Lecture 3

Stereochemistry

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HINT

Stereochemistry is a difficult topic for many students. Use your models to help you see the relationships between structures.

Isomerism in Organic Chemistry

Stereoisomerism

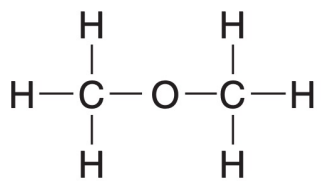
Isomers

Constitutional isomers

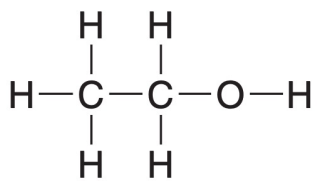
Same molecular formula but different constitution (order of connectivity of atoms)

Stereoisomers

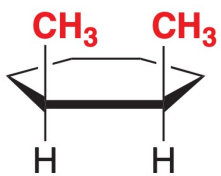
Same molecular formula and constitution but different spatial arrangement of atoms



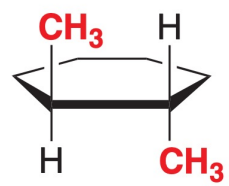
Methoxymethane
Boiling point = –23°C



Ethanol
Boiling point = 78.4°C

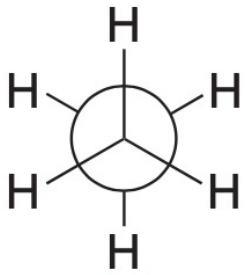


cis-
1,2-Dimethylcyclohexane

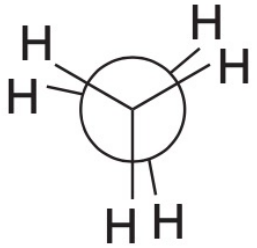


trans-
1,2-Dimethylcyclohexane

- Conformational Isomerism

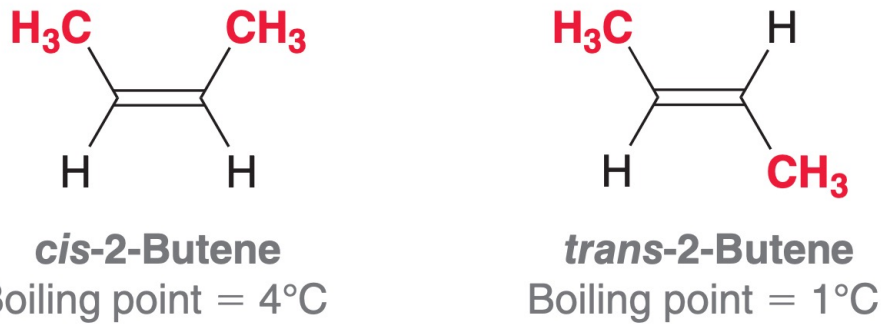


Staggered conformation
Lowest in energy

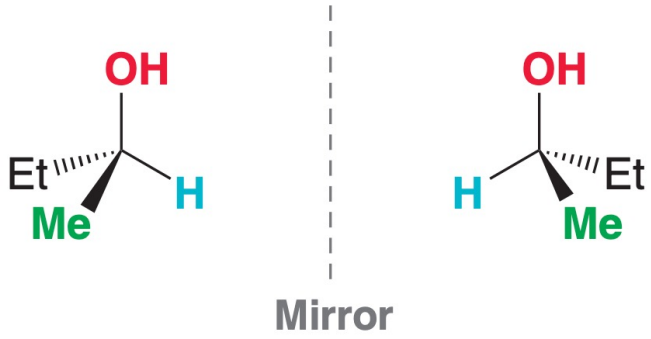


Eclipsed conformation
Highest in energy

- Configuration Isomerism



cis-trans isomerism

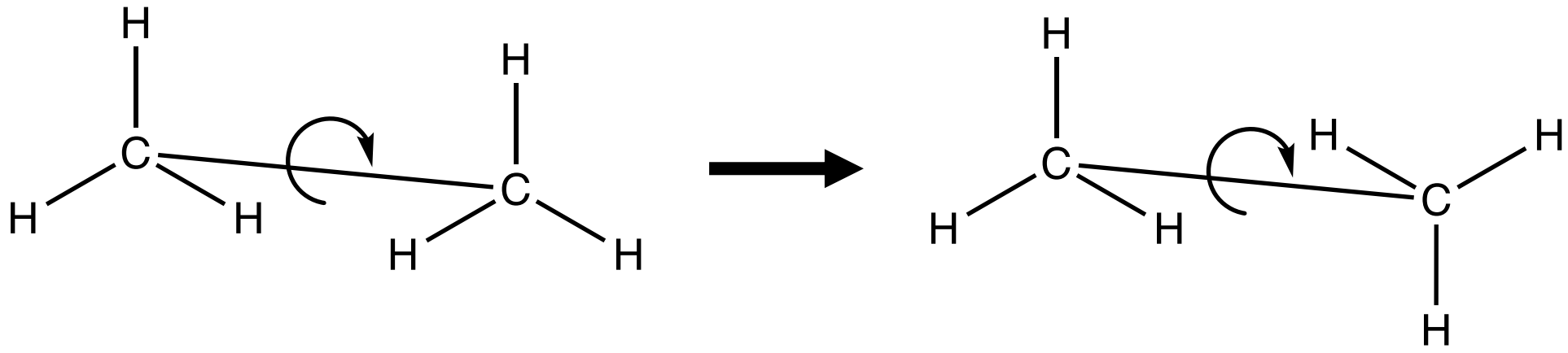


optical isomerism

Conformational Isomerism

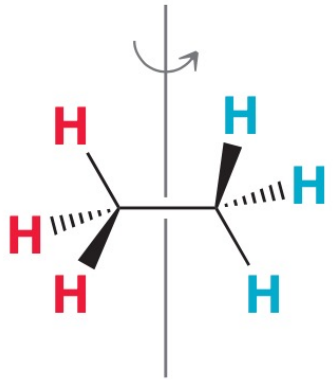
Conformation of Alkane & Cycloalkane

- Conformational isomerism: stereoisomerism of molecules due to the rotation of single bonds



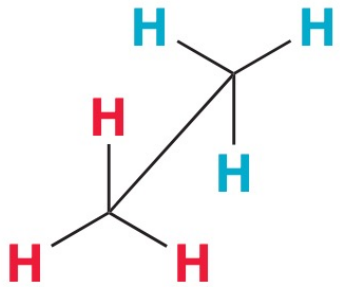
single bond can rotate freely

- Methods of drawing molecule conformations



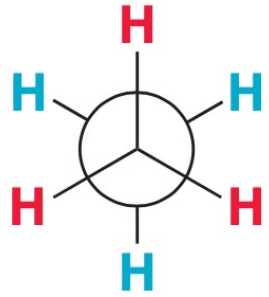
Wedge and dash

楔形式



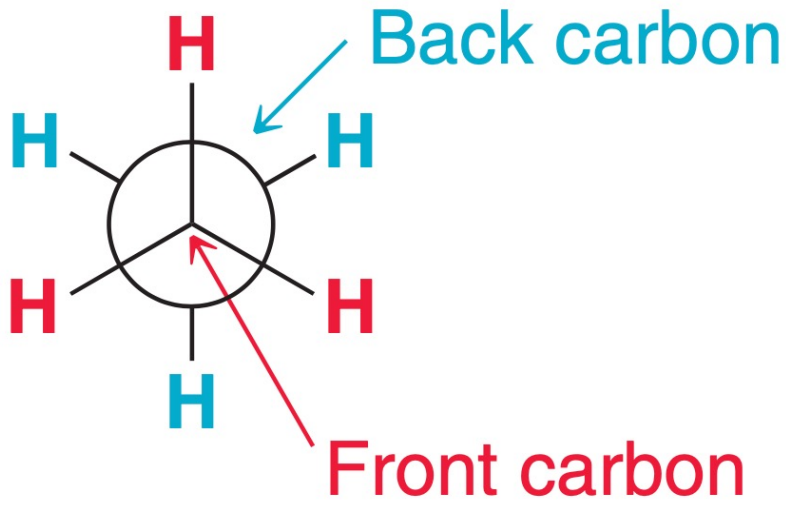
Sawhorse

锯架式



Newman projection

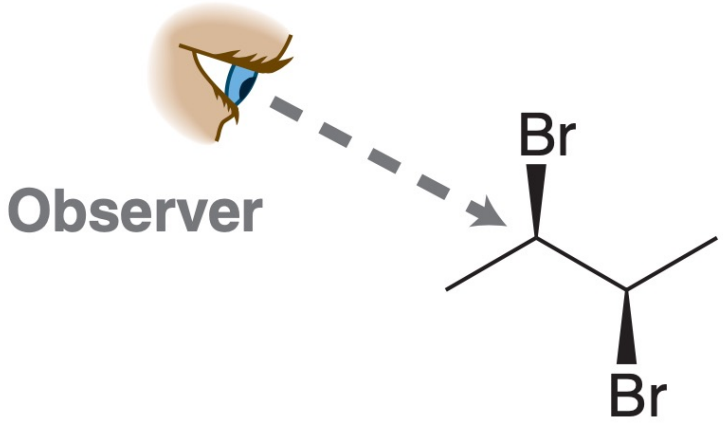
Newman投影式



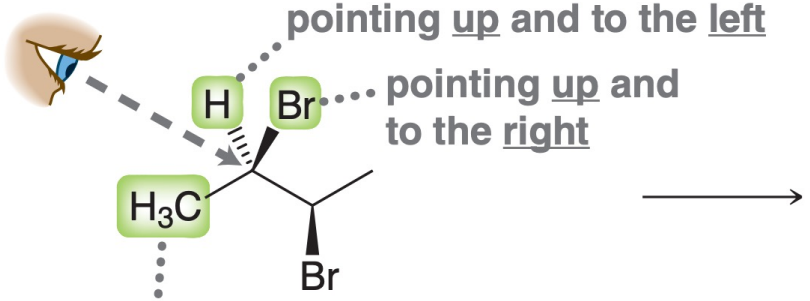
≡

H_3C——CH_3

- Practice: draw a Newman projection of the following compound, as viewed from the angle indicated:



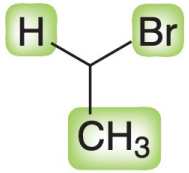
When viewed from the perspective of the observer...



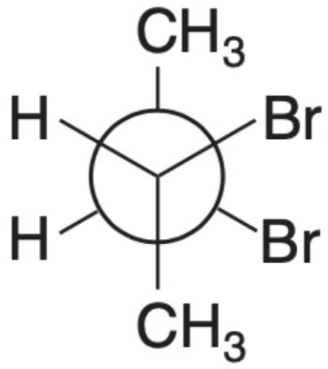
Front carbon

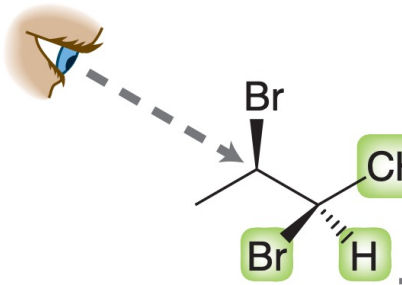
up and to the left

up and to the right



straight down





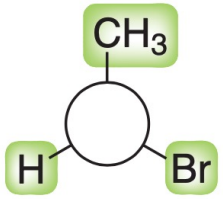
...this group is pointing straight up

...the Br is pointing down and to the right

...this H is pointing down and to the left

Back carbon

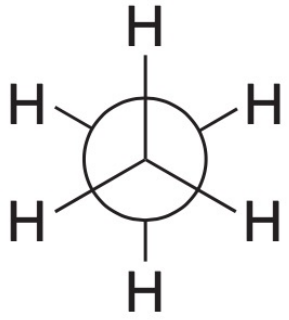
straight up



down and to the left

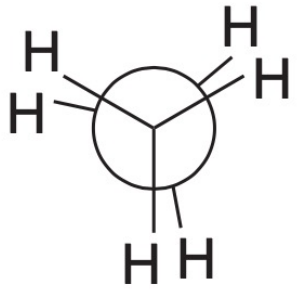
down and to the right

- Conformation of ethane



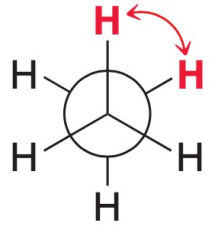
Staggered conformation
Lowest in energy

交叉式
（能量低）



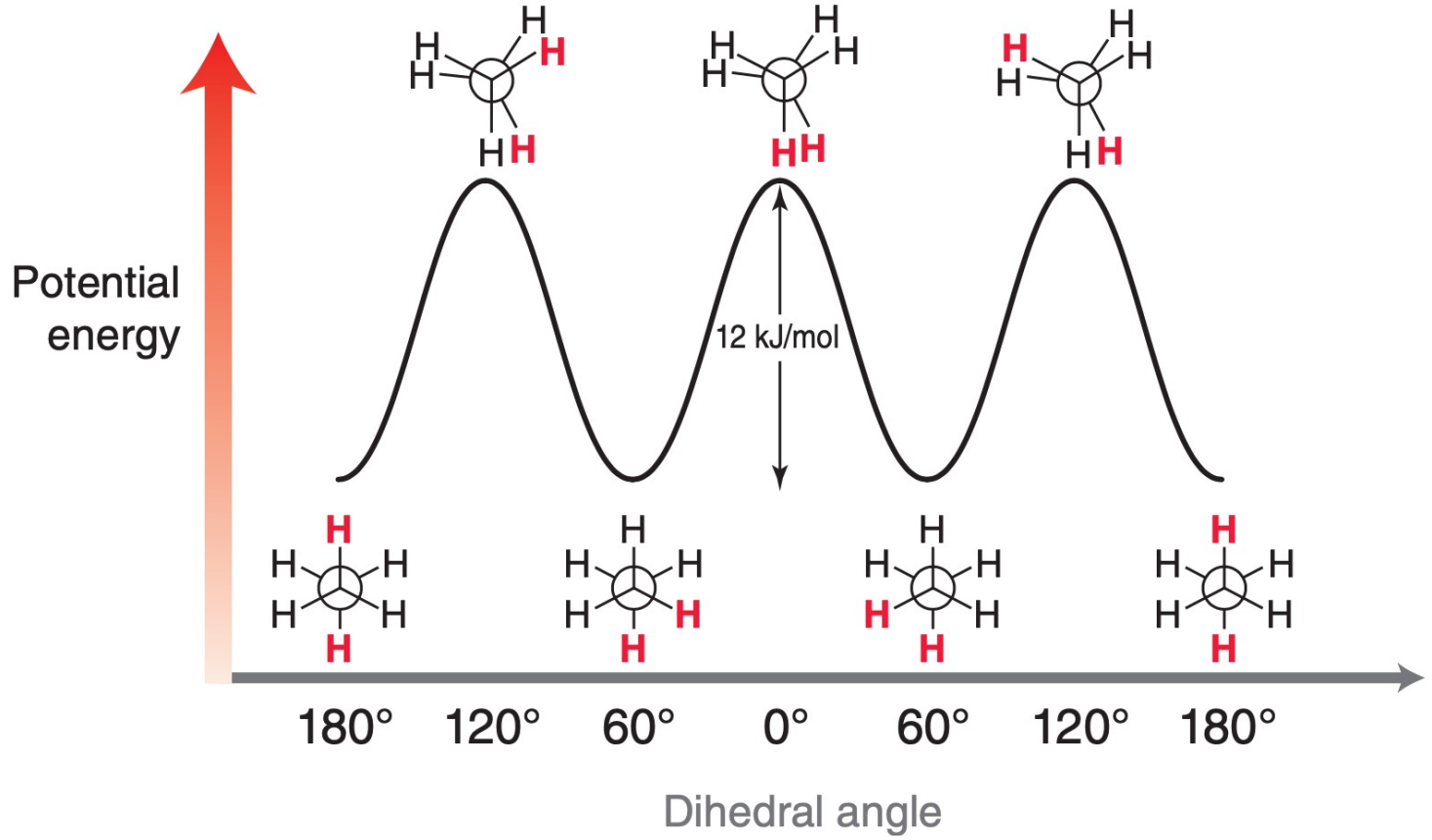
Eclipsed conformation
Highest in energy

重叠式
（能量高）



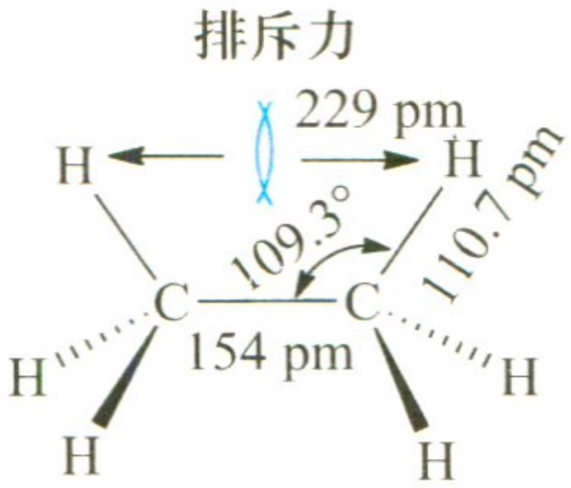
Dihedral angle=60°

- Conformation of ethane

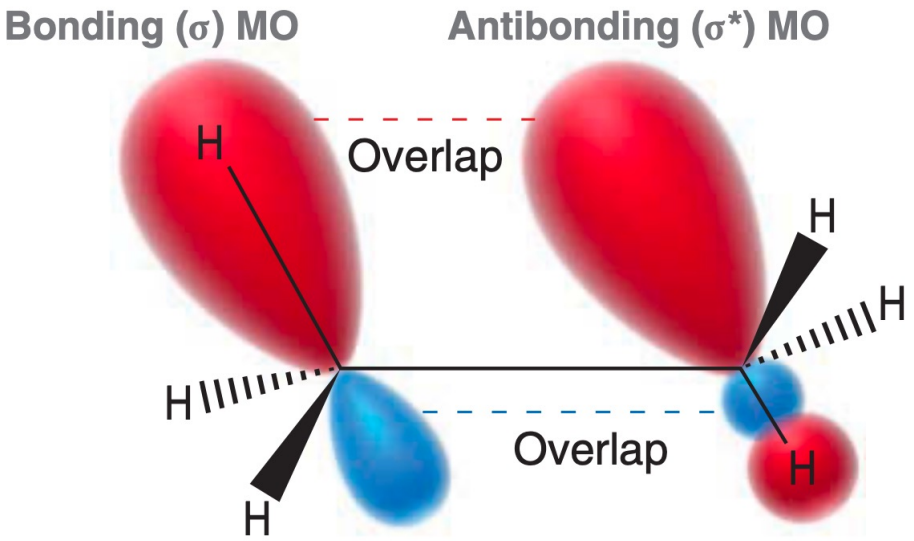


all staggered & eclipsed conformations are **degenerate**

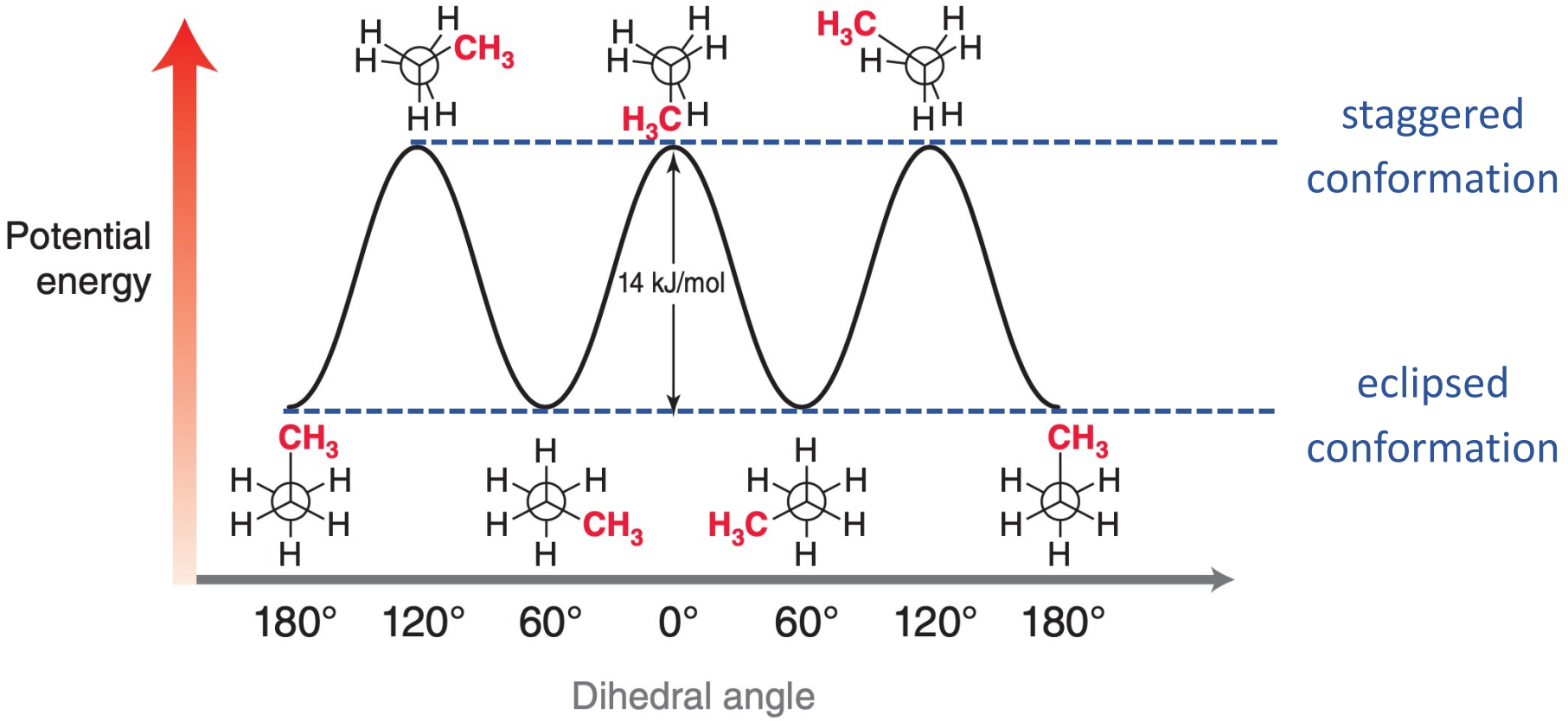
- Classical explanation: steric hindrance



- Modern explanation: orbital interaction

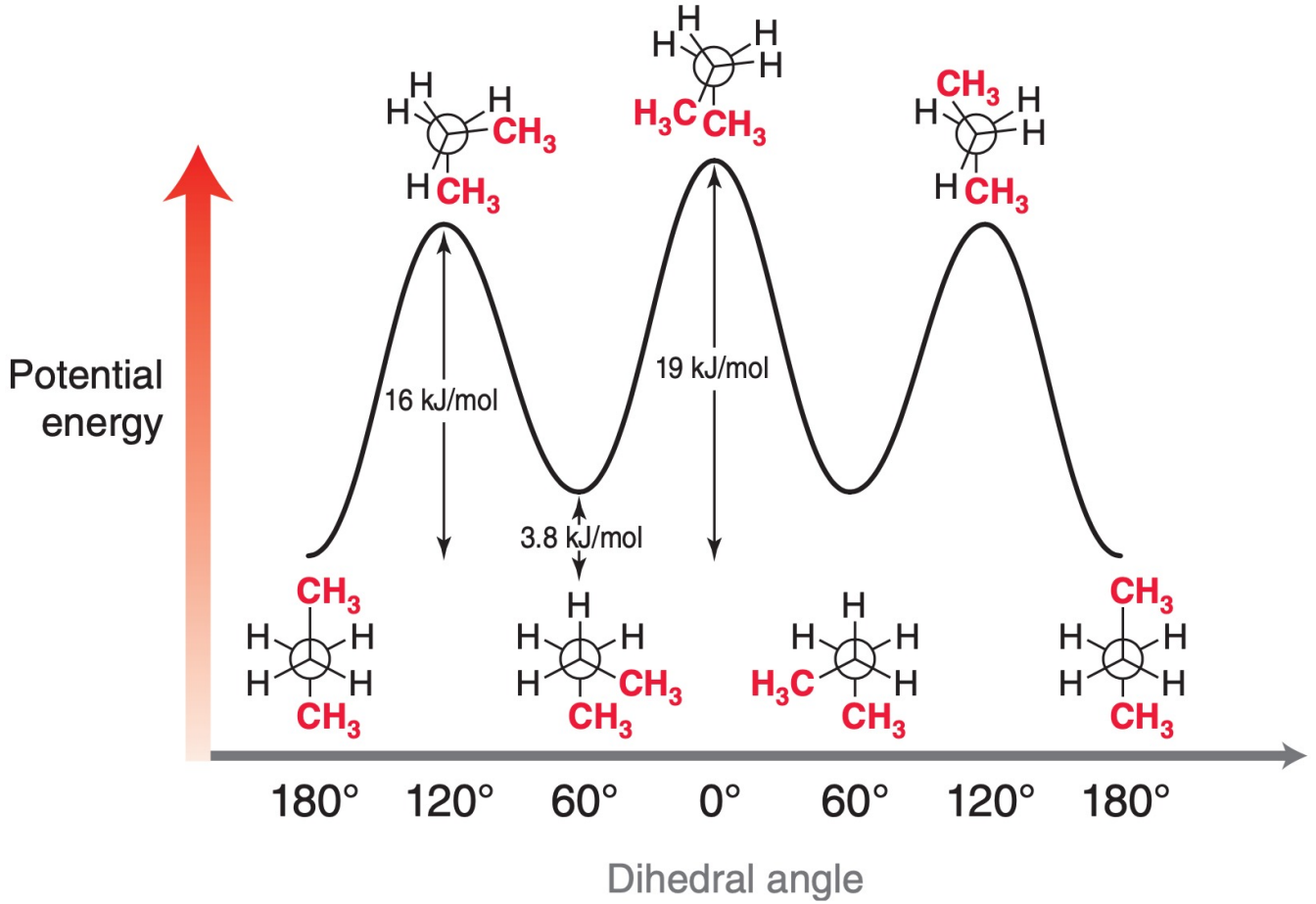


- Conformation of propane

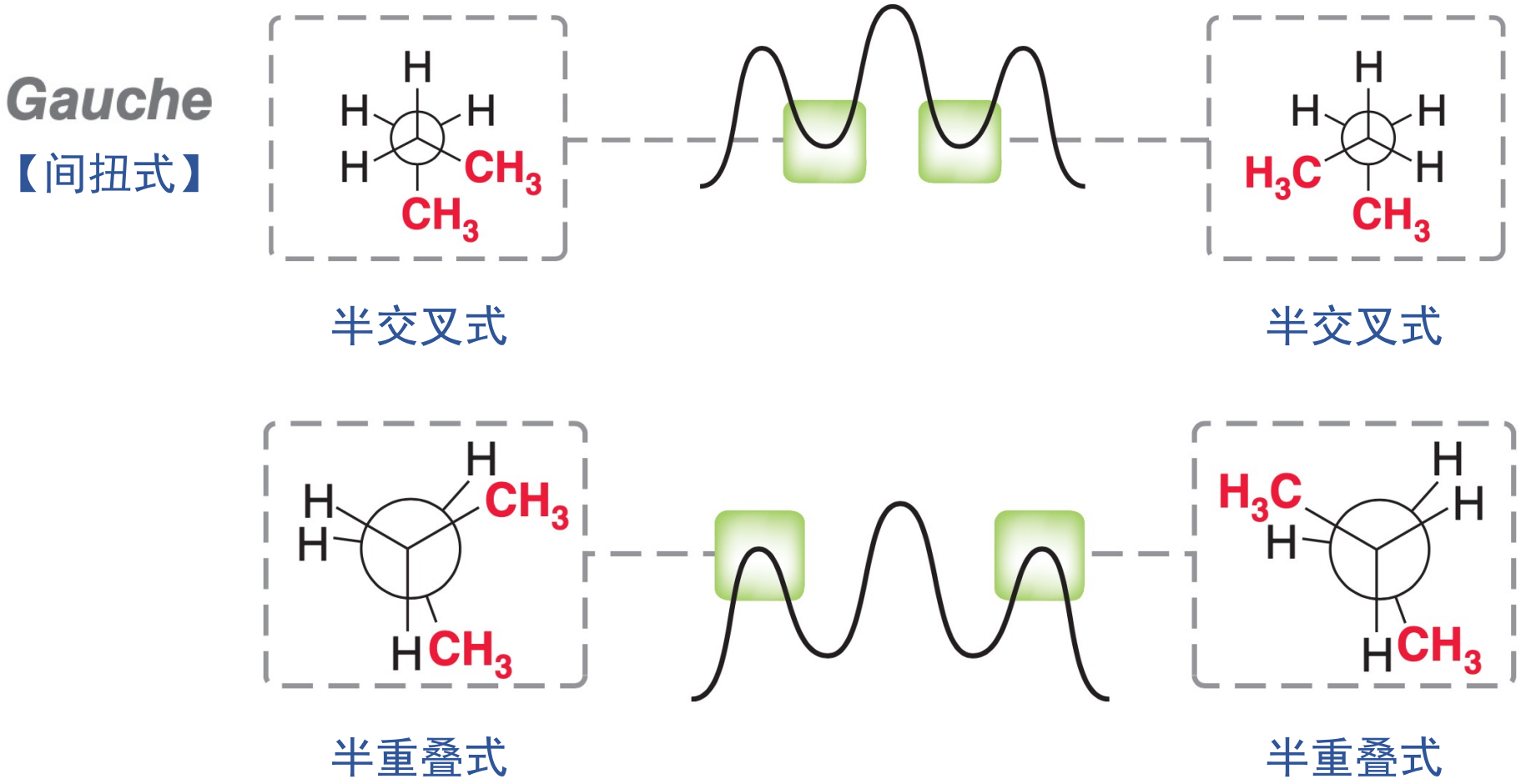


all staggered & eclipsed conformations are **degenerate**

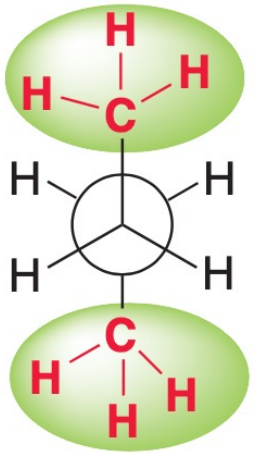
- Conformation of butane



- Conformation of butane

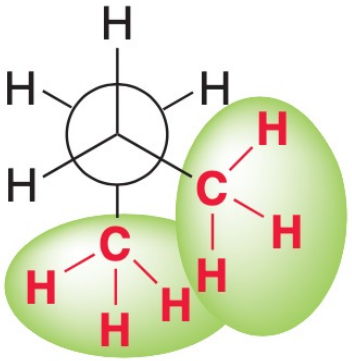


- *Gauche* interactions



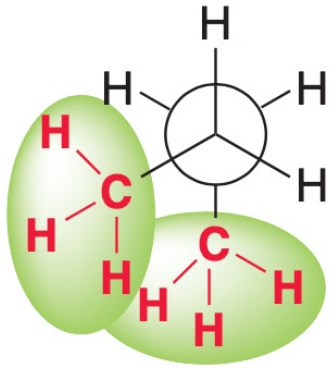
Anti

Methyl groups are farthest apart



Gauche

Methyl groups experience a gauche interaction



Gauche

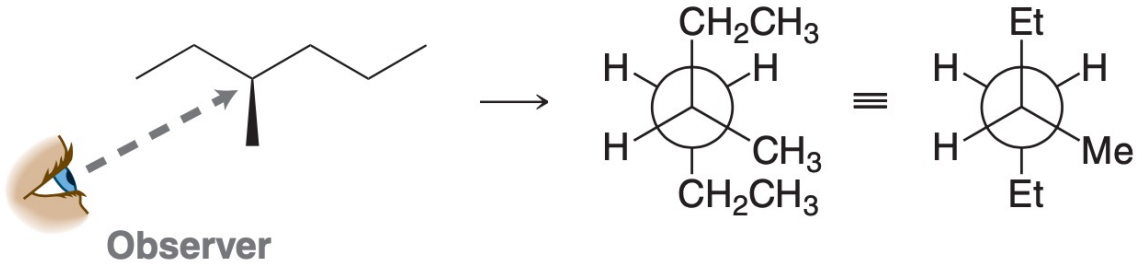
Methyl groups experience a gauche interaction

- Practice

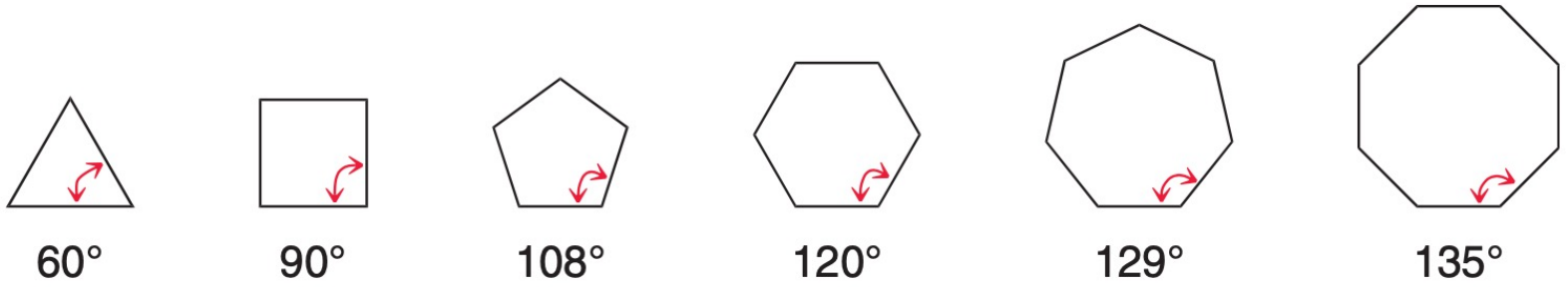
Consider the following compound:

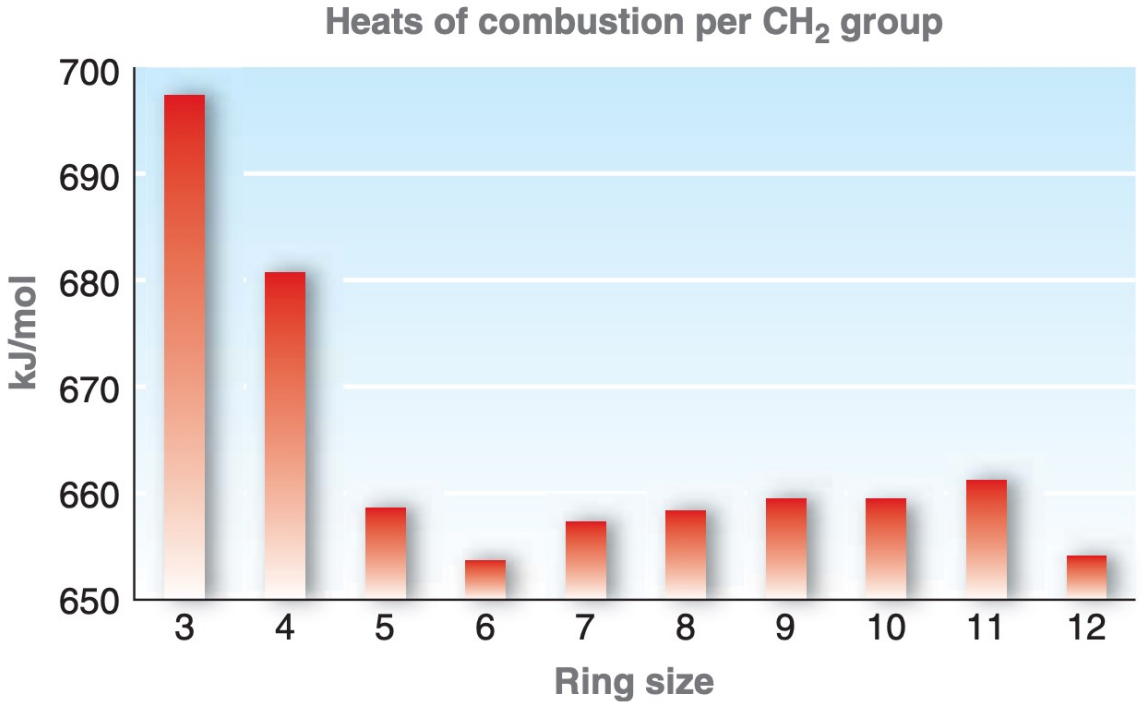
(a) Rotating only the C3—C4 bond, identify the lowest energy conformation.

(b) Rotating only the C3—C4 bond, identify the highest energy conformation.



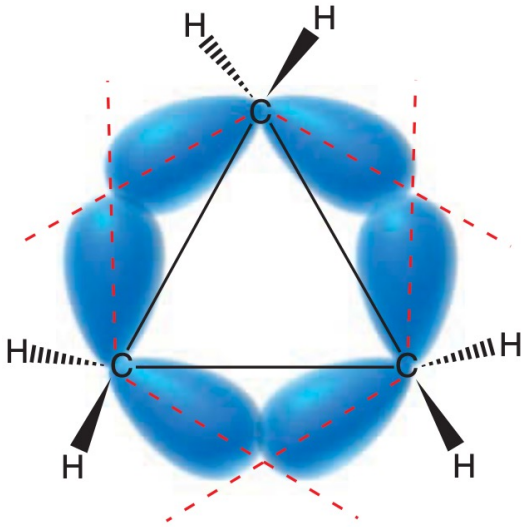
- Cycloalkanes: angle and stability – angle strain…?



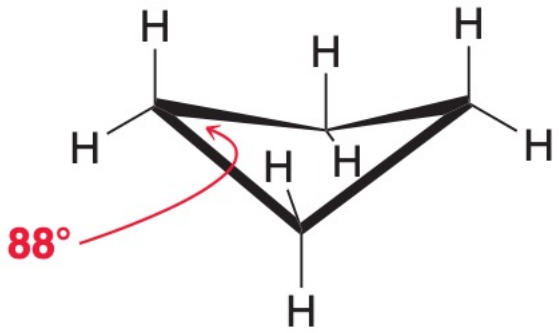


与事实并不同诶:)

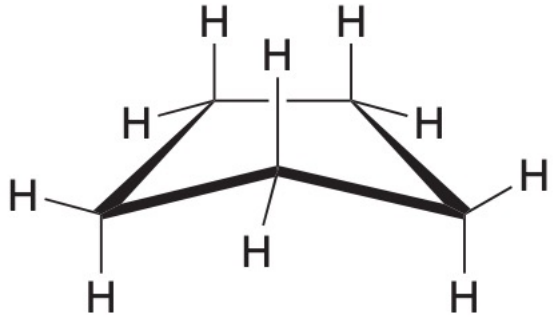
- Conformation of cycloalkanes



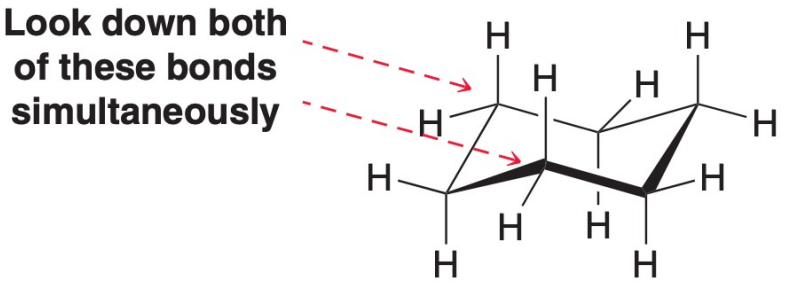
cyclopropane



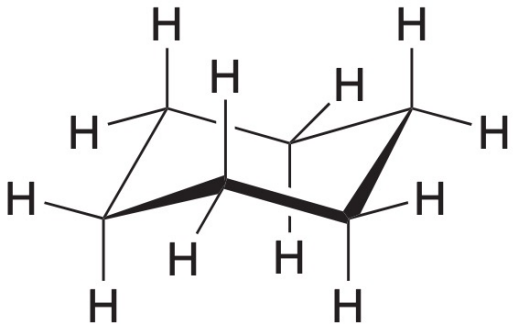
cyclobutane



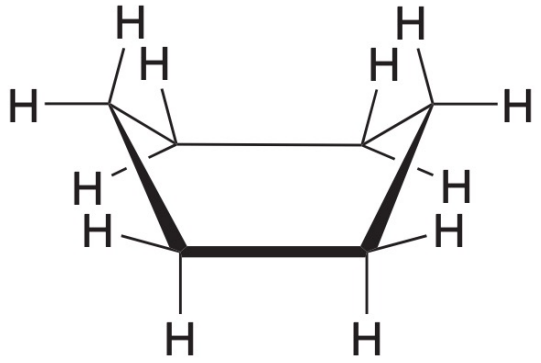
cyclopentane



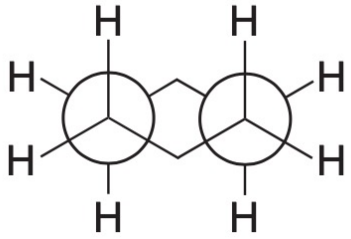
- Conformation of cyclohexane

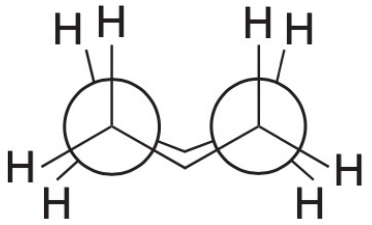


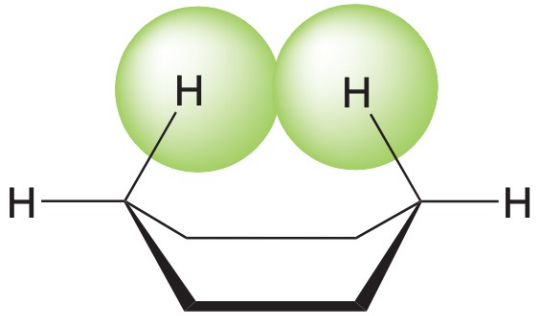
Chair



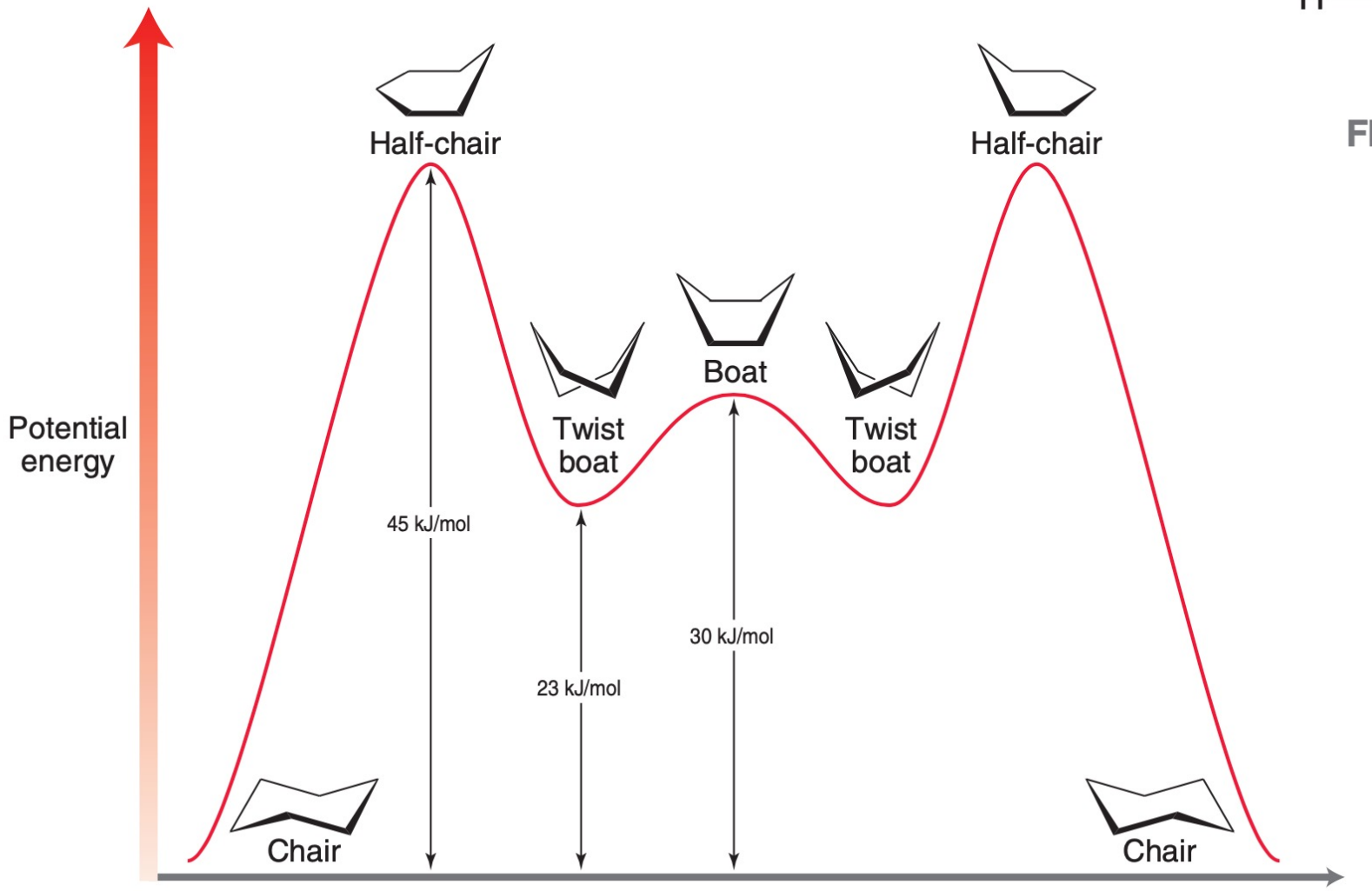
Boat







Flagpole interactions



- Drawing chair conformations

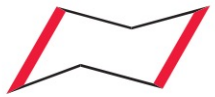
Step 1  Draw a ***wide*** V.

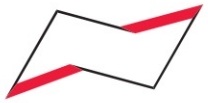
Step 2  Draw a line going down at a 60° angle, ending just before the center of the V.

Step 3  Draw a line parallel to the left side of the V, ending just before the left side of the V.

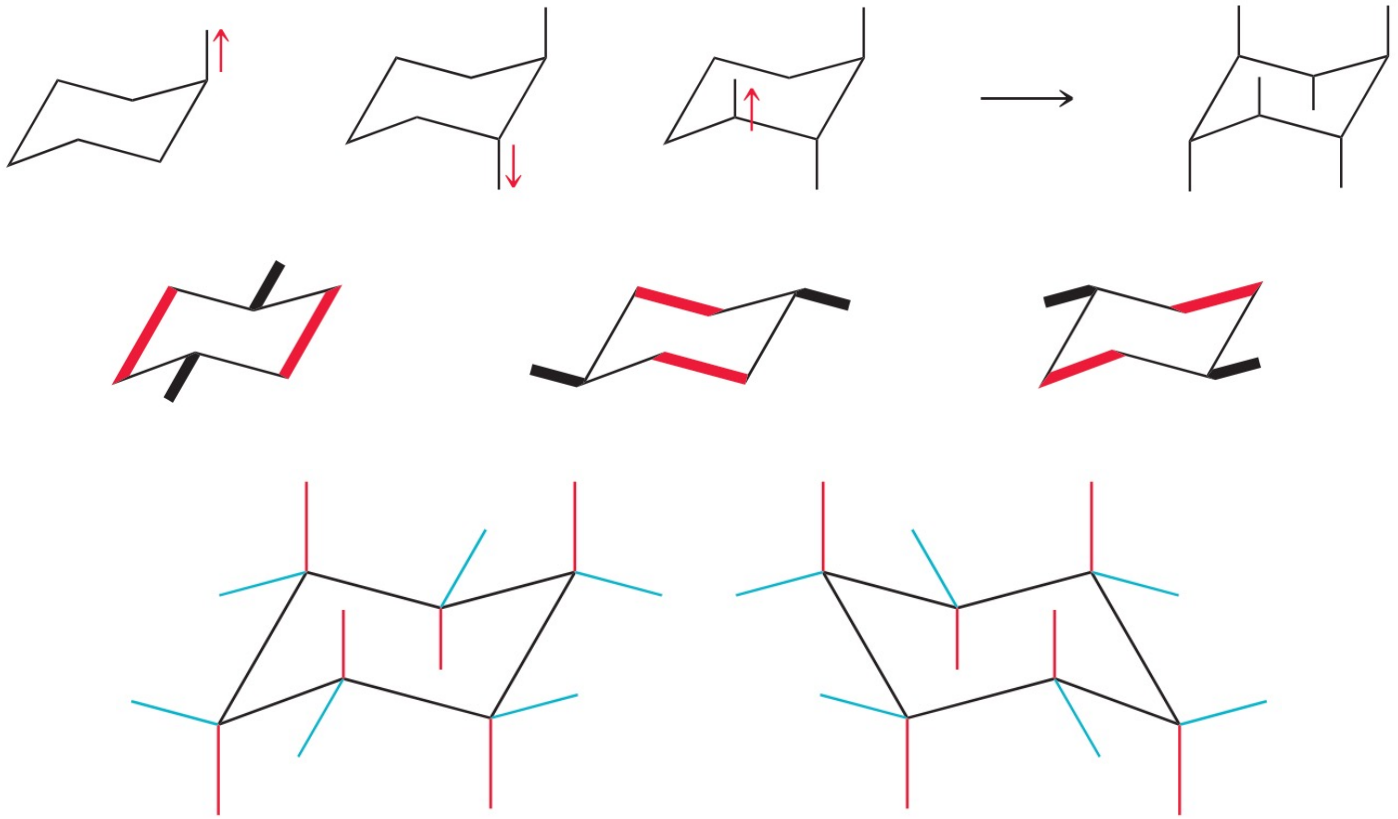
Step 4  Draw a line parallel to the line from Step 2, going down exactly as low as that line.

Step 5  Connect the dots.

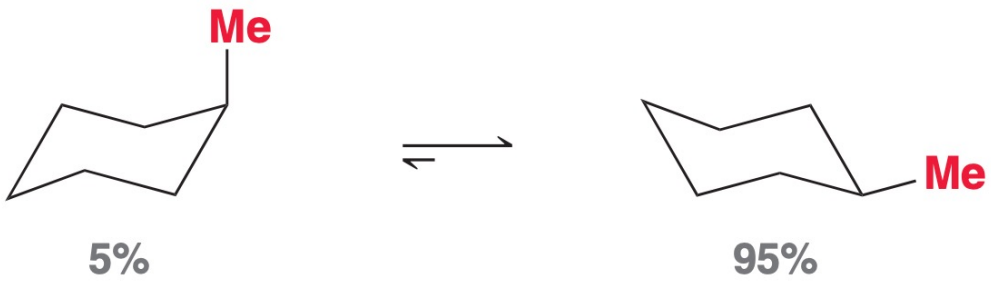




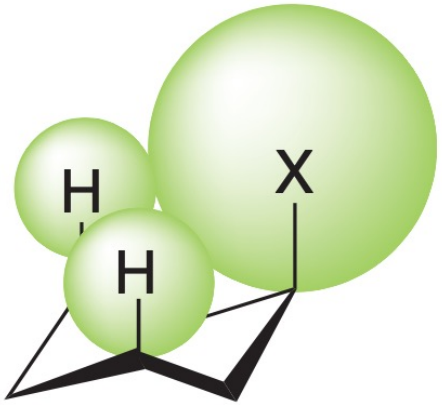
- Drawing chair conformations



- Monosubstituted cyclohexane



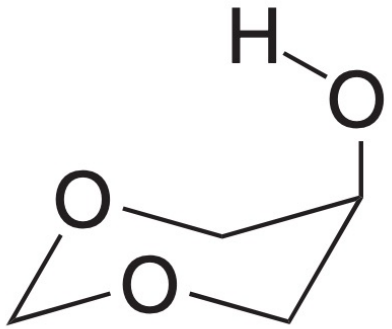
取代基处于E键时更加稳定



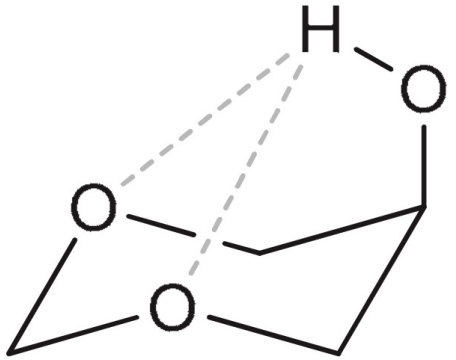
1,3-diaxial interactions

1,3-竖键相互作用

- Practice: the most stable conformation of 5-hydroxy-1,3-dioxane has the OH group in an axial position, rather than an equatorial position. Provide an explanation for this observation.

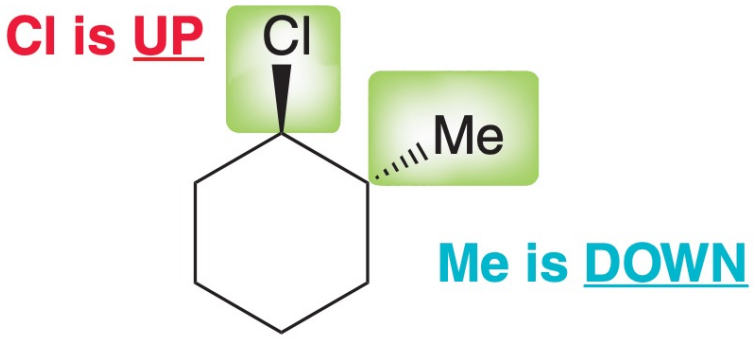


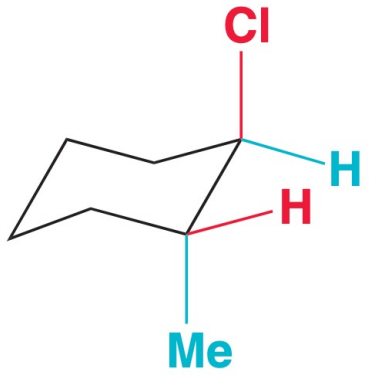
5-hydroxy-1,3-dioxane

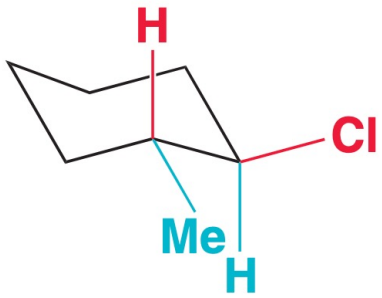


forming *intra*molecular hydrogen bonding

- Disubstituted, polysubstituted cyclohexanes



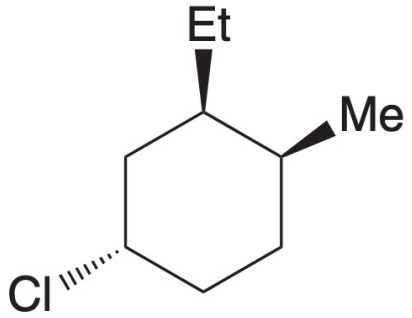


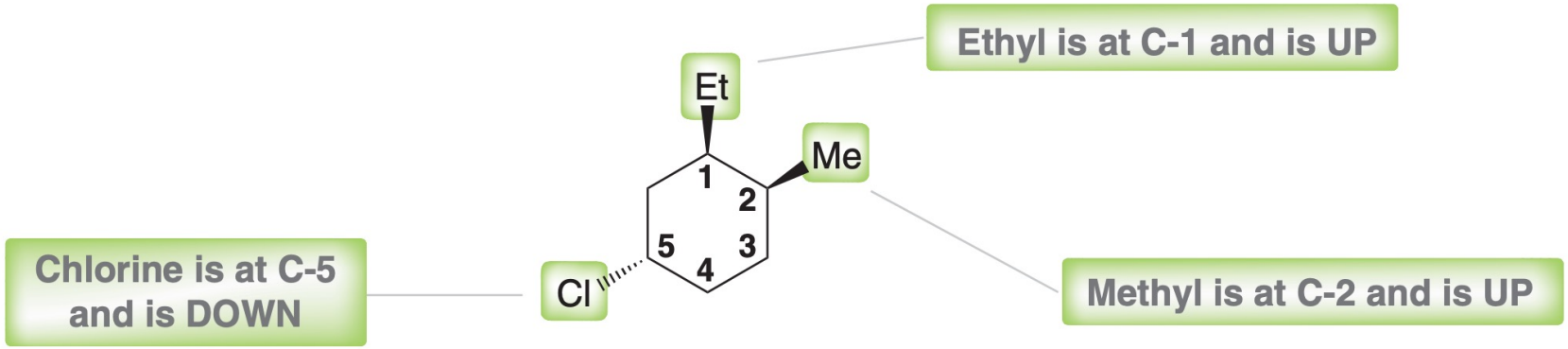


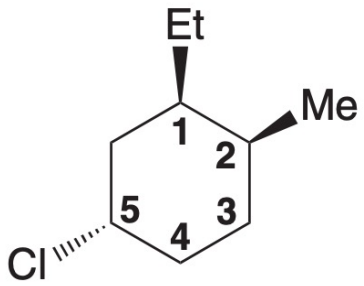
- Comparison of 1,3-diaxial interactions

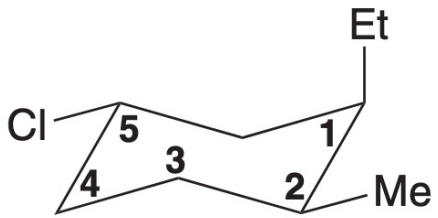
SUBSTITUENT	1,3-DIAXIAL INTERACTIONS (KJ/MOL)	EQUATORIAL-AXIAL RATIO (AT EQUILIBRIUM)
—Cl	2.0	70 : 30
—OH	4.2	83 : 17
—CH_3	7.6	95 : 5
—CH_2CH_3	8.0	96 : 4
—$CH(CH_3)_2$	9.2	97 : 3
—$C(CH_3)_3$	22.8	9999 : 1

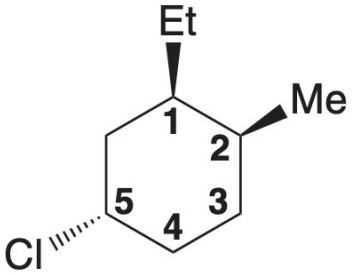
- Practice: draw the more stable chair conformation of the following compound:

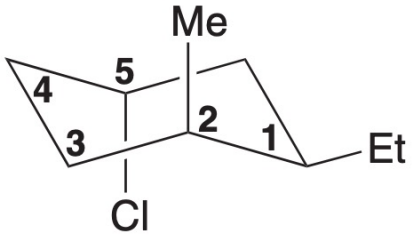


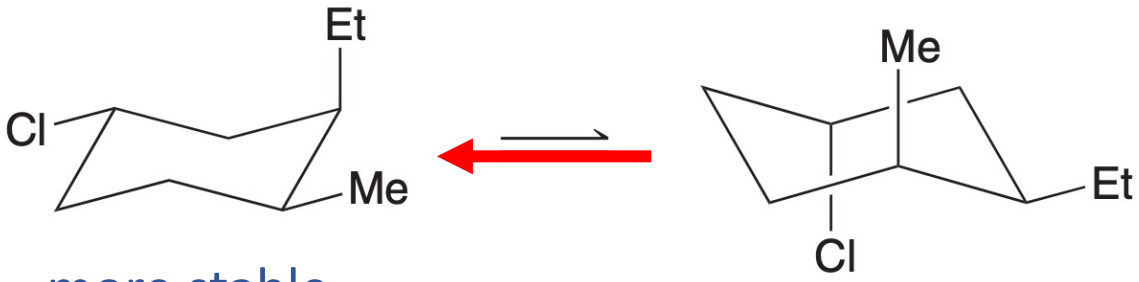



Et
Me
1
2
5
3
4
Cl


Et
Cl
5
1
3
4
2
Me


Et
Me
1
2
5
3
4
Cl


Me
5
4
2
3
1
Et
Cl

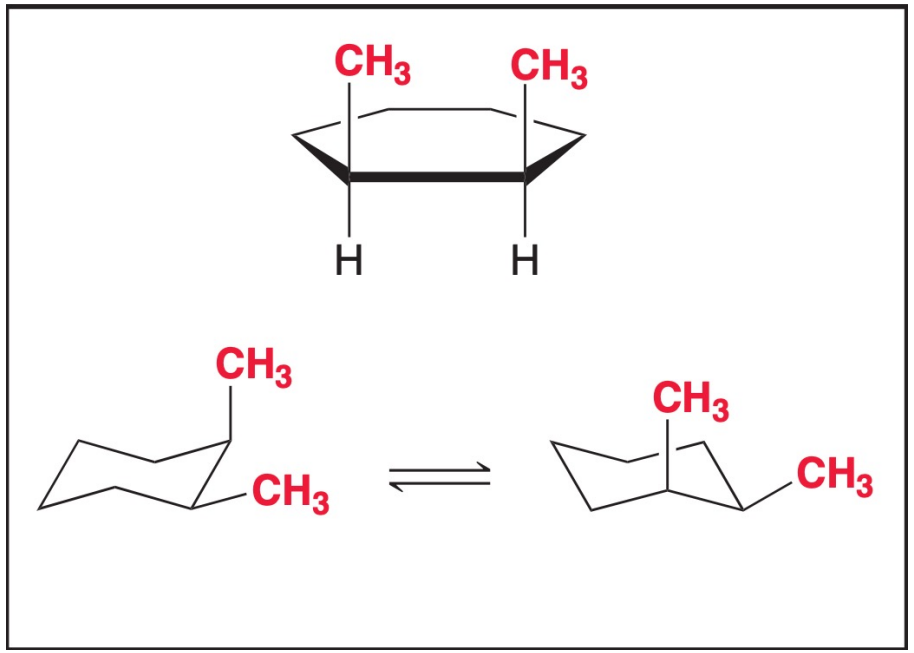

Et
Cl
Me
Me
Et
Cl

more stable

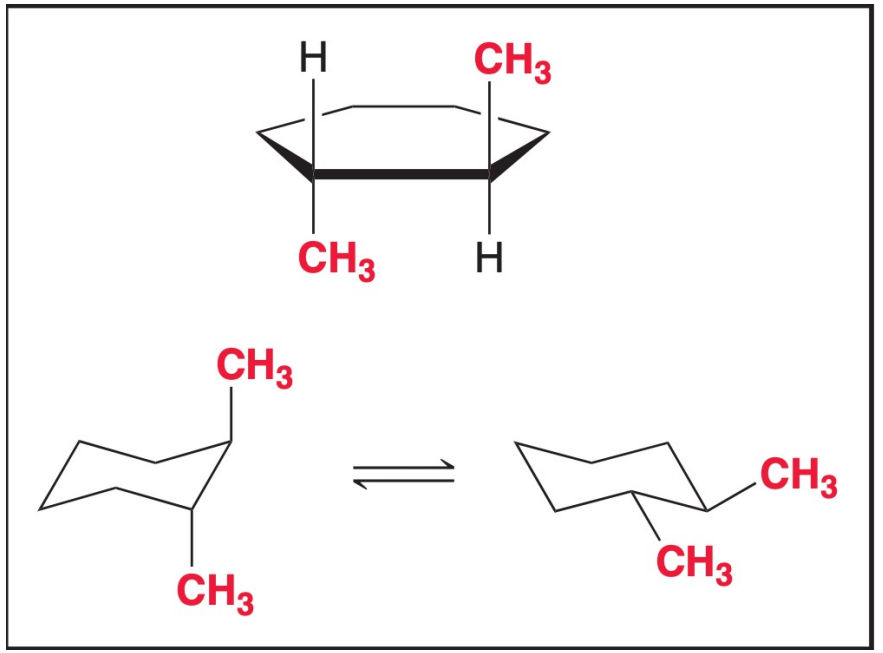
Configuration Isomerism

cis-trans Stereoisomerism, Chirality & Optical Activity

- *cis-trans* isomerism of cycloalkanes

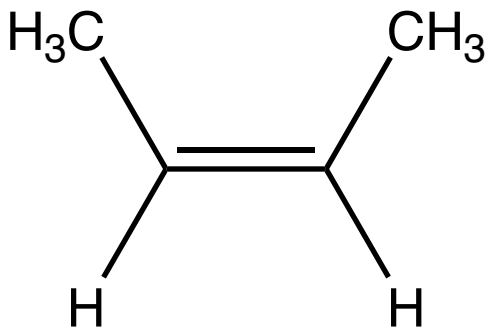


***cis*-1,2-Dimethylcyclohexane**

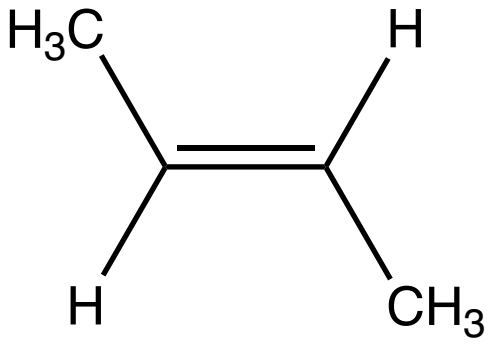


***trans*-1,2-Dimethylcyclohexane**

- *cis-trans* isomerism of alkenes

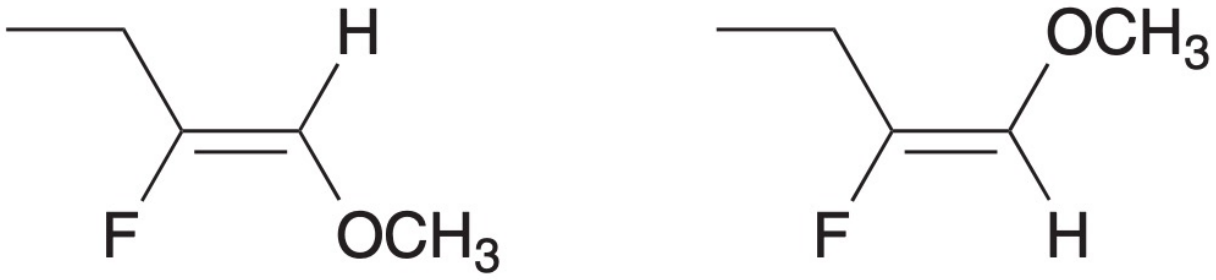


cis-but-2-ene



trans-but-2-ene

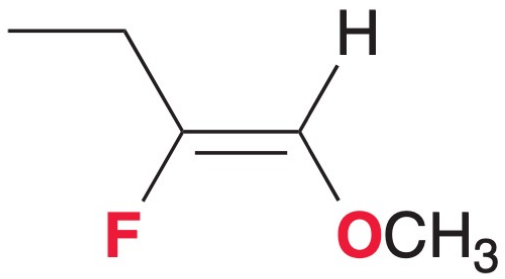
- Defects of cis-trans isomerism



For four different groups…

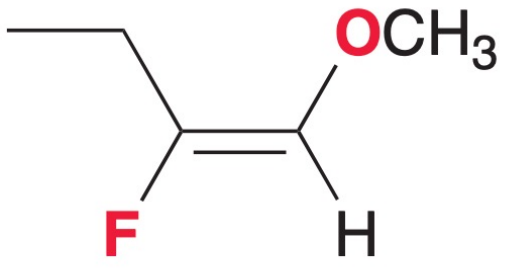
cannot use *cis*/*trans* to indicate configuration!

- *Z*/*E* configurations



Z

for German word
"zusammen"
(together)

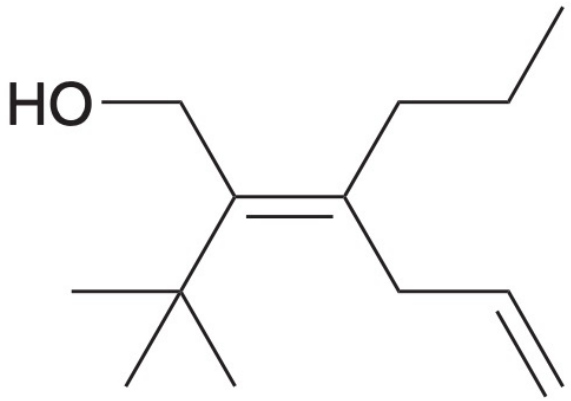


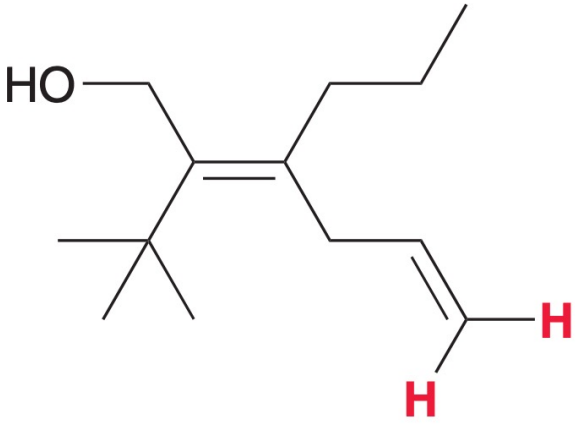
E

for German word
"entgegen"
(opposite)

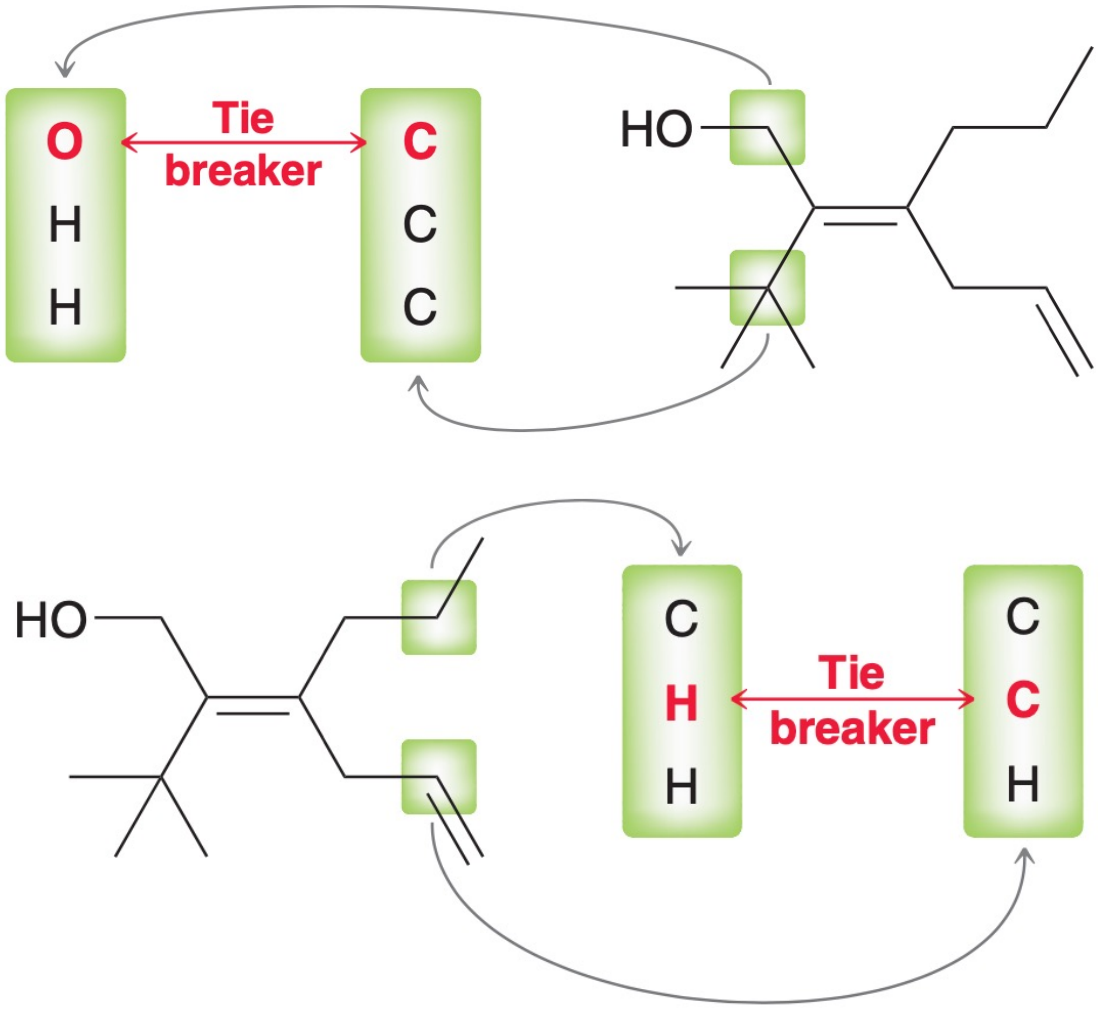
- 顺序规则(Cahn-Ingold-Prelog System)
  - 比较每个单原子基团的原子序数大小，原子序数大在前
  - 如果两个多原子基团的第一个原子相同，则比较与之相连的其它原子
  - 含双键/三键的基团可以认为连有两个或三个相同的原子
  - 若参与比较的原子连接的键不足四个，则可以补充原子序数为0的假想原子作为参照

- Practice: identify the configuration of the following alkene:

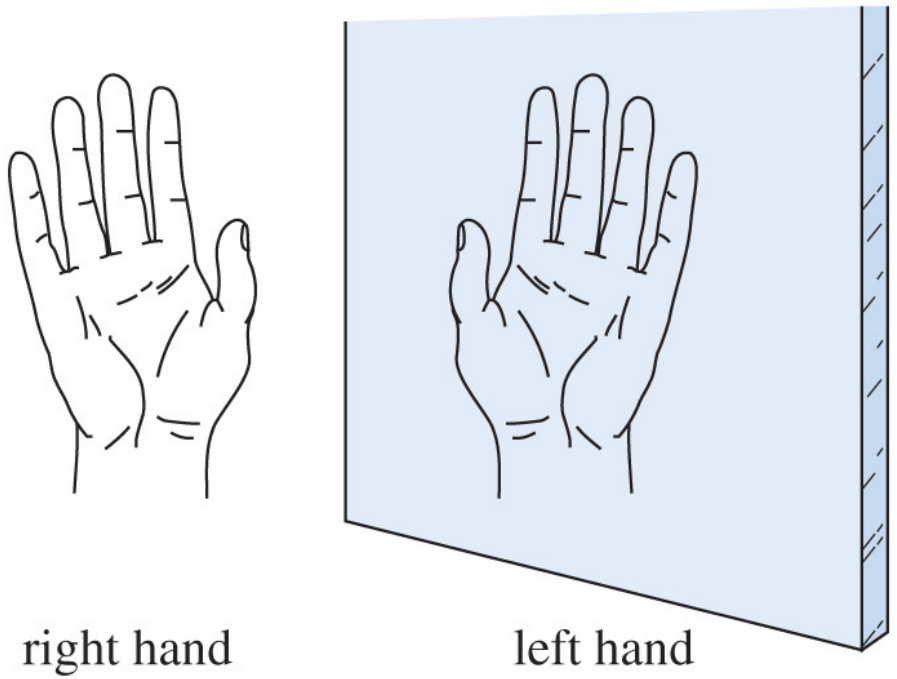




右下角的双键不存在立体异构

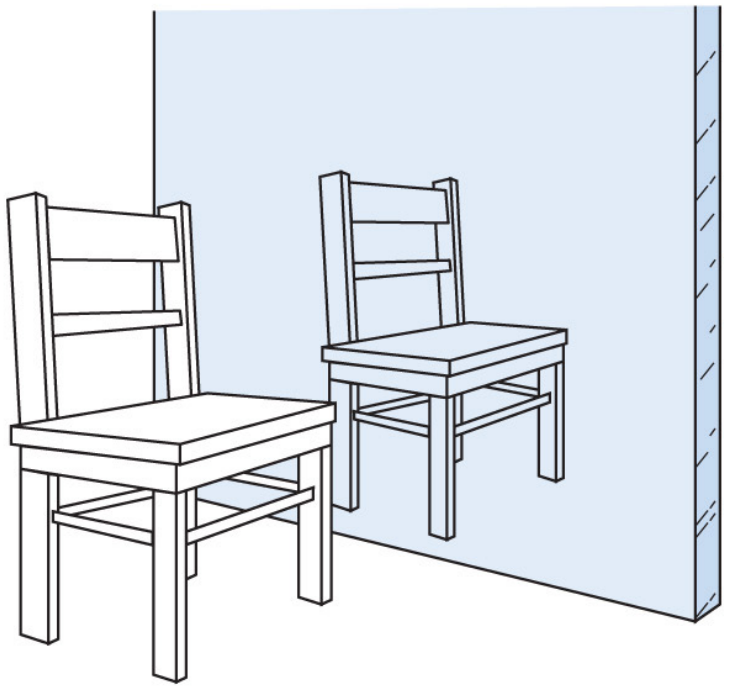


- Chirality and chiral objects



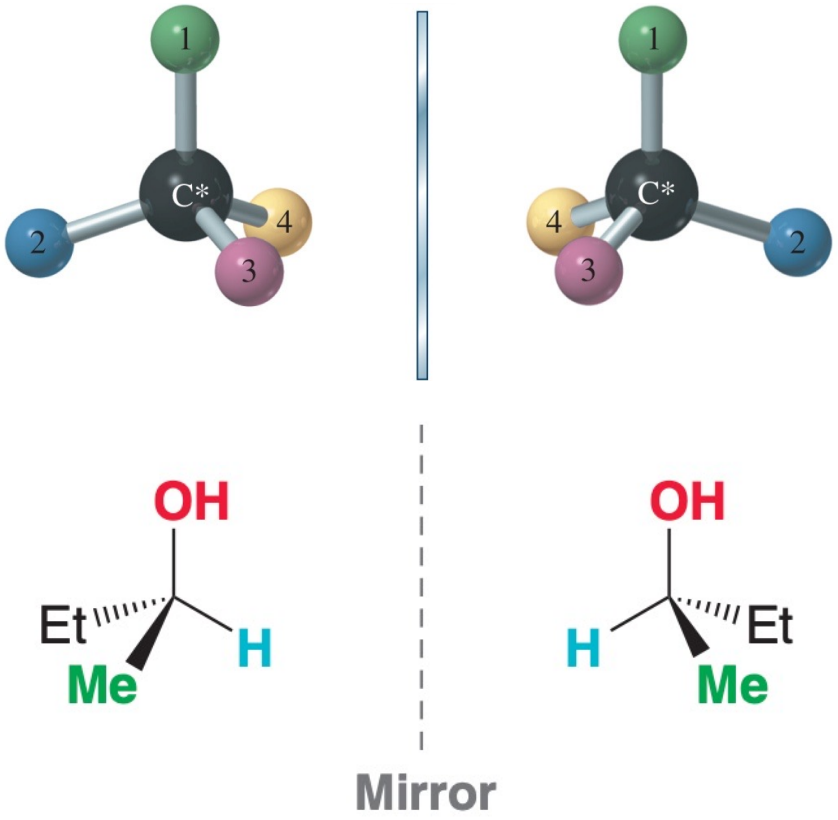
nonsuperimposable

- Achiral objects

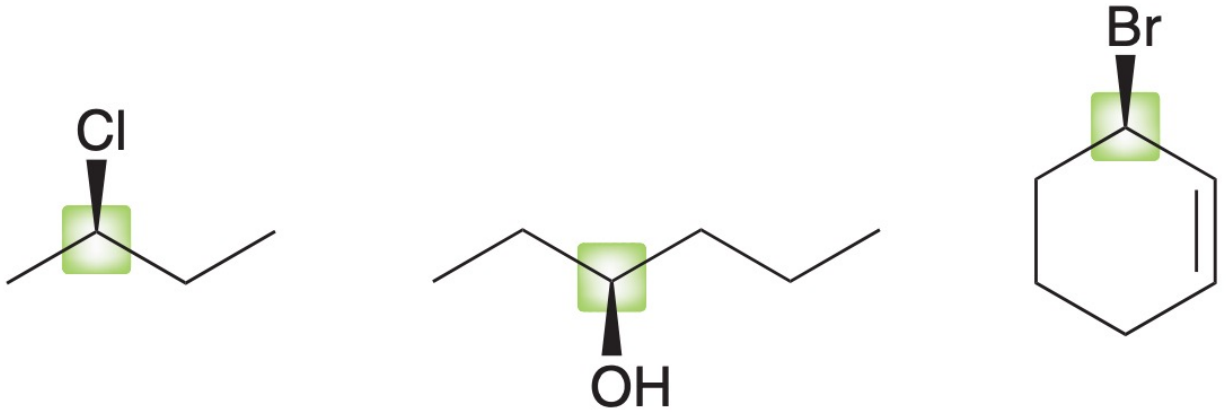


superimposable

- Molecular chirality

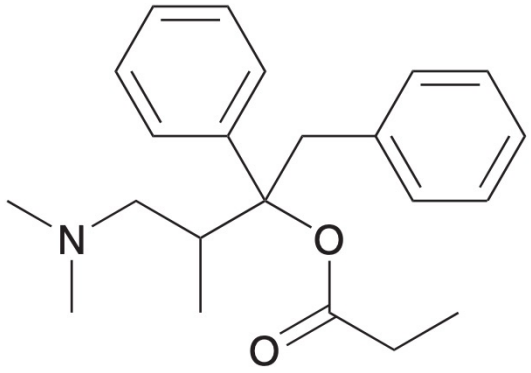


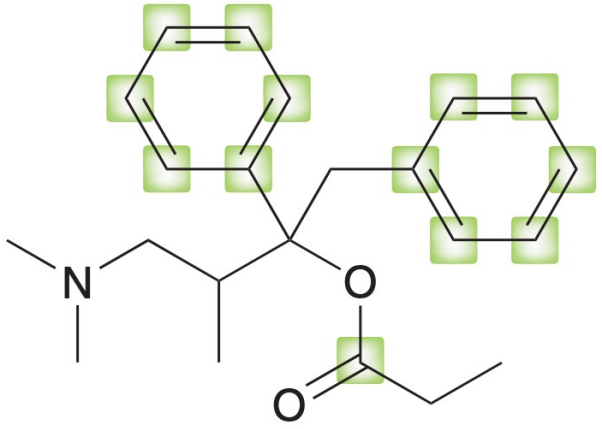
- Chirality center: a tetrahedral carbon bearing four different groups



- Practice

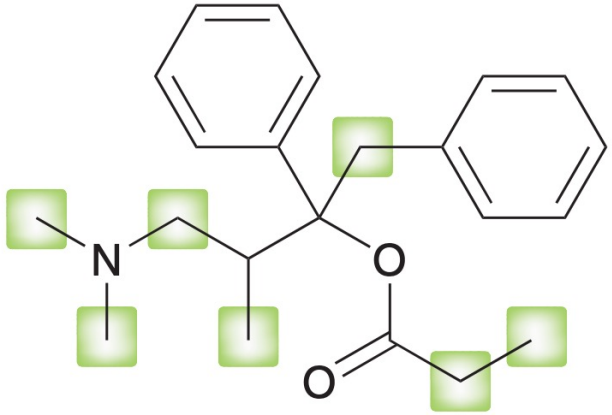
Propoxyphene, sold under the trade name Darvon, is an analgesic (painkiller) and antitussive (cough suppressant). Identify all chiral centers in propoxyphene:





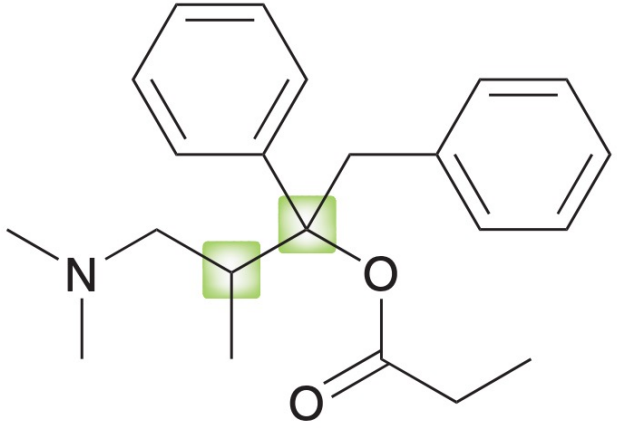
These carbon atoms cannot be chiral centers

排除sp^2杂化的碳原子

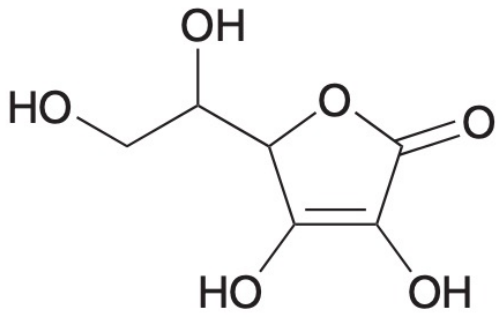


These carbon atoms cannot be chiral centers

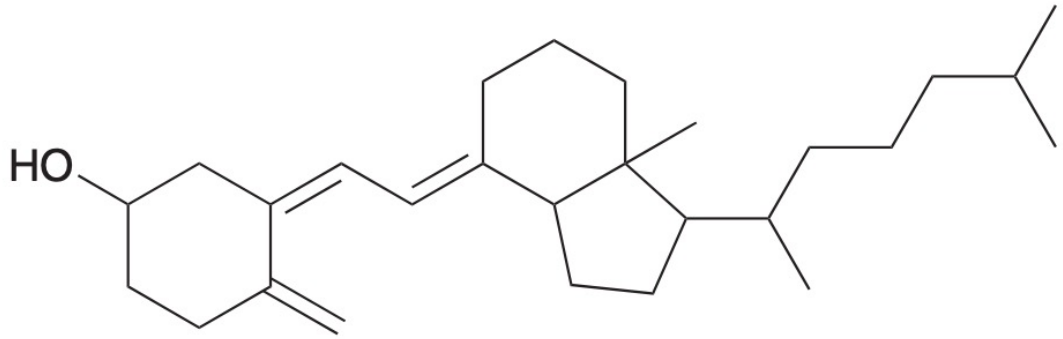
排除CH_2和CH_3



- Practice: identify all chiral centers in each of the following compounds:

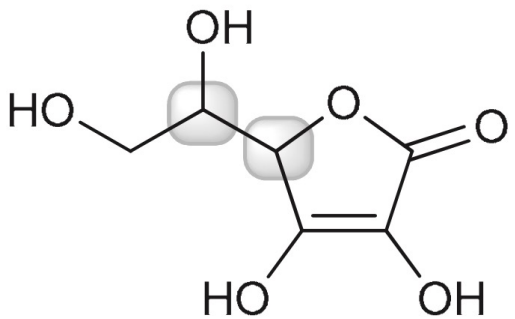


(a) Ascorbic acid (vitamin C)

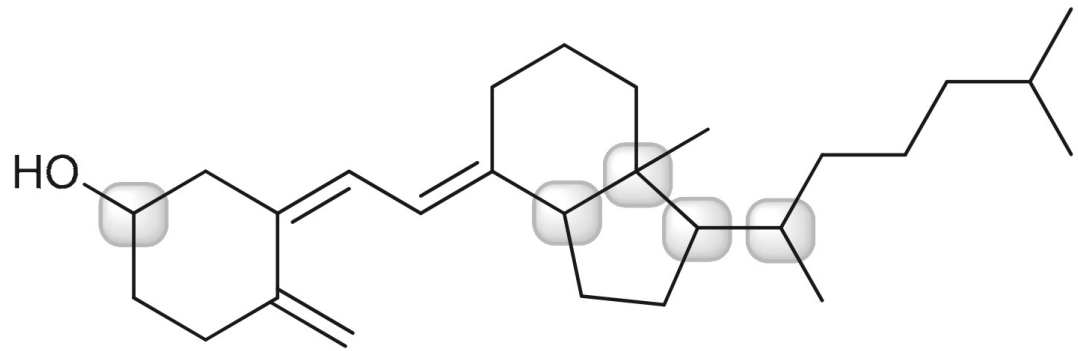


(b) Vitamin D_3

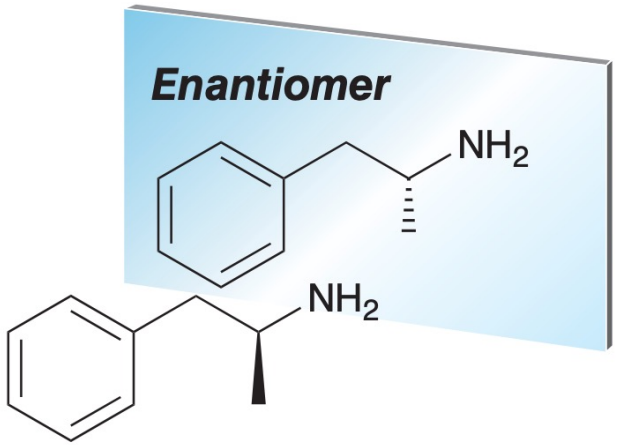
(a) This compound has two chiral centers:



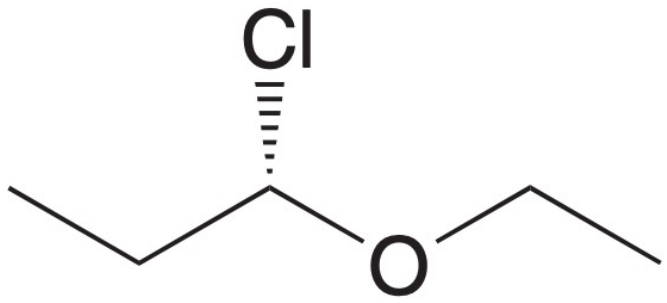
(b) This compound has five chiral centers:



- 对映异构体(enantiomer)
- 互为实物与镜像而不可重叠(nonsuperimposable)的立体异构体，称为对映异构体，简称为对映体
- 当两个化合物是一对对映体时，每一个化合物都被称为另一个的对映体
- 一个手性化合物只有一个对映体

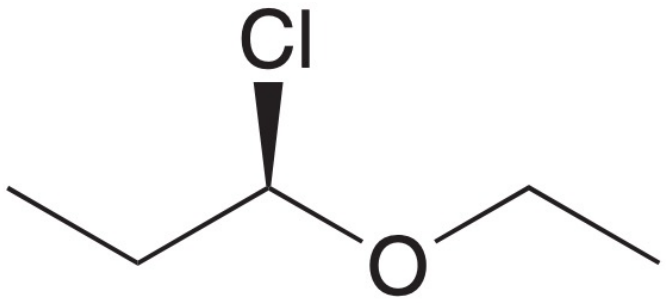


- Absolute configurations: *R*/*S* designation



R

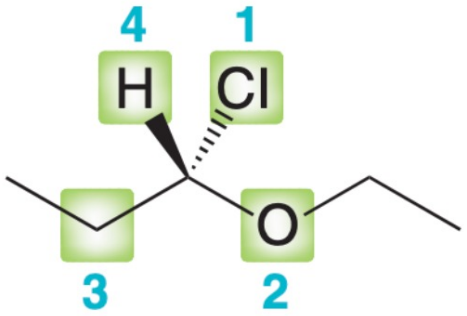
for Latin word "*rectus*"
(right)



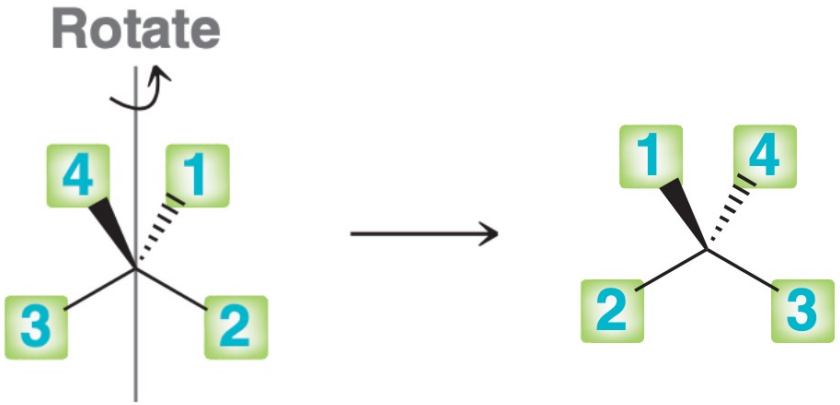
S

for Latin word "*sinister*"
(left)

- Designating configuration using the Cahn-Ingold-Prelog system

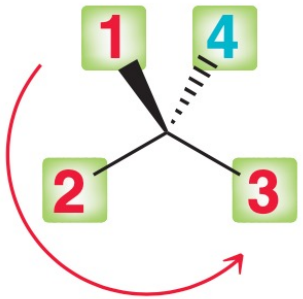


按照顺序规则给取代基编次序



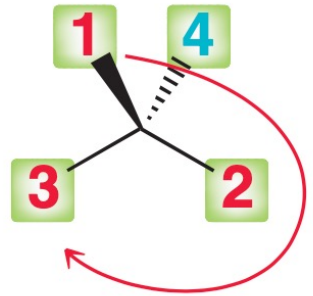
通过旋转将最小的基团放在离自己最远处
（伸向纸面后的那根键上）

剩下的三个基团按大小排序



Counterclockwise = ***S***

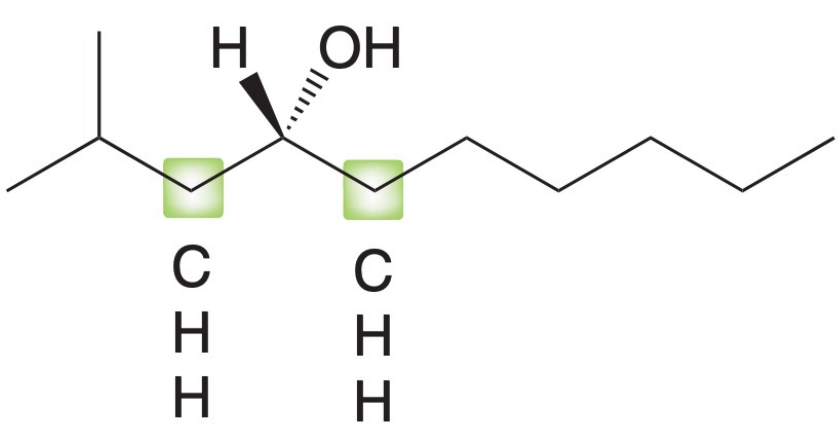
逆时针为S构型

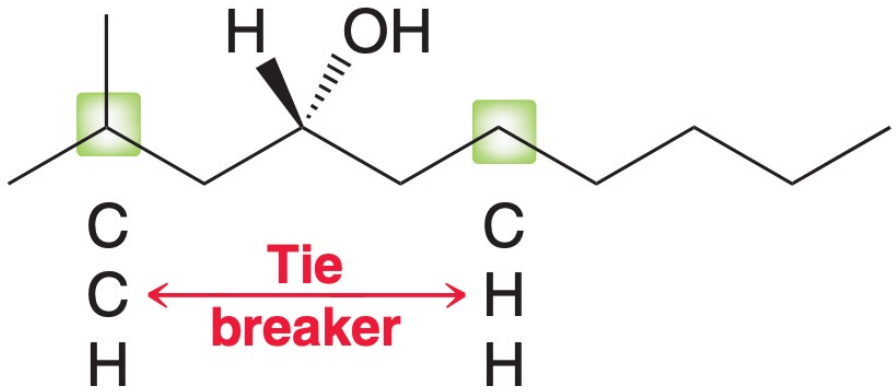


Clockwise = ***R***

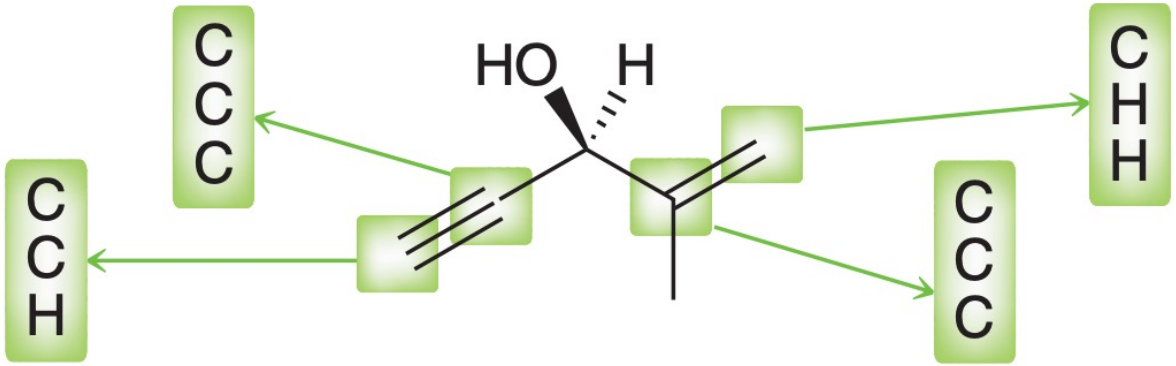
顺时针为R构型

- 当第一个原子相同时，比较其它基团

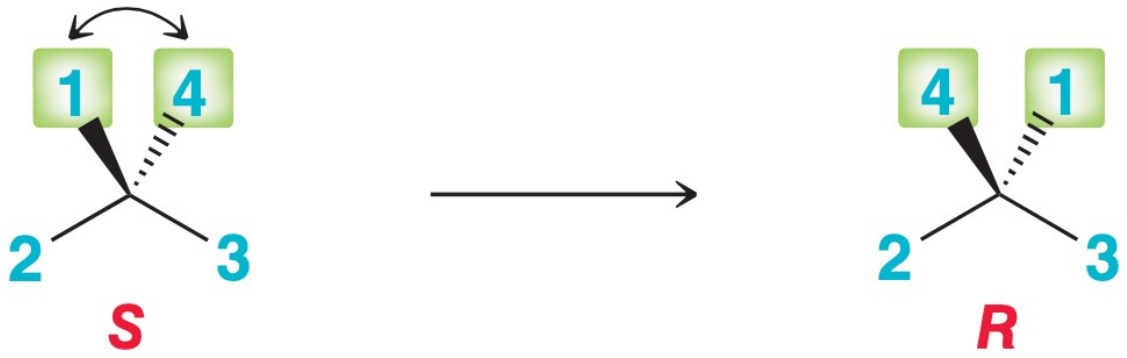




- 比较多重键时，反复计算多重键所连接的原子



- 变换基团对R/S构型的影响



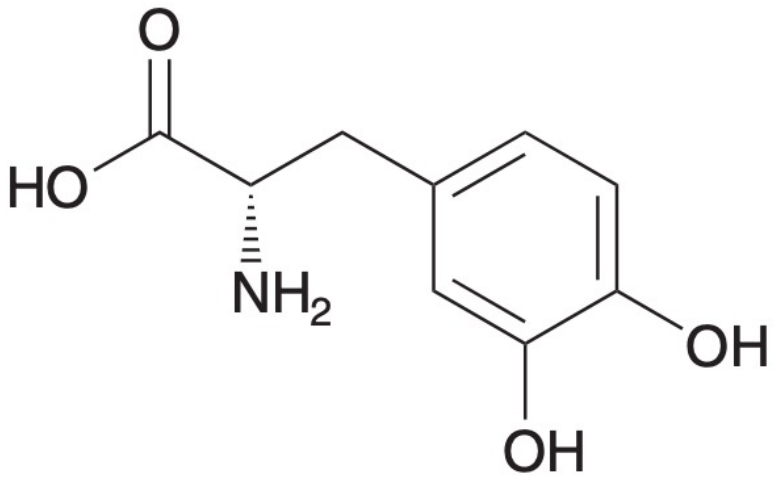
在手性中心上任意两个基团的交换都会使构型发生反转

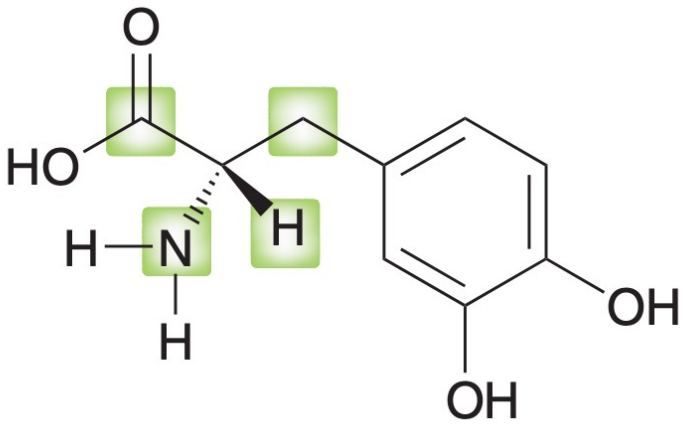
A REVIEW OF CAHN-INGOLD-PRELOG RULES: ASSIGNING THE CONFIGURATION OF A CHIRAL CENTER

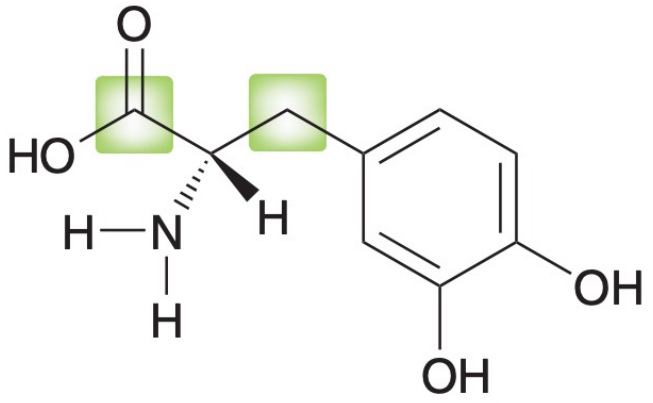
STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Identify the four atoms directly attached to the chiral center.	Assign a priority to each atom based on its atomic number. The highest atomic number receives priority 1, and the lowest atomic number (often a hydrogen atom) receives priority 4.	If two atoms have the same atomic number, move away from the chiral center looking for the first point of difference. When constructing lists to compare, remember that a double bond is treated as two separate single bonds.	Rotate the molecule so that the fourth priority is on a dash (going behind the plane of the page).	Determine whether the sequence 1-2-3 follows a clockwise order (*R*) or a counterclockwise order (*S*).

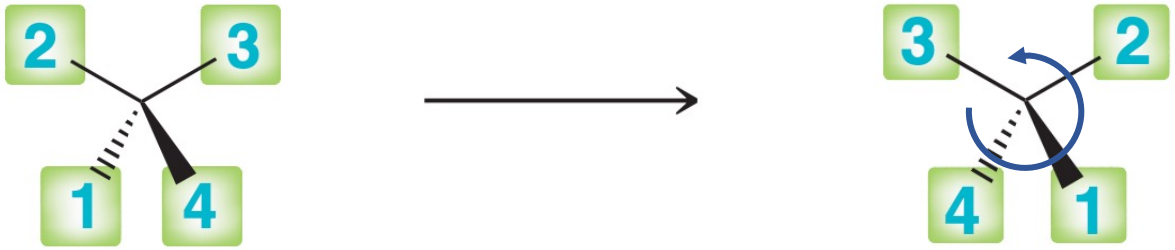
- Practice

The following bond-line structure represents one enantiomer of 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid, used in the treatment of Parkinson's disease. Assign the configuration of the chiral center in this compound.





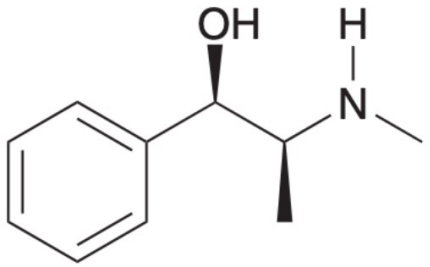




S

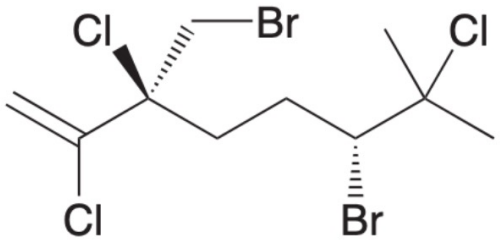
- Practice: each of the following compounds possesses carbon atoms that are chiral centers. Locate each of these chiral centers and identify the configuration of each one:

(a)



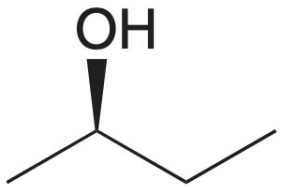
Ephedrine
A bronchodilator and decongestant obtained from the Chinese plant *Ephedra sinica*

(b)

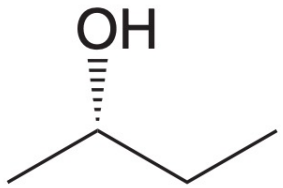


Halomon
An antitumor agent isolated from marine organisms

- Nomenclature of monochiral central compounds

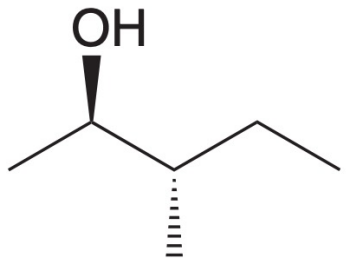


(*R*)-2-Butanol



(*S*)-2-Butanol

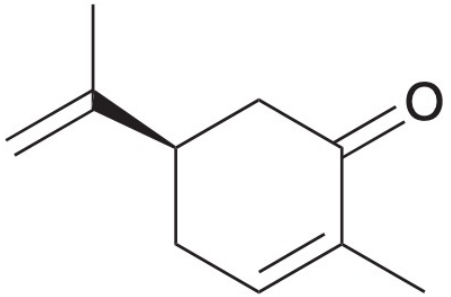
- Nomenclature of polychiral central compounds



(2*R*,3*S*)-3-Methyl-2-pentanol

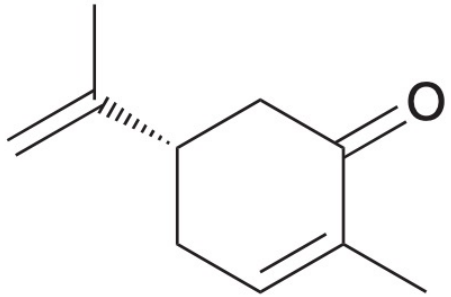
- Enantiomers have the same physical properties

(*R*)-Carvone



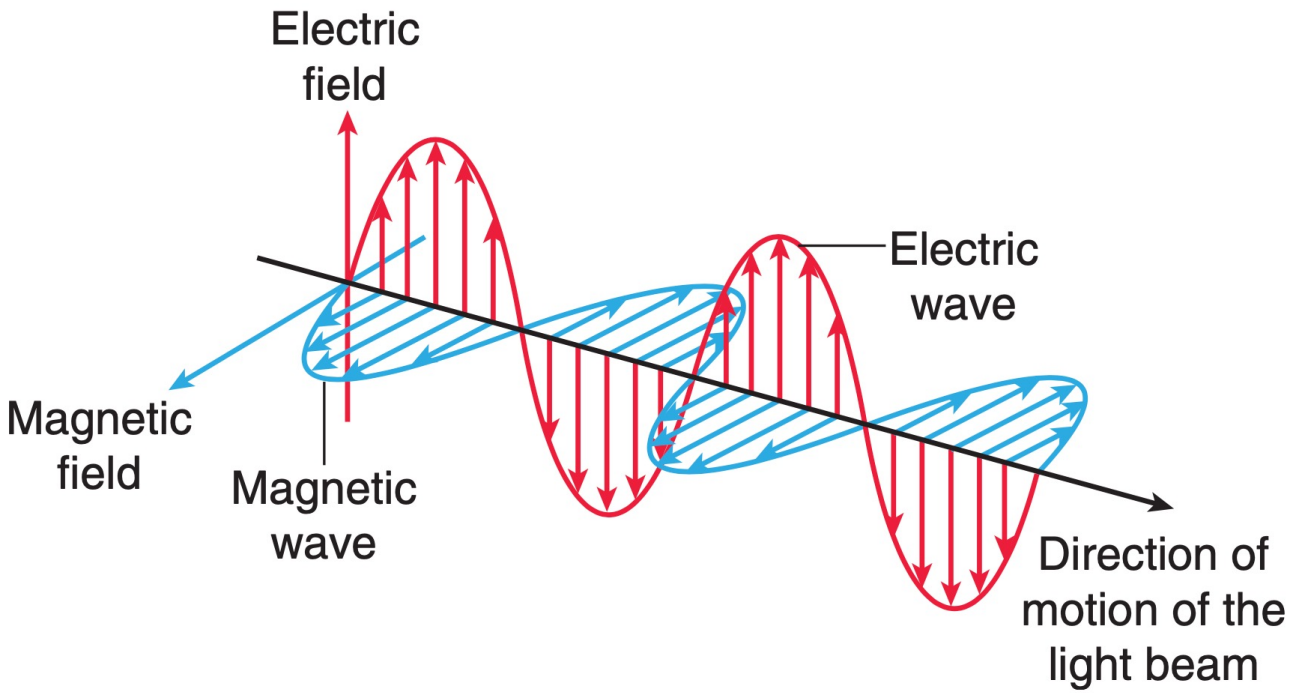
Melting point = 25°C
Boiling point = 231°C

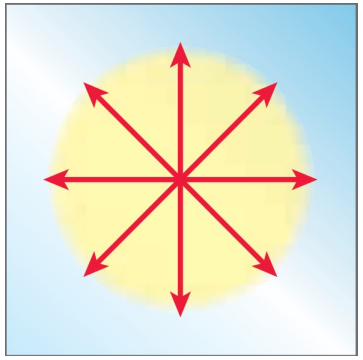
(*S*)-Carvone



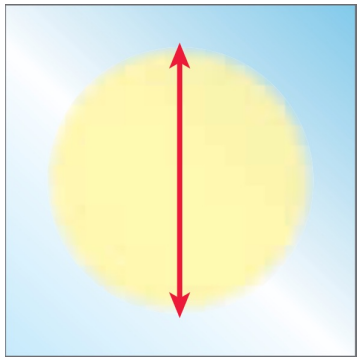
Melting point = 25°C
Boiling point = 231°C

- Plane-polarized light



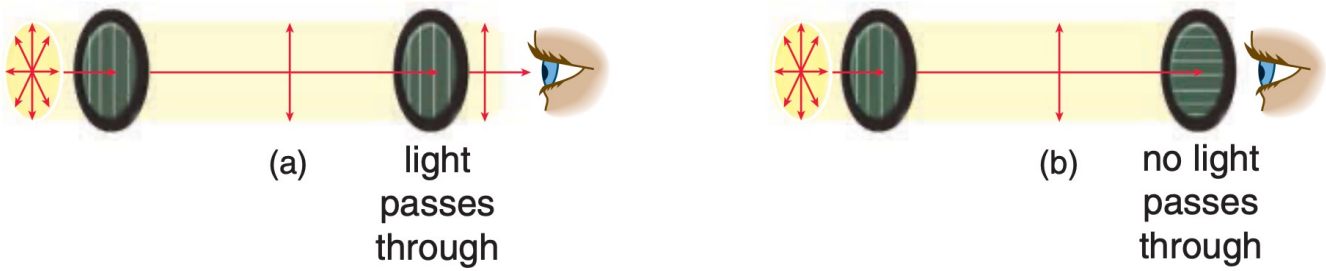


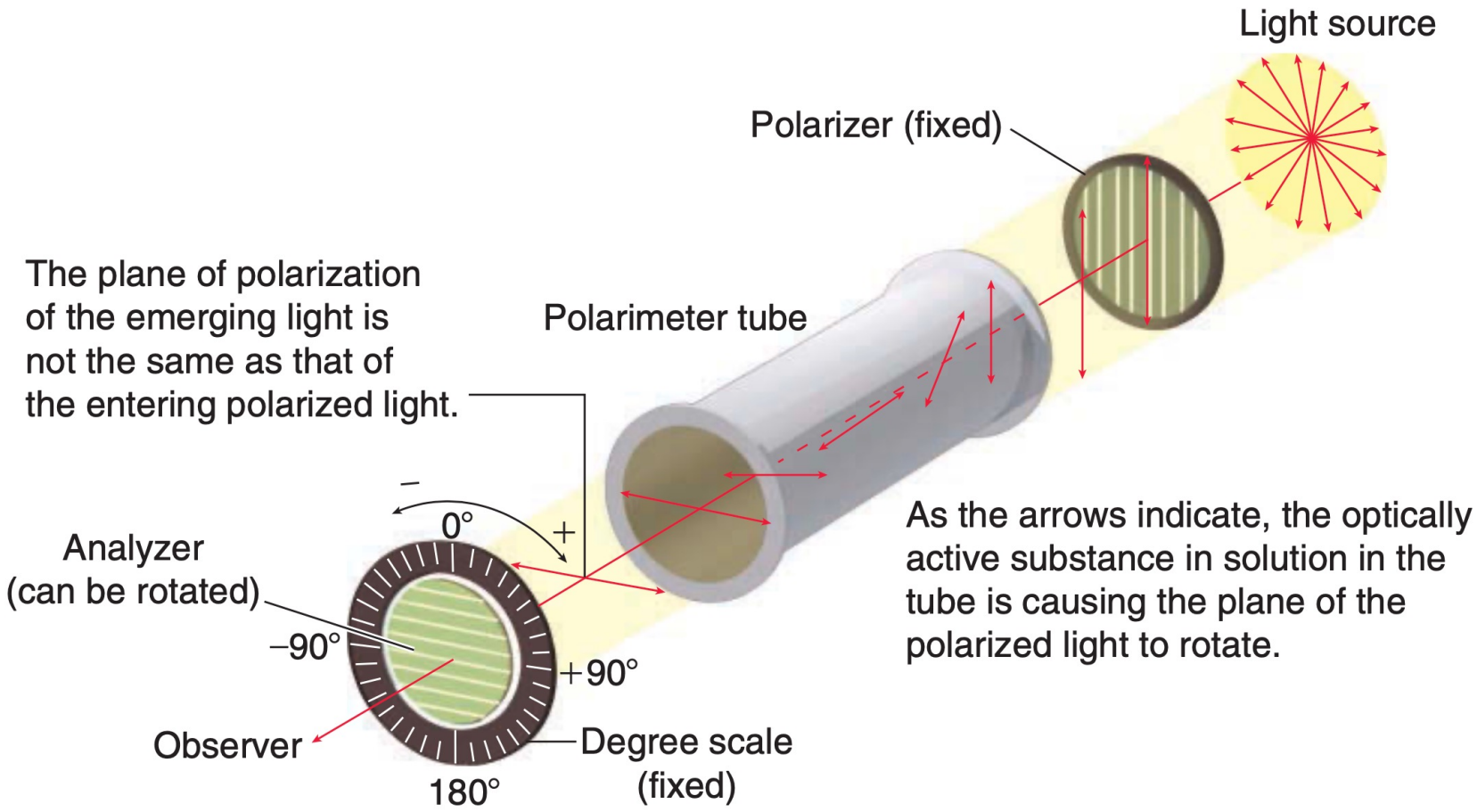
unpolarized light



plane-polarized light

- Polarimetry





- Specific rotation

observed rotation (degree)

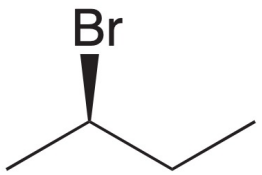
$$\text{Specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

concentration (g/mL)

path length (dm)

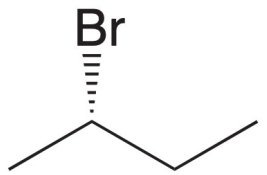
for compounds in a certain state, the specific rotation is a **constant**

$[\alpha]_{\lambda}^{T}$ temperature
wavelength



(*R*)-2-Bromobutane

$[\alpha]_{D}^{20} = -23.1$



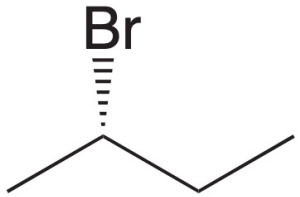
(*S*)-2-Bromobutane

$[\alpha]_{D}^{20} = +23.1$

D stands for the D line of sodium (589 nm)

the specific rotation is affected
by temperature and measured light wavelength

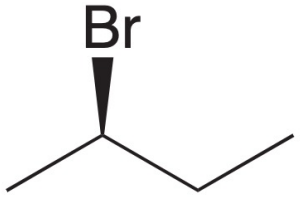
- Positive specific rotation (+): dextrorotatory (*D*)



$[\alpha]_D^{20} = +23.1$

(*S*)-2-Bromobutane

- Negative specific rotation (-): levorotatory (*L*)



$[\alpha]_D^{20} = -23.1$

(*R*)-2-Bromobutane

- **Practice** When 0.300 g of sucrose is dissolved in 10.0 mL of water and placed in a sample cell 10.0 cm in length, the observed rotation is +1.99° (using the D line of sodium at 20°C). Calculate the specific rotation of sucrose.

$$\text{Specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

$$\text{Specific rotation} = [\alpha] = \frac{\alpha}{c \times l} = \frac{+1.99°}{0.03\ \text{g/mL} \times 1.00\ \text{dm}} = +66.3$$

$$[\alpha]_D^{20} = +66.3$$

- Optically pure/enantiomerically pure: a solution containing a single enantiomer
- Racemic mixture: a solution containing equal amounts of both enantiomers
- Enantiomeric excess, *ee*: the amount of an enantiomer is excess than the another enantiomer

- Calculation of % *ee*

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\%$$

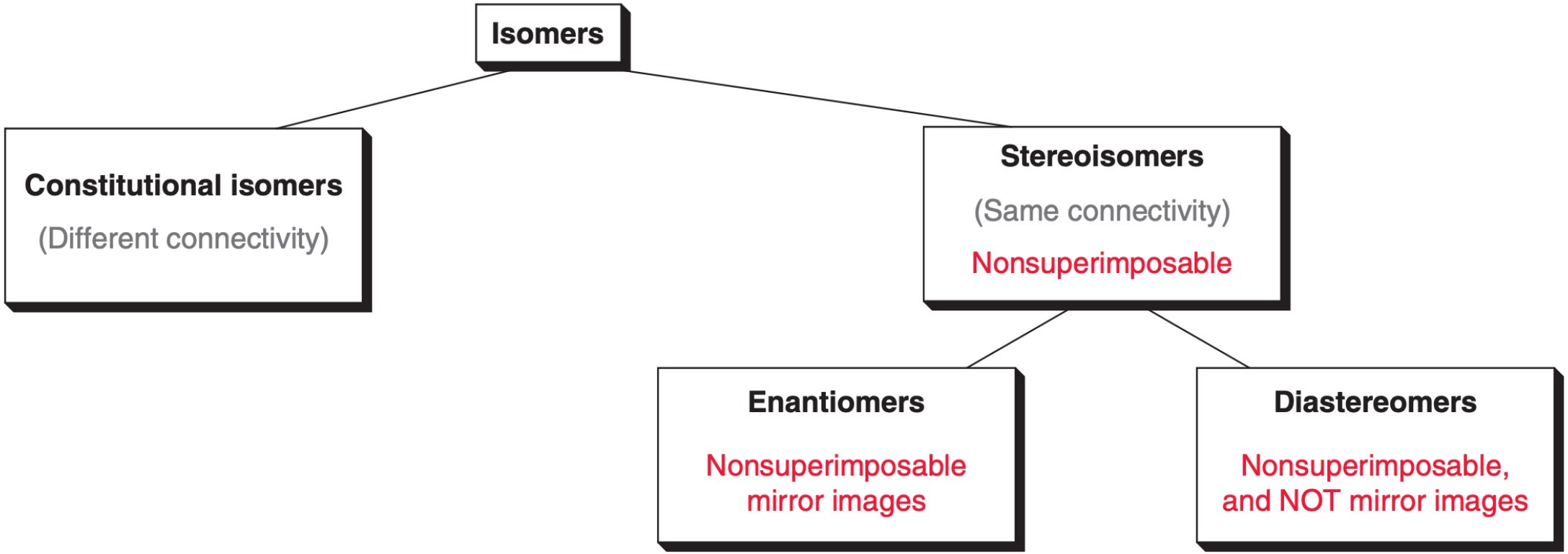
- **Practice**

The specific rotation of optically pure adrenaline in water (at 25°C) is −53. A chemist devised a synthetic route to prepare optically pure adrenaline, but it was suspected that the product was contaminated with a small amount of the undesirable enantiomer. The observed rotation was found to be −45°. Calculate the % *ee* of the product.

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\%$$

$$\%\ ee = \frac{45}{53} \times 100\%$$
$$= 85\%$$

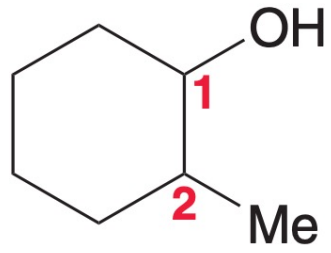
An 85% *ee* indicates that 85% of the product is adrenaline, while the remaining 15% is a racemic mixture of adrenaline and its enantiomer (7.5% adrenaline and 7.5% of the enantiomer). An 85% *ee* therefore indicates that the product is comprised of 92.5% adrenaline and 7.5% of the undesired enantiomer.



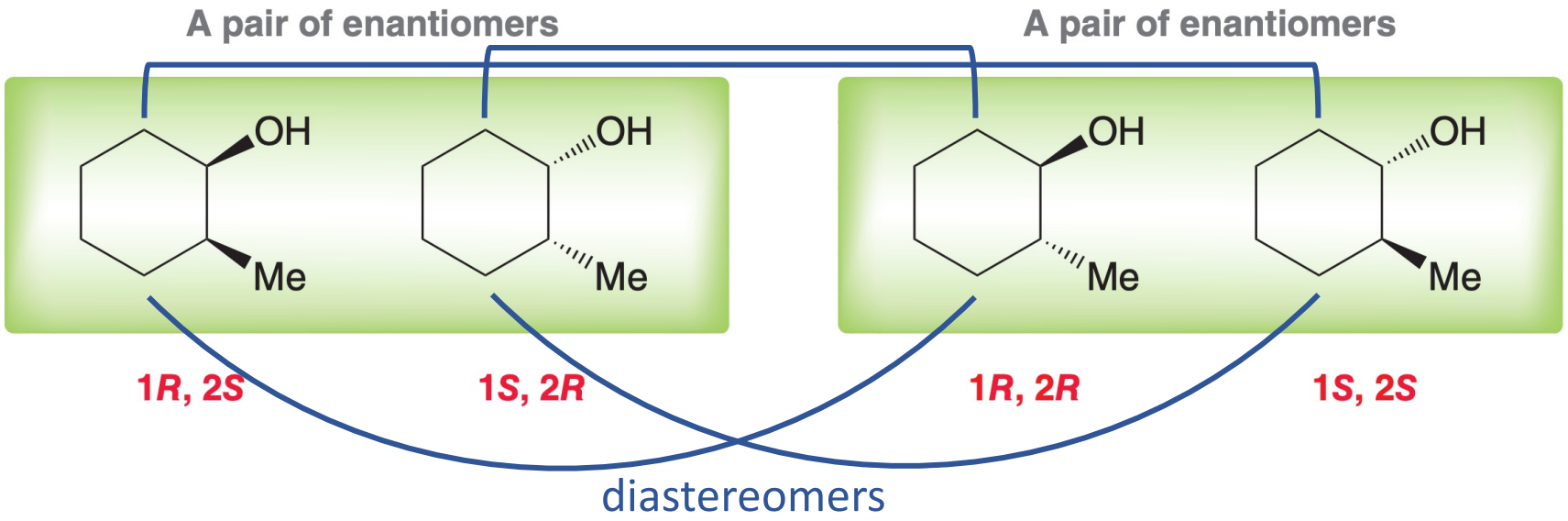
对映异构体

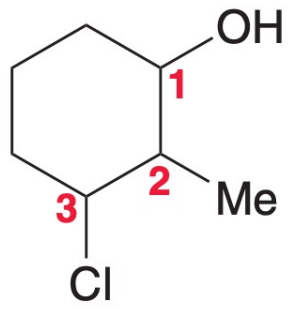
非对映异构体

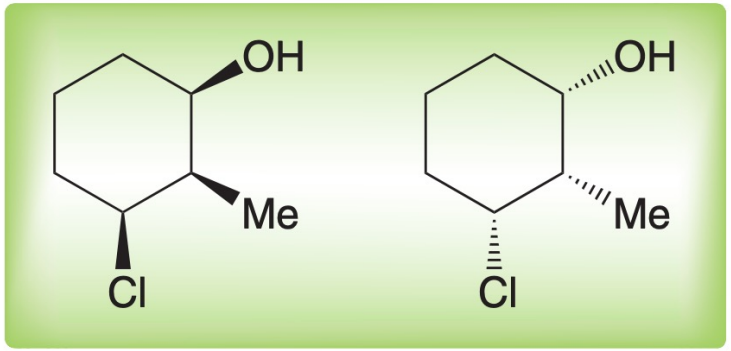
- 非对映异构体(diastereomer)



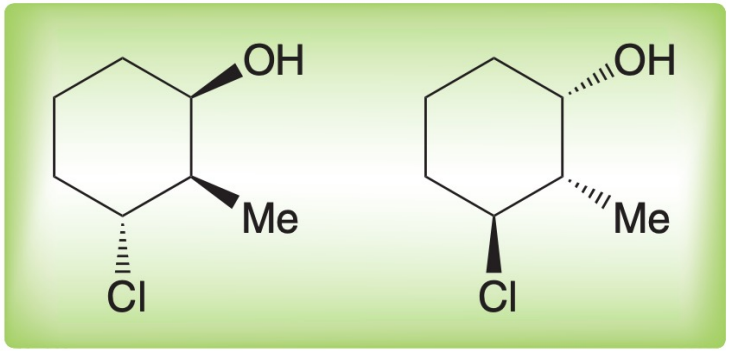
Maximum number of stereoisomers $= 2^n$



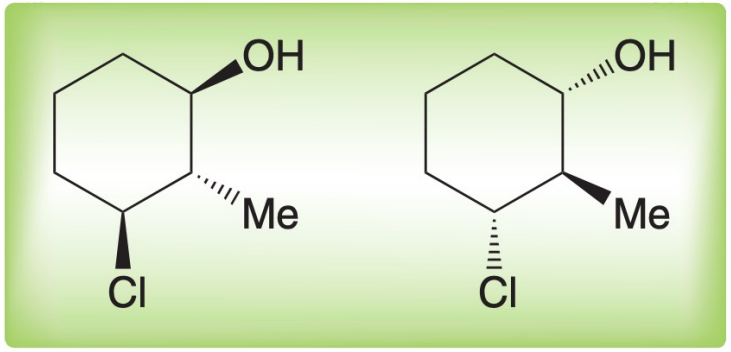




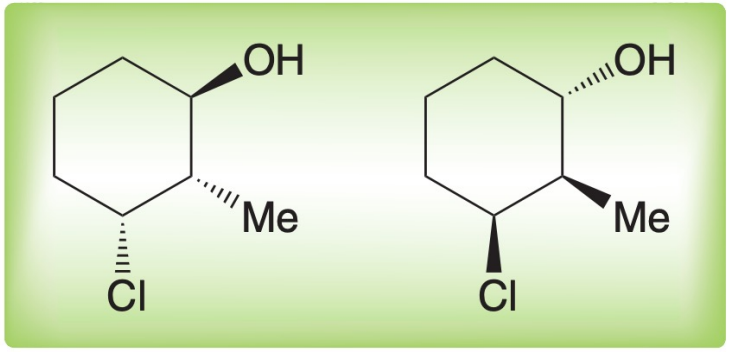
1*R*, 2*R*, 3*S* **1*S*, 2*S*, 3*R***



1*R*, 2*R*, 3*R* **1*S*, 2*S*, 3*S***

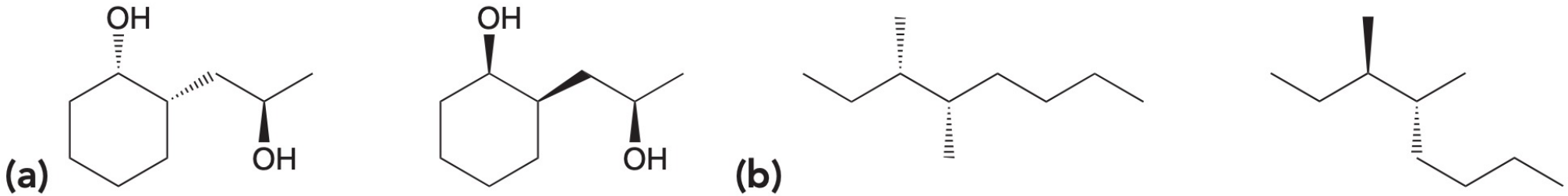


1*R*, 2*S*, 3*S* **1*S*, 2*R*, 3*R***

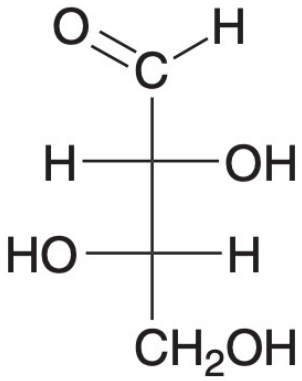


1*R*, 2*S*, 3*R* **1*S*, 2*R*, 3*S***

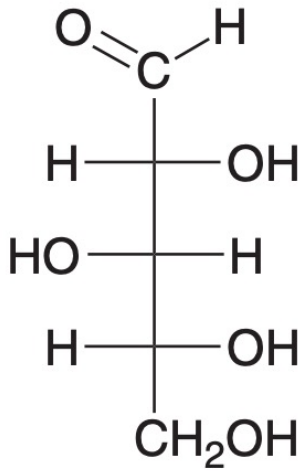
- Practice: identify whether each pair of compounds are enantiomers or diastereomers:



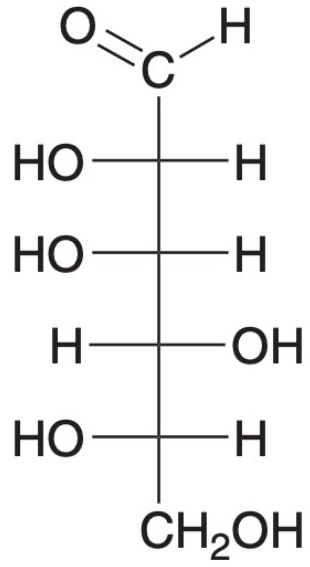
- Fischer projections



Two chiral centers

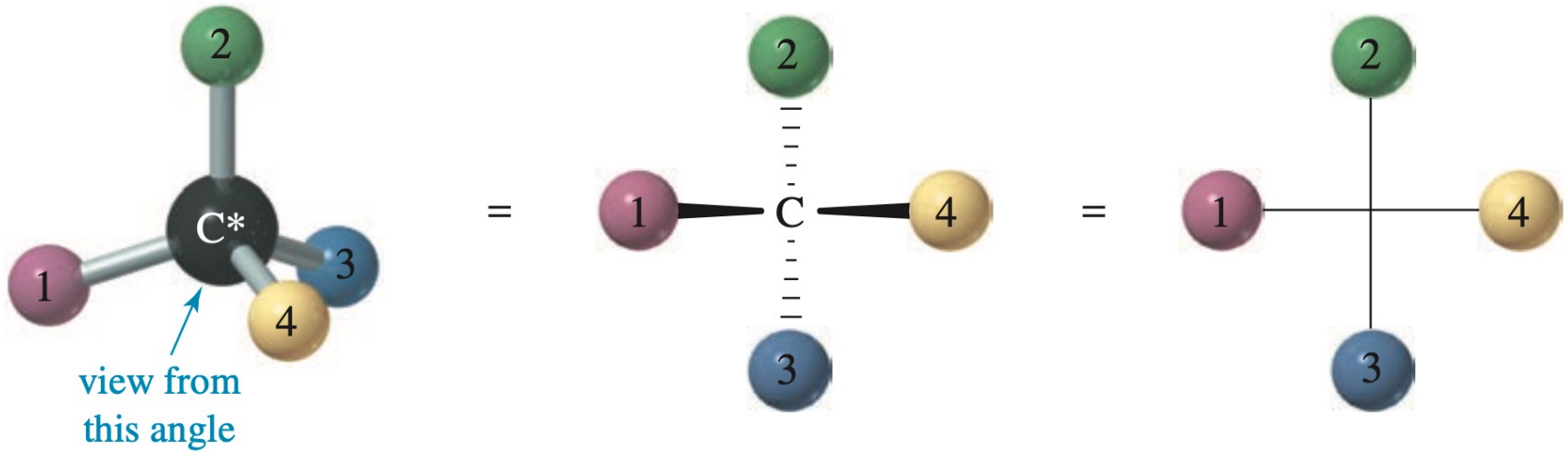


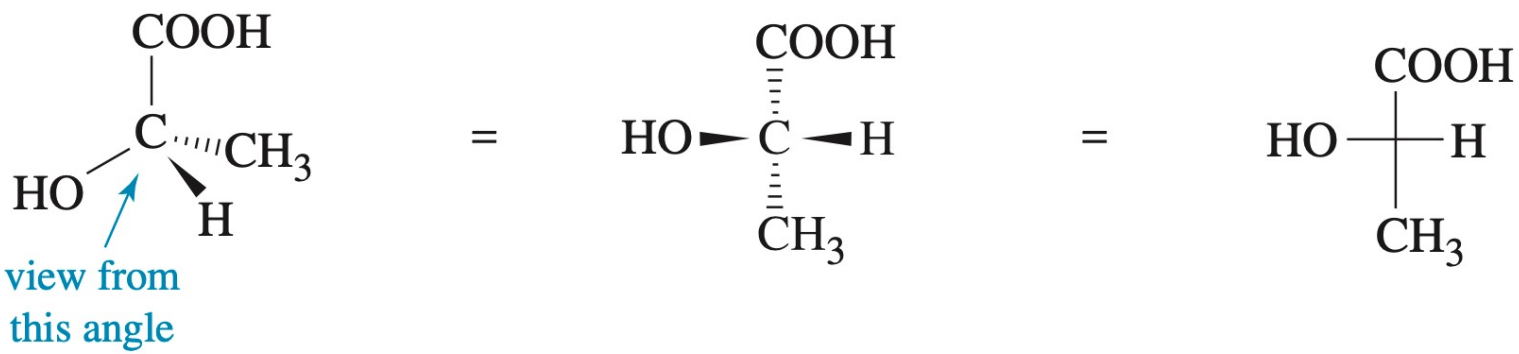
Three chiral centers



Four chiral centers

- 碳链放在垂直方向上，命名时编号最小的碳原子放在最上端
- 投影时假定手性碳原子放在纸平面上，与垂直线相连的原子或基团表示伸向纸面后方；与水平线相连的原子或基团表示伸向纸面前方——“横前竖后”
- 手性碳位于横线与竖线交叉处，用一个“+”号的交点表示

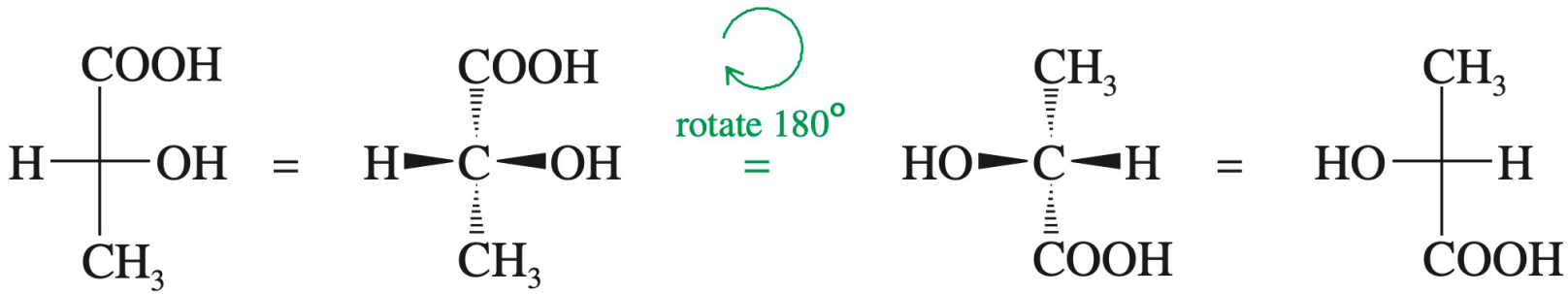




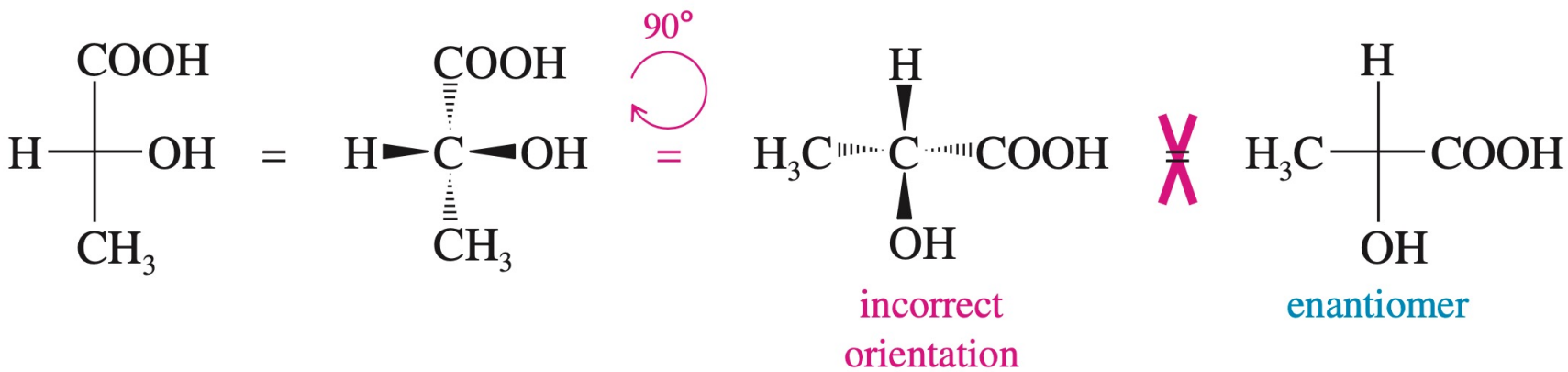
(*S*)-lactic acid
perspective drawing

(*S*)-lactic acid
Fischer projection

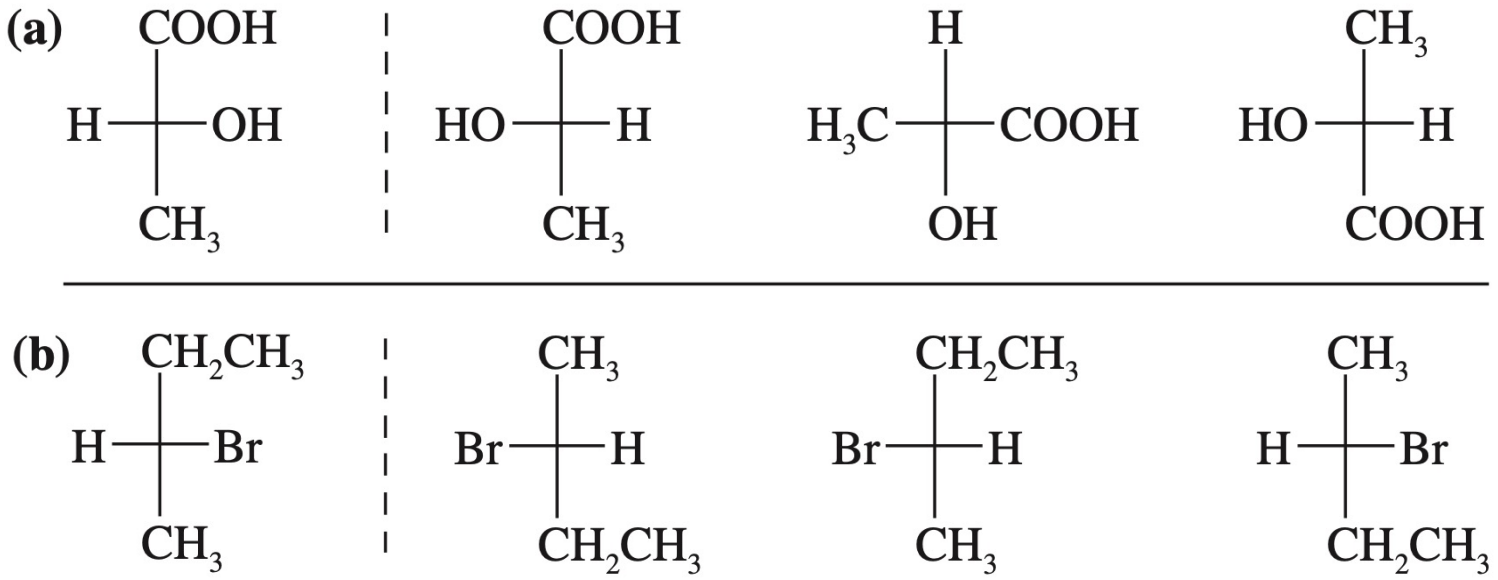
Rotation by 180° is allowed.



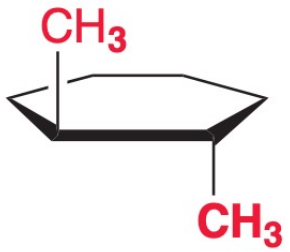
A 90° rotation is NOT allowed.



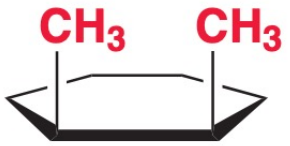
- Practice: for each set of examples, indicate the relationship of each of the other structures to the first structure. Examples of relationships: same compound, enantiomer, structural isomer.



- Rotational symmetry versus reflectional symmetry

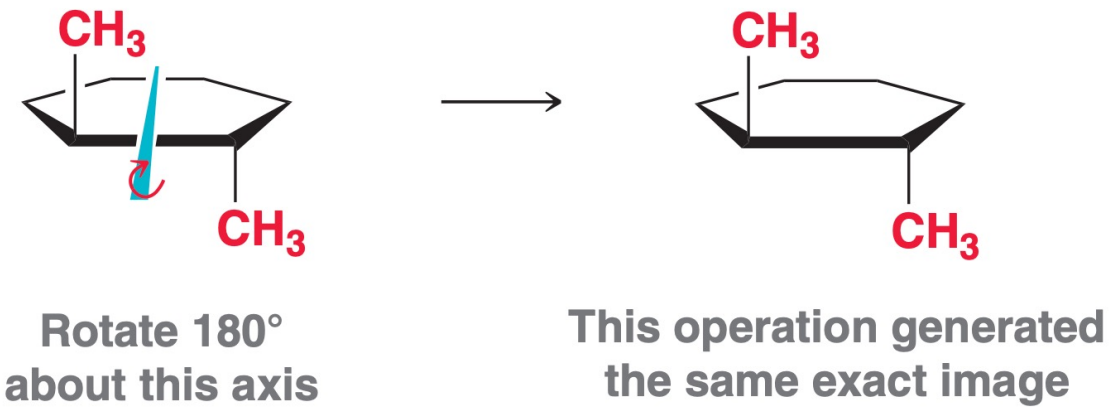


trans-
1,2-Dimethylcyclohexane



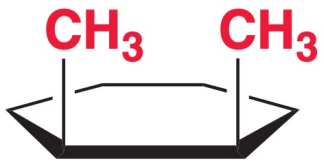
cis-
1,2-Dimethylcyclohexane

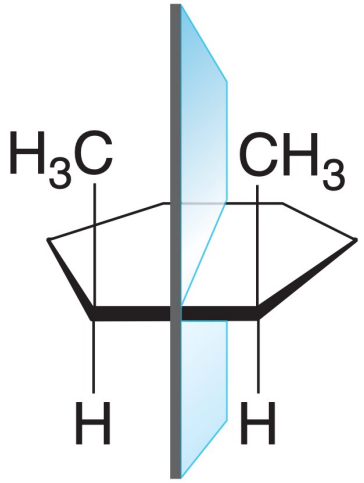
- Rotational symmetry



an **axis** of symmetry

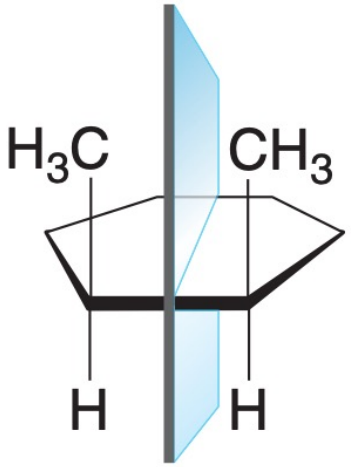
- Reflectional symmetry



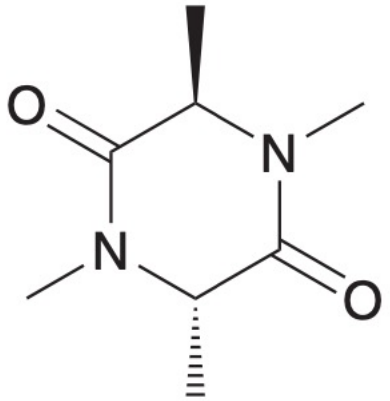


a **plane** of symmetry

- Two symmetry factors



plane symmetry

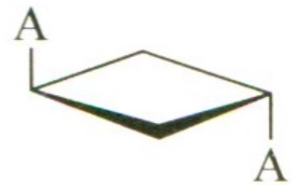


centro symmetry
(*inversion*)

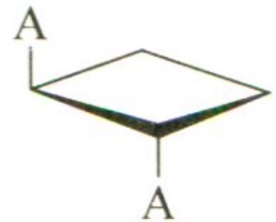
The compounds in the above two cases do not have chirality!

无旋光性(对称面)

有旋光性



无旋光性(对称中心)



有旋光性

无旋光性(对称面)

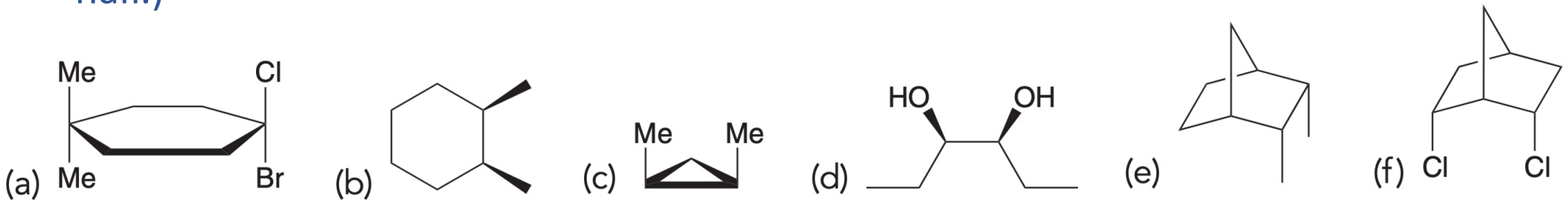
有旋光性

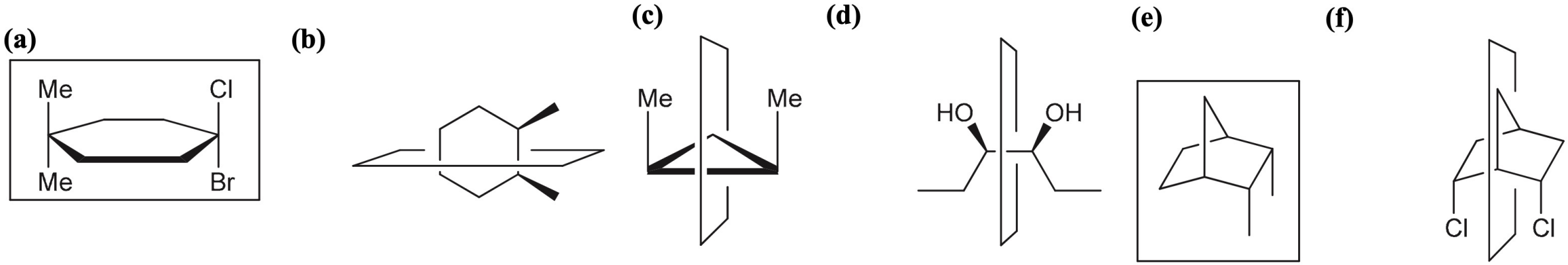
无旋光性(对称面)

有旋光性

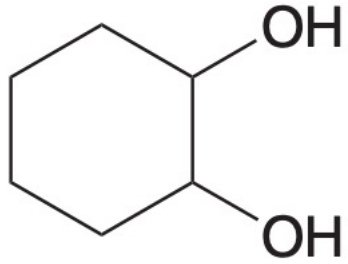
- Conclusions
  - The presence or absence of rotational symmetry is **irrelevant** to chirality
  - A compound that has a **plane of symmetry** will be **achiral**
  - A compound that lacks a plane of symmetry will *most likely* be chiral (although there are rare exceptions, which can mostly be ignored for our purposes)

- Practice: each of the following molecules has one plane of symmetry. Find the plane of symmetry in each case: (*Hint*: A plane of symmetry can slice atoms in half.)

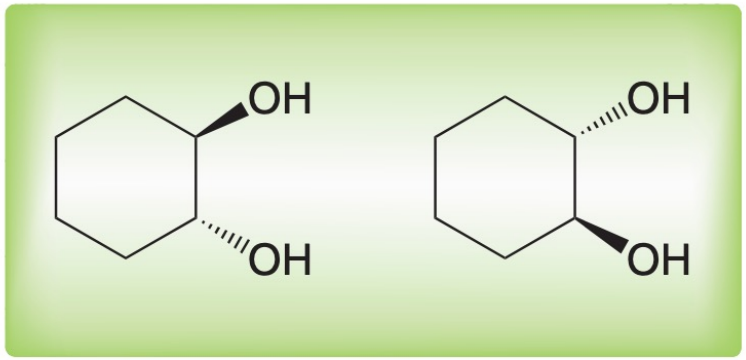




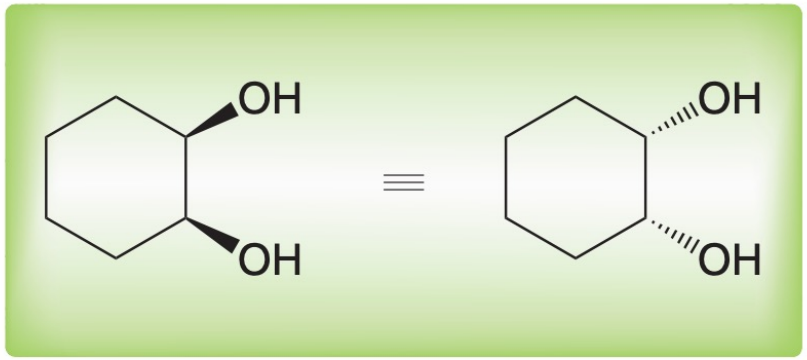
- *meso* compounds



possible isomers: 2^2 $(=4)$

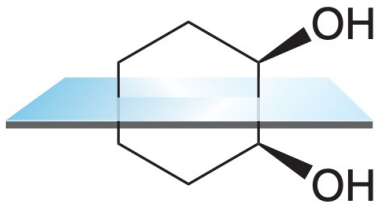


A pair of enantiomers

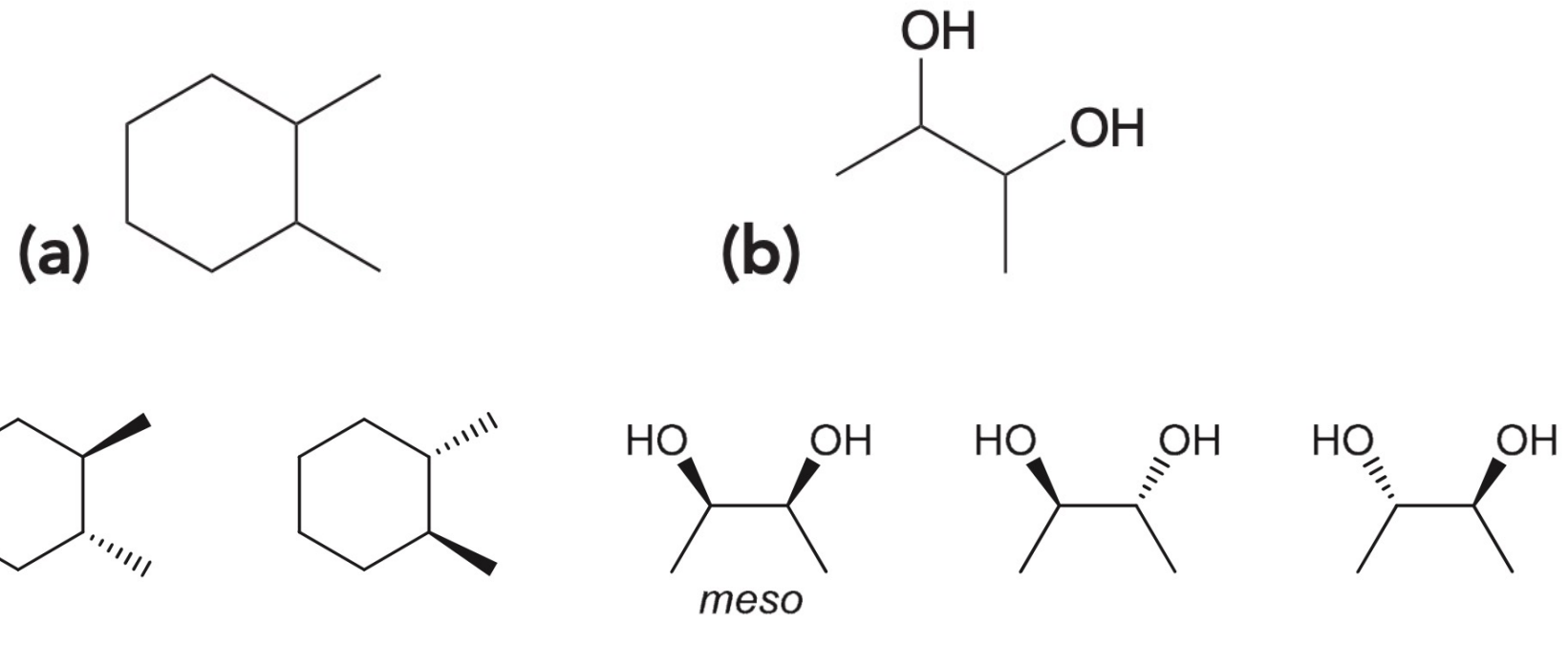


But these two drawings represent the same compound

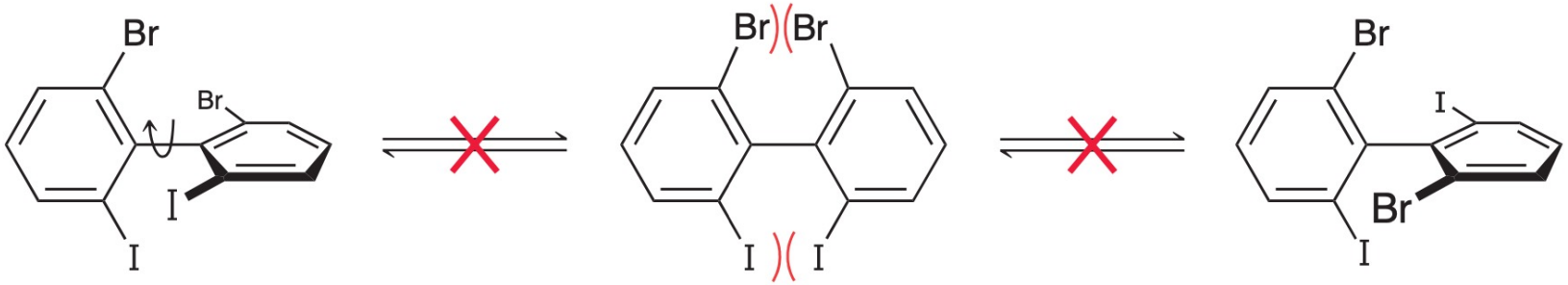
Plane of symmetry



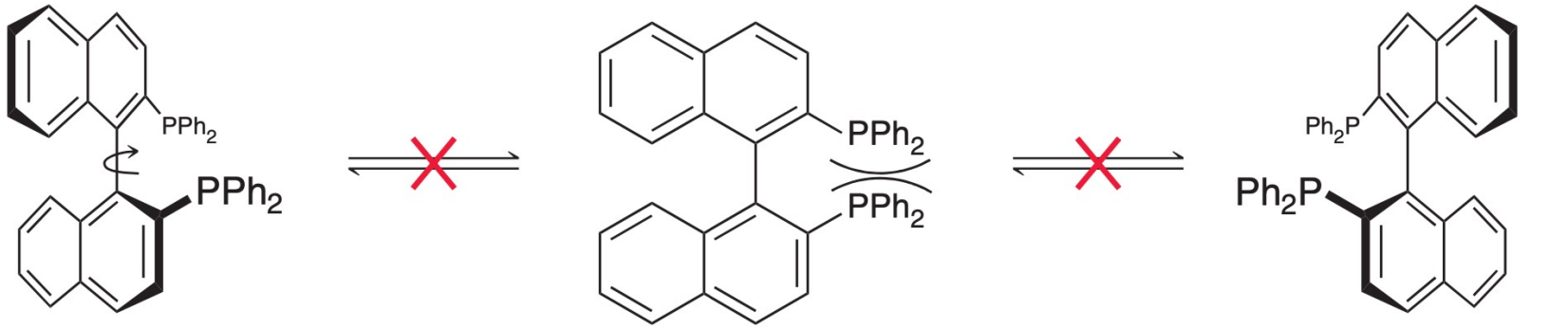
- Practice: draw all possible stereoisomers for each of the following compounds. Each possible stereoisomer should be drawn only once:



- 阻转异构体(atropisomer)



Does not form
(too high in energy)

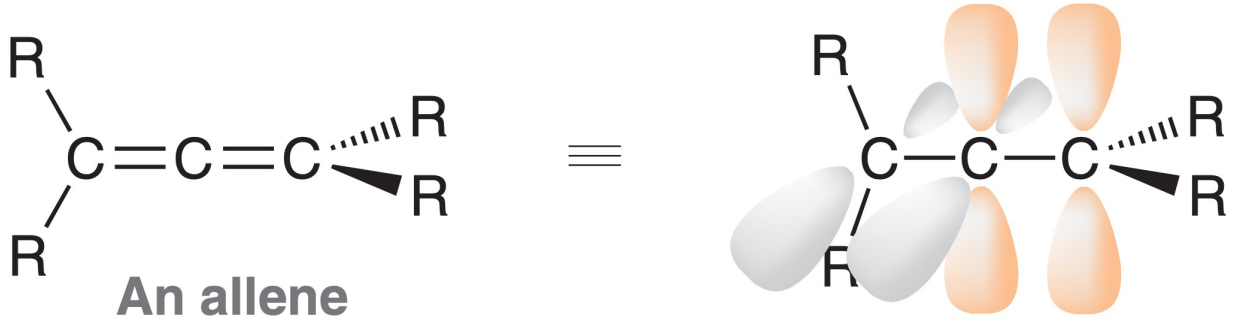


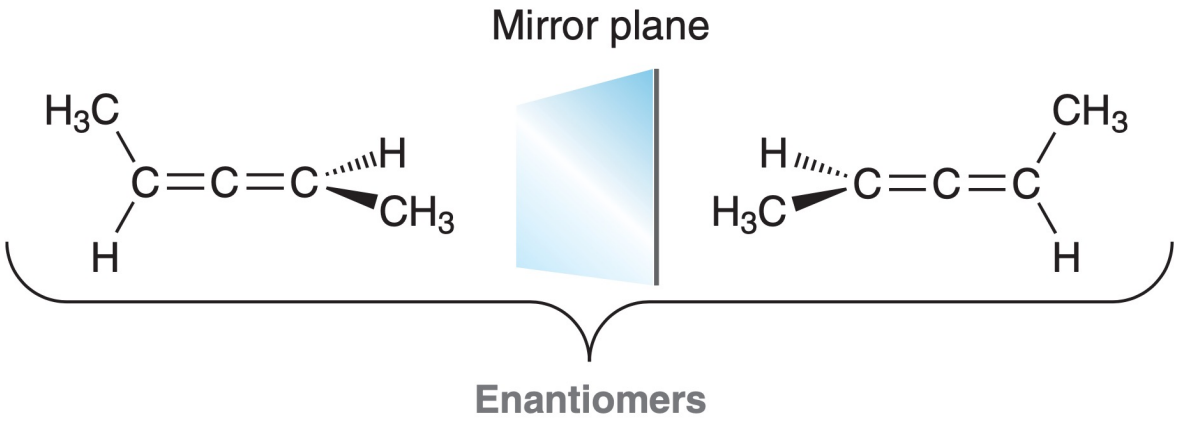
(*S*)-BINAP
(*S*)-2,2'-Bis(diphenyl phosphino)-1,1'-binaphthyl

Does not form
(too high in energy)

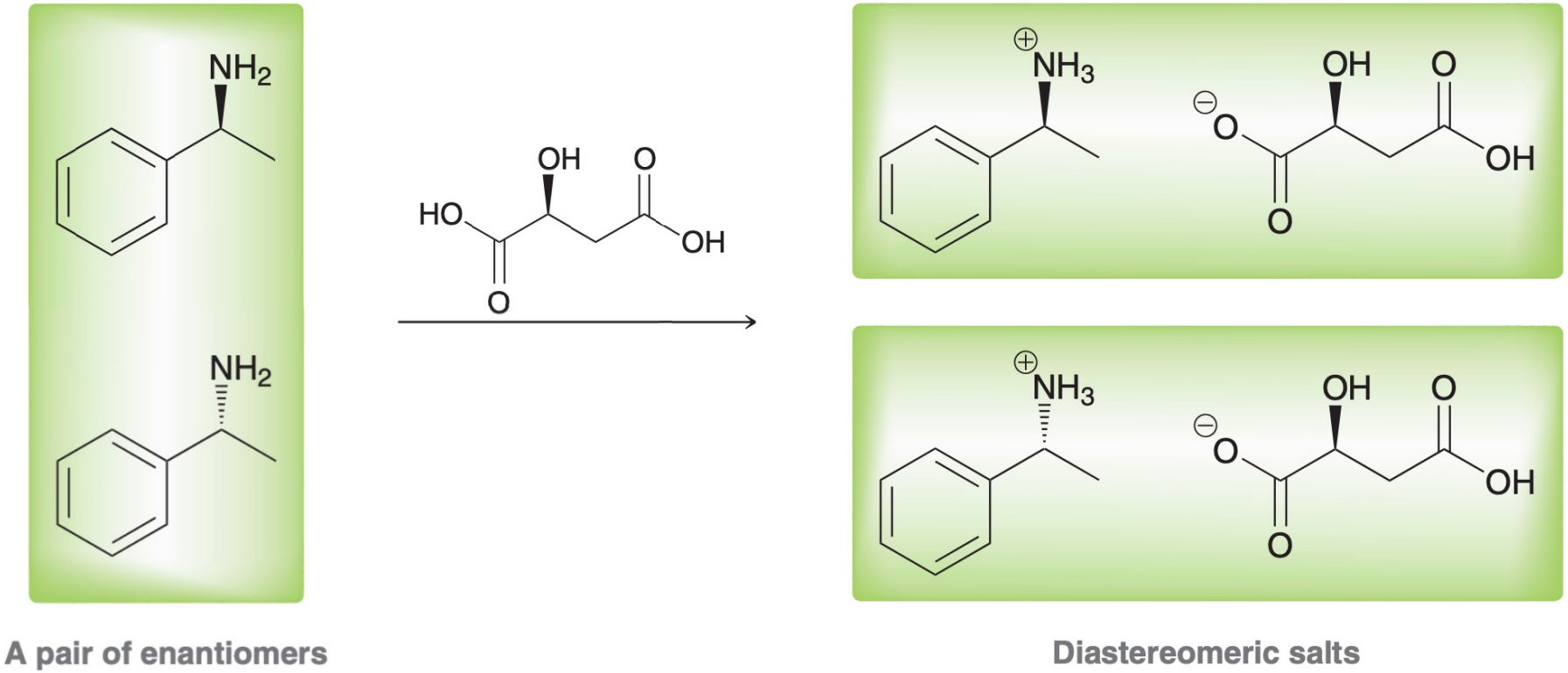
(*R*)-BINAP
(*S*)-2,2'-Bis(diphenyl phosphino)-1,1'-binaphthyl

- 联烯(allene)


R
R
C=C=C
R
R
An allene
R
R
C—C—C
R
R


Mirror plane
H3C
H
C=C=C
H
CH3
H
H3C
CH3
C=C=C
H
Enantiomers

- Resolution of enantiomers



A pair of enantiomers

Diastereomeric salts

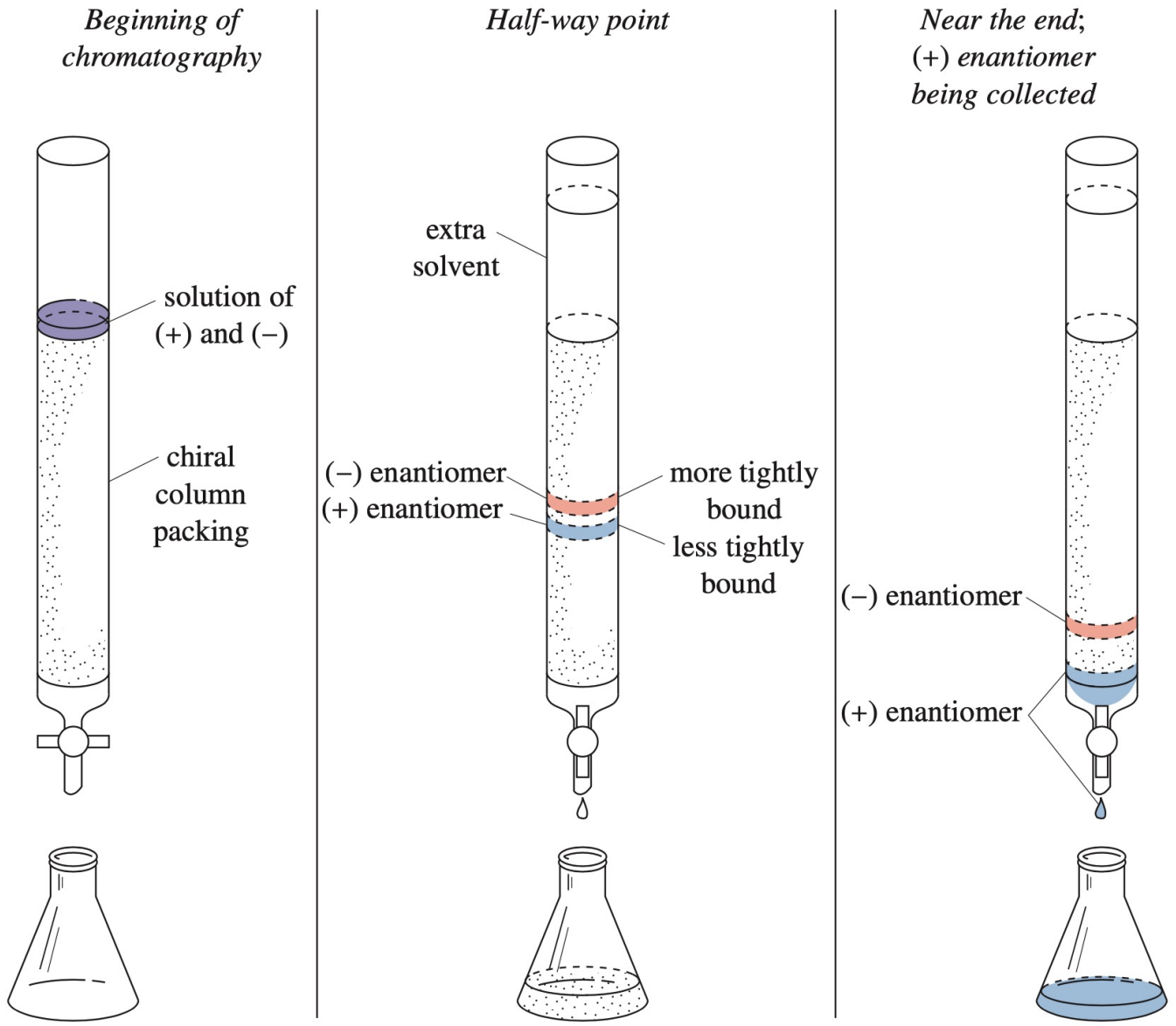
- Chiral column chromatography

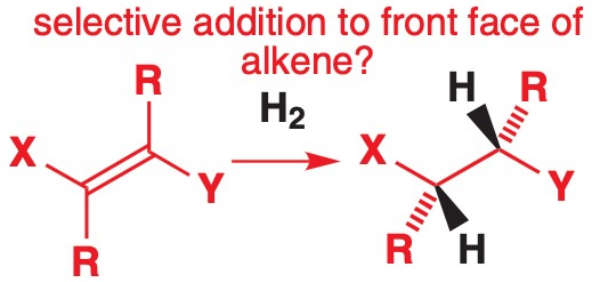
stationary phase – chiral compound

using the different attraction

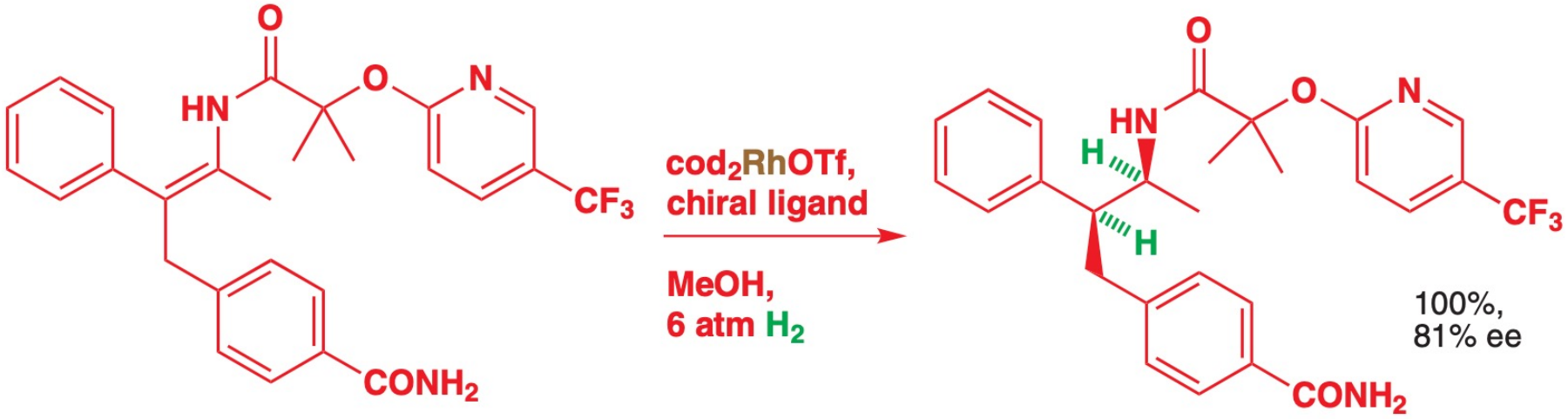
to compounds with different configurations

to separate racemic mixtures





- Asymmetric synthesis



using chiral catalysts to achieve asymmetric synthesis