine have? How many stereoisomers of morphine are possible in principle?



**Morphine**

# Meso compounds

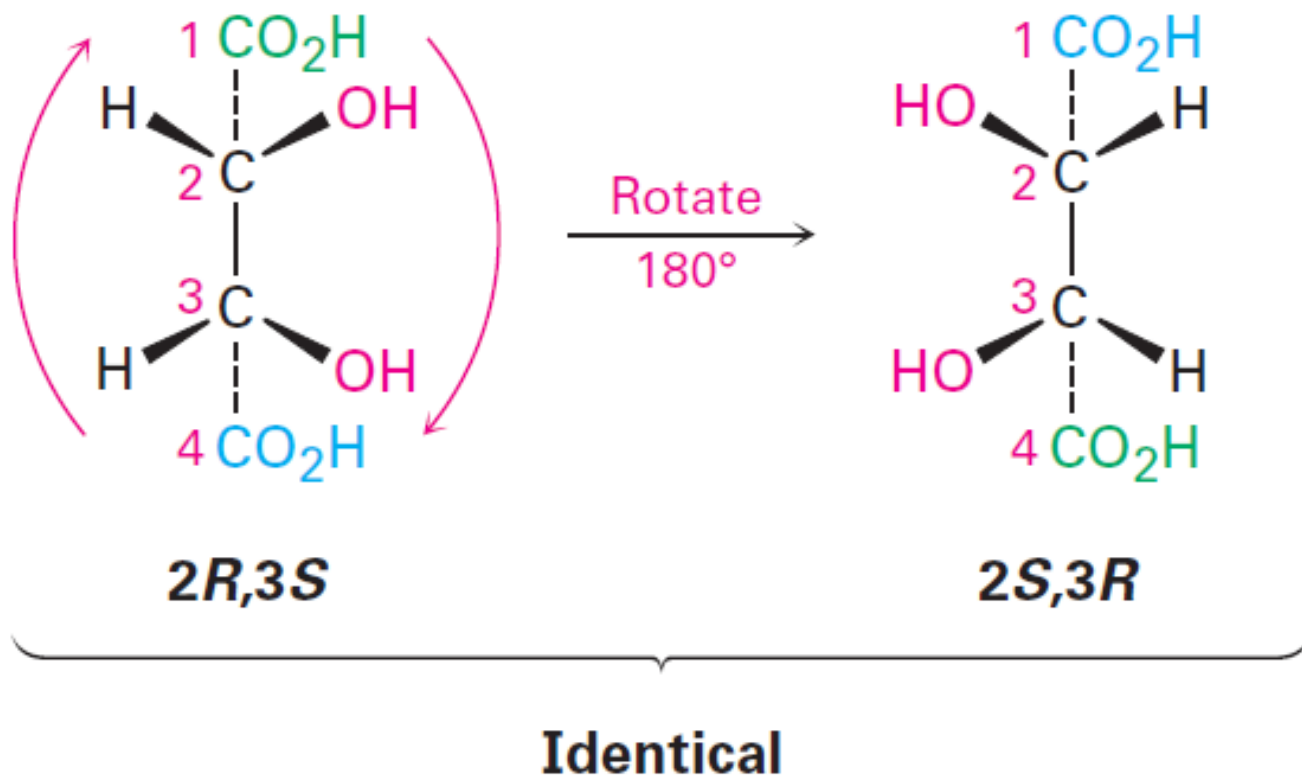
Tartaric acid



Superimposable?  
(vật và ảnh trùng khít nhau?)

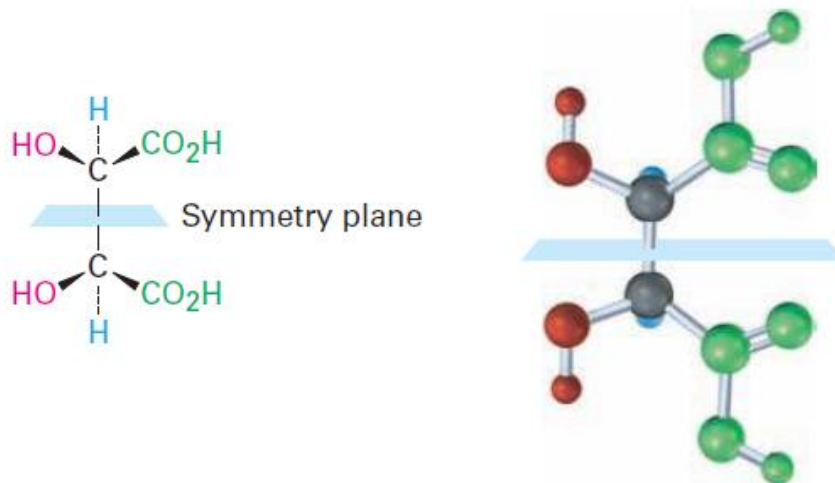


# Meso compounds



Achiral compounds that contain chirality centers are called **meso** compounds.

# Meso compounds



**TABLE 5-3** Some Properties of the Stereoisomers of Tartaric Acid

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

# Meso compounds

Compounds that are achiral, and containing chirality centers, are meso compounds

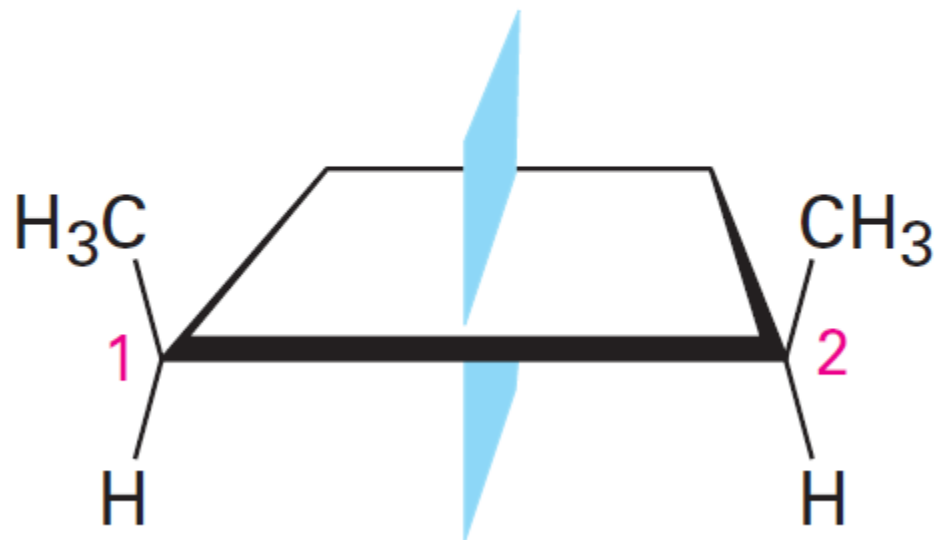
# Problem

cis-1,2-dimethylcyclobutane

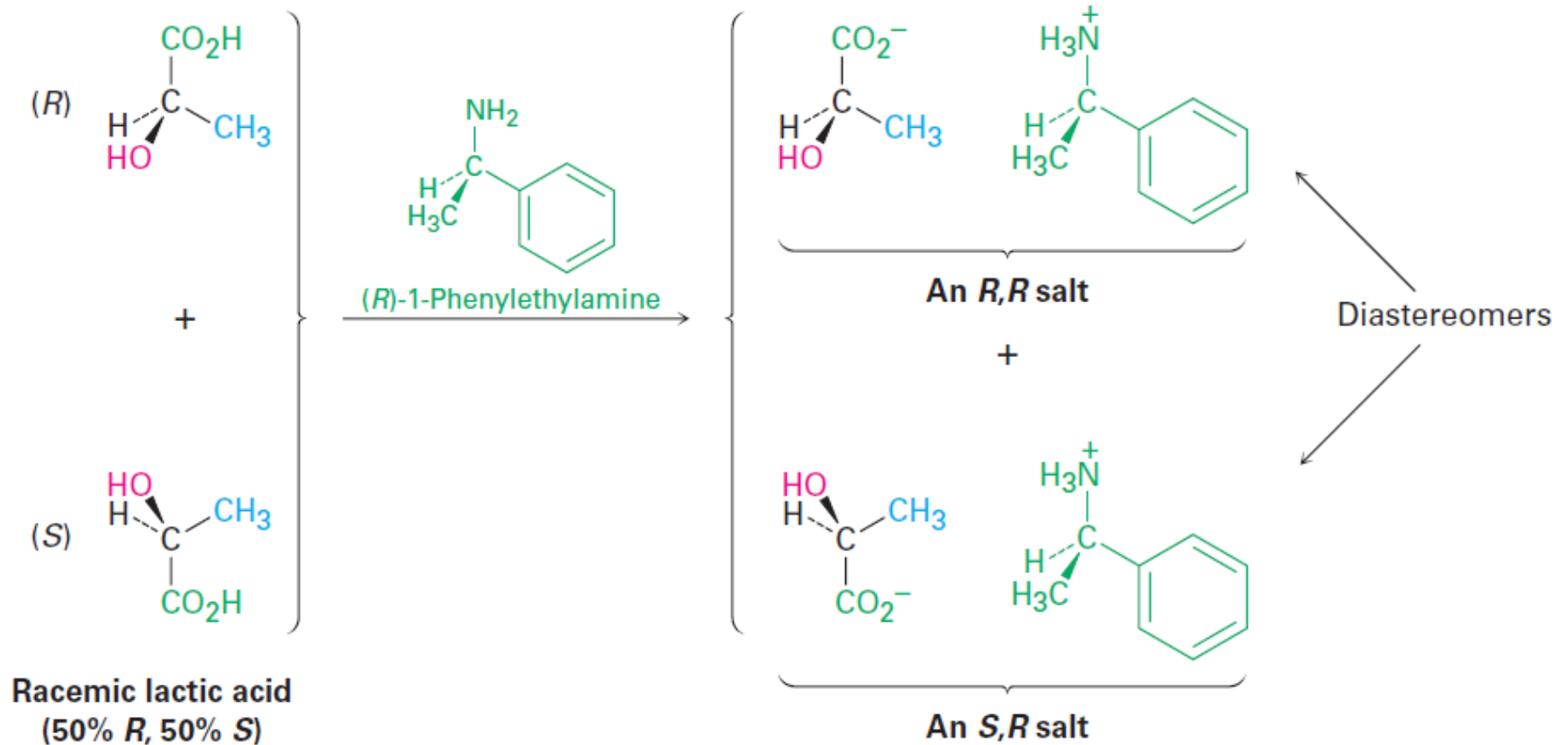
chirality centers?

chiral or achiral?

# Symmetry plane



# Racemic mixtures (hỗn hợp racemic)



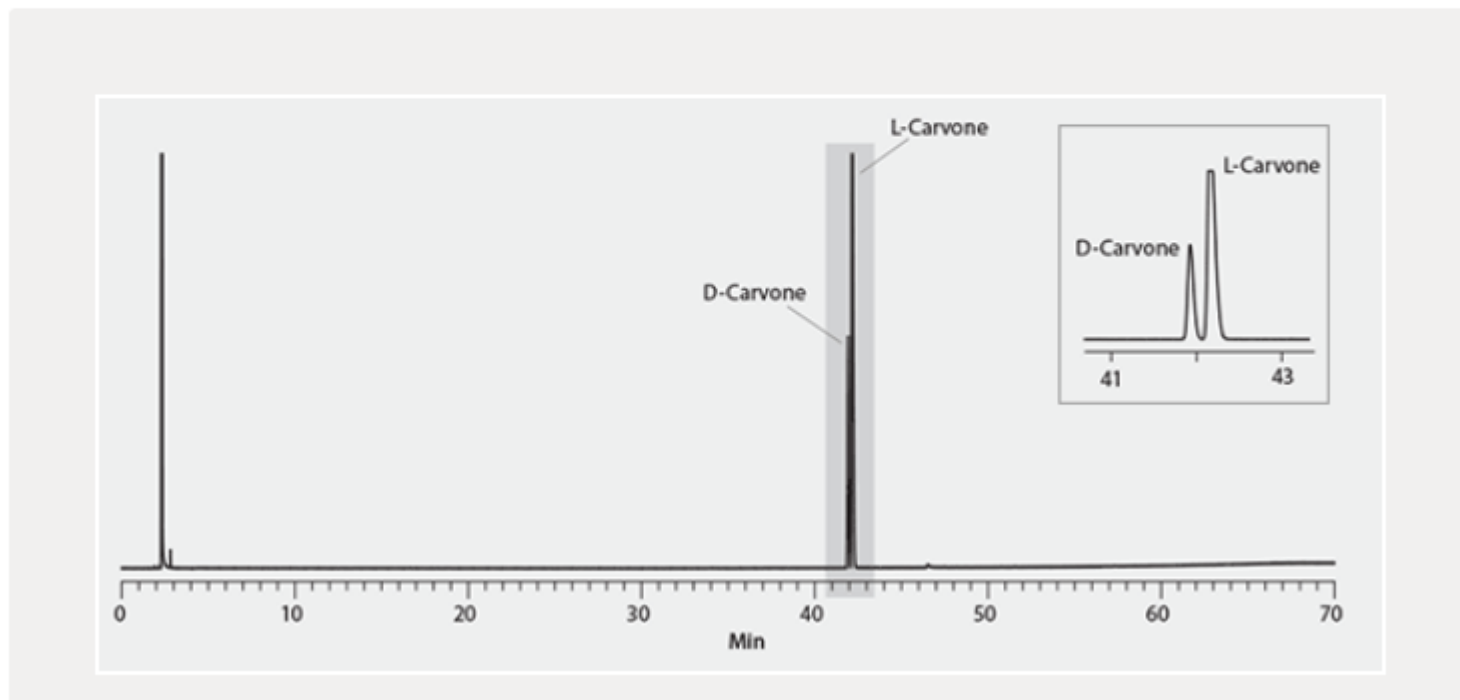
# Chiral GC Analysis of Carvone Enantiomers in Essential Oils

By: Leonard M. Sidisky, *Reporter US Volume 32.1*

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## Results and Discussion

**Figure 1** demonstrates that the D-carvone enantiomer elutes before L-carvone. **Figures 2, 4, 6 and 8** show the chromatograms resulting from analysis of neat samples of caraway seed, dill seed, native spearmint and scotch spearmint essential oils. Spiked sample chromatograms are shown in **Figures 3, 5, 7 and 9**, and show that the spiked enantiomer is resolved and can be identified. This demonstrates the chiral selectivity of the Astec CHIRALDEX G-TA capillary GC column.



## Why Do I Have to Learn This Stuff?

"One day a chemistry professor was discussing a particularly complicated concept. A pre-med student rudely interrupted to ask 'Why do we have to learn this stuff?' 'To save lives,' the professor responded quickly and continued the lecture. A few minutes later the same student spoke up again. 'So how does organic chemistry save lives?' he persisted. 'It keeps idiots out of medical school.' replied the professor." --Modified from Frank Gorga, Bridgewater State College