Damascus University
Faculty of Pharmacy
Pharmaceutical Organic Chemistry I

الكيمياء الفراغية والمراكز رباعية الوجوه

5. Stereochemistry at Tetrahedral centers (Chapter 5, McMurry)

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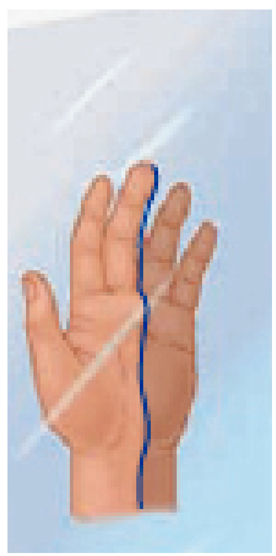
Symmetrical and unsymmetrical objects
الأجسام المتناظرة وغير المتناظرة

- Symmetrical object has a plane of symmetryمستوى تناظر, thus can superimpose تنطبقon its mirror image صورة في المرآة (example conical flask)
- Unsymmetrical object has no plane of symmetry, thus can not superimpose on its mirror image (example a hand). This property is called "**handedness اليدوية** "
- Left hand is not identical to its mirror image right hand



Enantiomers
المتصاوغات المرآتية

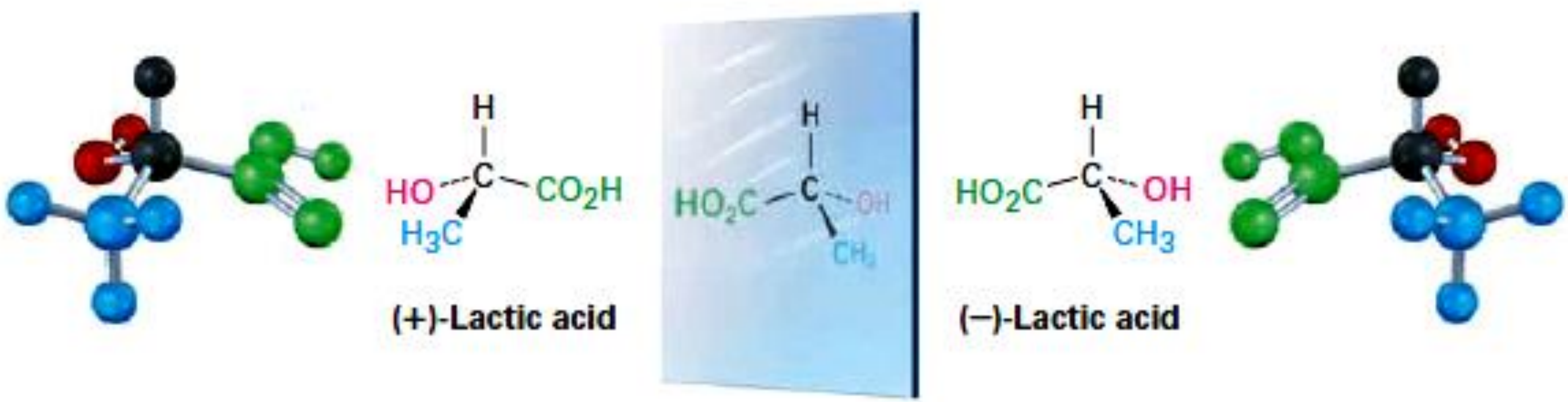
- Molecules exist as three-dimensional objects
- Some molecules are the same as their mirror image
- Some molecules are different than their mirror image
  - These are stereoisomers متصاوغات فراغية called: enantiomers متصاوغات (متماكبات) مرآتية

4.1 Enantiomers and the Tetrahedral Carbon
المصاوغات المرآتية والكربون رباعي الوجوه

- Molecules that are not identical to their mirror images are called enantiomers:

  - Lactic acid occurs as a pair of enantiomers.

Lactic acid: a molecule of general formula CHXYZ



4.2 The reason of handedness in Molecules: chirality اليدوية

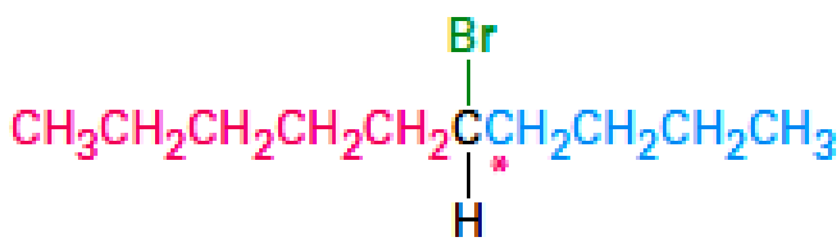
• Molecules that are not superimposable with their mirror images are chiral يدوي(have handedness يدوية).

• Chiral molecule has no plane of symmetry.

• The lack of a plane of symmetry is called “handedness”, chirality.

• A molecule with a plane of symmetry is the same as its mirror image and is said to be **achiral** غير يدوي

• The most common cause of chirality in an organic molecule is the presence of a tetrahedral carbon atom bonded to four different groups— Such carbon is referred to as **chirality center مركز لليدوية.**

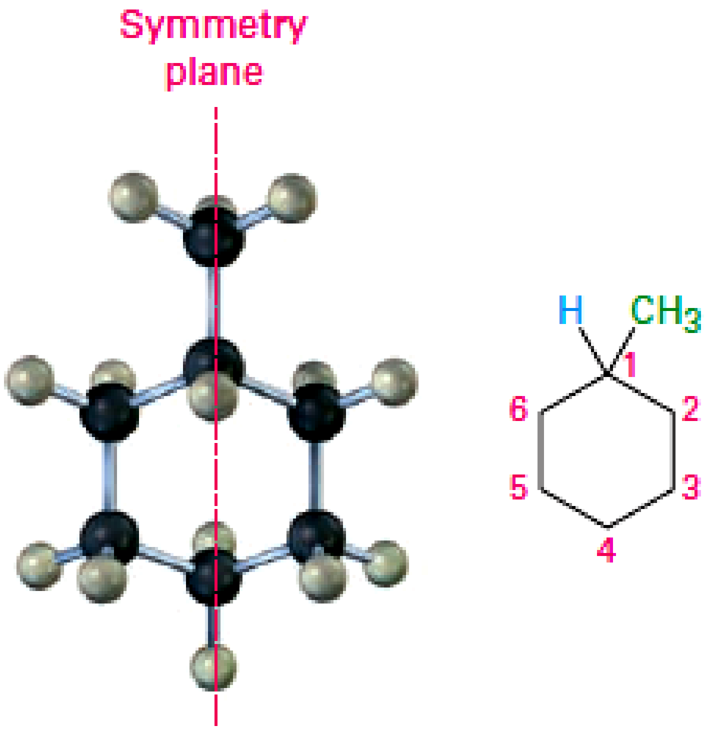


5-Bromodecane (chiral)

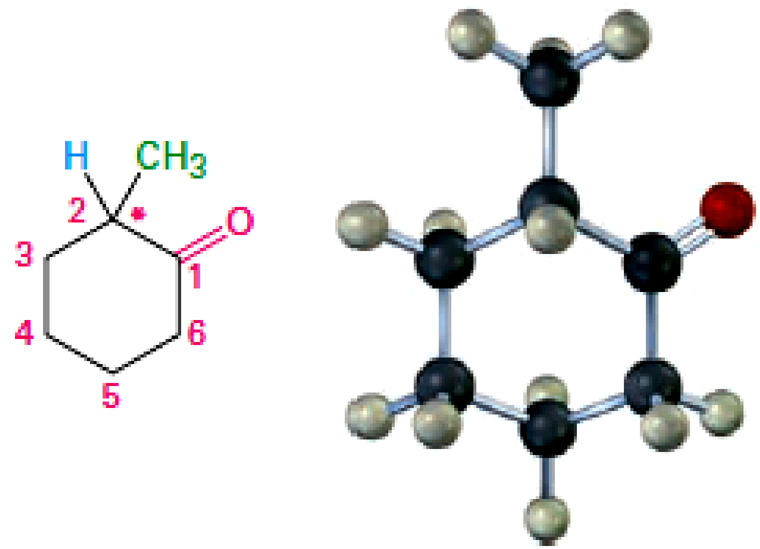
Chiral and Achiral Molecules

الجزيئات اليدوية وغير اليدوية

- In cyclic molecules, we compare by following in each direction in a ring.



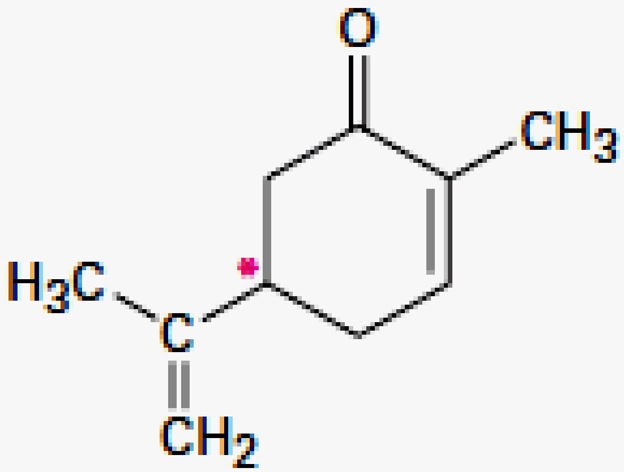
Methylcyclohexane
(achiral)



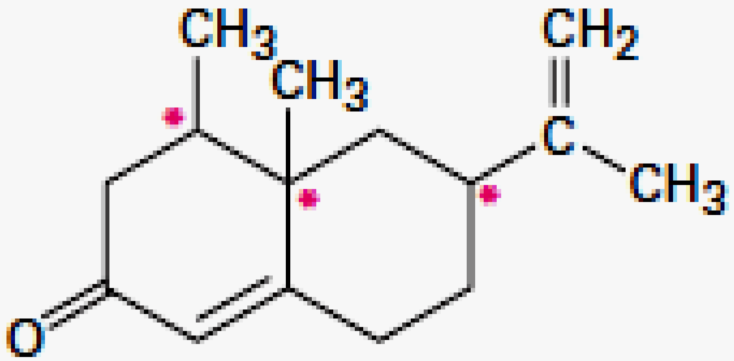
2-Methylcyclohexanone
(chiral)

Examples of Chirality Centers in Chiral Molecules

أمثلة على مراكز اليدوية والجزيئات اليدوية



Carvone (spearmint oil)



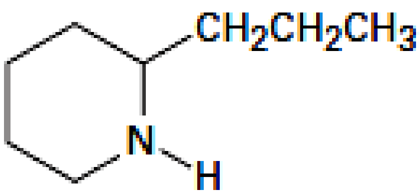
Nootkatone (grapefruit oil)

Examples of Chirality Centers in Chiral Molecules

Problem 5.2

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

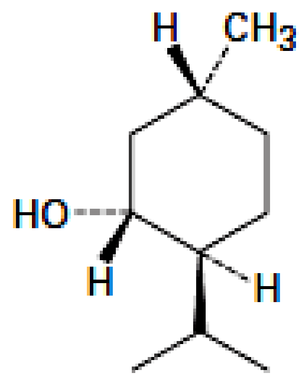
(a)



Coniine
(poison hemlock)

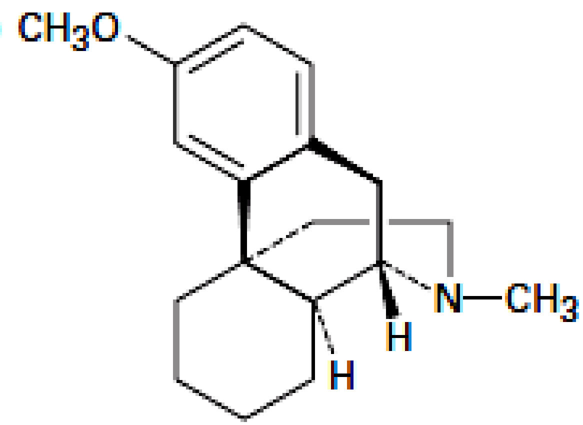
سم الشوكران

(b)



Menthol
(flavoring agent)

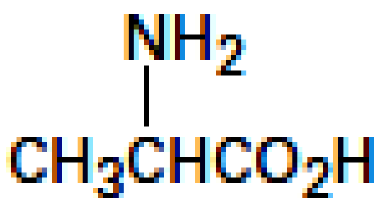
(c)



Dextromethorphan
(cough suppressant)

Problem 5.3

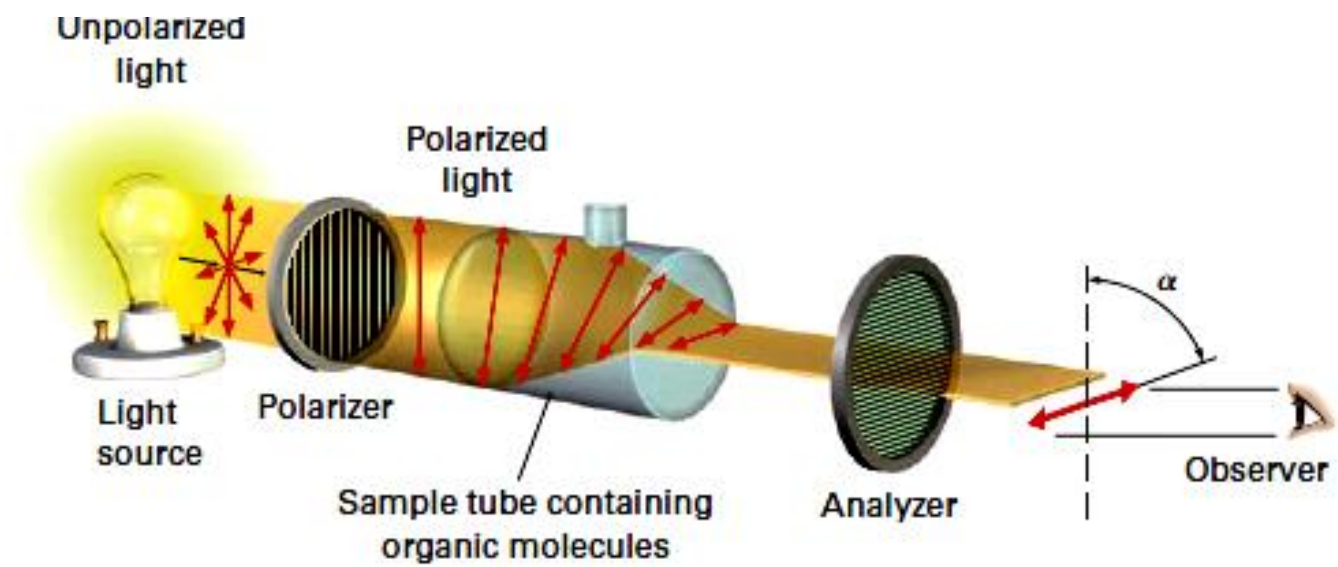
Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.



Alanine

5.3 Optical Activity الفعالية البصرية

- Light restricted to pass through a plane is *plane-polarized*
- Plane-polarized light (ضوء مستقطب في مستوى(مسطح 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** فعال بصريا .
- Molecules that cause right- rotation are dextrorotatory ميمن or (+)
- Molecules that cause left- rotation is called levorotatory ميسر or (-)
- Rotation in degree (α) is measured by a polarimeter) مقطاب مقياس استقطاب.



Specific Rotation الدوران النوعي

• Specific rotation is that observed for 1 g/mL in solution in cell with a 10 cm (1dm) path using light from sodium metal vapor بخار الصوديوم (589 nanometers)

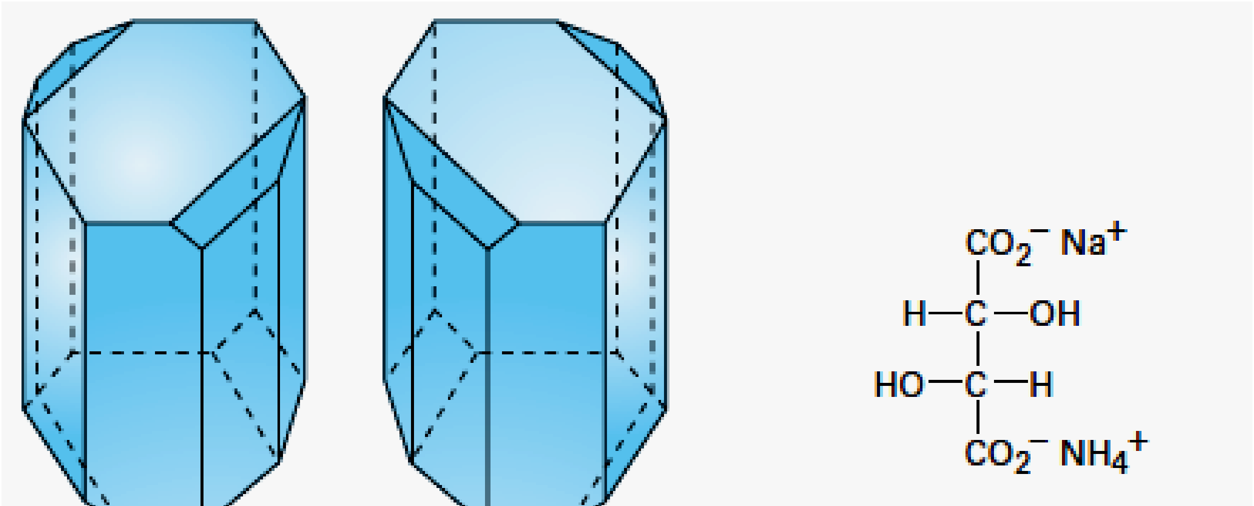
$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{Concentration, } c \text{ (g/cm}^3\text{)}} \quad \frac{\alpha}{l \times c}$$

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

4.4 Pasteur's Discovery of Enantiomers (1849)

- Louis Pasteur discovered that concentrated solution of **sodium ammonium salts of tartaric** acid crystallize يتبلور distinctly into two different shapes (right handed and left handed), called enantiomers. – such an event is rare
- Enantiomers مصاوغات مرآتية ,(also called optical isomers مصاوغات بصرية), have <u>identical physical properties</u>, but differ in the direction in which their solutions rotate plane-polarized light.



Sodium ammonium tartrate

4.5 Sequence Rules (Cahn–Ingold–Prelog rules) for Specification of Configuration

قواعد السلسلة لتعيين نوع التهايؤ الفراغي لمركز اليدوية

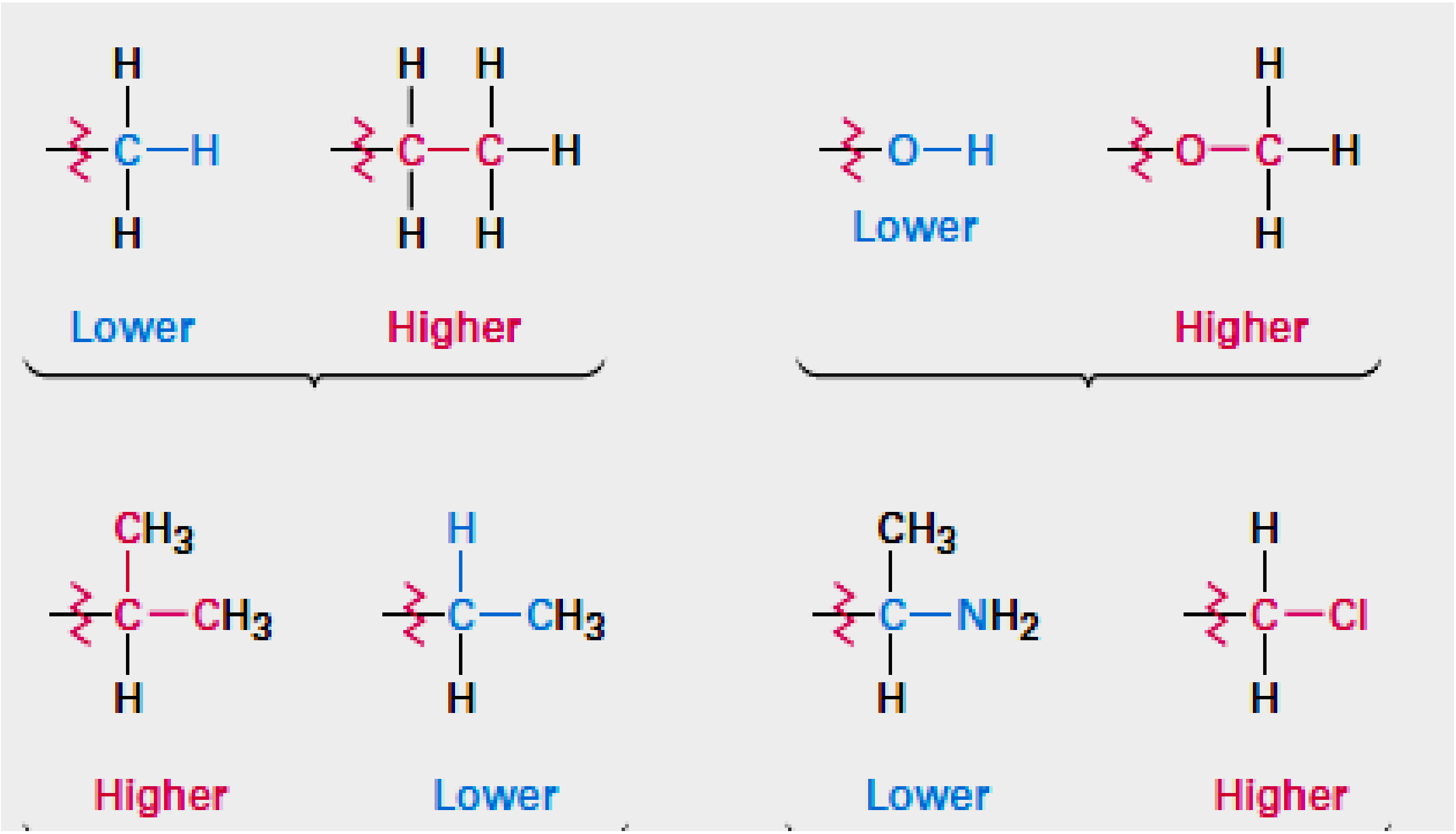
- A set of sequence rules are employed to rank the four groups and then to specify the three-dimentional arrangements at the chirality center: R or S configuration.

Rule 1 Look at the four atoms directly attached المرتبطة مباشرة to the chirality center, and rank رتب them from 1 to 4 according to atomic number, in decreasing order وفق الترتيب المتناقص لأعدادها الذرية ; the highest is the first and the lowest is the fourth.

Atomic number	35		17		16		15		8		7		6		(2)		(1)		
Higher ranking	Br	>	Cl	>	S	>	P	>	O	>	N	>	C	>	^{2}H	>	^{1}H		Lower ranking

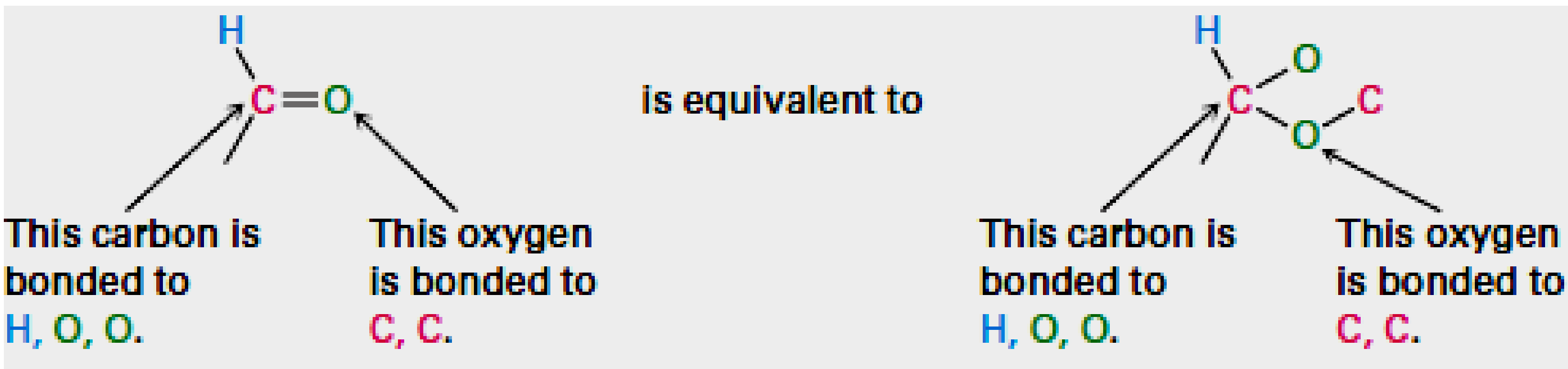
Sequence Rules(Cahn–Ingold–Prelog rules)

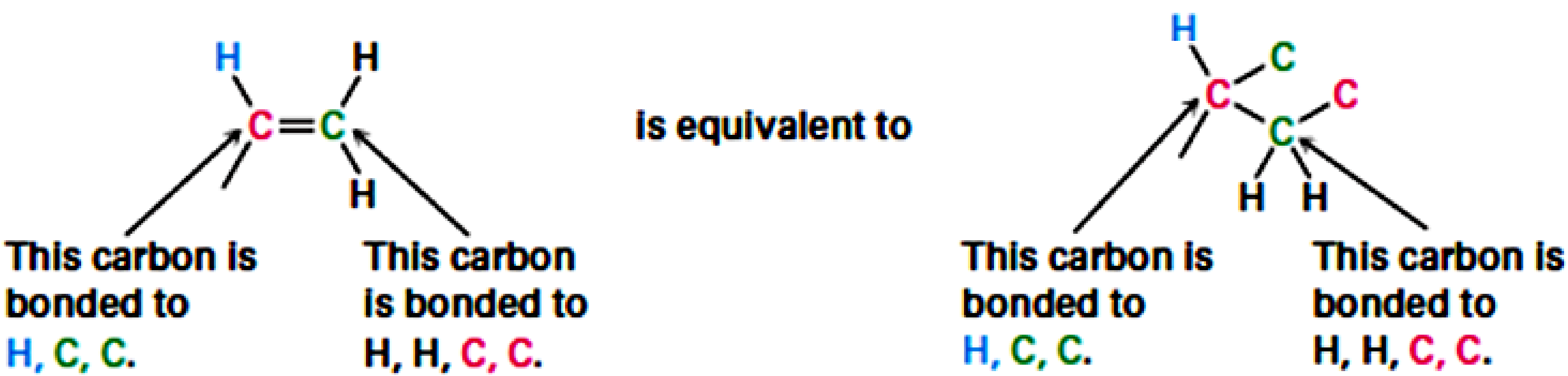
Rule 2 If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found.



Sequence Rules(Cahn–Ingold–Prelog rules)

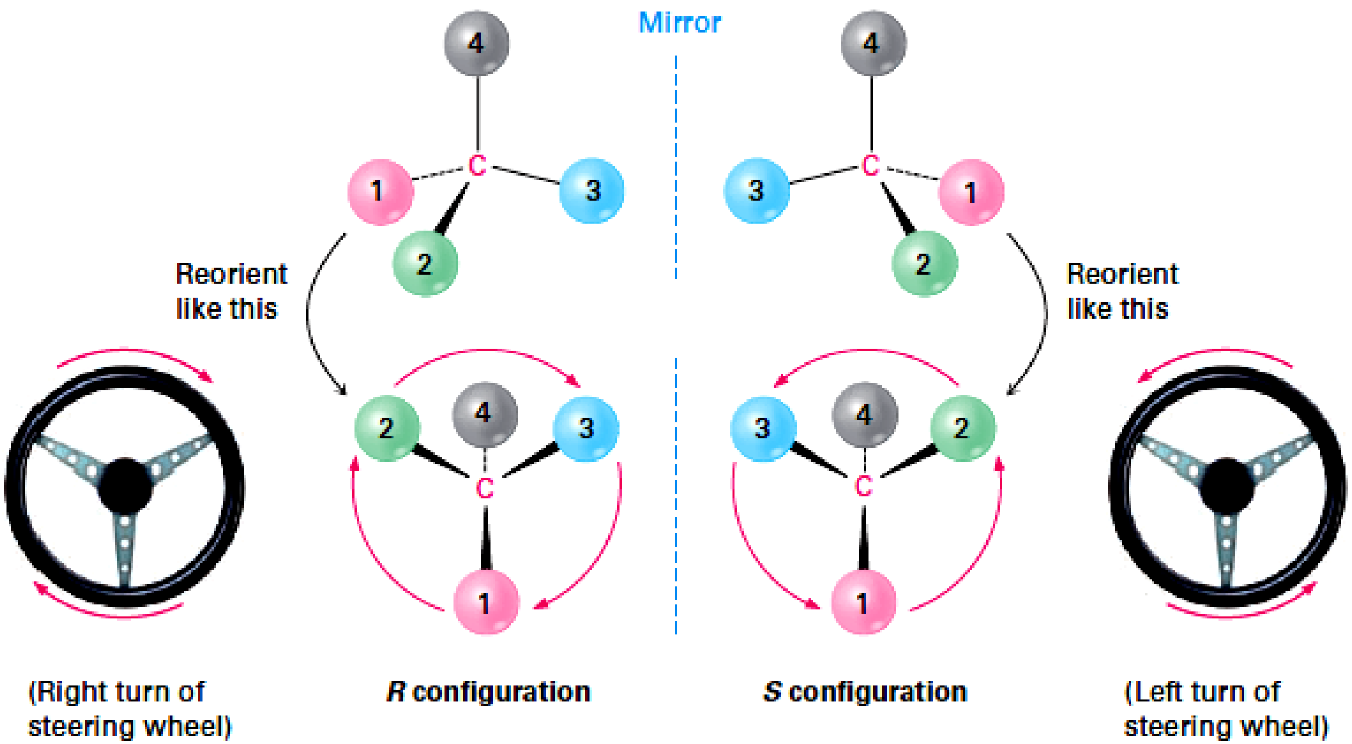
Rule 3 Multiple-bonded atoms are equivalent to the same number of single bonded atoms





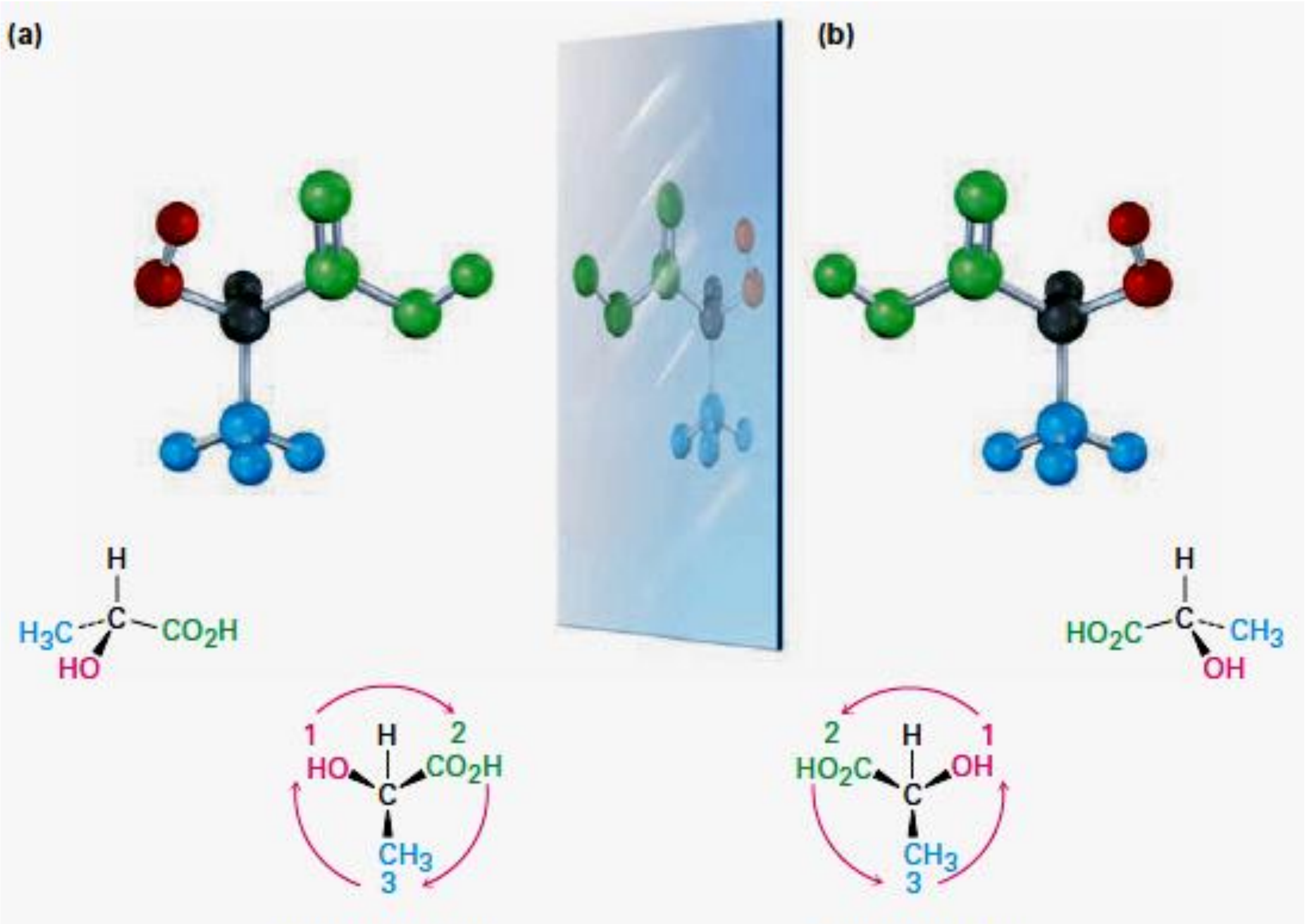
Specification of Configuration: R or S تعيين التهايؤ

• Ranking the four groups in decreasing priority order وفق ترتيب الأولوية المتناقص; 1 to 4
• Orient the molecule so that the lowest priority group goes away from you.
• Look at the remaining three groups:
- If the movement from 1 to 3 is clockwise باتجاه عقارب الساعة , the configuration is R
- If the movement from 1 to 3 is counterclockwise عكس اتجاه عقارب الساعة the configuratio



Assigning Configuration to Lactic acid Enantiomers

تعيين التهايؤ للمصاوغات المرآتية لحمض اللاكتيك

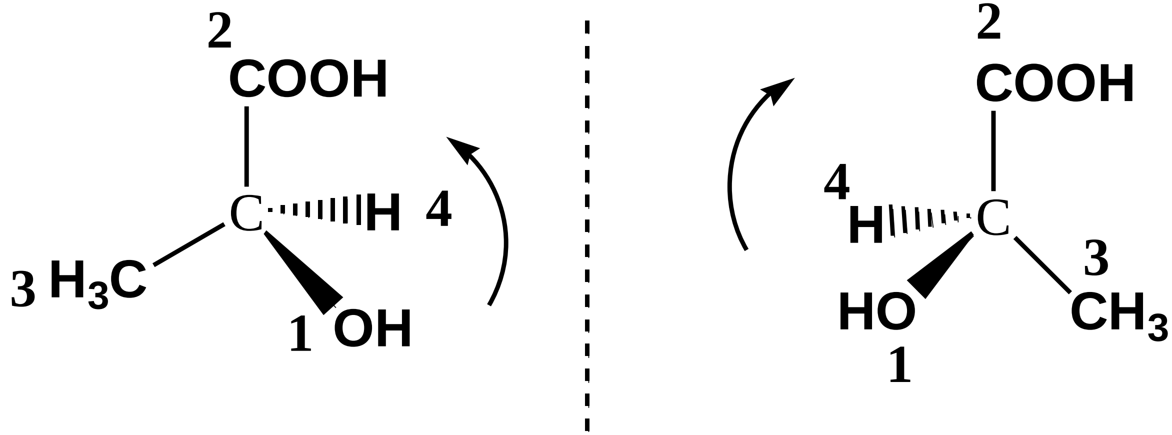


R **configuration**
(−)-Lactic acid

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

Other Method for Specification of Configuration of the chirality center

- If the lowest priority group is pointed back (placed at dashed line),assign the configuration directly (movement from 1 to 3).

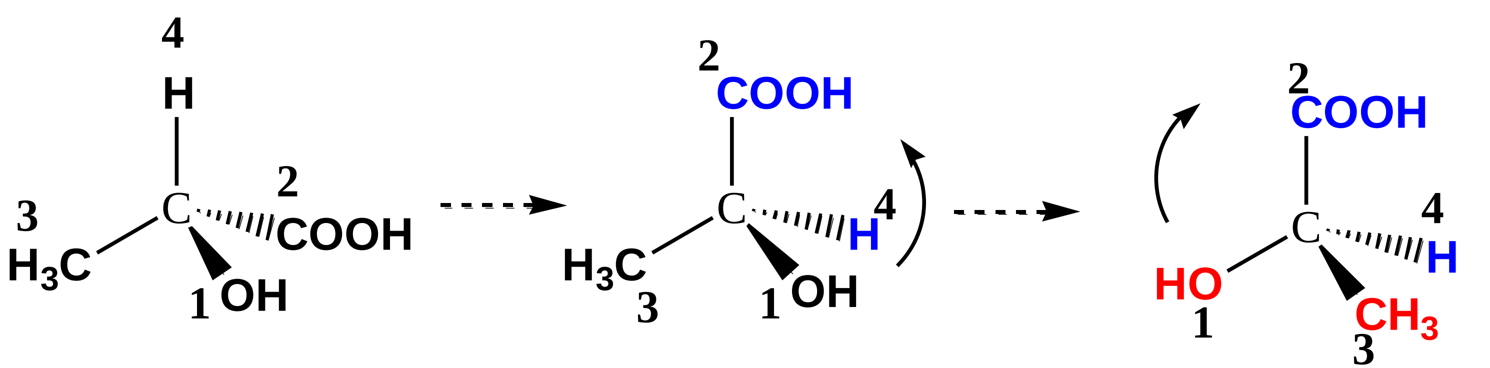


(*S*)-Lactic acid

(*R*)-Lactic acid

Other Method for Specification of Configuration of the chirality center

- Exchange H with the dashed line- group (COOH) and then assign the configuration directly on the new structure representation -**Note here** that the new structure has the opposite configuration of the original one.
- If you do another exchange between the two other groups (e.g. CH_3 for OH) the resulted representation will retain configuration of the original one.



original
(unknown configuration)

configuration opposite
to the original

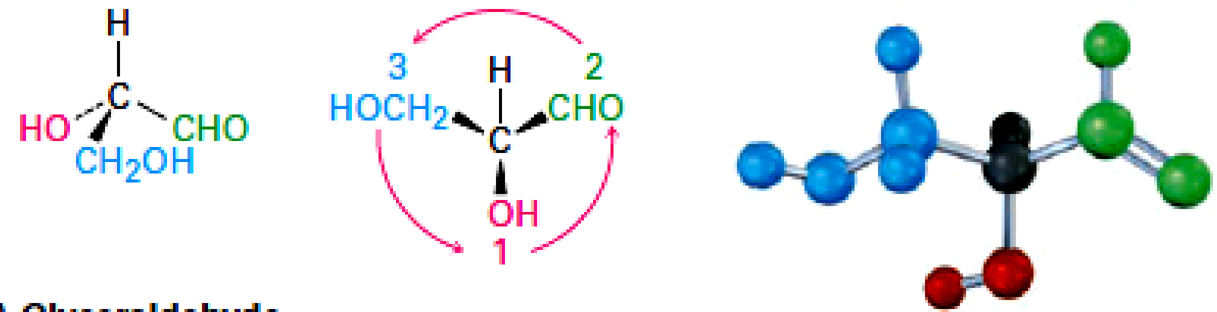
(S)- configuration

same configuration
as the original

(R)- configuration

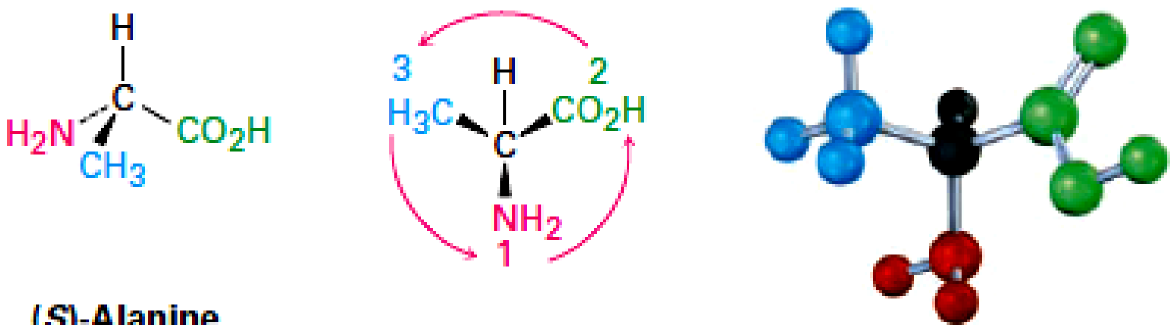
Sign of optical rotation, (+) or (-), is not related to the R,S designation

(a)



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

(b)



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

Drawing the Three-Dimensional Structure of a Specific Enantiomer

Worked Example 5.4

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

Strategy.

Solution

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 $-CH{=}O$

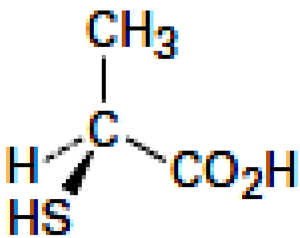
Problem 5.8

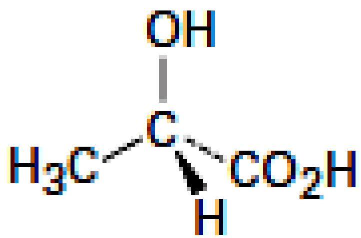
Rank the following sets of substituents:

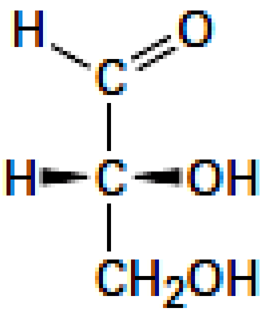
(a) $-H$, $-OH$, $-CH_2CH_3$, $-CH_2CH_2OH$
(b) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, $-OH$
(c) $-CN$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-NH_2$
(d) $-SH$, $-CH_2SCH_3$, $-CH_3$, $-SSCH_3$

Problem 5.10

Assign R or S configuration to the chirality center in each of the following molecules:

(a)


(b)


(c)


Problem 5.11

Draw a tetrahedral representation of (*S)-2-pentanol (2-hydroxypentane).*

Number of stereoisomers of chiral molecules
عدد المتصاوغات الفراغية للجزيئات اليدوية

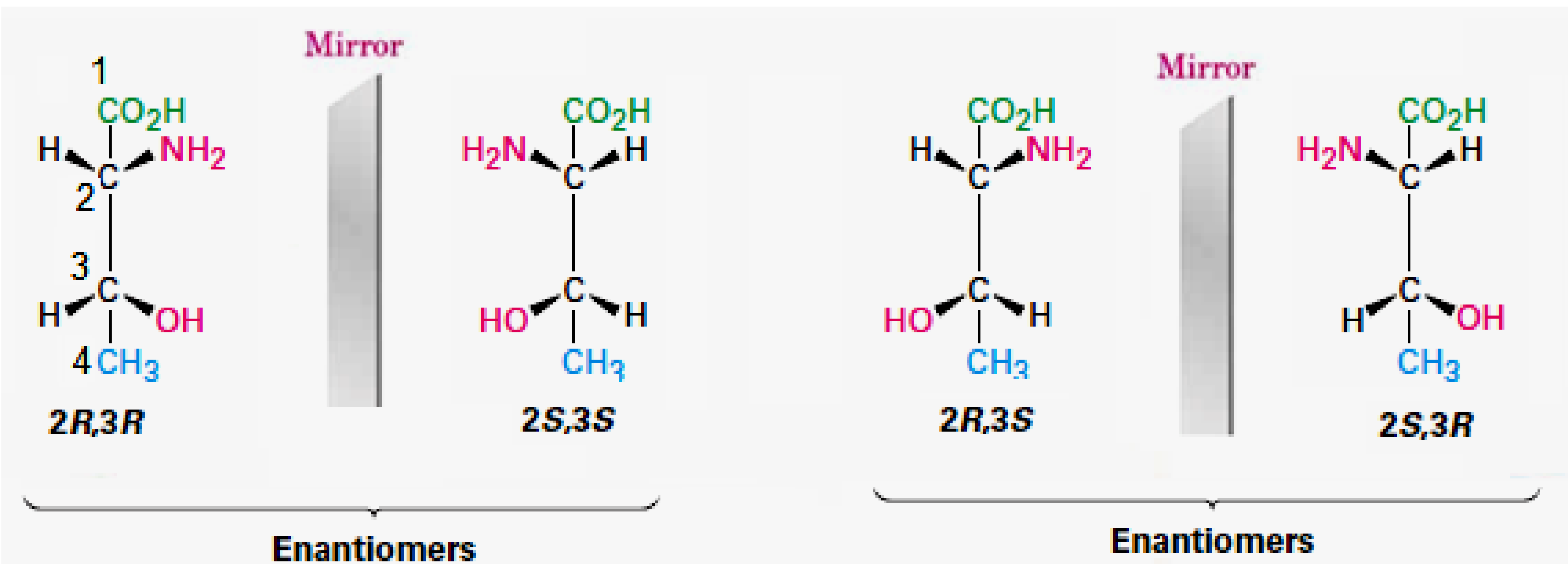
- Molecule with one chirality center has only two stereoisomers.
- As a general rule, a molecule with n chirality centers can have up to **2^n stereoisomers** (although it may have fewer, as we'll see below).

4.6 Diastereomers (دياستيرية) متصاوغات فراقية

• Threonine ثريونين (2-amino-3-hydroxybutanoic acid) has two chirality centers (C2 and C3), thus there are four possible stereoisomers: two pair of enantiomers.

• The 2R,3R isomer and the 2R,3S isomers are diastereomers: they are not mirror images, they have the same configurations at one chirality center and the opposite configuration at the other.

• Indicate the other diastereomeric pairs……



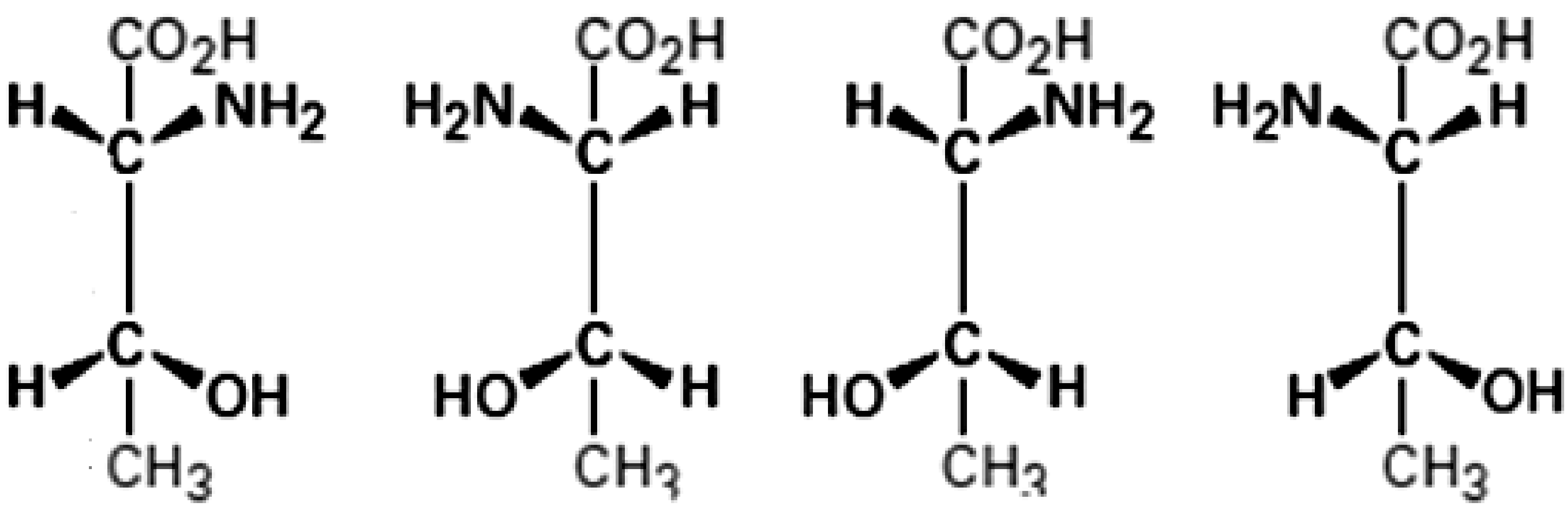
Enantiomers Compared to Diastereomers

مقارنة المتصاوغات المرآتية مع المتصاوغات الفراقية

• Enantiomers have opposite configuration at all chirality Centers (mirror images).

• Diastereomers have the same configuration in at least one center but opposite configurations at the others.

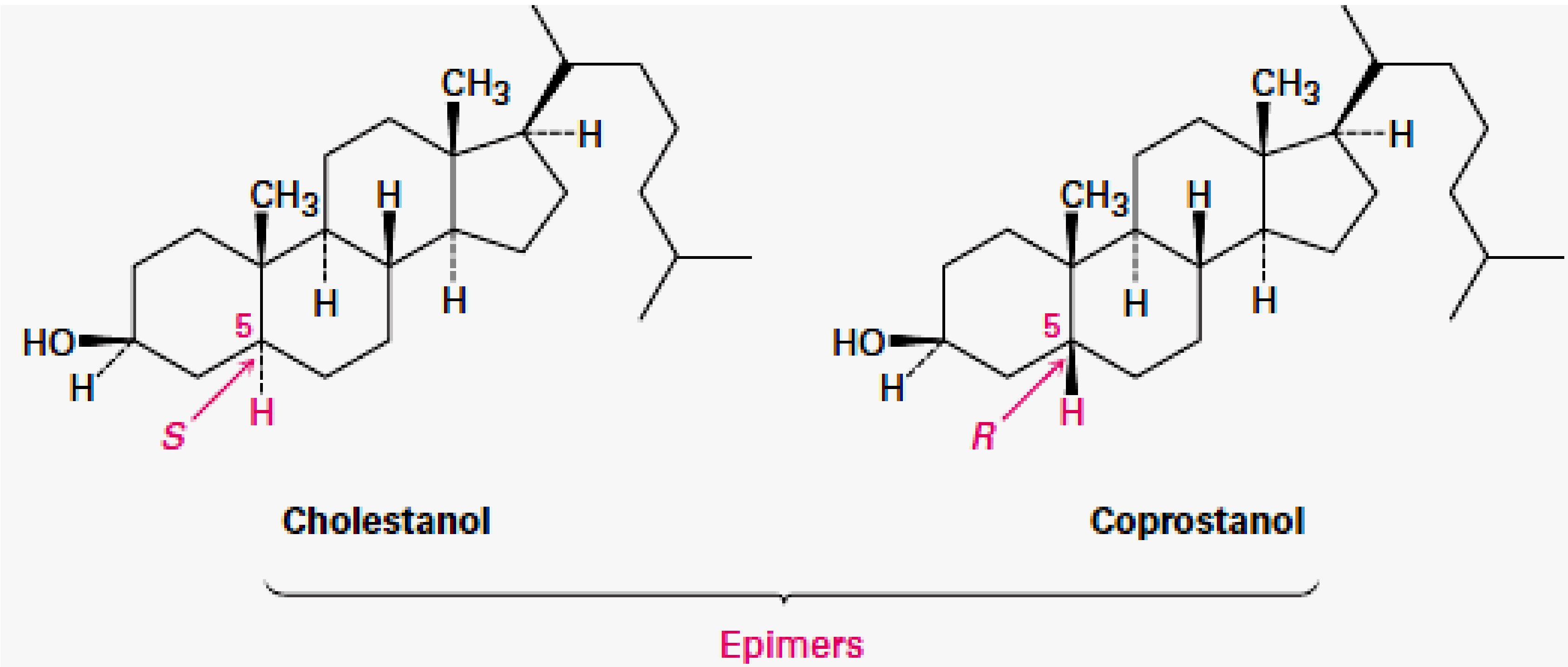
Problem Which of the following structures are enantiomers, and which of are stereoisomers.



A B C D

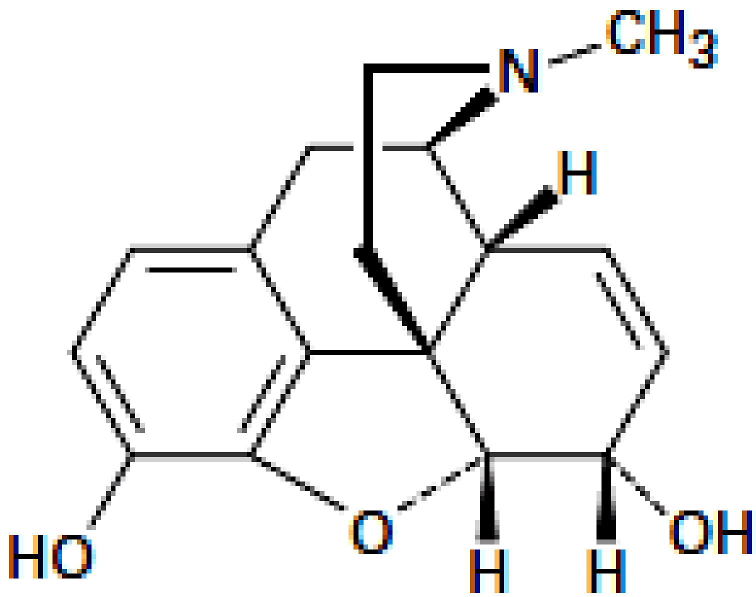
Epimers
مصاوغات صنوية

Cholestanol and coprostanol, for instance, are both found in human feces, and both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric at C5*



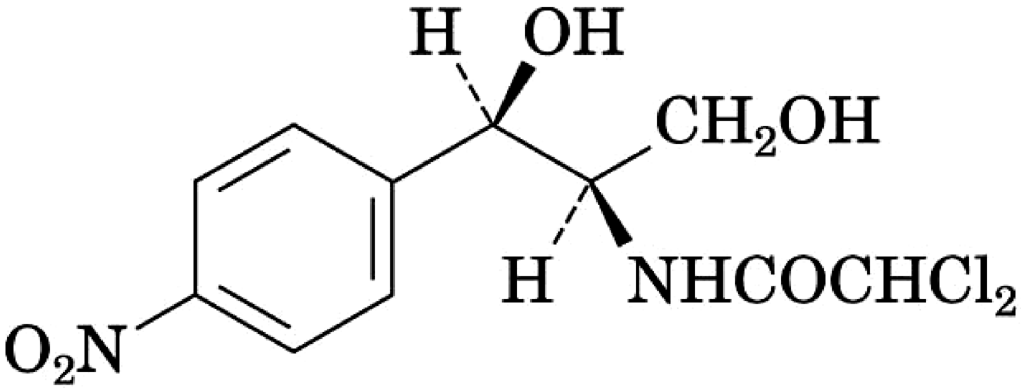
Problem 5.14

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



Morphine

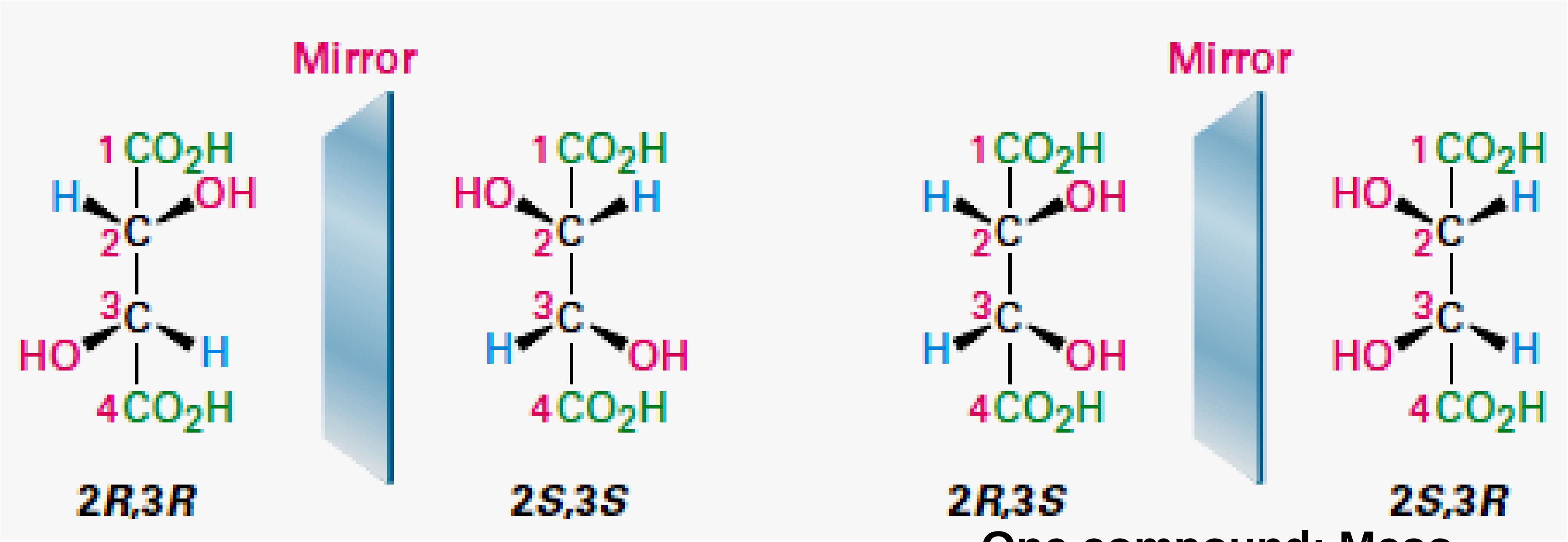
Assign the configuration of the chirality centers



Chloramphenicol

4.7 Meso Compounds مركبات ميزو

- Although tartaric acidحمض الطرطير has two chirality centers, it exists in three stereoisomeric forms: two enantiomers and one meso form.
- 2R,3R and 2S,3S structures are a pair of enantiomers.
- The 2R,3S and 2S,3R structures are superimposable, and thus identical (symmetrycal), thus represent one compund called meso ميزو

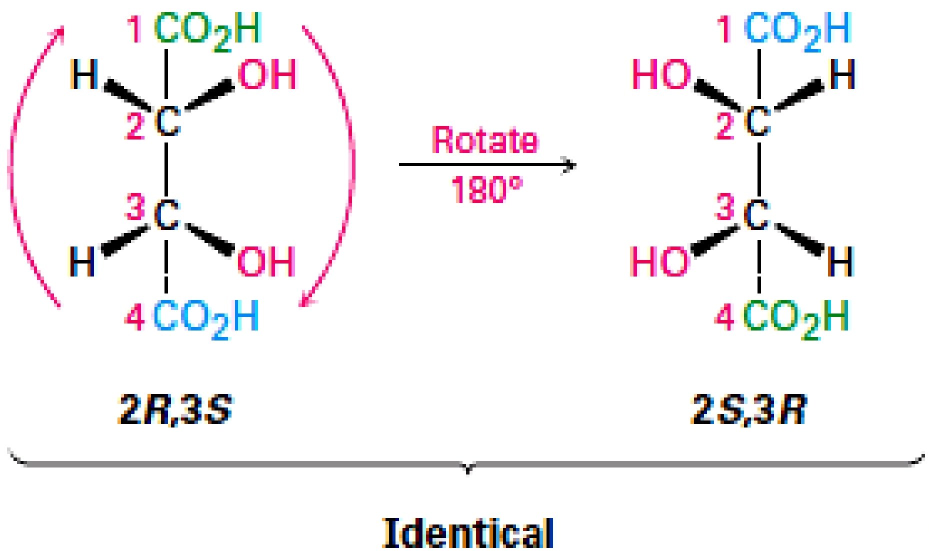


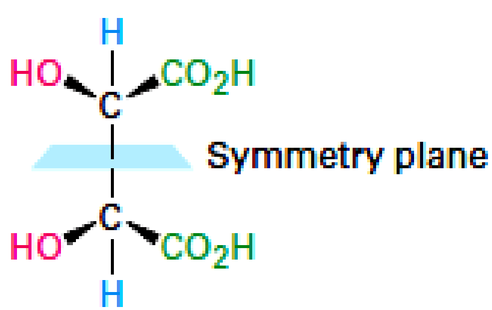
Enantiomers

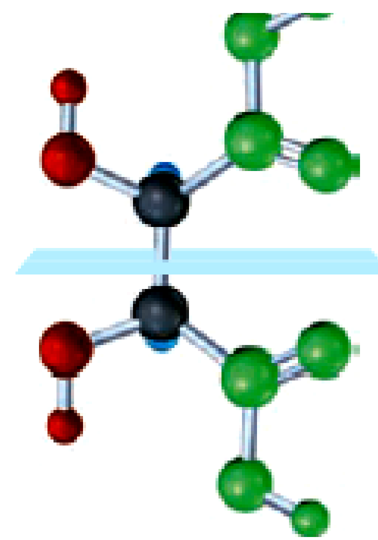
One compound: Meso (achiral)

Meso compounds

- Meso compounds, in general, contain chirality centers but are achiral overall (e.g. meso tartaric acid).







Phsical properties of meso tartaric acid
الخواص الفيزيائية لميزو حمض الطرطير

- The enantiomers (+)- and (-)-tartaric acids have identical melting points, solubilities, and densities, but they differ only in the sign of their rotation of plane-polarized light.
- The meso isomer, by contrast, is diastereomeric with the (+) and (-) forms, and has different physical properties.

Table 5.3 Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm^3)	Solubility at 20 °C (g/100 mL H_2O)
(+)	168–170	+12	1.7598	139.0
(−)	168–170	−12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

Distinguishing Chiral Compounds from Meso Compounds

Worked Example 5.5

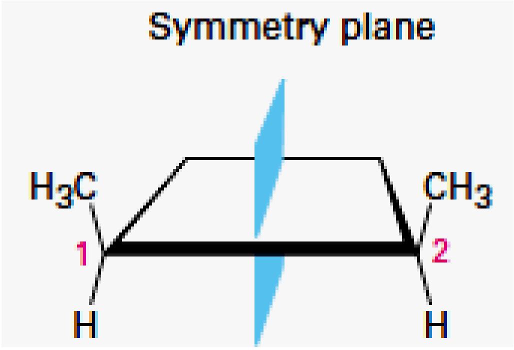
Does *cis-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?*

Strategy

To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for the presence or absence of a symmetry plane. Not all molecules with chirality centers are chiral overall—meso compounds are an exception.

Solution

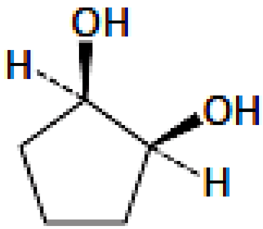
A look at the structure of *cis-1,2-dimethylcyclobutane shows that both methyl-bearing ring* carbons (C1 and C2) are chirality centers. Overall, though, the compound is achiral because there is a symmetry plane bisecting the ring between C1 and C2. Thus, the molecule is a meso compound.



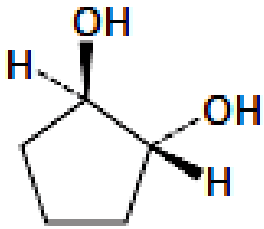
Problem 5.16

Which of the following structures represent meso compounds?

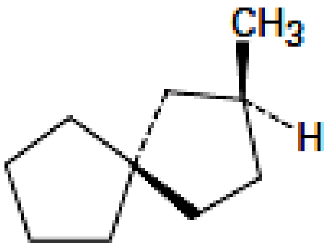
(a)



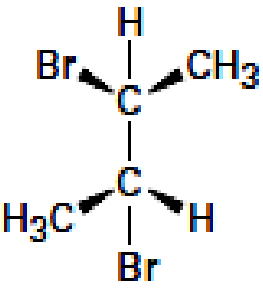
(b)



(c)



(d)



Problem 5.17

Which of the following have a meso form?

(a) 2,3-Butanediol (b) 2,3-Pentanediol (c) 2,4-Pentanediol

4.8 Racemic Mixtures المزائج الراسيمية

• Racemic mixture is a 50:50 mixture of (+) and (-) enantiomers
• It is also called racemate or racemic mixture or denoted by either the symbol (±) or (d,l) mixture.
• It is optically inactive غير فعالة ضوئيا (does not rotate the plane polarized light).

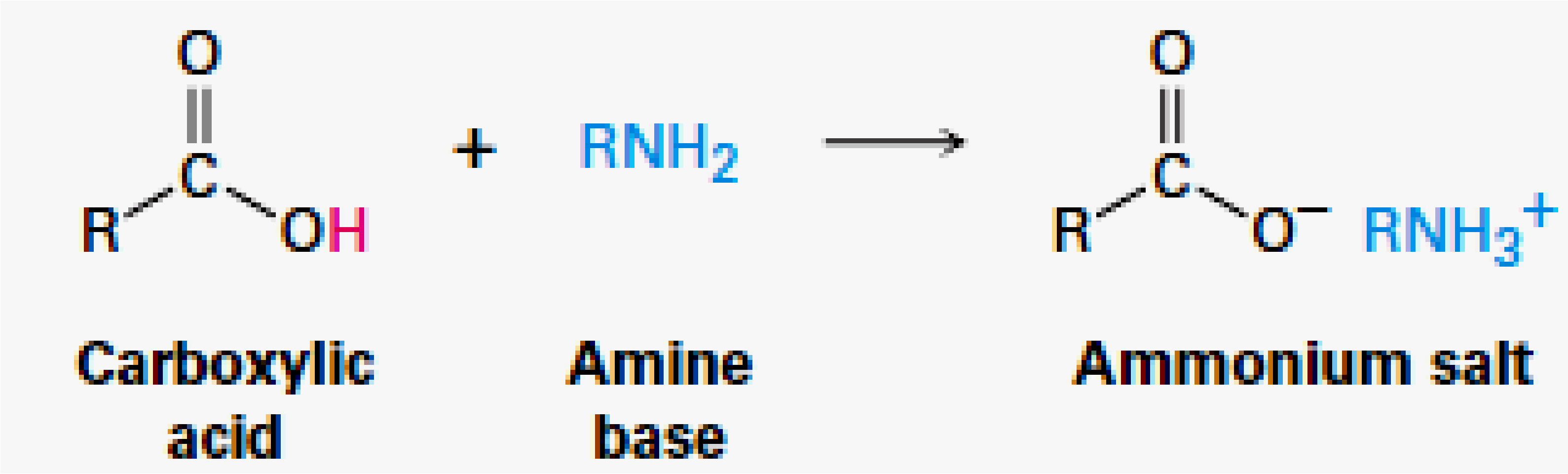
Resolution of Racemic Mixture

فصل المتصاوغين المرآتيين للمزيج الراسيمي عن بعضهما

- Resolution (separation) is done by reaction of racemic mixture (RCO_2H) with an amine base (RNH_2) enantiomer (pure R or S) to yield an ammonium salt.

-This gives diastereomers that are separated by their differing solubility.

-The amine base is then removed from each diastereomer.



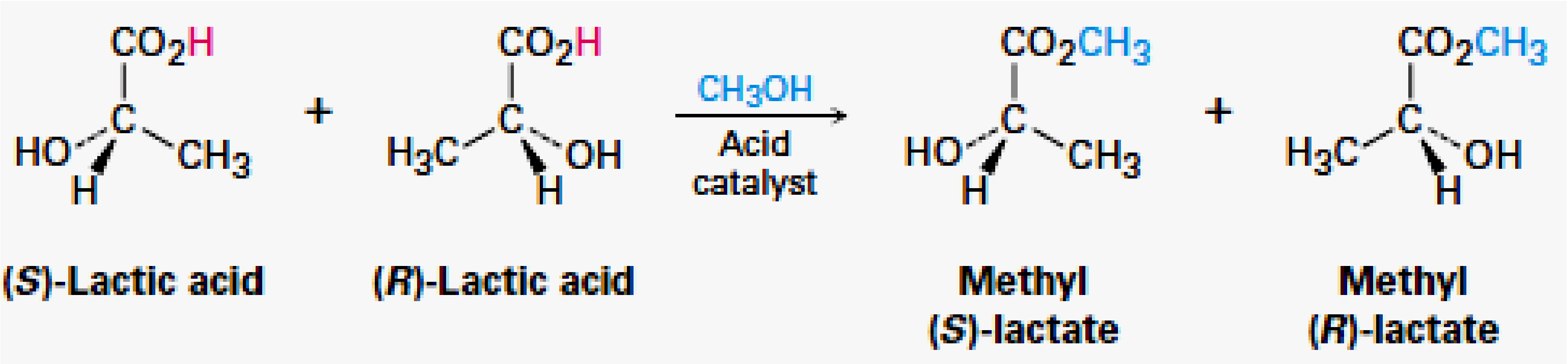
Predicting the Chirality of a Reaction Product

Worked Example 5.6

Suppose that (±)-lactic acid reacts with CH3OH to form the ester, methyl lactate. What stereochemistry would you expect the product(s) to have? What is the relationship of the products?

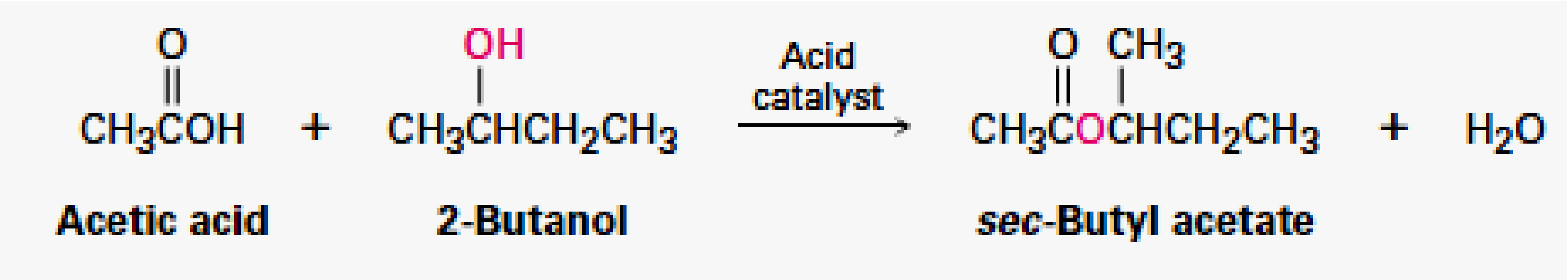
Solution

Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products



Problem 5.19

Suppose that acetic acid (CH3CO2H) reacts with (*S)-2-butanol to form an ester* .What stereochemistry would you expect the product(s) to have? What is the relationship of the products



Problem 5.20

What stereoisomers would result from reaction of (±)-lactic acid with (*S)-1-phenylethylamine,* and what is the relationship between them?

Review Of Isomerism

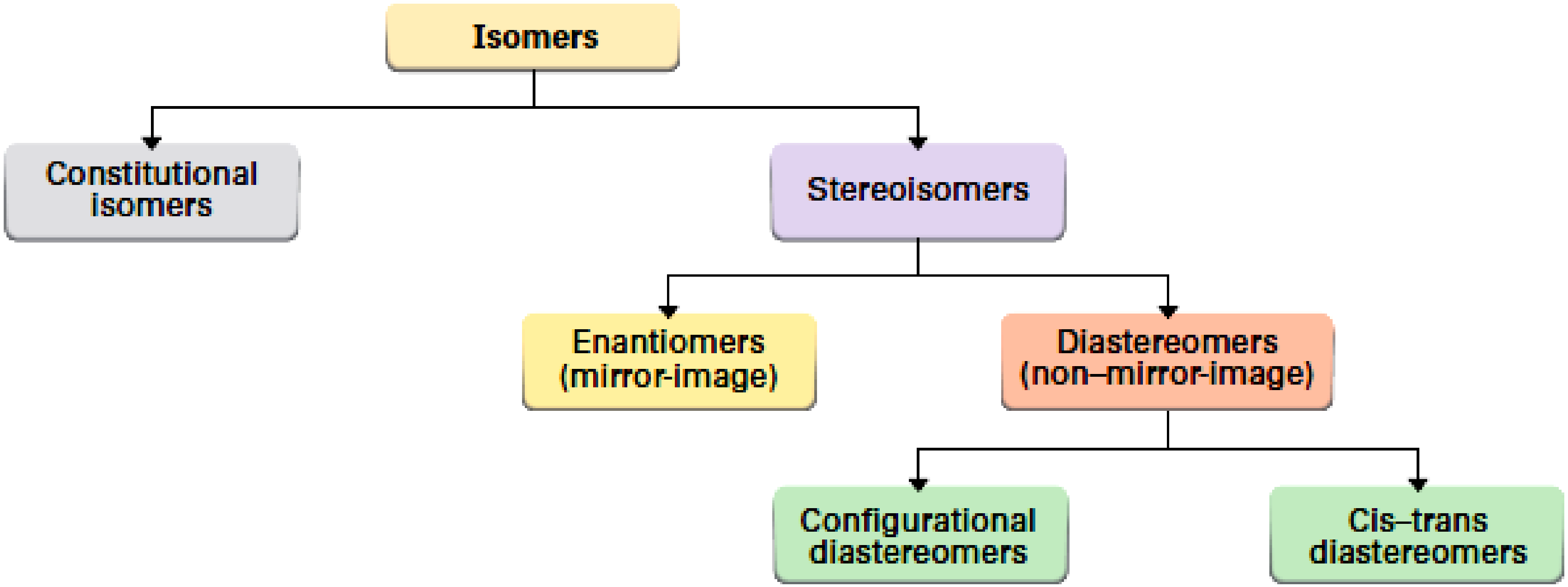
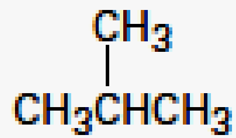
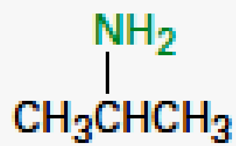


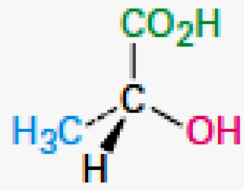
Figure 5.14 A summary of the different kinds of isomers.

Constitutional isomers (Section 3.2)

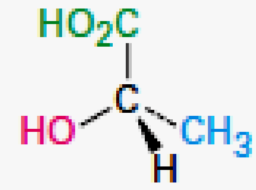
Different carbon skeletons	 **2-Methylpropane**	and	$CH_3CH_2CH_2CH_3$ **Butane**
Different functional groups	CH_3CH_2OH **Ethyl alcohol**	and	CH_3OCH_3 **Dimethyl ether**
Different position of functional groups	 **Isopropylamine**	and	$CH_3CH_2CH_2NH_2$ **Propylamine**

Stereoisomers (Section 4.2)

Enantiomers (nonsuperimposable mirror-image stereoisomers)



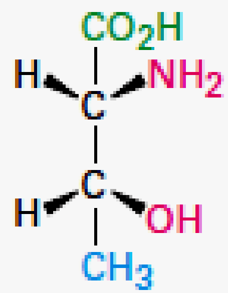
(*R*)-Lactic acid



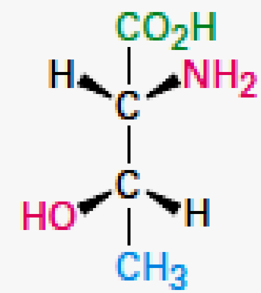
(*S*)-Lactic acid

Diastereomers (nonsuperimposable non–mirror-image stereoisomers)

Configurational diastereomers

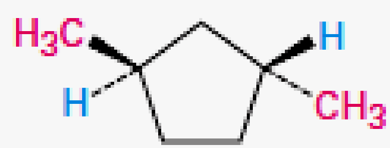


2*R*,3*R*-2-Amino-3-hydroxybutanoic acid



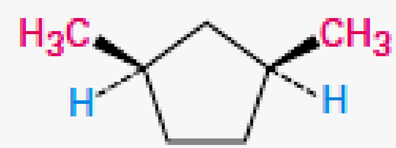
2*R*,3*S*-2-Amino-3-hydroxybutanoic acid

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



trans-1,3-Dimethylcyclopentane

and



cis-1,3-Dimethylcyclopentane

4.9 Chiral drugs and Chiral receptors
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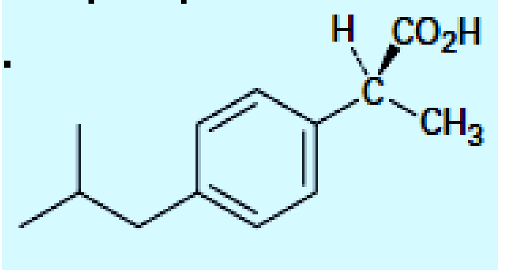
- Change in chirality of can affect the biological properties of a drug-this property is found in many drugs.

  Example: the nonsteroidal anti-inflammatory (NSAID,s) ibuprofen

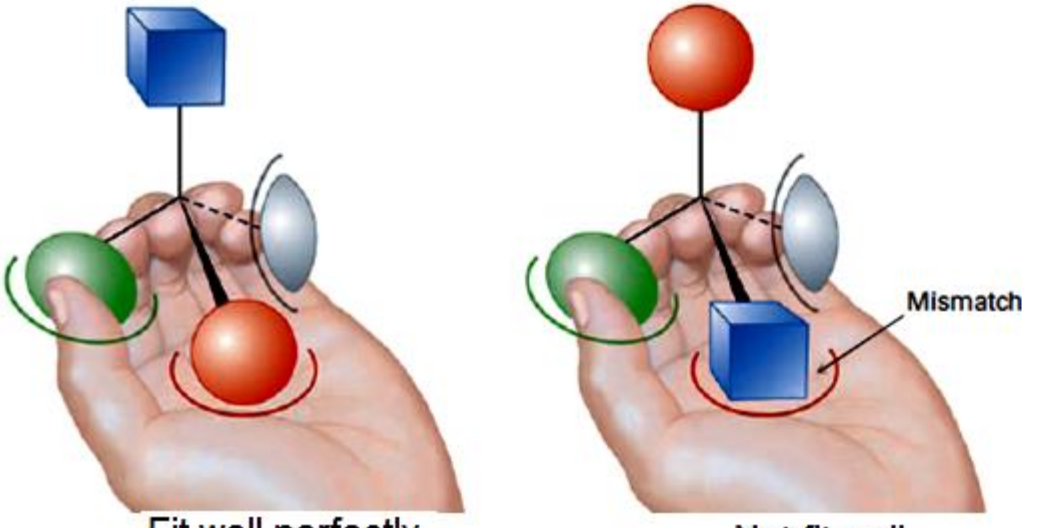
  - The S enantiomer is active
  - The R enantiomer is inactive, although it is slowly converted in the body to the active S form.



(*S*)-Ibuprofen
(an active analgesic agent)

- Reason:

  To have a biological effect, the chiral drug typically must have the correct stereochemistry to fit well into chiral receptor.



Fit well perfectly

Not fit well