Advanced Organic Chemistry

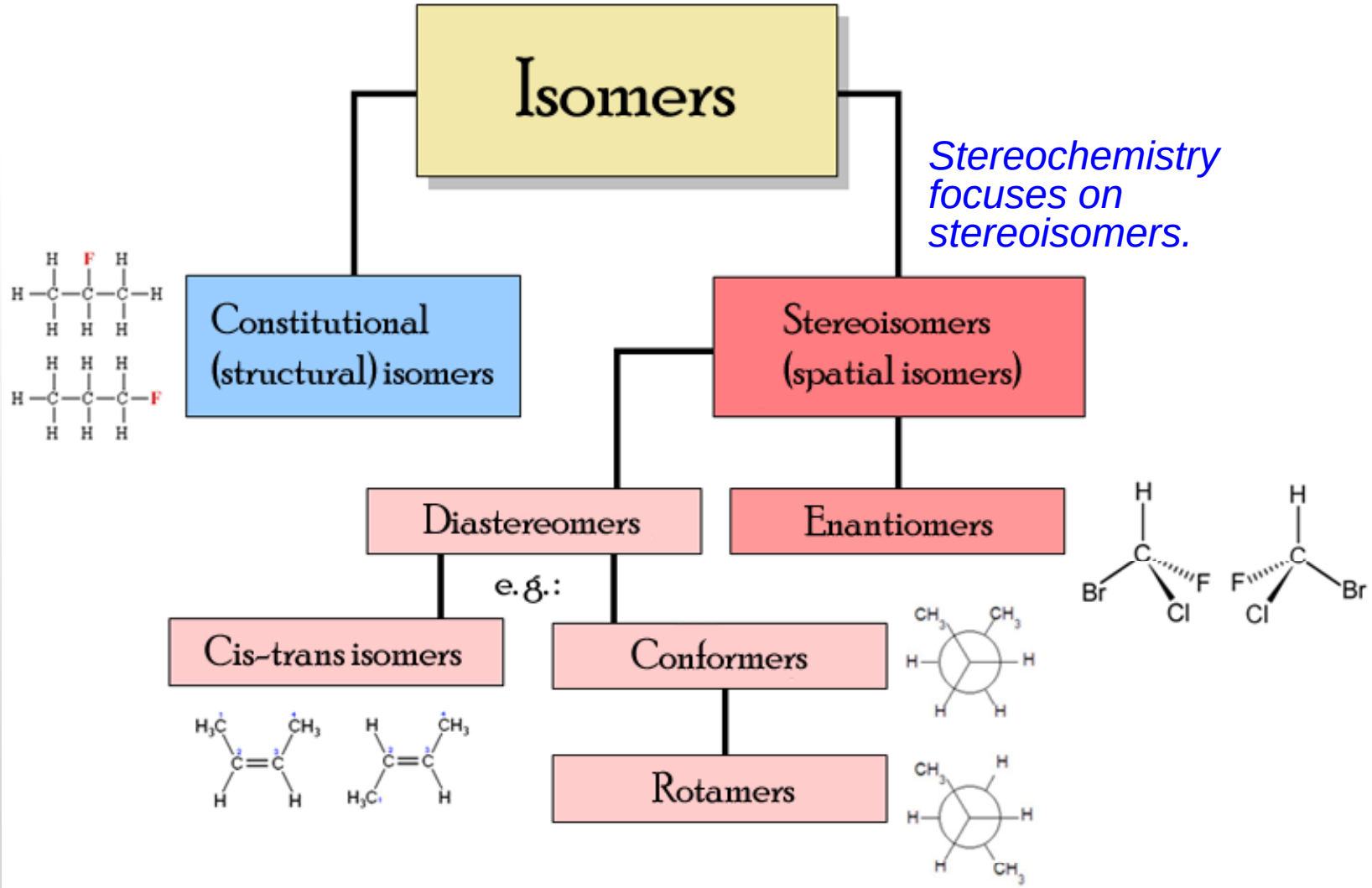
By LIMING JIANG & WEIPU ZHU (朱蔚璞)

Department of Polymer Science & Engineering
Zhejiang University
Email: zhuwp@zju.edu.cn
13735471052 (581052)

Chapter 3

Stereochemistry

3.1 Stereoisomerism, Optical Activity and Chirality

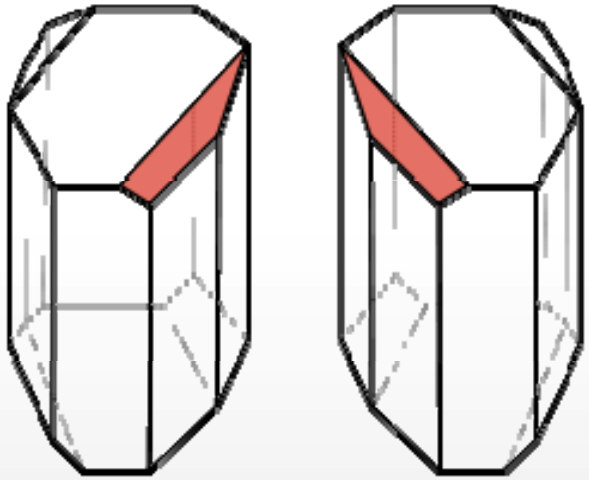


i. Optical activity

♦ Any material that rotates the plane of polarized light is said to be ***optically active***. Optical rotation is the turning of the plane of *planar polarized light* about the direction of motion as the light travels through certain materials.

♦ If a pure compound is optically active, the molecule is ***nonsuperimposable*** on its mirror image. 不可重疊的

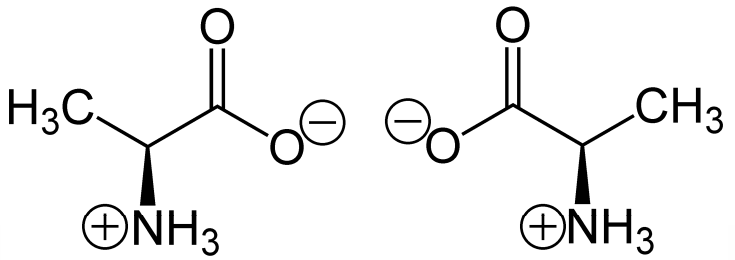
♦ If a molecule is ***superimposable*** on its mirror image, the compound does not rotate the plane of polarized light; it is ***optically inactive***.

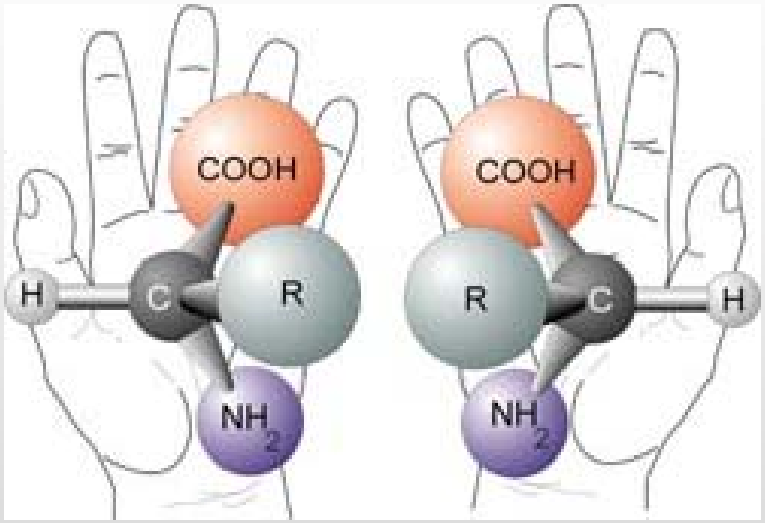


Pasteur *separated the left and right crystal shapes from each other to form two piles of crystals: in solution one form rotated light to the left, the other to the right, while an equal mixture of the two forms canceled each other's rotation. Hence, the mixture does not rotate polarized light.*

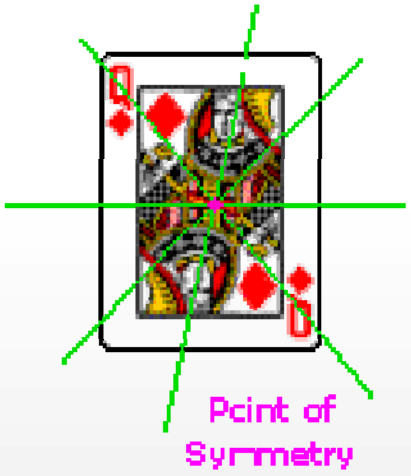
ii. Chirality and Symmetry

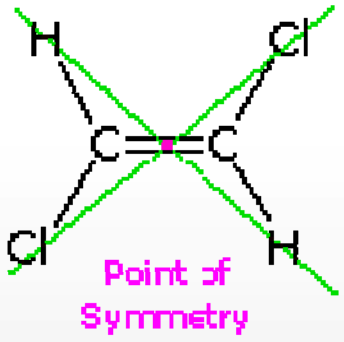
All objects may be classified with respect to a property we call **chirality** (from the Greek *cheir* meaning hand). A **chiral object** is not identical in all respects (i.e. nonsuperimposable) with its mirror image. An **achiral object** is identical with (superimposable on) its mirror image. The relation between optical activity and chirality is absolute. No exceptions are known, and many thousands cases have been found in accord with it. The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This is both a necessary and a sufficient condition.

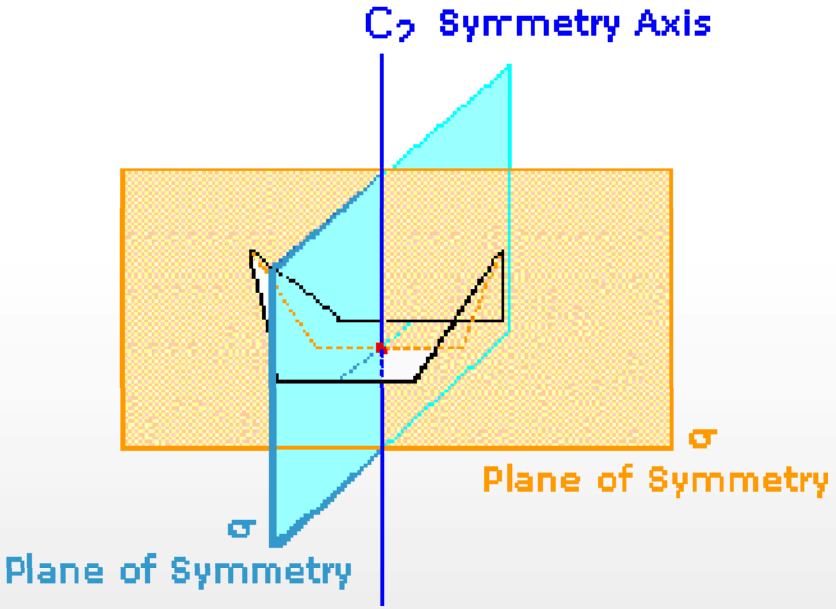




Two enantiomers of a generic amino acid







The existence of a reflective symmetry element (a point or plane of symmetry) is sufficient to assure that the object having that element is **achiral**. 反射对称元素

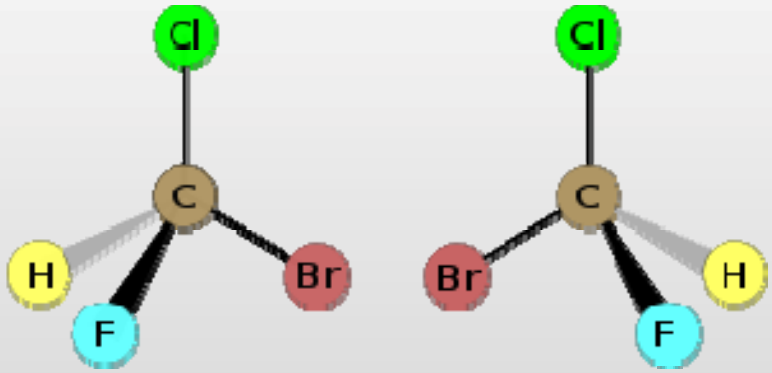
Dissymmetry: The absence of reflective symmetry elements. All dissymmetric objects are chiral. 非对称性

Asymmetry: The absence of all symmetry elements. All asymmetric objects are chiral. 不对称性

iii. Enantiomer

Stereoisomer are compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable. These three-dimensional structures are called **configurations**. 构型

- If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity.
- In each case of optical activity of a pure compound there are two and only two isomers, called enantiomers, which differ in structure only in the left- and right-handedness of their orientations. 对映异构体

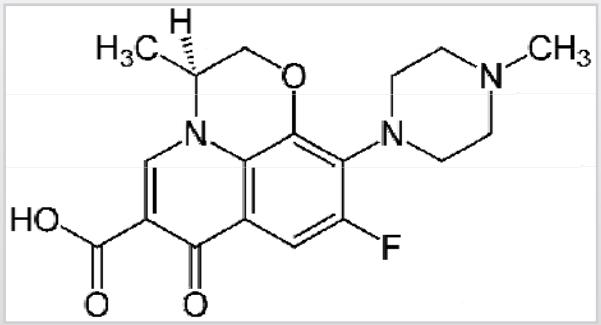


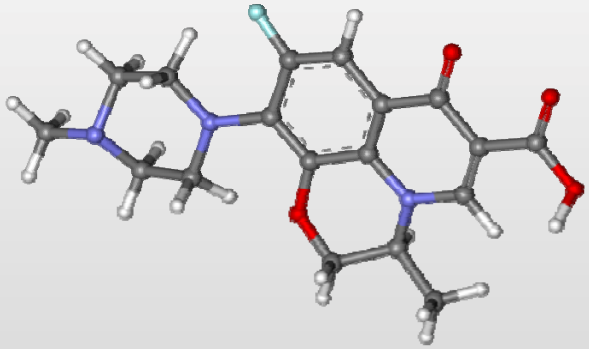
The two enantiomers of bromochlorofluoromethane

The properties of enantiomers

(a) They rotate the plane of polarized light in opposite directions, although in equal amounts; ***dextro*** isomer (+), ***levo*** isomer (–). 右旋体/左旋体

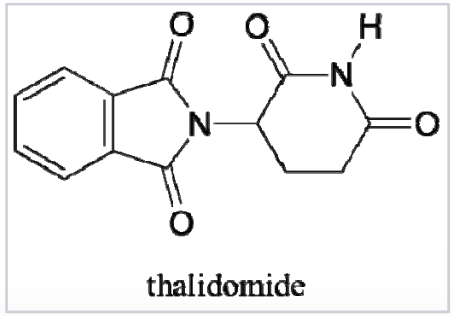
(b) They react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. Enantiomers react at the same rate with achiral compounds.

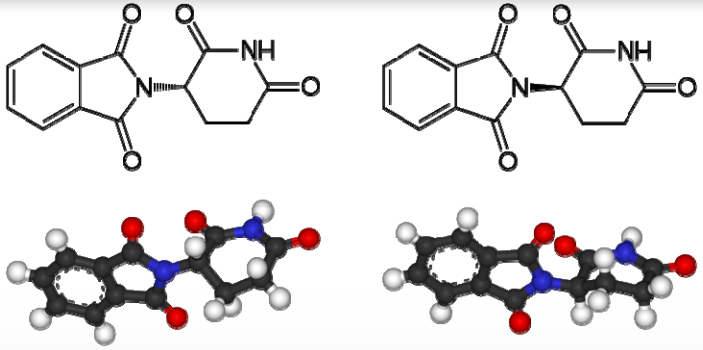




Levofloxacin 左氧氟沙星

IUPAC name: (-)-(*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

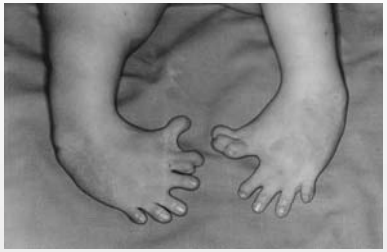




(沙利度胺)

2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione
German Pharmaceutical Co.
1957-1961
"反应停"—"孕妇的理想选择"

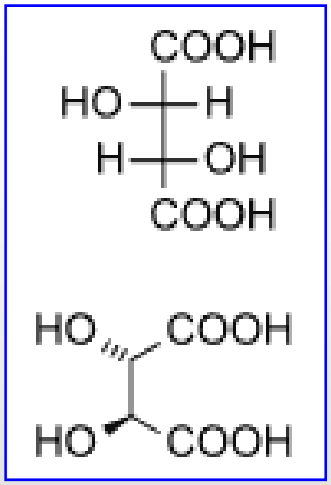
(*R*)-isomer: sedative, hypnotic 镇静、催眠
(*S*)-isomer: birth defects 致畸
◆ 12000畸形儿——海豹肢症、腭裂、盲儿、聋儿、内脏畸形
◆ 4000名患儿不到1岁夭折



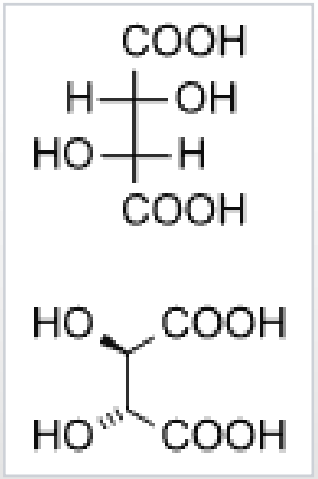
1962: FDA. pharmacologist Dr. Frances Oldham Kelsey (1914-2015) receives the President's Award

iv. Racemic mixtures (racemates)

A racemate is optically inactive, meaning that it does not rotate plane-polarized light. This is because the two isomers rotate plane-polarized light in opposite directions, and they optically cancel out. 外消旋体



(*D*-(−)-tartaric acid)



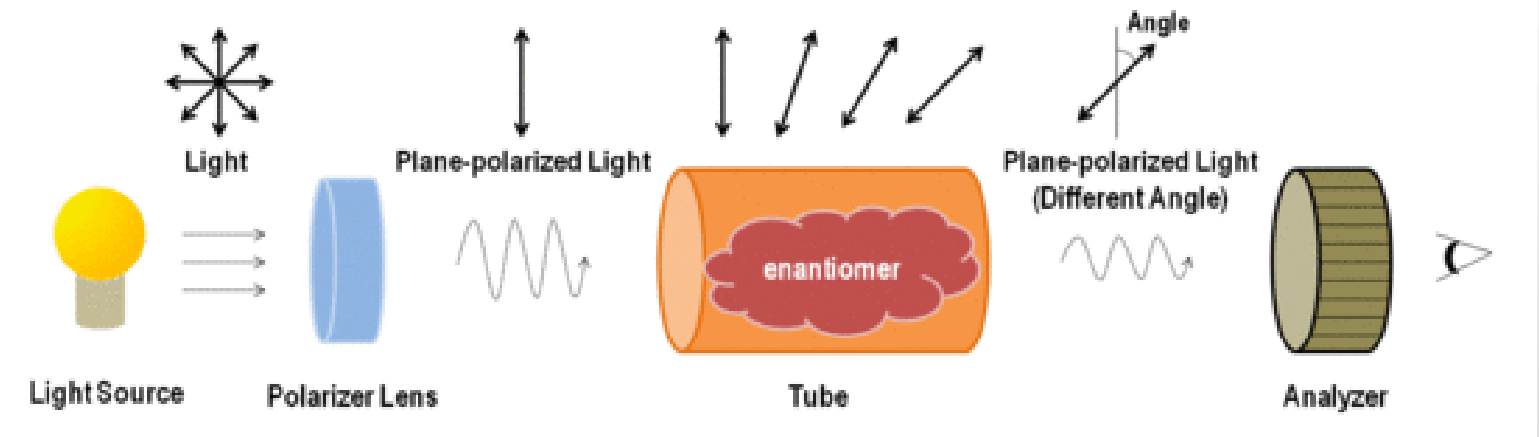
(*L*-(+)-tartaric acid)

	mp	solubility (in water, 20°C)
(±)-	204-6	206 g/L
(+)- or (-)-	170	1390 g/L

♦ The separation of a racemic mixture into its two optically active components is called chiral resolution. Their properties in the gaseous or liquid or in solution usually are the same, since such a mixture is nearly ideal. 手性拆分

v. Specific rotation

The **specific rotation** of a chemical compound [α] is defined as the observed angle of optical rotation α when plane-polarized light is passed through a sample with a path length of 1 decimeter and a sample concentration of 1 gram per 1 millilitre. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]^{25}_{546}$.



$[\alpha] = \alpha / lc$ for solutions

$[\alpha] = \alpha / ld$ for pure compounds

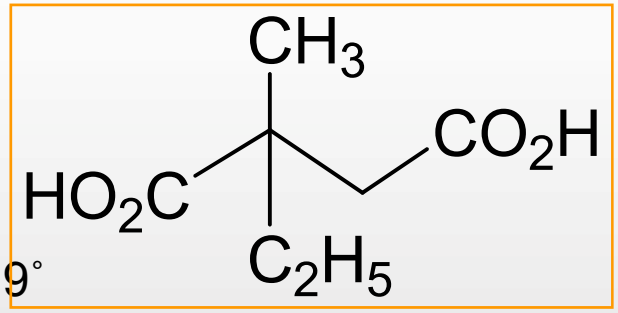
α : the observed rotation; c : the concentration (g/mL)

l : cell length in decimeters; d : the density (g/mL)

♦ In theory, there should be no change in [α] with concentration, since this is taken into account in the formula, but associations, dissociations, and solute-solvent interactions often cause nonlinear behavior.

Example:

(-)-2-ethyl-2-methylsuccinic acid



[Conc.]	16.5	10.6	8.5	2.2
$[\alpha]_D$(24˚C, $CHCl_3$)	-5.0˚	-0.7˚	+1.7˚	+18.9˚

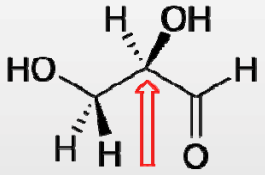
NOTE:

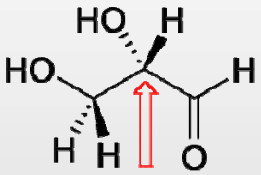
The value of α changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation but even the direction.

3.2 The kinds of optically active molecules

A. Molecules with stereogenic centers

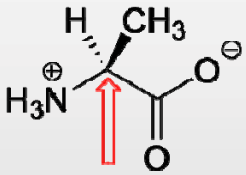
In general, chiral molecules have point chirality at a single stereogenic atom, usually carbon, which has four different substituents. The two enantiomers of such compounds are said to have different absolute configurations at this center. This center is thus stereogenic (i.e., a grouping within a molecular entity that may be considered a focus of stereoisomerism).

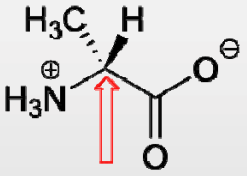




glyceraldehyde

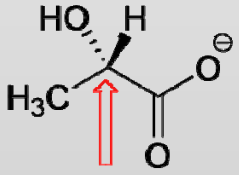
甘油醛

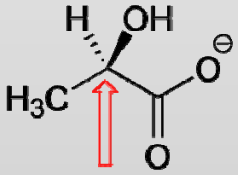




alanine

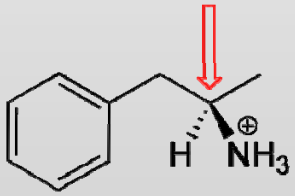
丙氨酸

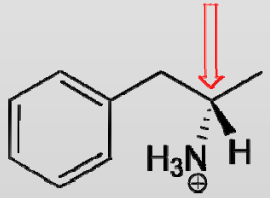




lactate

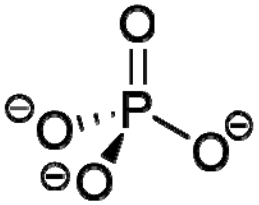
乳酸



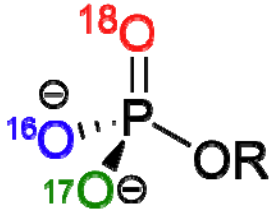


amphetamine

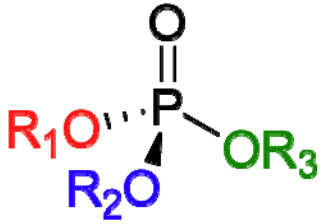
苯丙胺



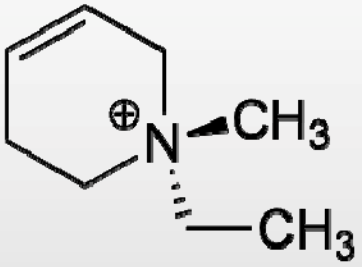
phosphate
(achiral)



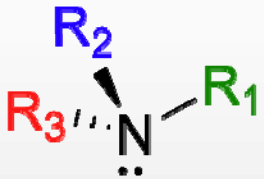
labeled phosphate ester
(chiral)



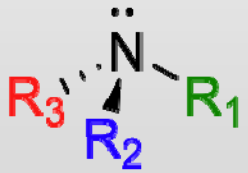
a chiral phosphate triester



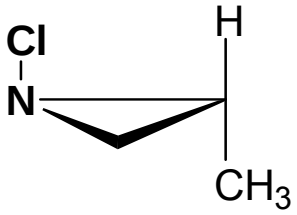
a chiral quaternary ammonium

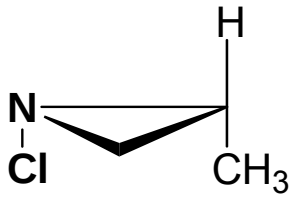


the rapid inversion of amines makes them achiral



Pyramidal inversion 2×10^{11} inversions every second for NH_3

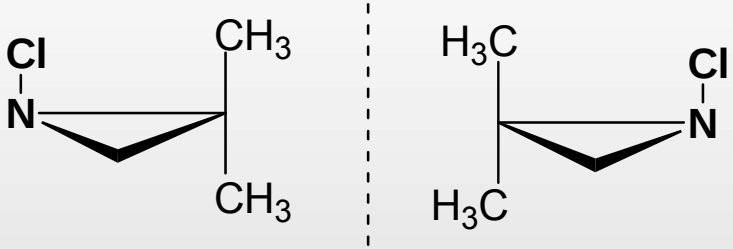


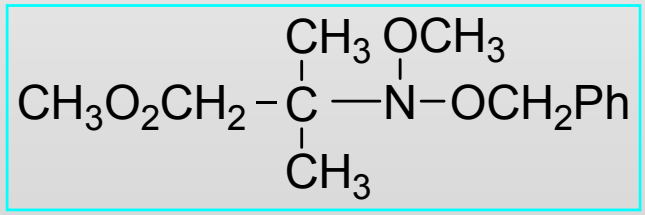


trans (1-chloro-2-methylaziridine)

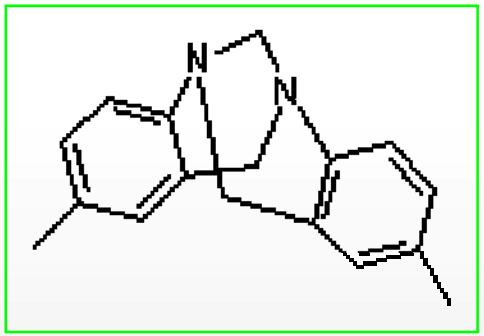
cis

Mirror





racemization at r.t. with half-life of 1.22 h



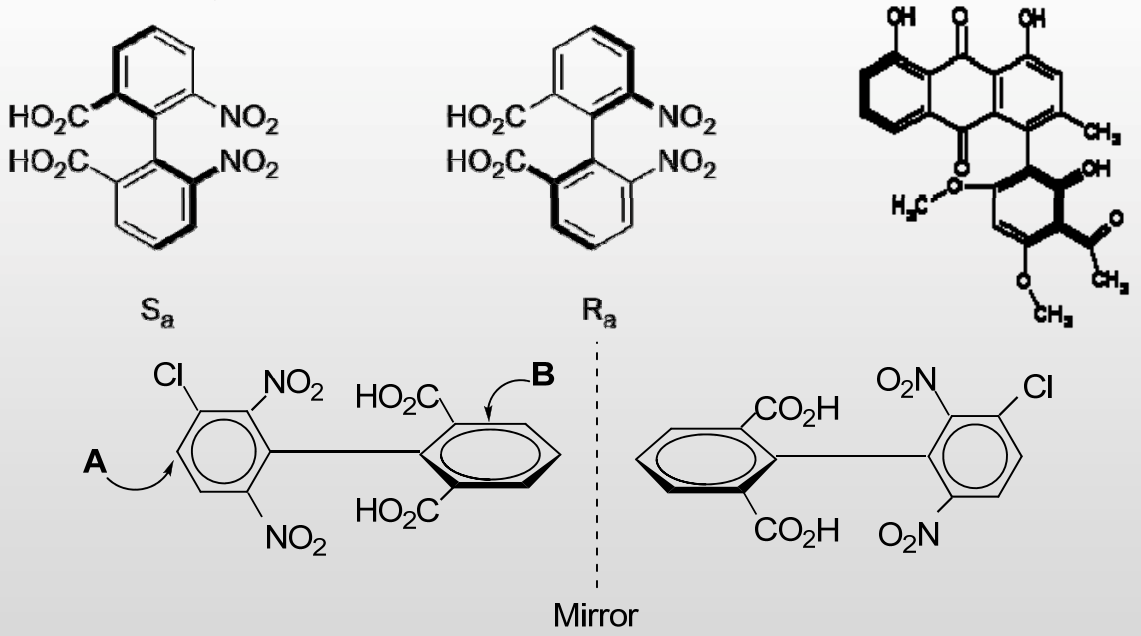
Tröger's base (1887)

a molecular tweezer, the bicyclic skeleton forces the molecule in a rigid locked conformation with the aromatic rings in proximity

B. Molecules without stereogenic centers

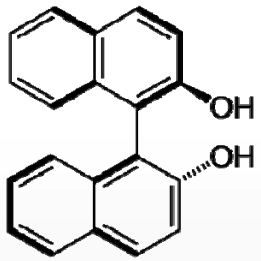
Axial chirality is a special case of chirality in which a molecule does not possess a stereogenic center but an **axis of chirality** - an axis is about which a set of substituents is held in a spatial arrangement that is not superposable on its mirror image.

Atropisomers 阻转异构体

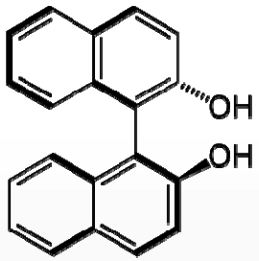


Biphenyls: If either ring is symmetrically substituted, the molecule has a plane of symmetry; the compound is achiral.

Binaphthalene derivatives:

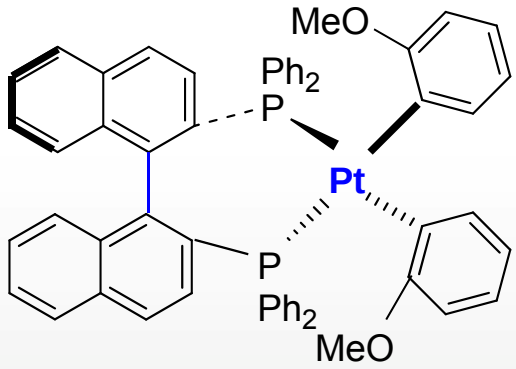


(R)-BINOL

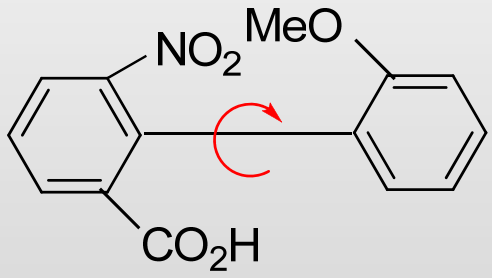


(S)-BINOL

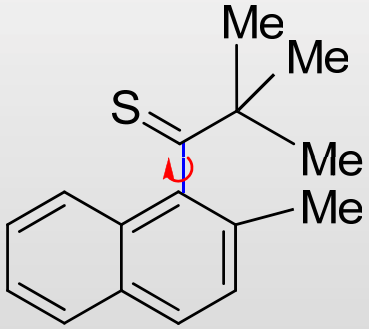
[α] = +/- 35.5º (c=1 in THF)



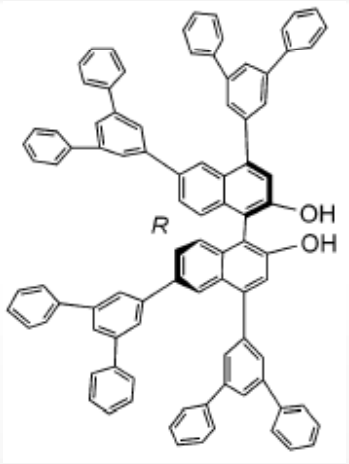
a chiral Pt-complex

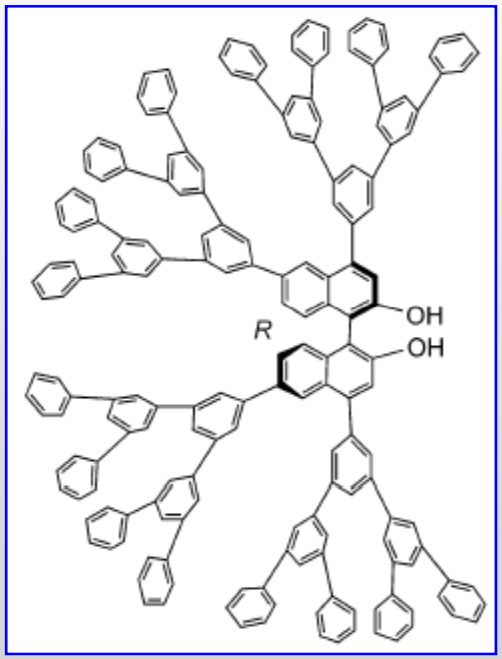


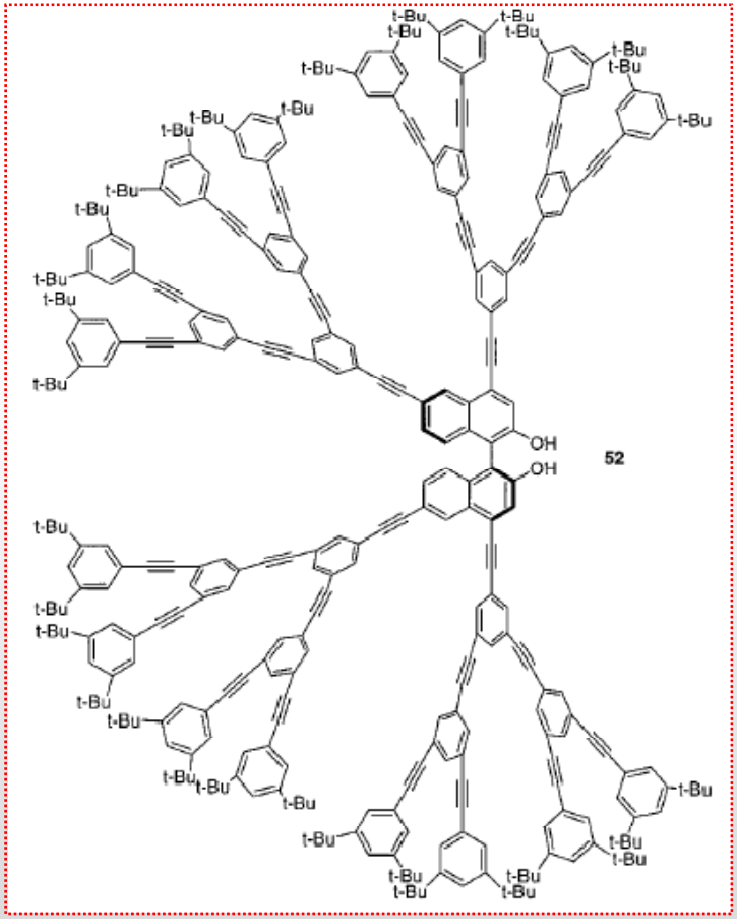
a half-life 9.4 min.
(EtOH, 25˚C)

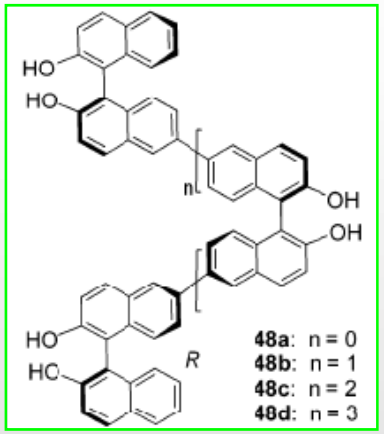


Atropisomerism
an interconversion
barrier: 18~19 kcal/mol



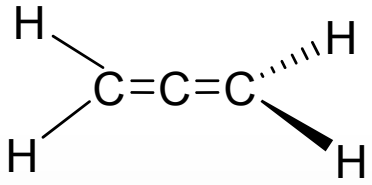


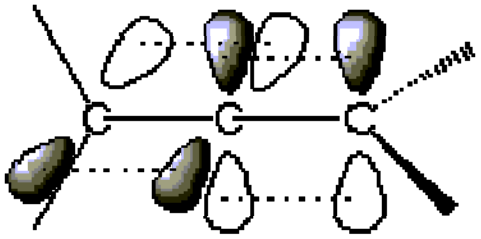




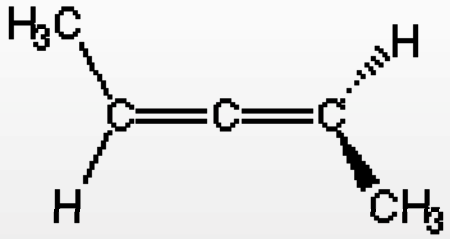
Binaphthyl dendrimer oligomeric and polymeric binaphthyls:
Enantioselective Fluorescent Sensor

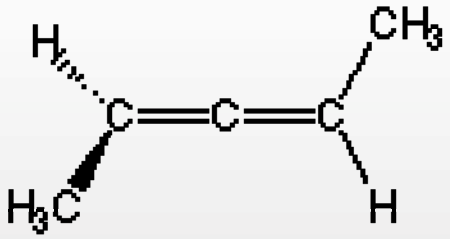
Allenes 丙二烯型衍生物



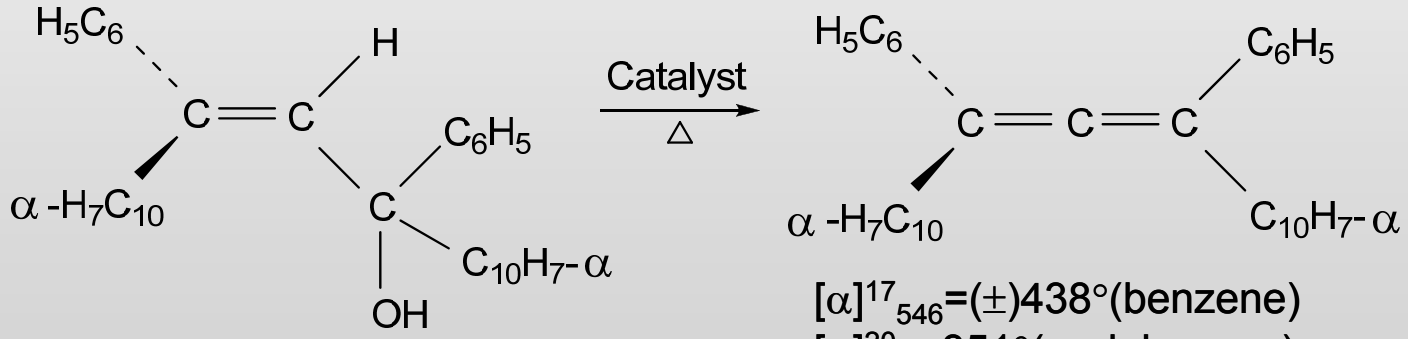


Two ends of allene are perpendicular

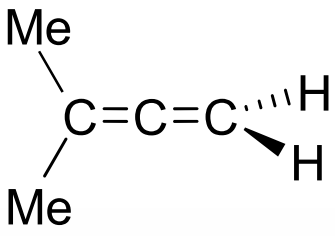




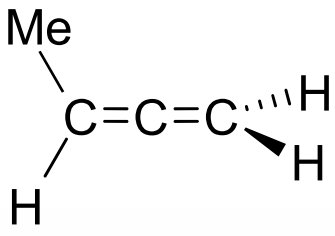
Enantiomers of chiral allenes



$[\alpha]^{17}_{546}=(\pm)438°$(benzene)
$[\alpha]^{20}_{D}=351°$(cyclohexane)



Inactive



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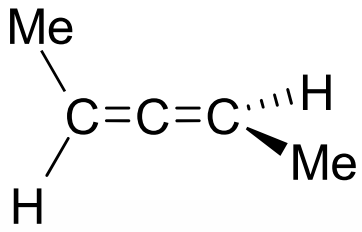
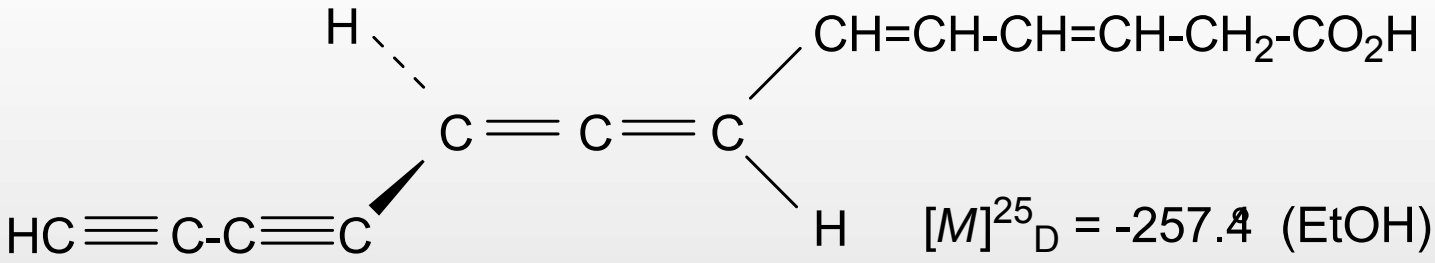
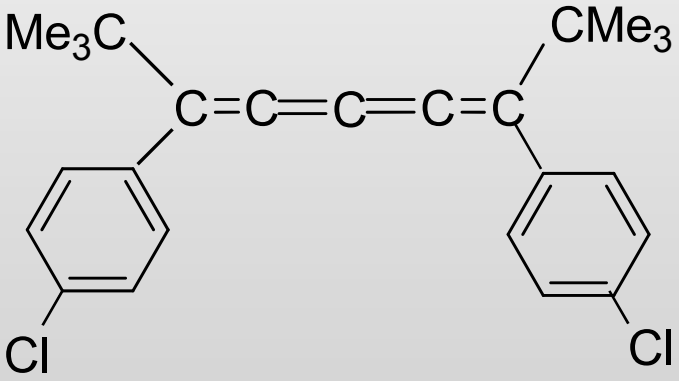
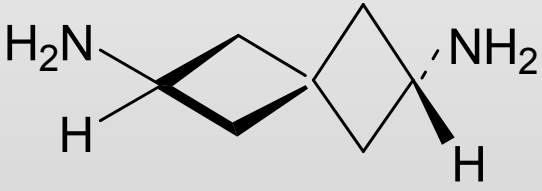


Active

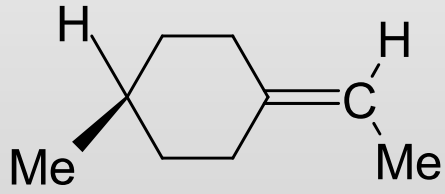


$[M]^{25}_{D}$ = -257.4 (EtOH)





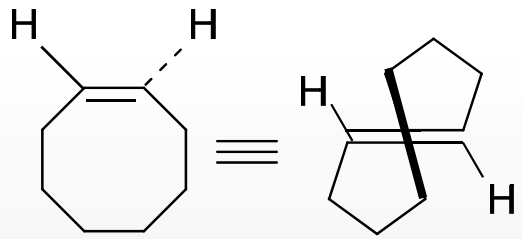
Spirane

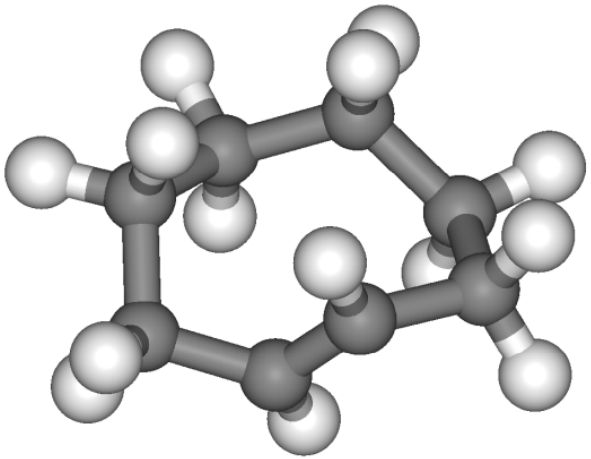


exocycdic double bonds

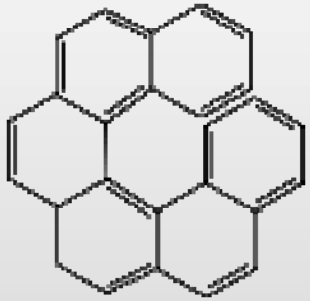
Chirality due to a helical shape

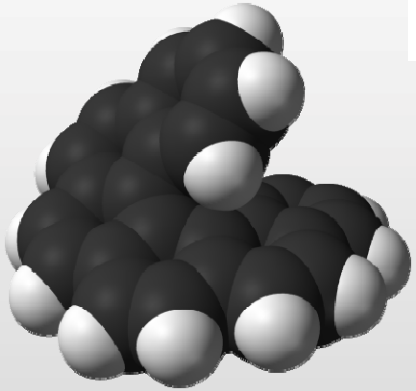
trans-cyclooctene





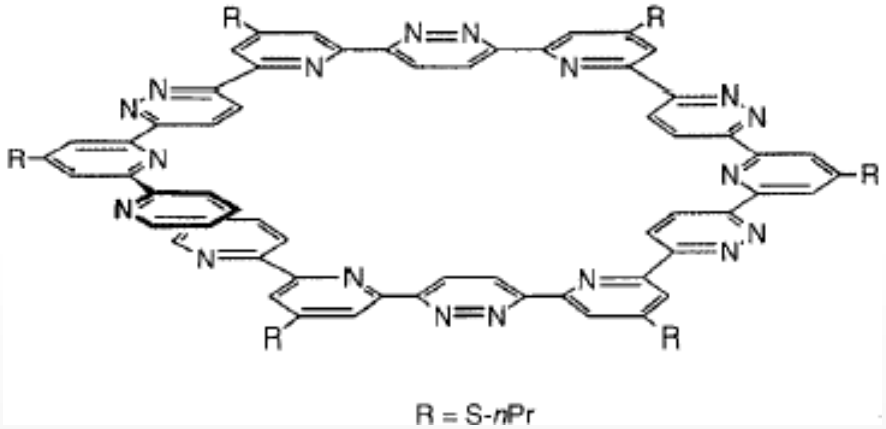
Helicenes

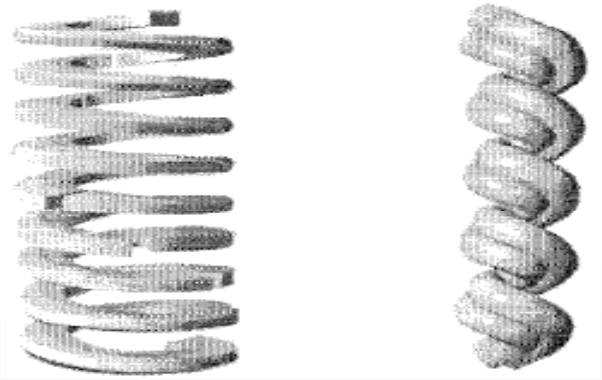


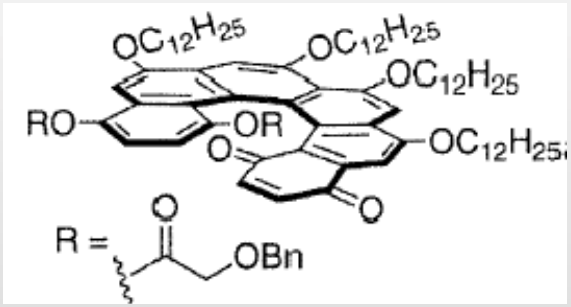


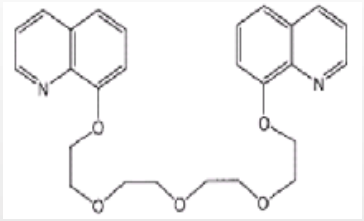
Hexahelicene
$[3640]^{24}_{589nm}$
Newman, 1956

Helicenes *are notable for having chirality while lacking both asymmetric carbons and chiral centers. Helicenes' chirality results from the fact that clockwise and counterclockwise helices are non-superimposable.*

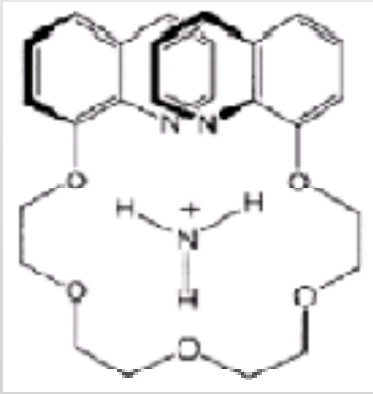








$R^-NH_3^+$



Liquid crystalline disc-shaped helicene and its mode of association into helical columns.

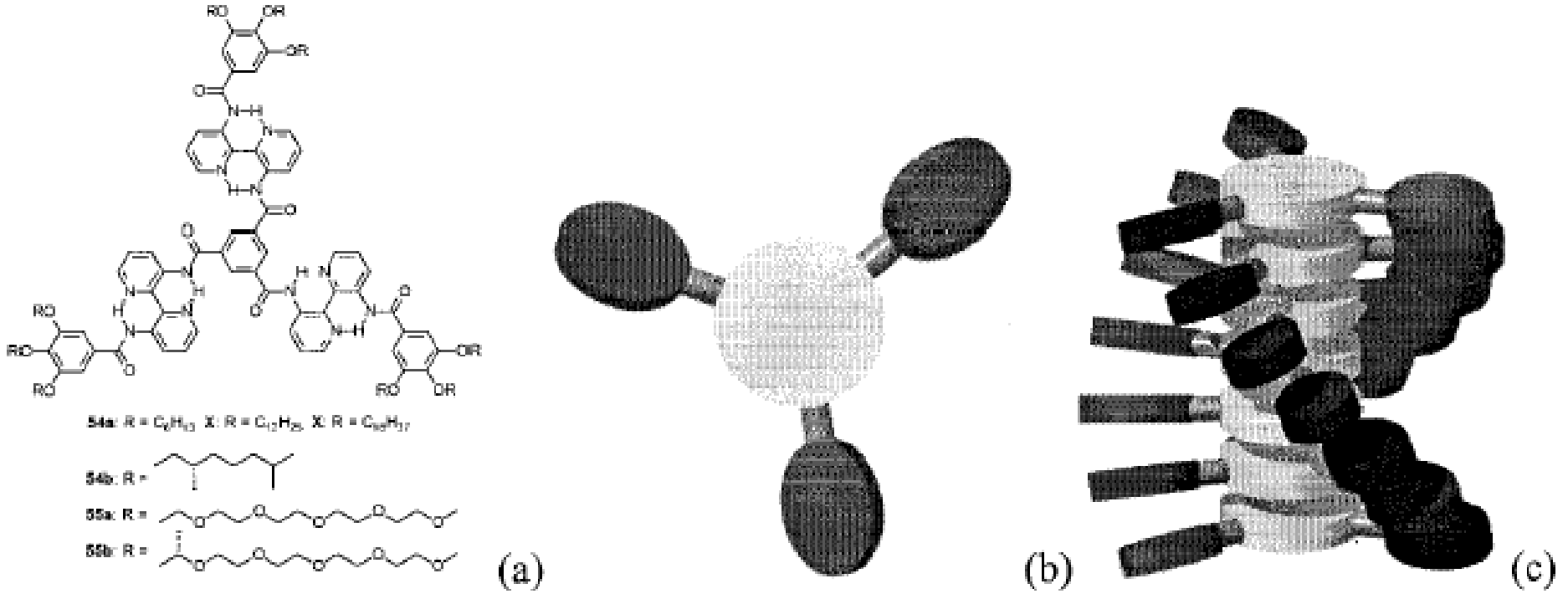
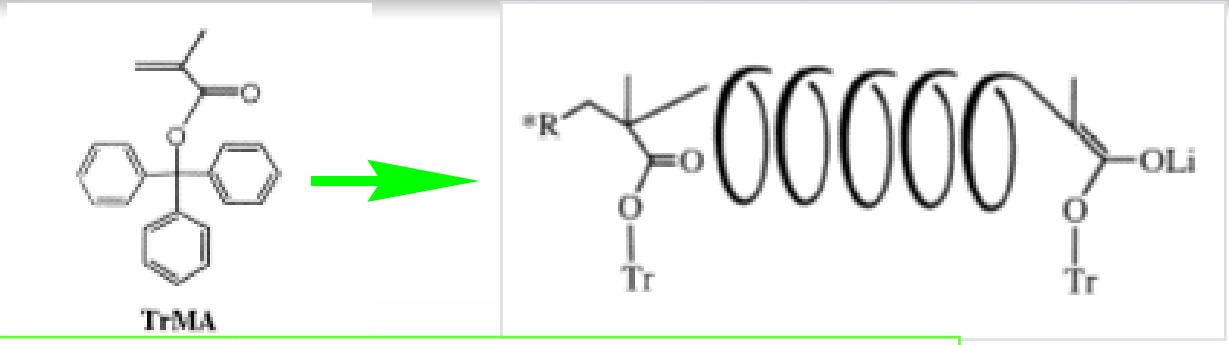
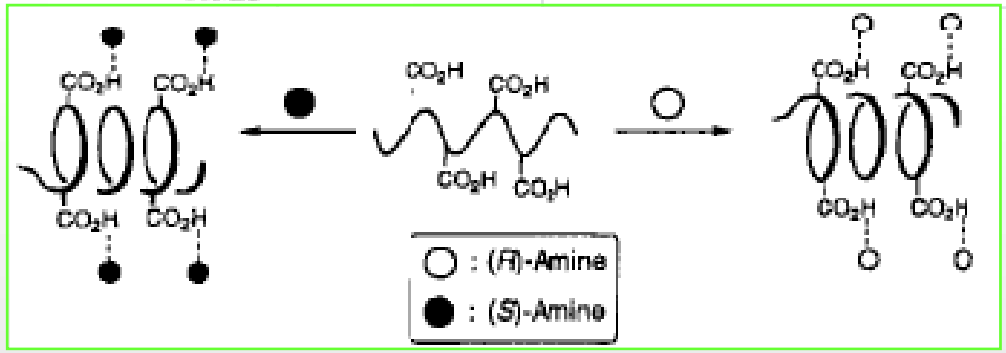
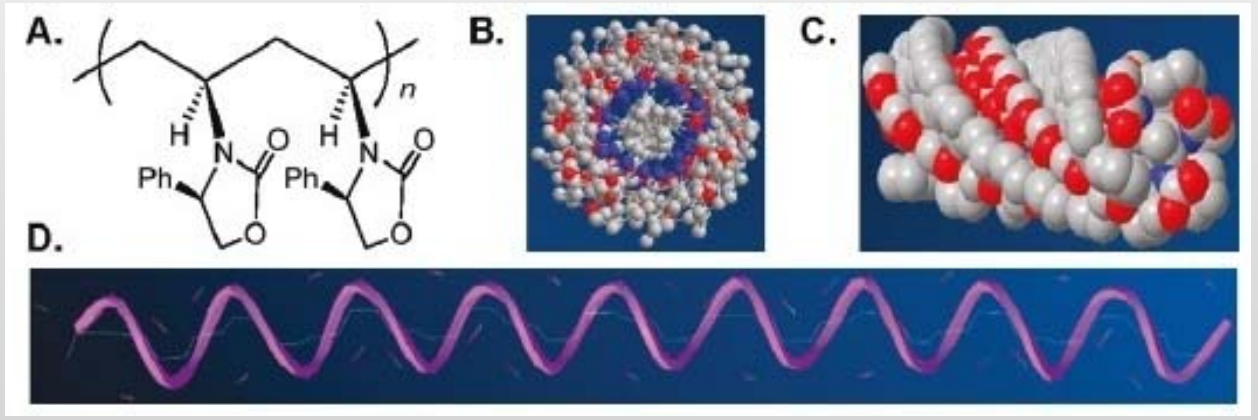


Figure.(a) C_3-asymmetrical disc-shaped molecules 54 and 55 with achiral and chiral side-chains. (b) a cartoon representation of the propeller-like conformation attained by the C_3-symmetrical molecular; and (c) formation of helical columns by the propellers.

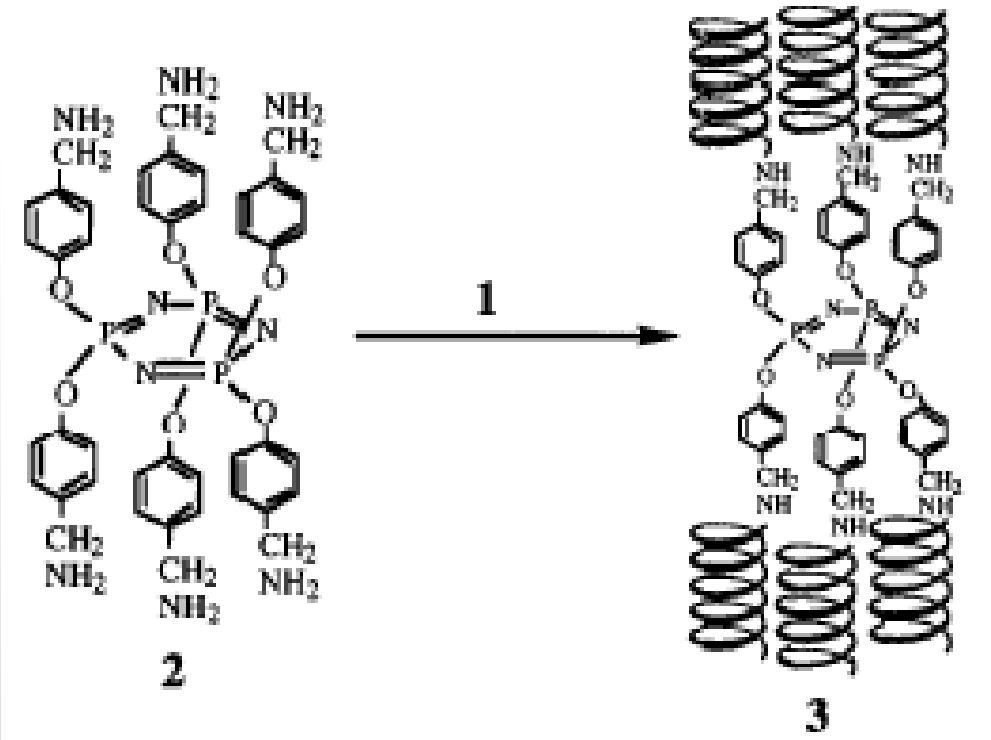




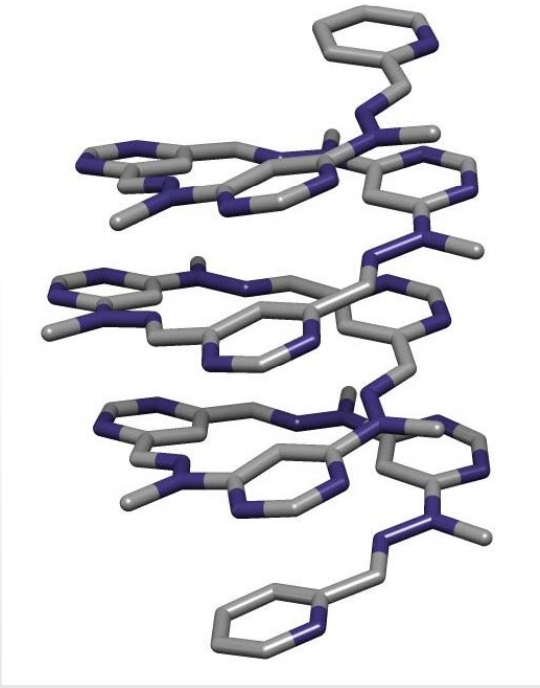
Inversion of polymeric helix initiated with chiral molecules



Macromolecules 2010, 43, 7504–7514

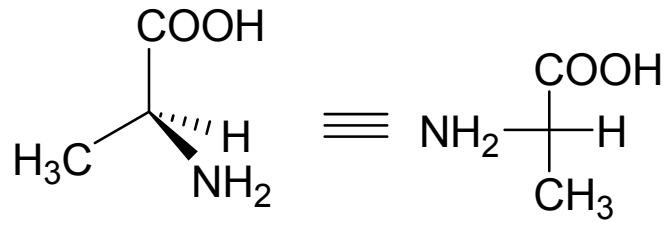


Star-shaped polymer with helical arms for optical resolution amino-acids.

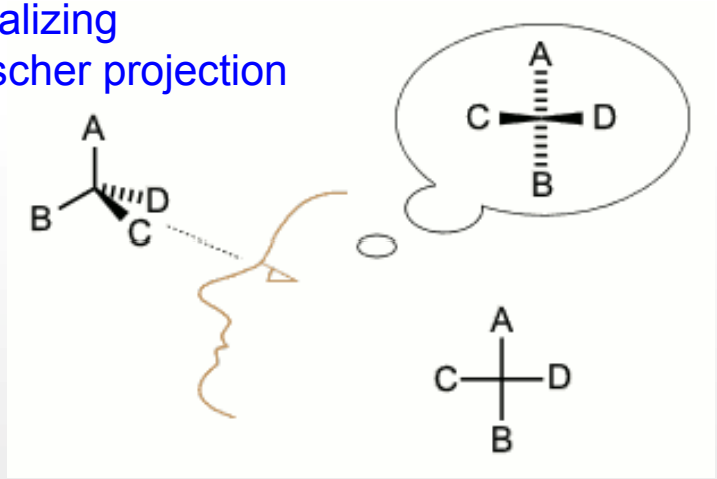


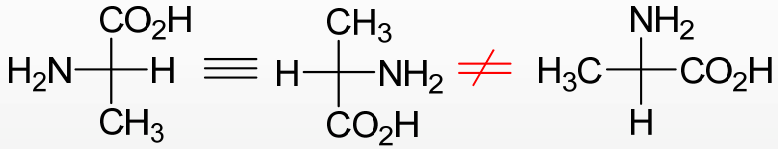
A foldamer: a discrete chain molecule or oligomer that adopts a secondary structure stabilized by non-covalent interactions. 折叠体
Lehn et al. Helv. Chim. Acta., 2003, **86**, 1598.

3.3 The Fisher Projection



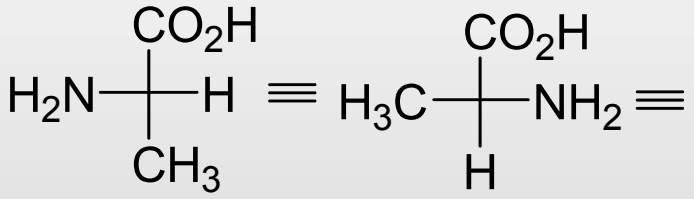
Visualizing
a Fischer projection

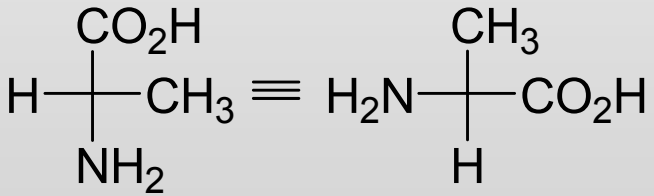




Restrictions

i. Projections may not be taken out of the plane of the blackboard or paper;
ii. They may not be rotated 90˚, 180˚ rotation is permissible;
iii. It is permissible to keep any group fixed and to rotate the other three clockwise or counterclockwise.

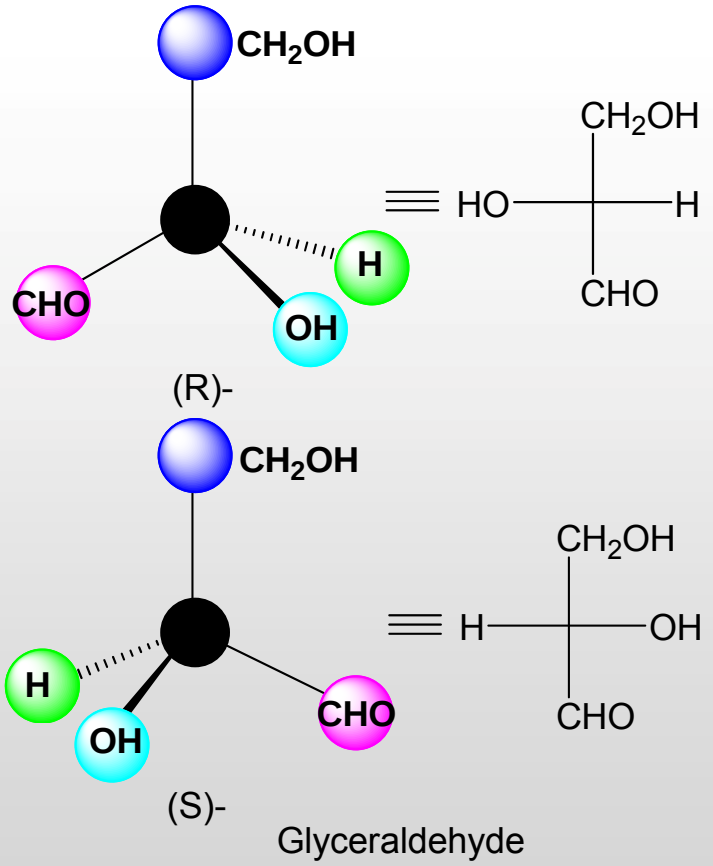




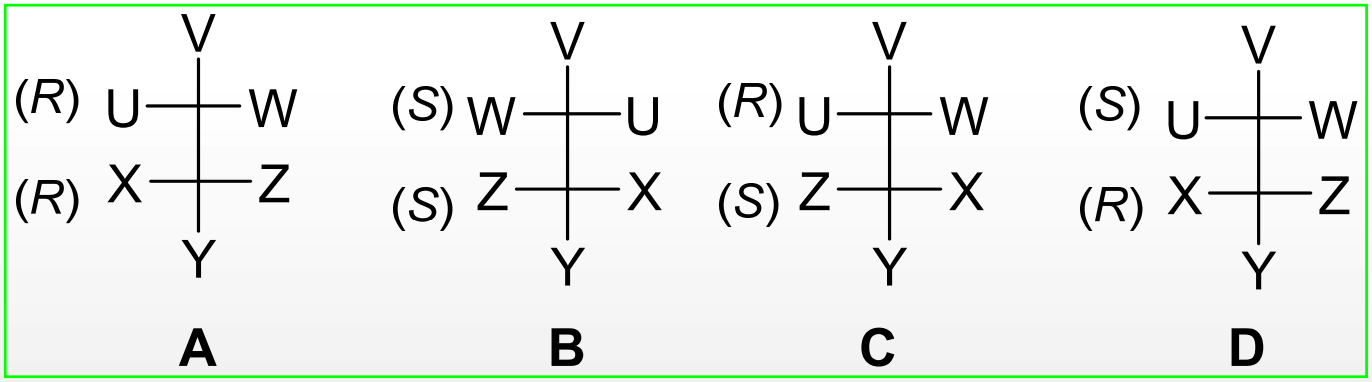
3.4 Assigning descriptors and Cahn–Ingold–Prelog priority rules (Sequence rule)

Some examples illustrating the sequence rule:

- **–OH > –CH_3**. The –OH groups directly attached to C* have a higher atomic number (8) than the –CH_3 groups directly attached to C* (6).
- **–CH(OH)CH_3 > –CH_2OH**. The directly attached atoms are both carbon, but the distance-2 lists differ: they are (O, C, H) and (O, H, H), respectively.
- **–CH(OCH_3)CH_3 > –CH(OH)CH_2OH**
- **–CH(CH_2F)OCH_3 > –CH(CH_3)OCH_2F**
- **–CDH_2 > –CH_3**
- **–CH(OD)CH_3 > –CH(OH)CTH_2**
- **–$CH_2CH_2CH_3$ > –CDHCH_3**
- **–CH=O > –CH_2OH**
- **–CH(OCH_3)$_2$ > –CH=O**
- **–CH=CH_2 > –CH(CH_3)$_2$**



3.5 Molecules with more than one chiral center. Diastereomer

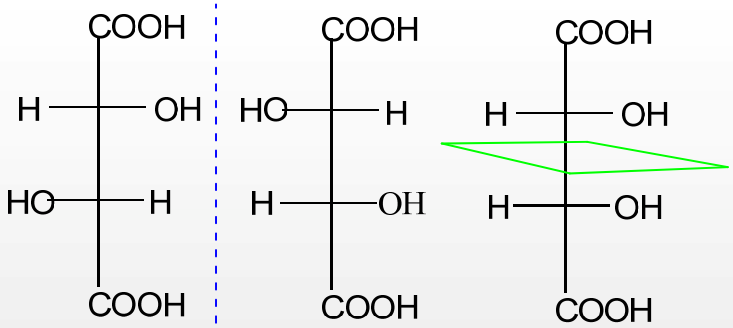


Diastereomer (or diastereoisomers) are stereoisomers that are not enantiomers (non-superimposable mirror images of each other). 非对映异构体
Being enantiomers, *C* and *D* must have identical properties; the same is true for *A* and *B*.

♦ Diastereomer have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all.

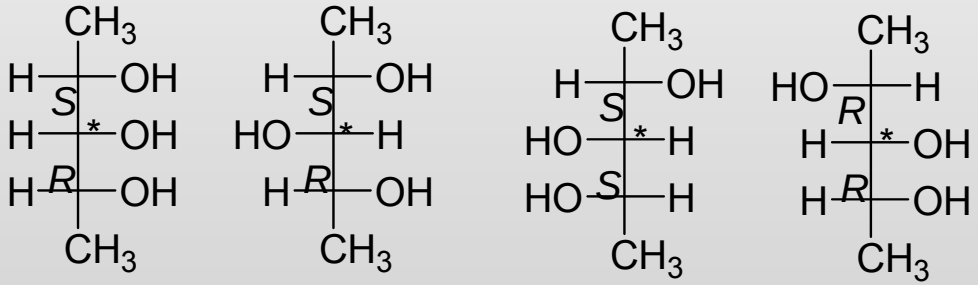
The maximum possible number of isomer:
2^n (n= the number of chiral centers)

- Example 1: the three stereoisomers of tartaric acid



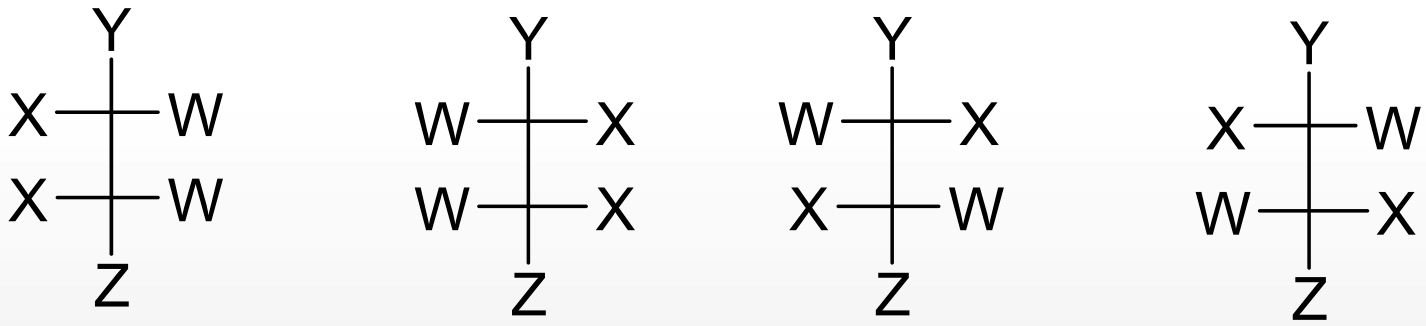
dl pair *meso-*

- Example 2: 2,3,4-pentanetriol



**pseudoasymmetric*

Prefixes: erythro- (赤式), threo-（苏式）



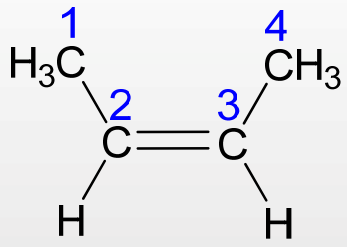
erythro *dl* Pair
(赤式)

threo *dl* Pair
(苏式)

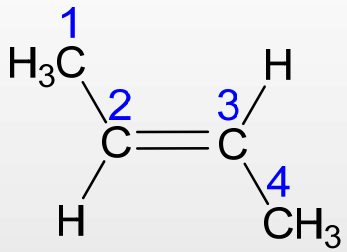
Two common prefixes used to distinguish diastereomers are **threo** and **erythro**. When drawn in the Fischer projection the *erythro* isomer has two identical substituents on the same side and the *threo* isomer has them on opposite sites.

3.6 Cis-trans isomerism

Cis-trans isomerism or geometric isomerism or configuration isomerism or E-Z isomerism is a form of stereoisomerism describing the orientation of functional groups within a molecule. In general, such isomers contain double bonds, which cannot rotate, but they can also arise from ring structures, wherein the rotation of bonds is greatly restricted.

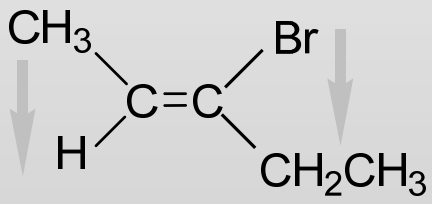


cis-2-butene

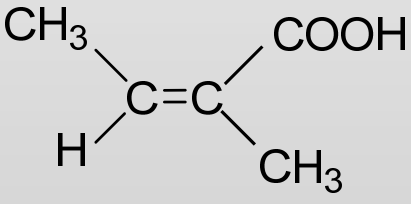


trans-2-butene

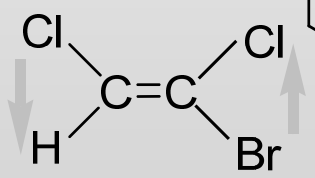
Z,*E* –designation (based on Sequence rules):



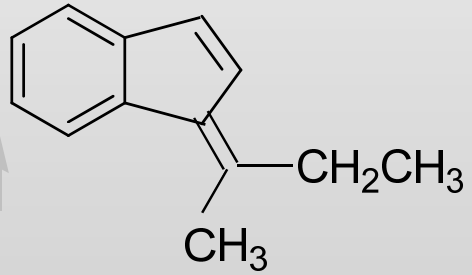
Z-



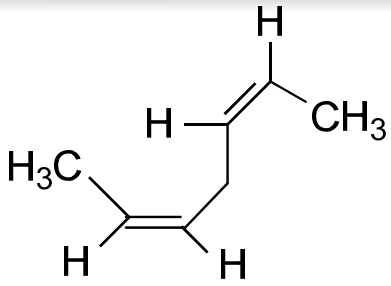
Z-



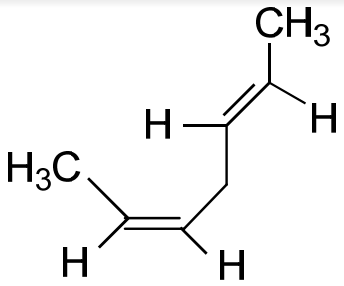
E-



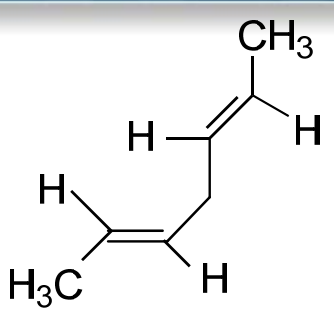
E-



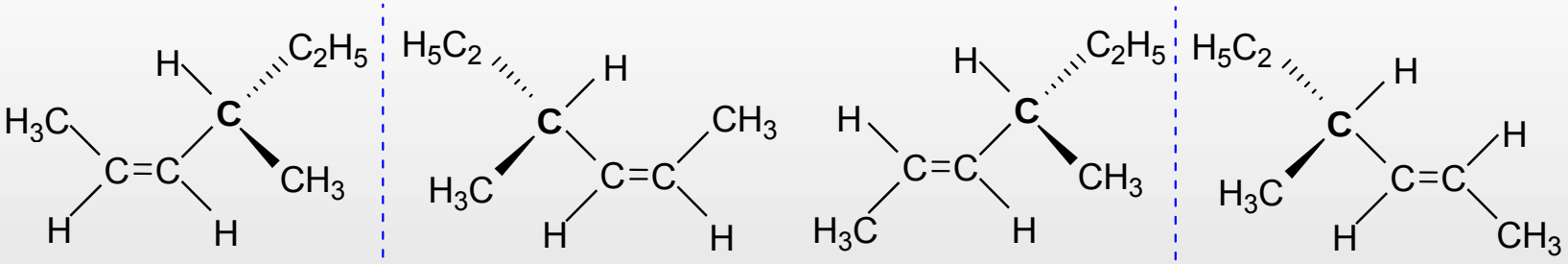
cis-cis or
(*Z*, *Z*-)



cis-trans or
(*Z*, *E*-)

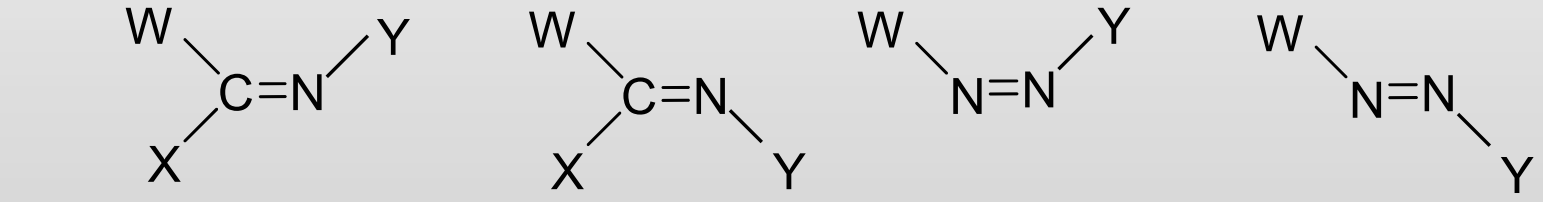


trans-trans or
(*E*, *E*-)



(*Z*) or cis *dl* pair

(*E*) or trans *dl* pair



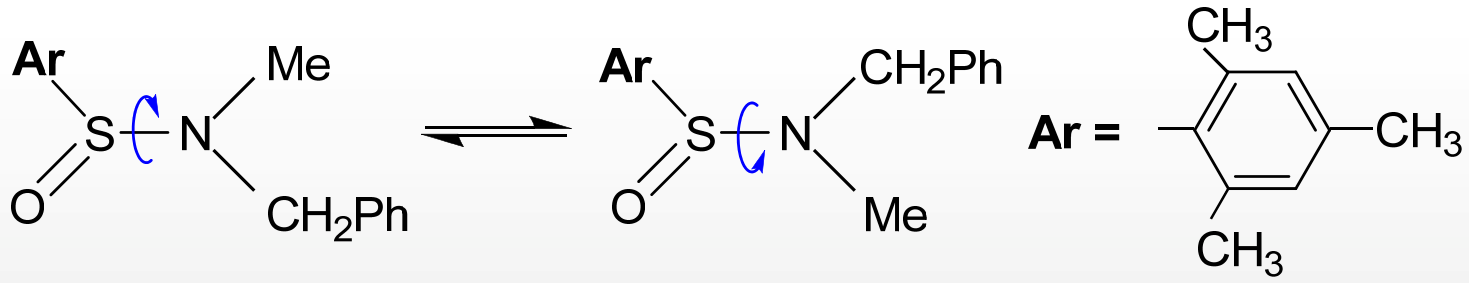
if W > X *Z*- *E*-

imine

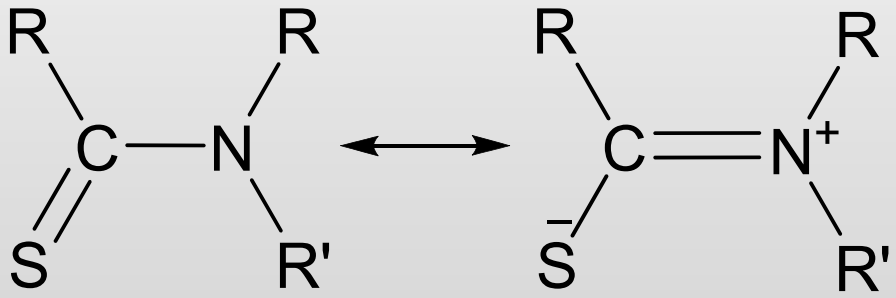
Z- *E*-

diazo compounds

- In a few cases, single-bond rotation is so slowed that *cis* and *trans* isomers can be isolated.

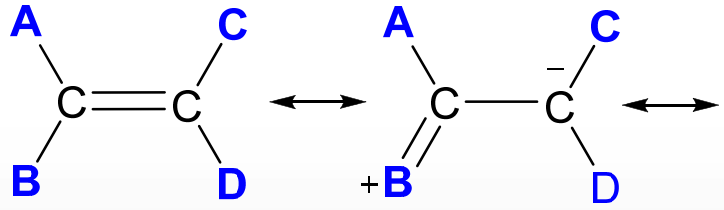


The interconversion with a half-life of ~25 hr in $CDCl_3$ at 50˚C.



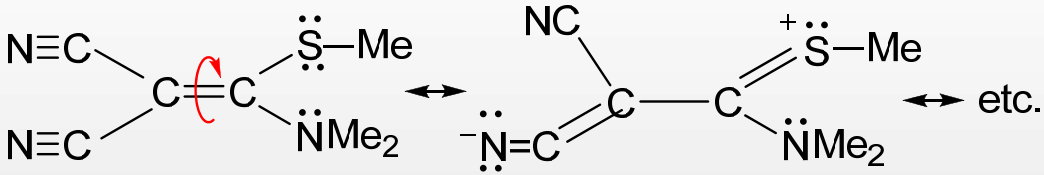
Resonance figure of thioamides

❑ Push-pull ethylenes: nearly free rotation around what are formally C=C double bonds

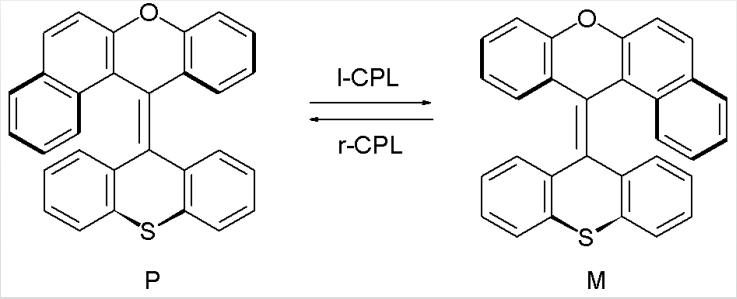


A, B = electron-withdrawing

C, D = elecron-donating

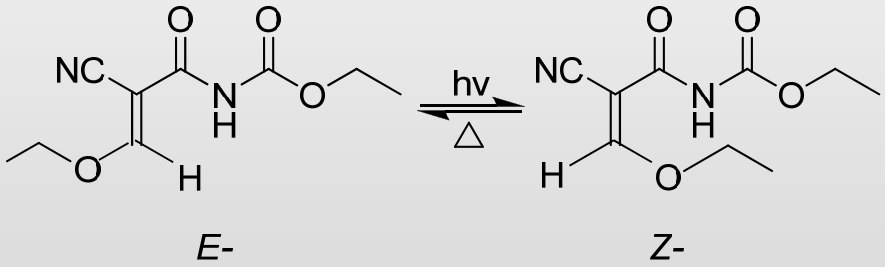


a barrier to rotation of 55 kJ/mol (260-270 kJ/mol for simple alkenes)



Chiroptical molecular switches

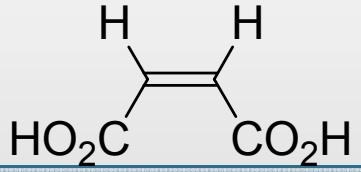
手光分子开关

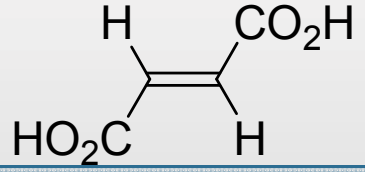


K.Sung, et al, ARKIVOC, 2005(Xiii),131-140

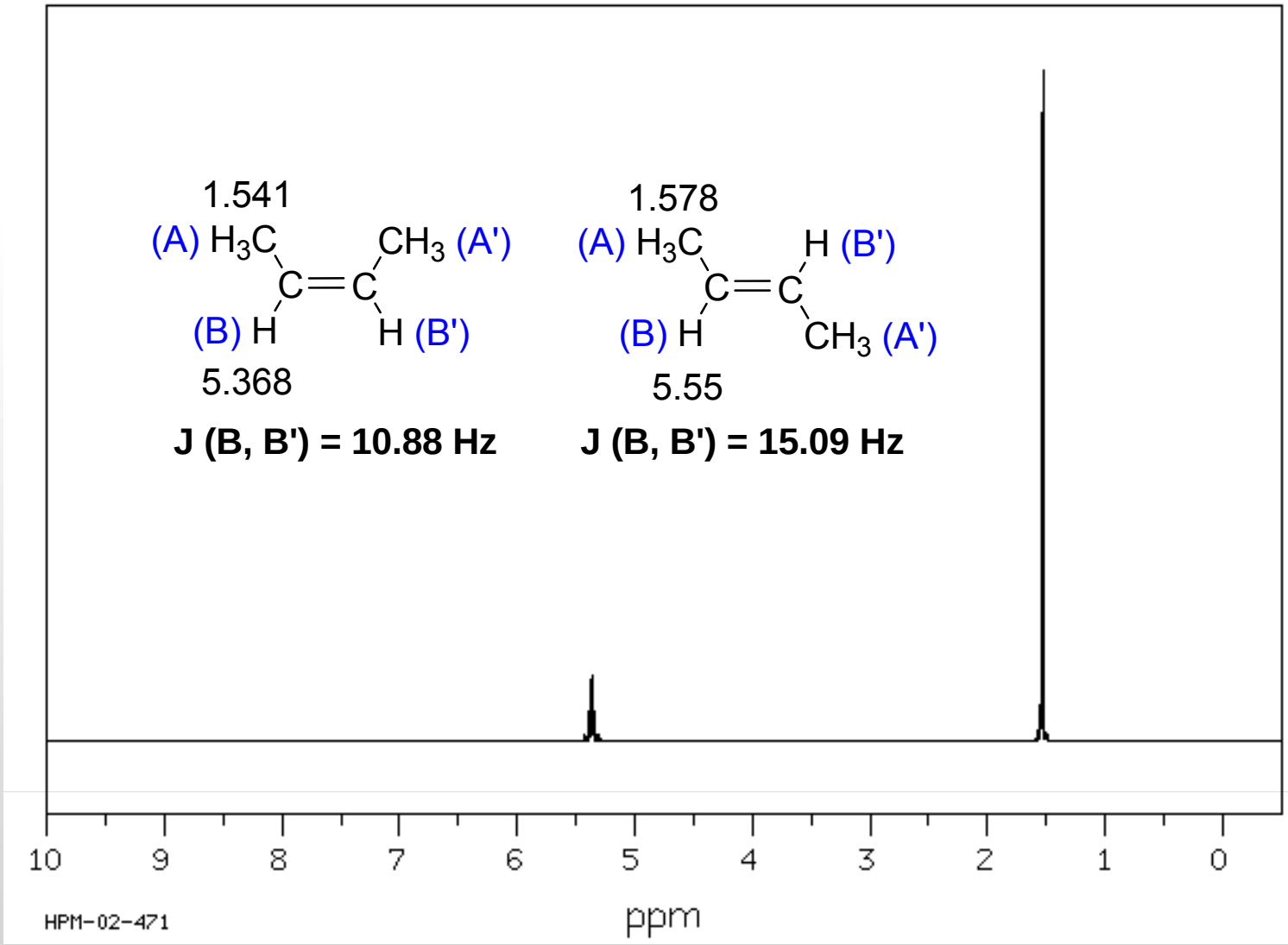
Cis isomers and trans isomers often have different physical properties. Differences between isomers, in general, arise from the differences in the shape of the molecule or the overall dipole moment.

	Cis-		Trans-
dipole		>	
density		>	
Melting point		<	
Solubility (in inert solvent)		>	
Thermochemical stability		<	
(heat of combustion)		>	
Vicinal coupling constant	0~12	<	12~18 Hz



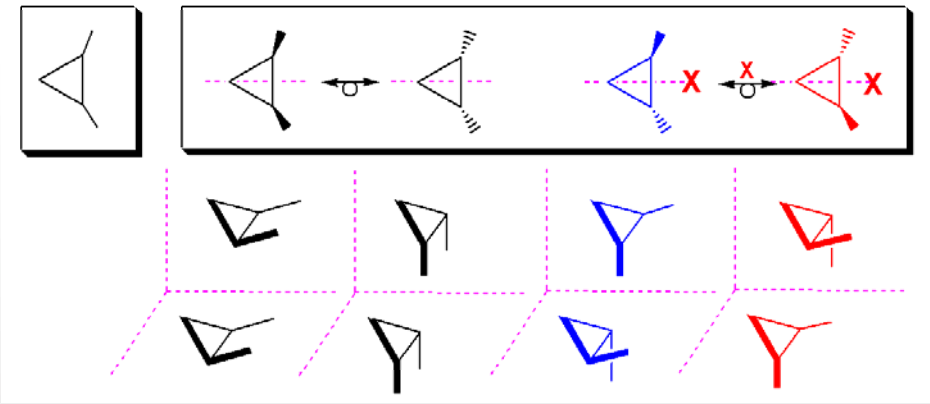


Properties	Maleic acid	Fumaric acid
Melting point, °C	130	286
Solubility, g/L, 25°C (water)	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

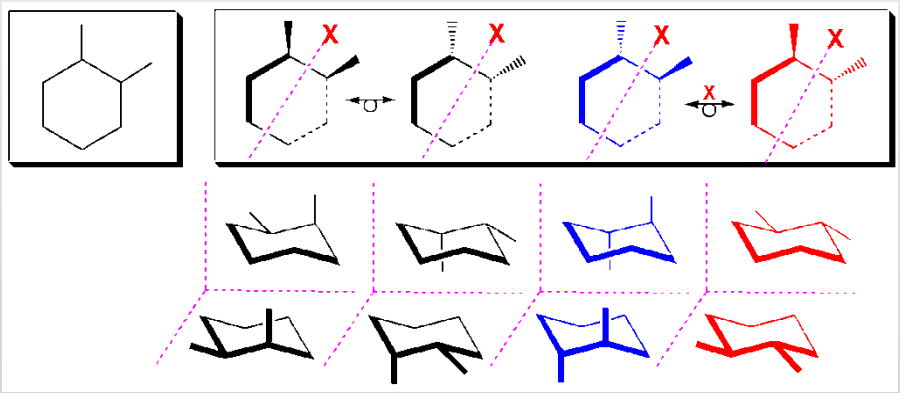


Cis-trans isomerism of cyclic compounds

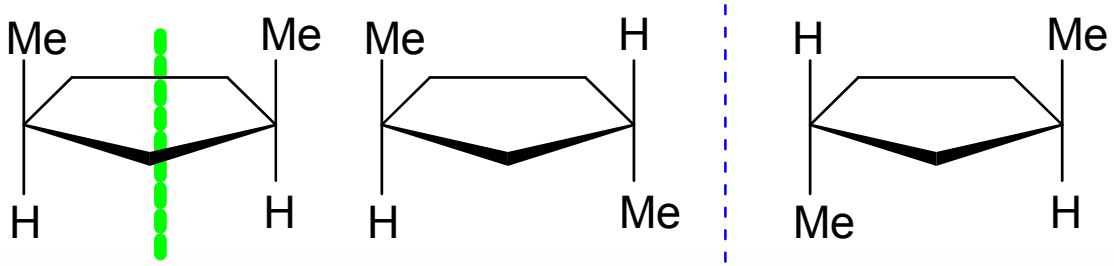
- 1,2-Substituted cyclopropane / cyclohexane



顺式异构体：
内消旋（分子具有镜面）
反式异构体：
对映异构



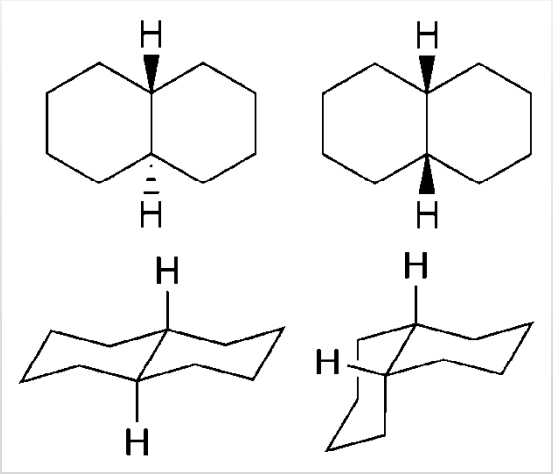
顺式异构体：
内消旋
反式异构体：
对映异构



cis, meso- *trans, dl pair*

1,3-dimethylcyclopentane

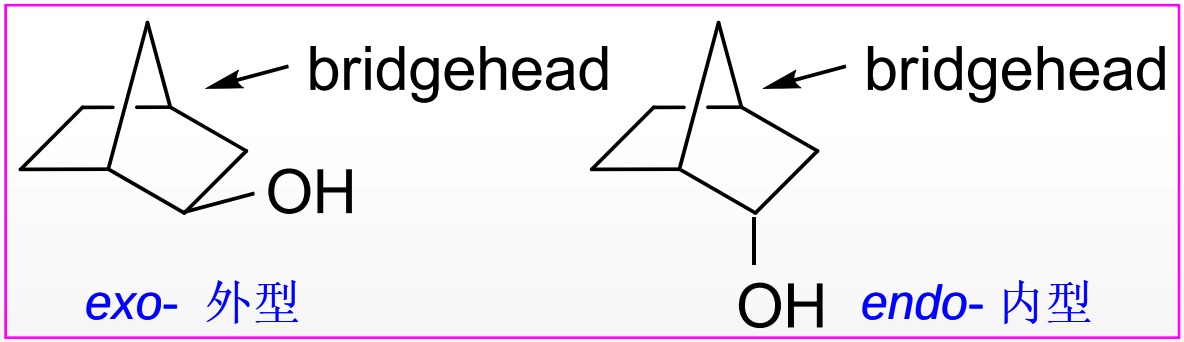
Fused and bridged bicyclic ring systems：

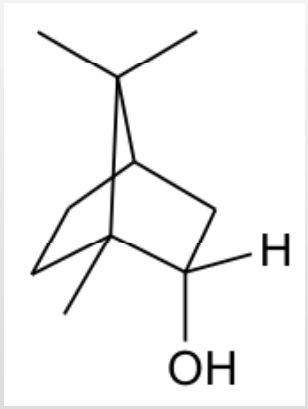


trans-decalin cis-decalin

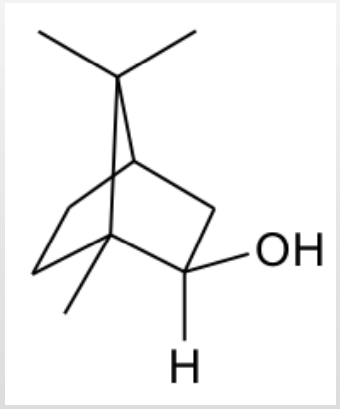
Prefix: *endo* and *exo* for bridged bicyclic isomers

2-Norborneol
（降冰片）

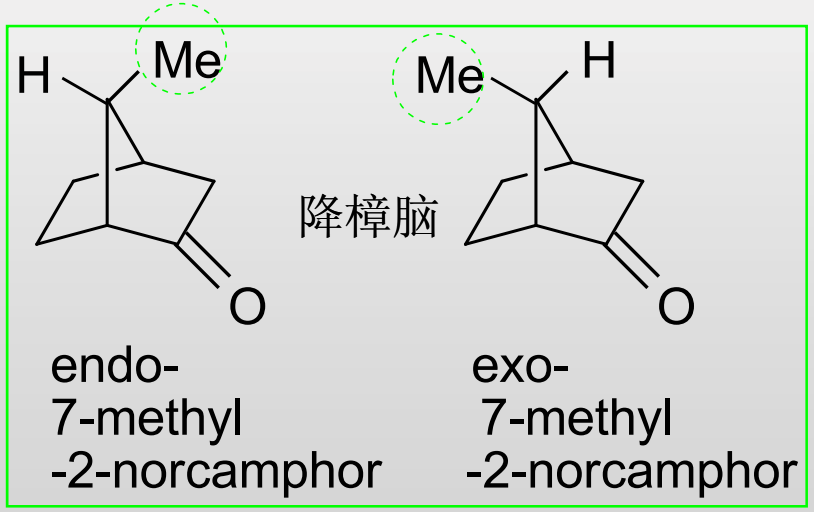




Borneol (*endo*-)
冰片



Isoborneol (*exo*-)
异冰片

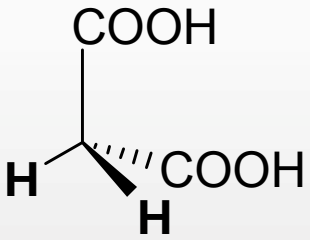


3.7 The stereochemical relationship: enantiotopic and diastereotopic 对映异位和非对映异位

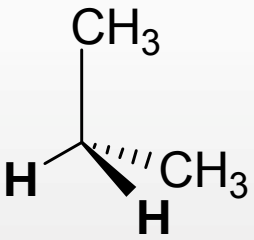
i. Enantiotopic and diastereotopic atoms and groups

CH_2Y_2:

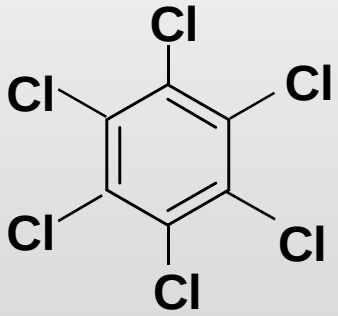
$CH_2(COOH)_2$



$CH_2(CH_3)_2$



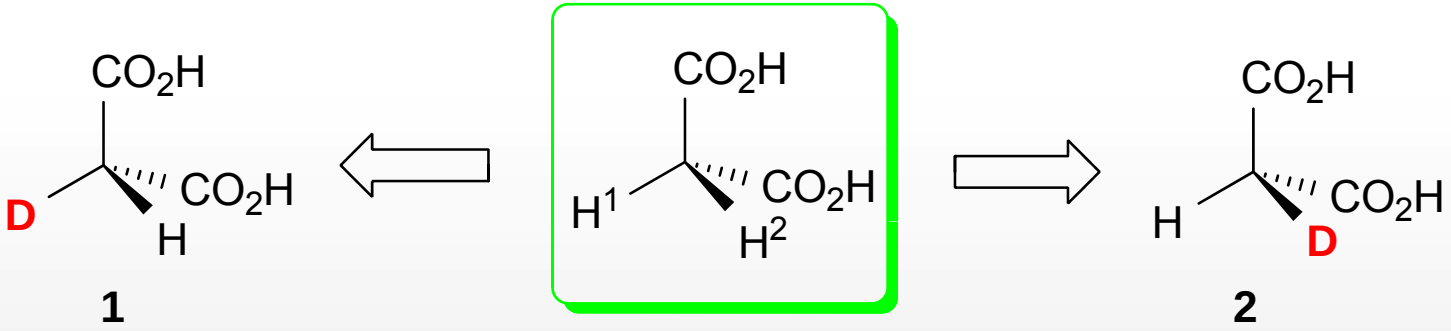
C_6Cl_6



$BrCH_2CH_2Br$

Homotopic groups in a chemical compound are equivalent groups.

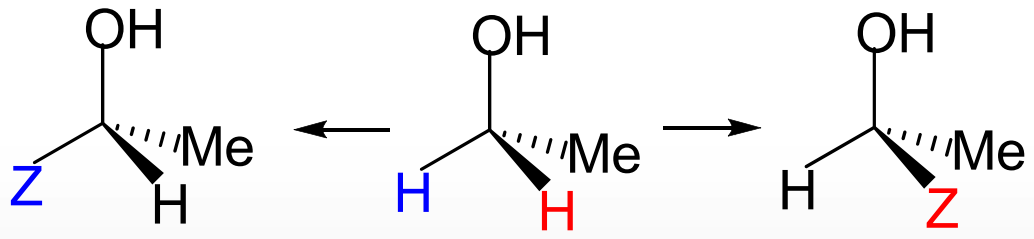
How to identify whether two atoms are equivalent?

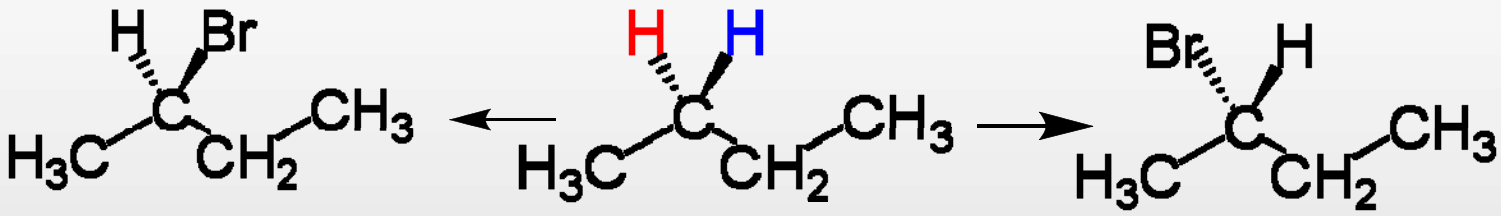


The new molecules created by this process are identical, the original atoms equivalent; otherwise not.

Two groups A and B are **homotopic** if the molecule remains the same (including stereochemically) when the groups are interchanged with the remaining parts of the molecule fixed. Homotopic atoms have the same chemical shift in an NMR spectrum: CH_4, CH_2Cl_2.

CH_3CH_2OH:

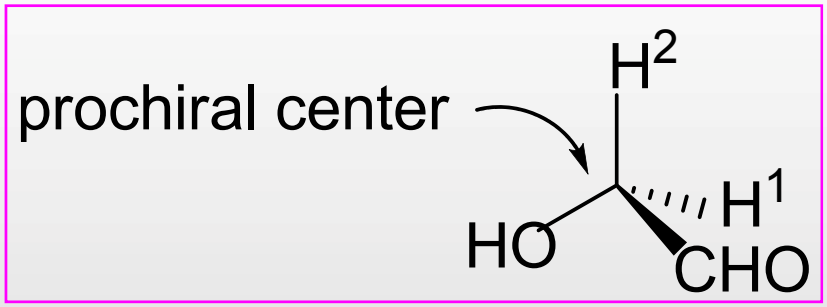




The stereochemical term **enantiotopic** refers to the relationship between two groups in a molecule which, if one or the other were replaced, would generate a chiral compound. The two possible compounds resulting from that replacement would be enantiomers.

♦ Any molecule: **CX2WY**, if neither W or Y is chiral, the X atoms or groups are always enantiotopic.

♦ The term **prochiral** is used for a compound or group that can be converted from achiral to chiral in a single step. 前手性

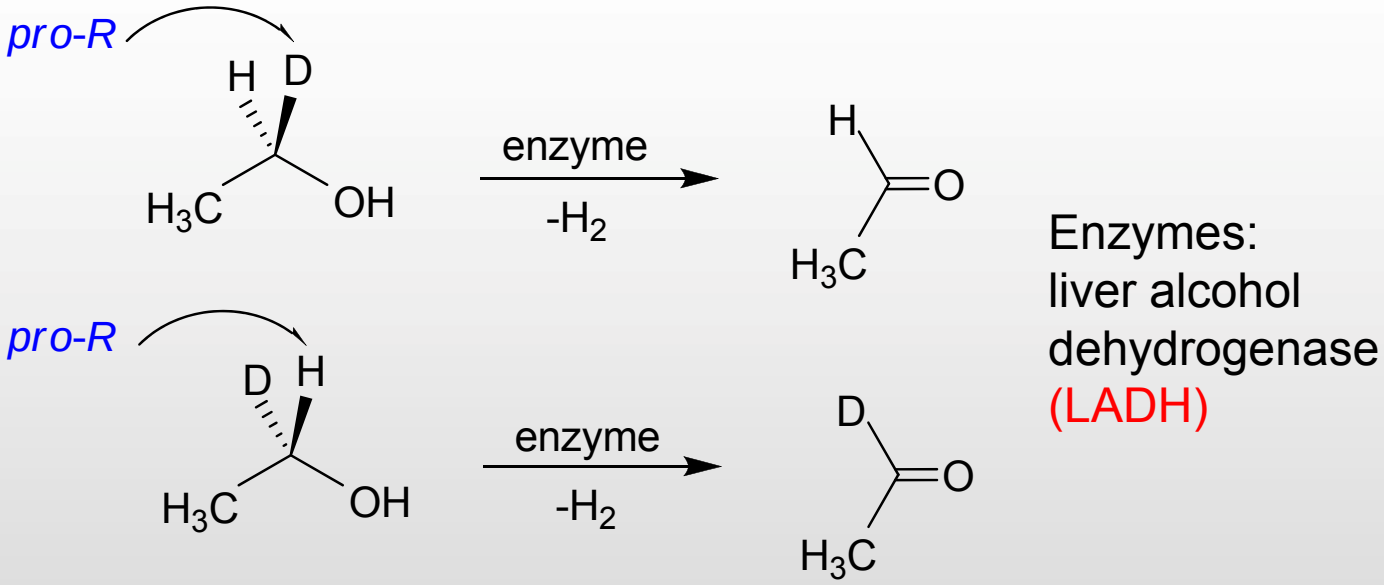


H^2 = *pro-S*
H^1 = *pro-R*

If two identical substituents are attached to an sp^3-hybridized atom, the descriptors *pro-R* and *pro-S* are used to distinguish between the two. Replacing the *pro-R* substituent results in an *R* chirality center at the original sp^3-hybridized atom, and *vice versa*.

DISCUSSION:

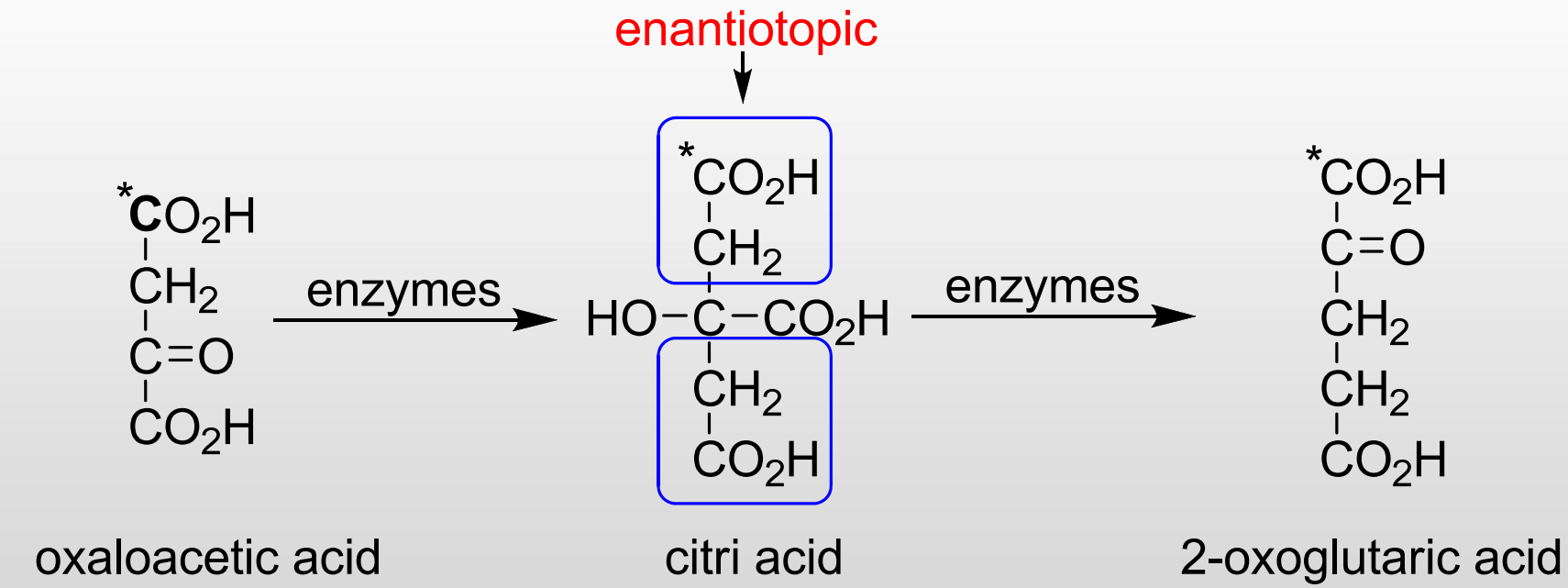
♦ Enantiotopic atoms or groups are equivalent in all chemical and physical respects **except toward a chiral regent**.



Enzymes:
liver alcohol dehydrogenase (LADH)

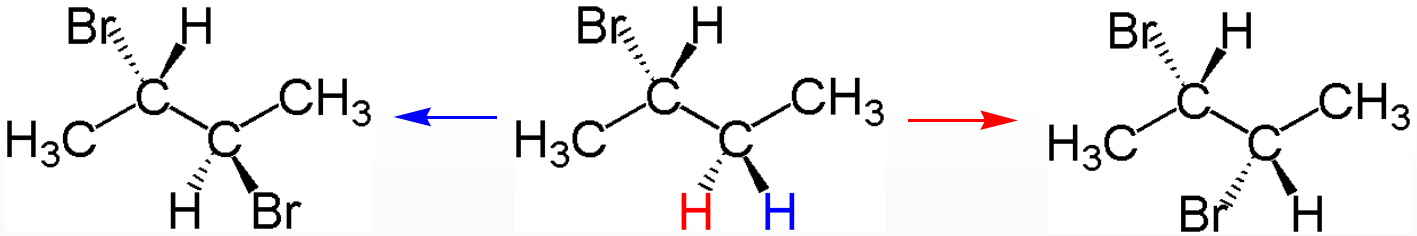
♦ **Enantiotopic pairs** of NMR-active nuclei are also indistinguishable by NMR and produce a single signal.

Krebs cycle, also known as the citric acid cycle, the tricarboxylic acid cycle (TCA cycle) is a series of enzyme-catalyzed chemical reactions of central importance in all living cells, especially those that use oxygen as part of cellular respiration.



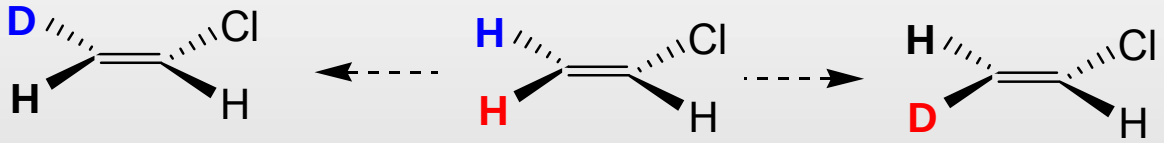
Krebs cycle 柠檬酸循环

Diastereotopic　非对映异位



(2*S*,3*R*)-2,3-dibromobutane　(*S*)-2-bromobutane　(*2S*,*3S*)-2,3-dibromobutane

(II)　(I)　(III)



(V)　(IV)　(VI)

vinyl chloride

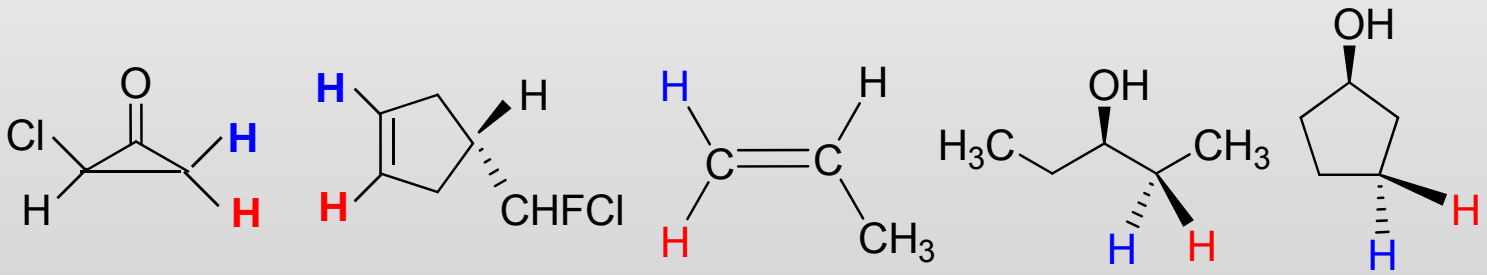
Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called diastereotopic.

DISCUSSION

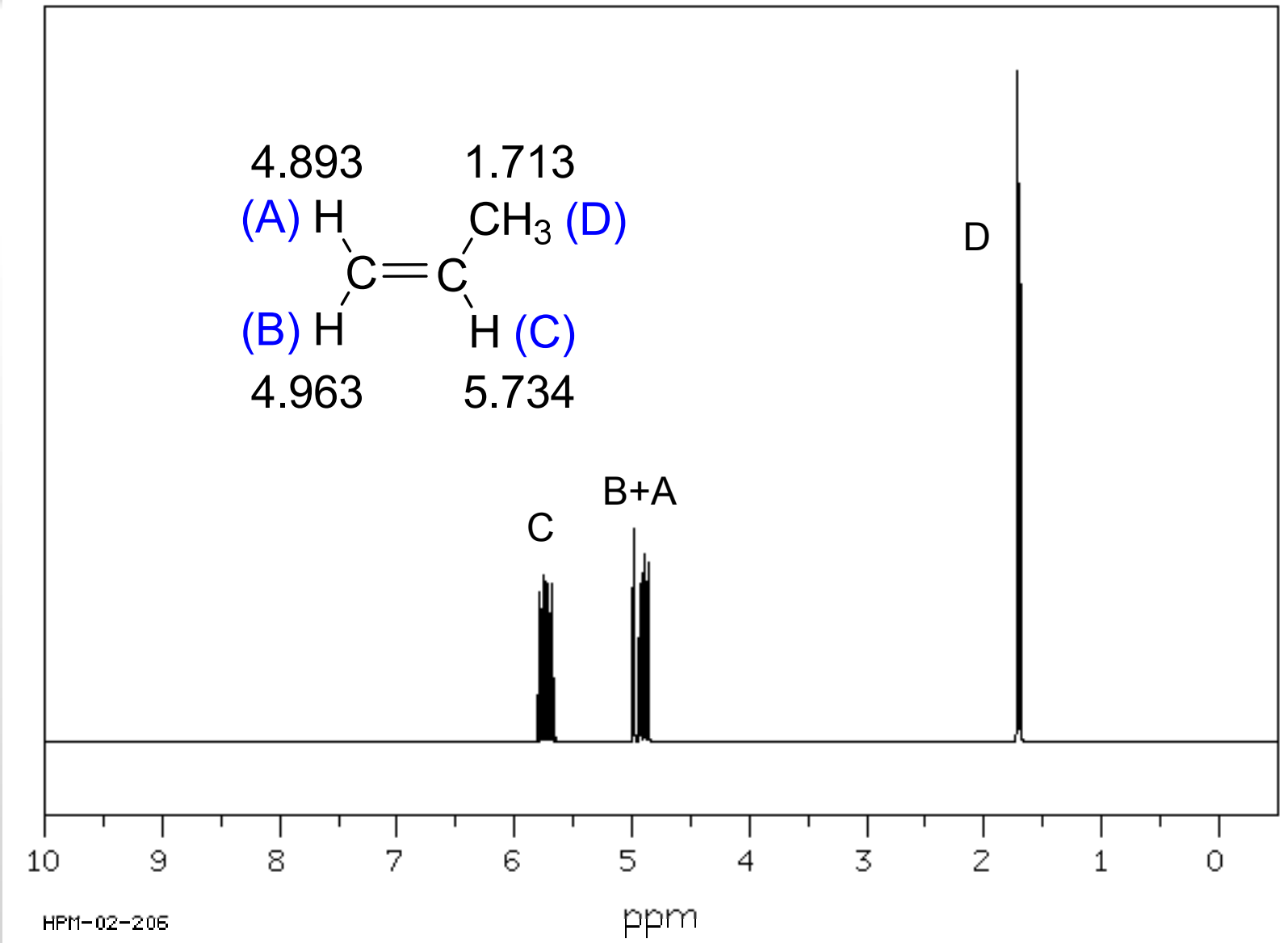
- **X** atoms or groups in **CX_2WY** are diastereotopic if either W or Y is chiral (I). Diastereotopic groups need not be attached to the same atom (II). Furthermore, diastereotopic groups also arise in achiral molecules (III, IV, V).

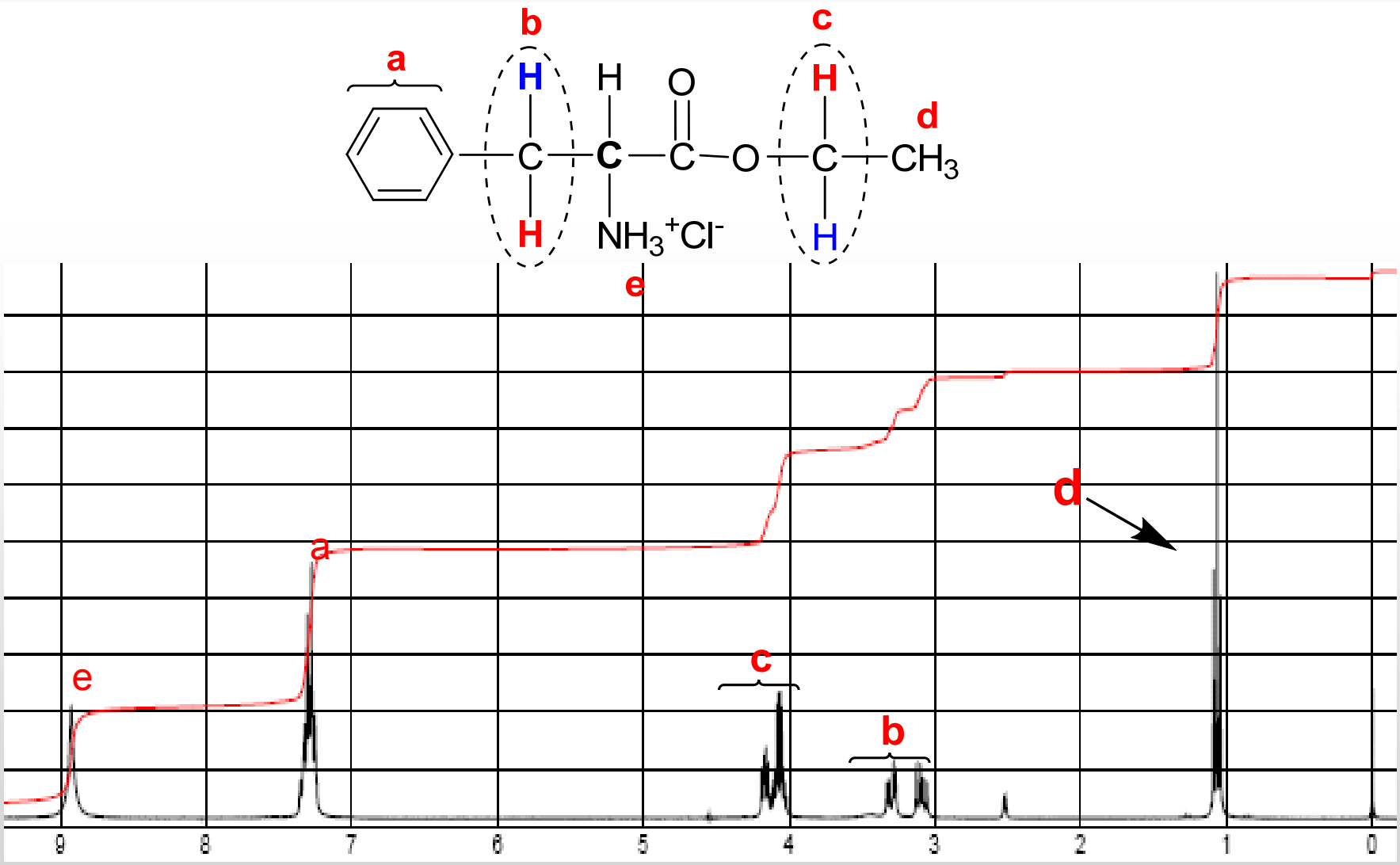
- **Diastereotopic atoms or groups are in different in any environment, chiral or achiral.**

- Diastereotopic hydrogens theoretically give different peaks and split each other, which are distinguishable in NMR. In practice, the NMR signals from diastereotopic protons are often found to be indistinguishable, but this merely because they are very close together.

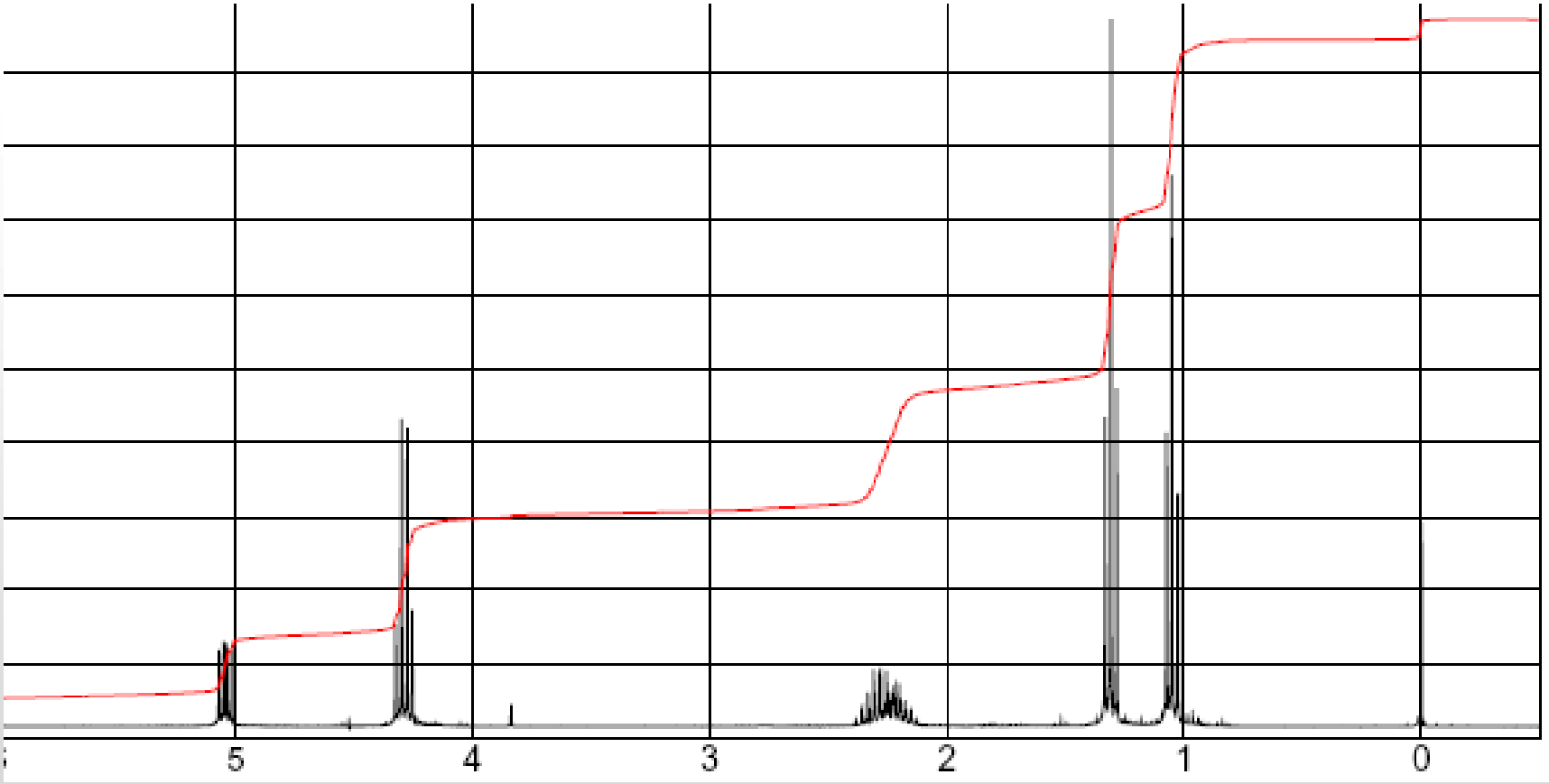


(I) (II) (III) (IV) (V)



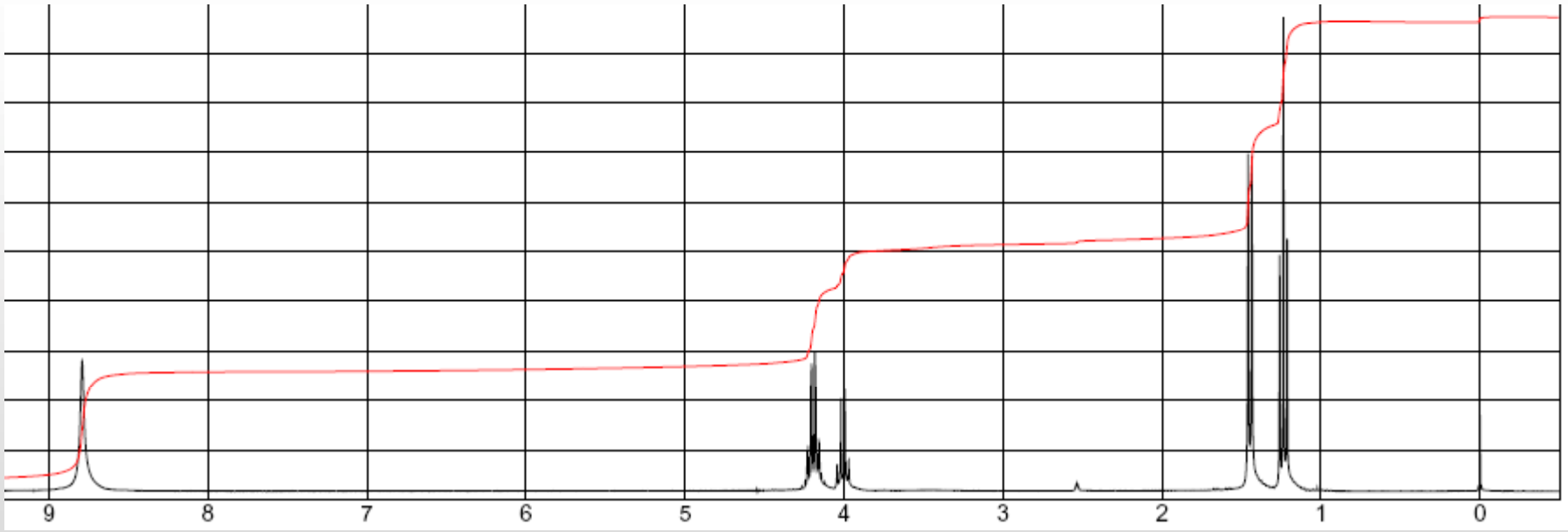


$CH_3CH_2\mathbf{C}H(NO_2)COOCH_2CH_3$



300 MHz ^{1}H-NMR spectrum of ethyl 2-nitrobutanoate in $CDCl_3$

$CH_3CH(NH_3^+)COOCH_2CH_3\ Cl^-$



300 MHz ^{1}H-NMR spectrum of ethyl alaninate hydrochloride in DMSO-d_6

ii. Enantiotopic and diastereotopic faces
对映异位/非对映异位面

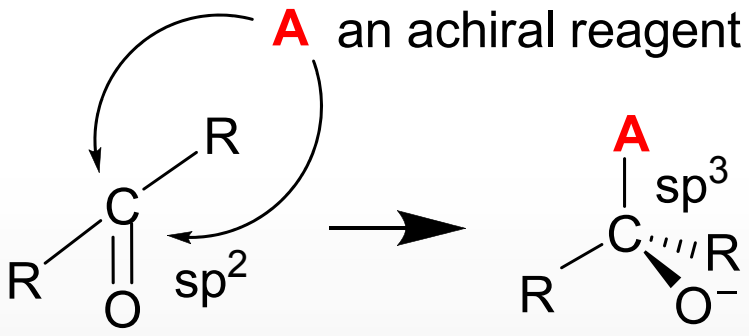
A trigonal planar sp^2-hybridized carbon:

♦ **Equivalent faces**

When an achiral nucleophile attacks acetone, both faces are identical and there is only one reaction product.

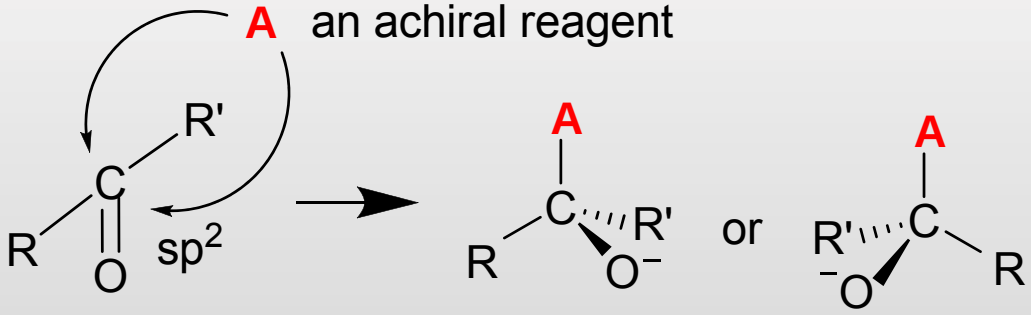
♦ **Enantiotopic faces**

When the nucleophile attacks butanone, the faces are not identical and a racemic product results.



formaldehyde or acetone

an sp^3 hybridized carbon

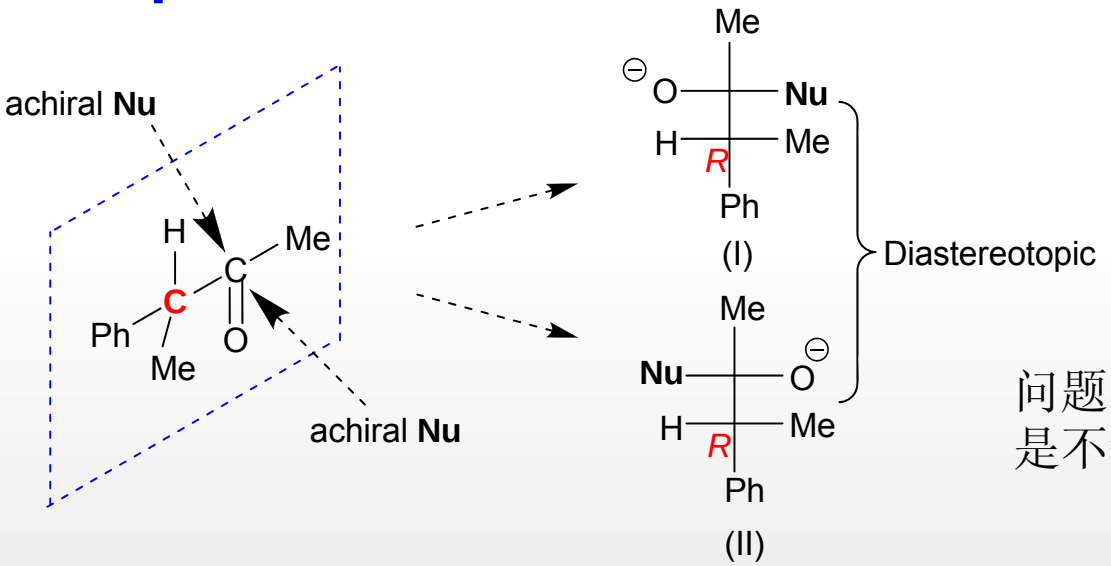


Butanone

a racemic mixture

If the nucleophile is a chiral molecule, which stereoisomers are formed?

Diastereotopic faces

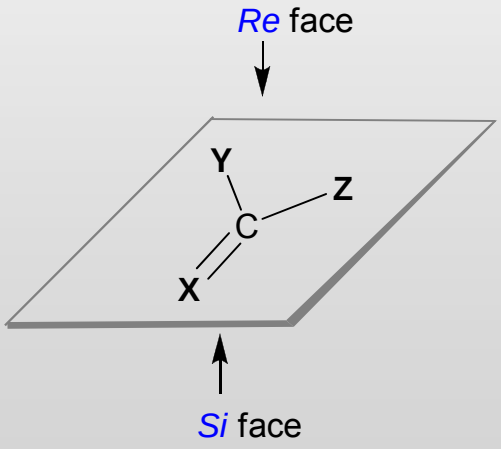


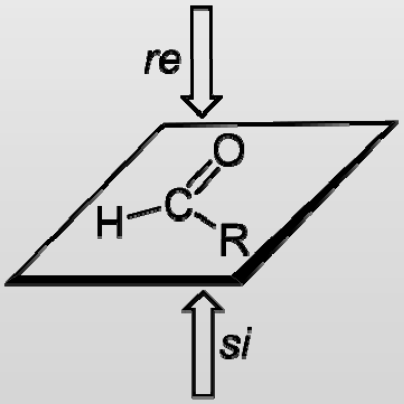
问题：I和II等量还是不等量？

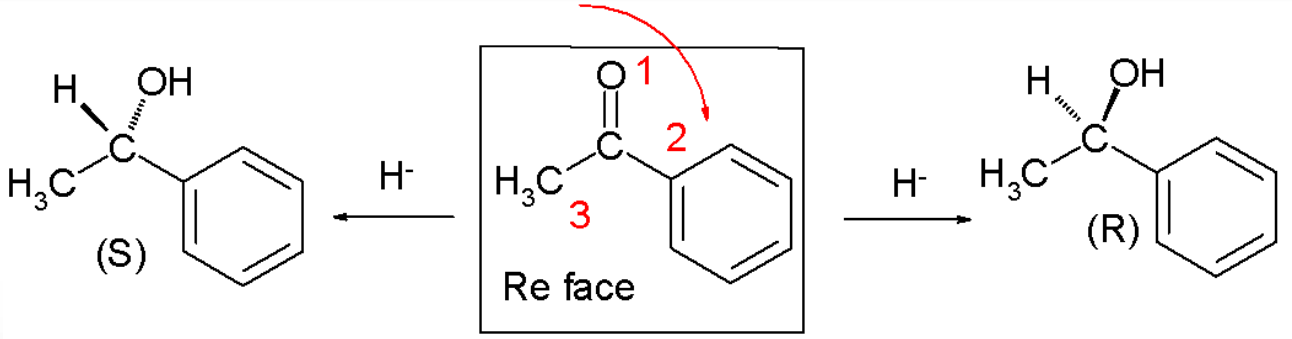
By the sequence rules, the order: X>Y>Z

Prochiral: an sp^2-hybridized carbon atom, with ***re*** and ***si*** faces.

前手性面

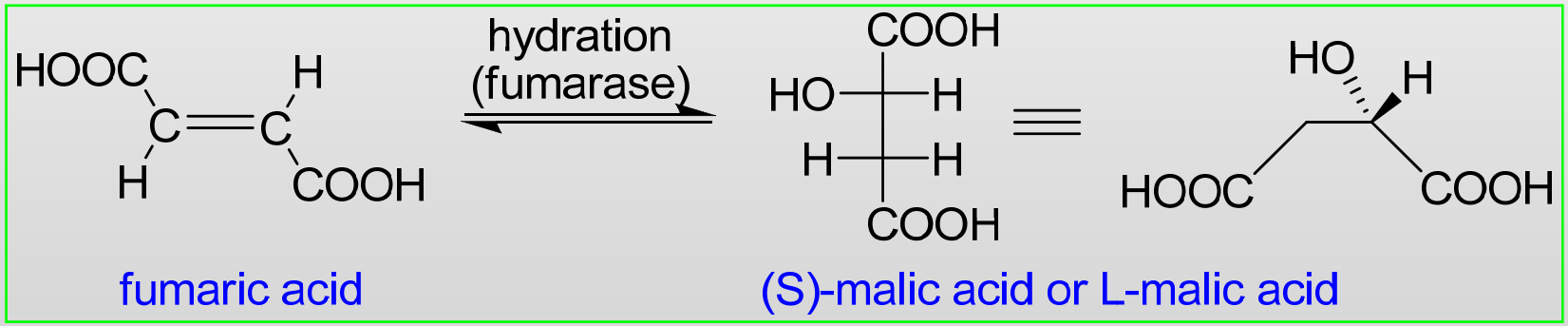






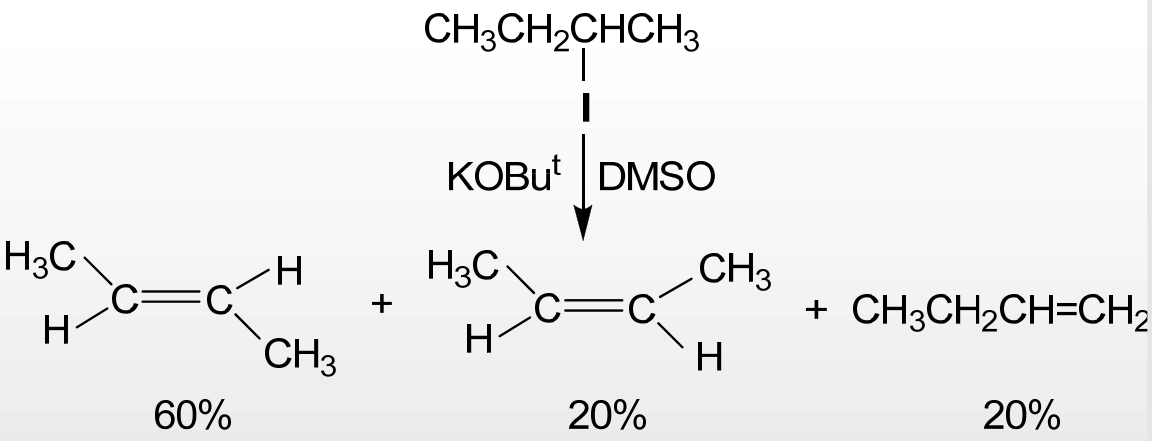
Hydride (H^-) addition in a reduction process of acetophenone

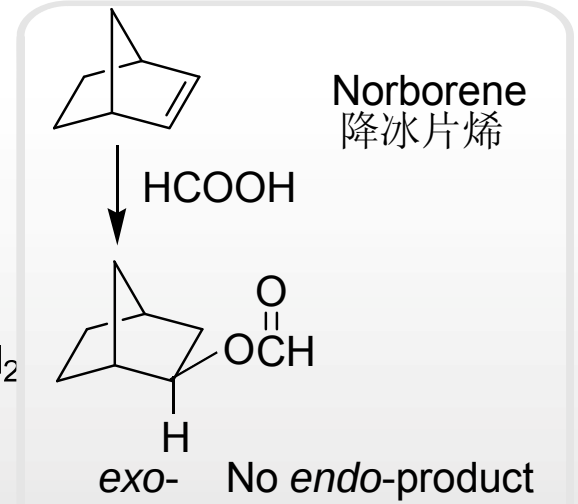
- Chiral reagents can discriminate between the prochiral faces, and can result in an optically active product.



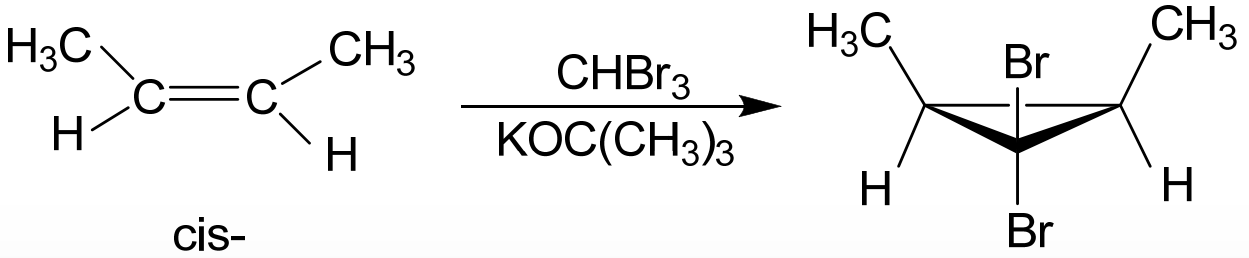
QUESTION: *re-re* addition or *si-si* addition?

3.8 Stereoselective and stereospecific reactions
立体选择性和立体专一性反应

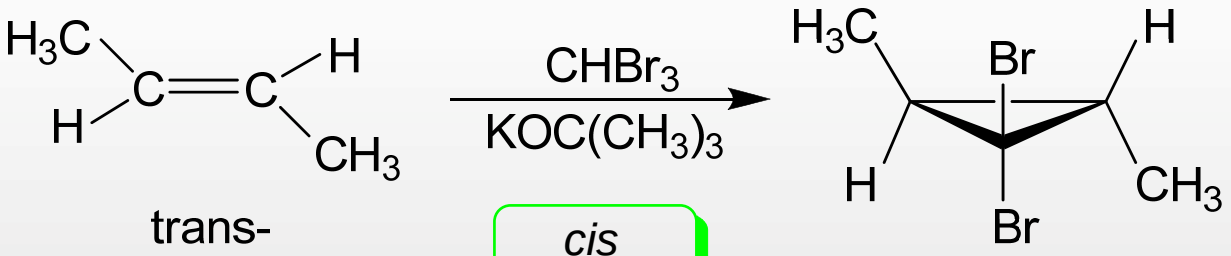




Stereoselectivity is the property of a chemical reaction that yields an unequal mixture of stereoisomers from a single reactant. Stereoselectivity may be partial, where the formation of one stereoisomer is favored over the other, or it may be total where only one stereoisomer is formed.



cis-



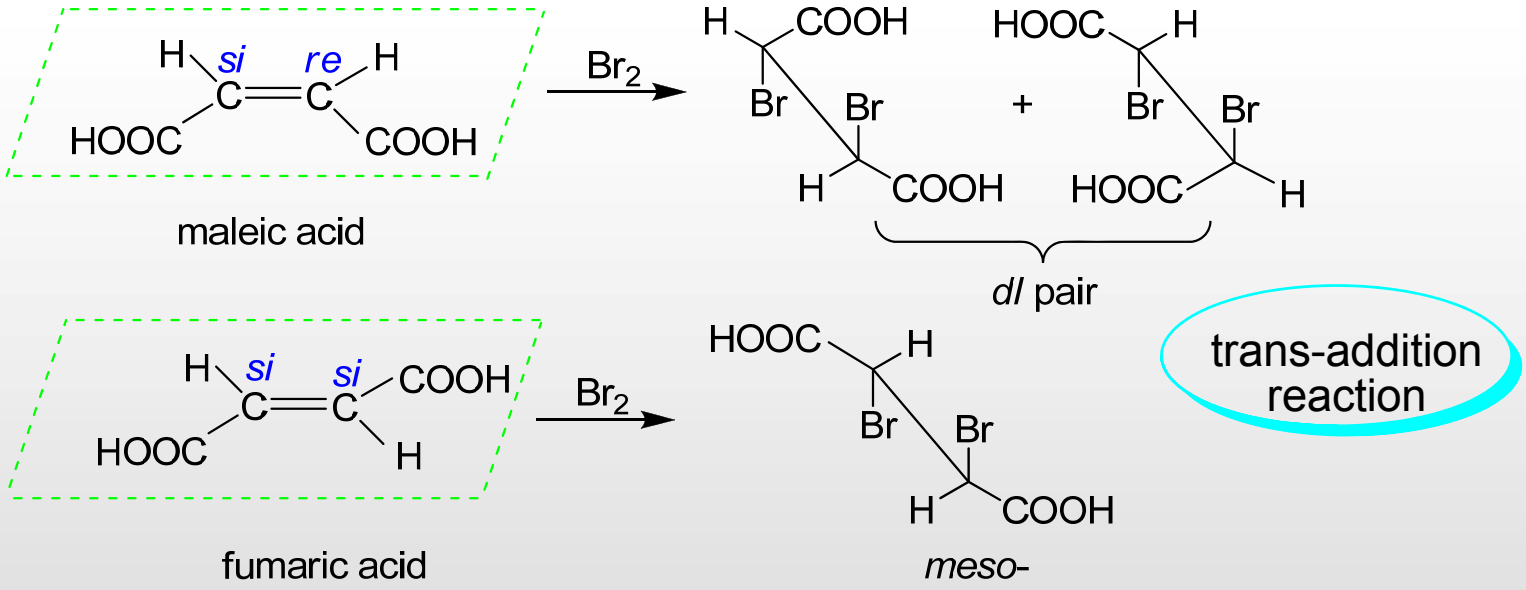
trans-

cis addition

Stereospecificity is the property of a reaction mechanism that yields different stereoisomeric reaction products from different stereoisomeric reactants, or which operates on only one (or a subset) of the stereoisomers. That is, a given isomer leads to one product while another stereoisomer leads to the opposite product.

DISCUSSION

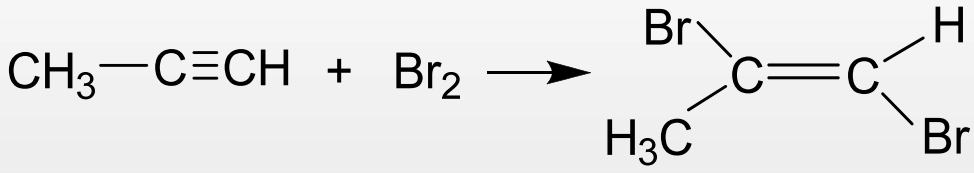
i. All stereospecific reactions are necessarily stereoselective, but the converse is not true.



If both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective but not stereospecific.

If more or less equal amounts of *dl* and *meso* forms were produced in each case, the reaction would be nonstereoselective. 非立体选择性

ii. **A stereospecific mechanism** *specifies* the stereochemical outcome of a given reactant, whereas **a stereoselective reaction** *selects* products from those made available by the same, non-specific mechanism acting on a given reactant. A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most stereoselective.



trans-1,2-dibromopropene
(predominated product)

iii. Stereospecificity is the property of a reaction mechanism, whereas stereoselectivity is the property of a reactant. 立体专一性描述反应机理的特性；立体选择性描述反应物的性质——按照相同的、非专一性机理优先形成某一立体异构产物

3.9 Asymmetric synthesis and the resolution of enantiomers

I. Asymmetric synthesis 不对称合成

Asymmetric synthesis (chiral synthesis, enantioselective synthesis or stereoselective synthesis) is organic synthesis which introduces one or more new and desired elements of chirality.

Three main approaches to asymmetric synthesis:

- **Chiral pool synthesis**
- **Chiral auxiliaries**
- **Asymmetric catalysis**

❑ **Asymmetric induction** What many strategies in chiral synthesis have in common is asymmetric induction. The aim is to make enantiomers into diastereomers, since diastereomers have different reactivity, but enantiomers do not. To make enantiomers into diastereomers, the reagents or the catalyst need to be incorporated with an enantiopure chiral center.

Enantiomeric excess

- **Enantiomeric excess** is defined as the absolute difference between the mole fraction of each enantiomer:

$ee = |F_+ - F_-|$ (where $F_+ + F_- = 1$)

- In practice, it is most often expressed as a ***percent enantiomeric excess***.

$ee = ([\alpha]_{abs}/[\alpha]_{max}) \times 100$

- The enantiomeric excess can be determined in another way if we know the amount of each enantiomer produced. If one knows the moles of each enantiomer produced then:

$ee = [(R - S)/(R + S)] \times 100$

- For example: a sample with 70% of *R* isomer and 30% of *S*

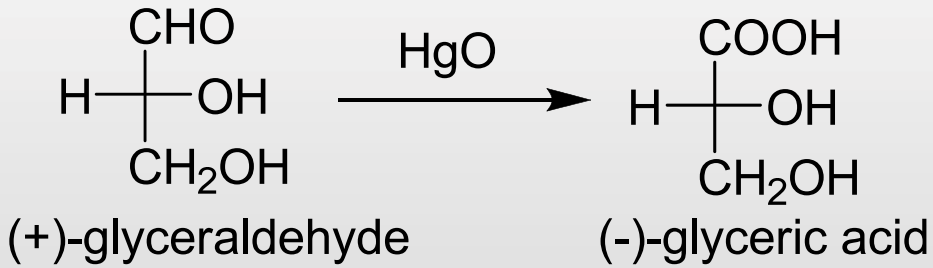
  ee = 40%

If given the enantiomeric excess of a mixture, the fraction of the major isomer, say *R*, can be determined using:

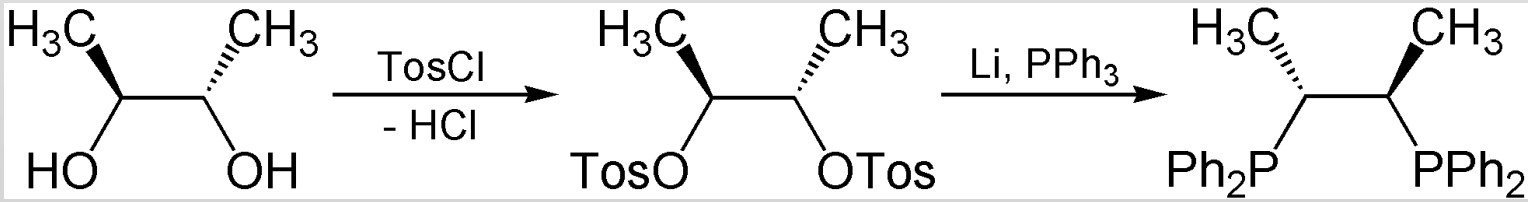
R = +ee/2 + 50% and the minor isomer *S* = –ee/2 + 50%

Chiral pool synthesis

Chiral pool synthesis is a strategy that aims to improve the efficiency of chiral synthesis. A chiral starting material is manipulated through successive reactions using achiral reagents which retain its chirality to obtain the desired target molecule. This is especially attractive for target molecules having the similar chirality to a relatively inexpensive naturally occurring building block such as a sugar or amino acid.



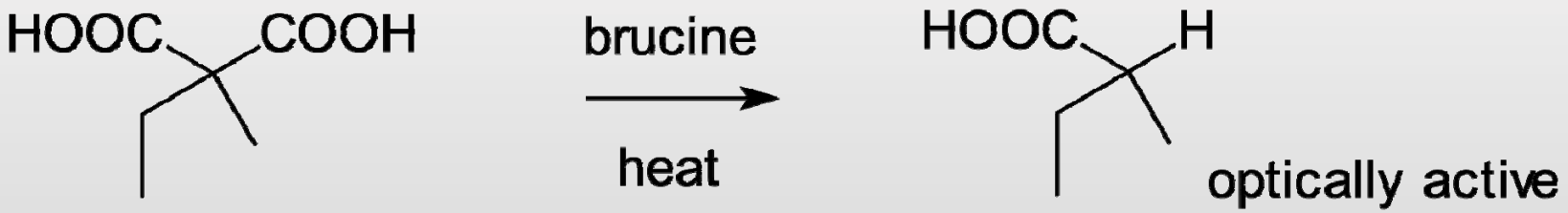
(+)-glyceraldehyde (-)-glyceric acid

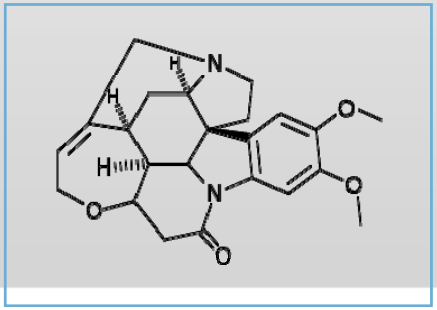


Chiral auxiliary 手性辅基/助剂

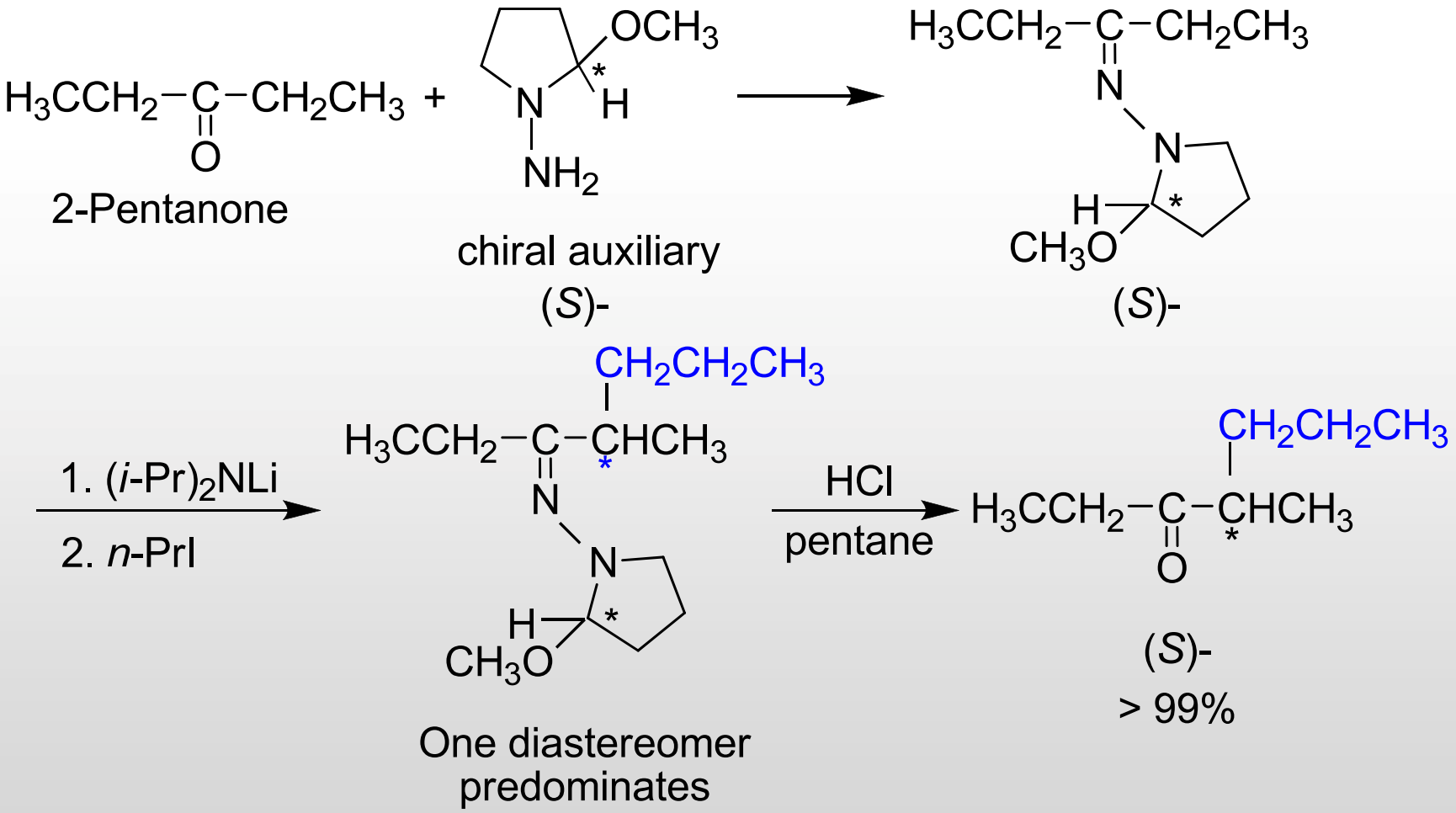
One asymmetric induction strategy is the use of a chiral auxiliary which forms an adduct to the starting materials and physically blocks the other trajectory for attack, leaving only the desired trajectory open. *Assuming the chiral auxiliary is enantiopure, the different trajectories are not equivalent, but diastereomeric.*

Willy Marckwald (1904): The oldest enantioselective synthesis is the enantioselective decarboxylation of the malonic acid.





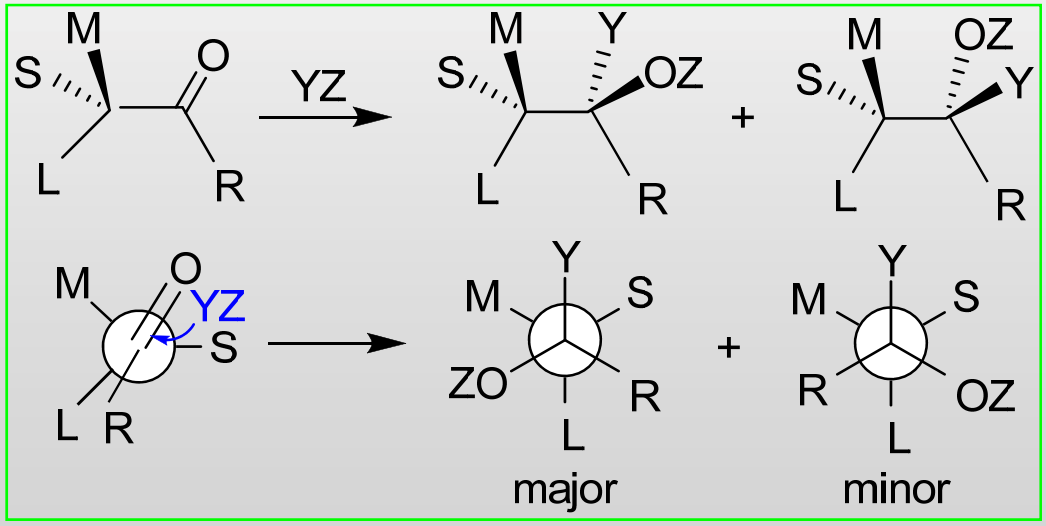
Brucine马钱子碱

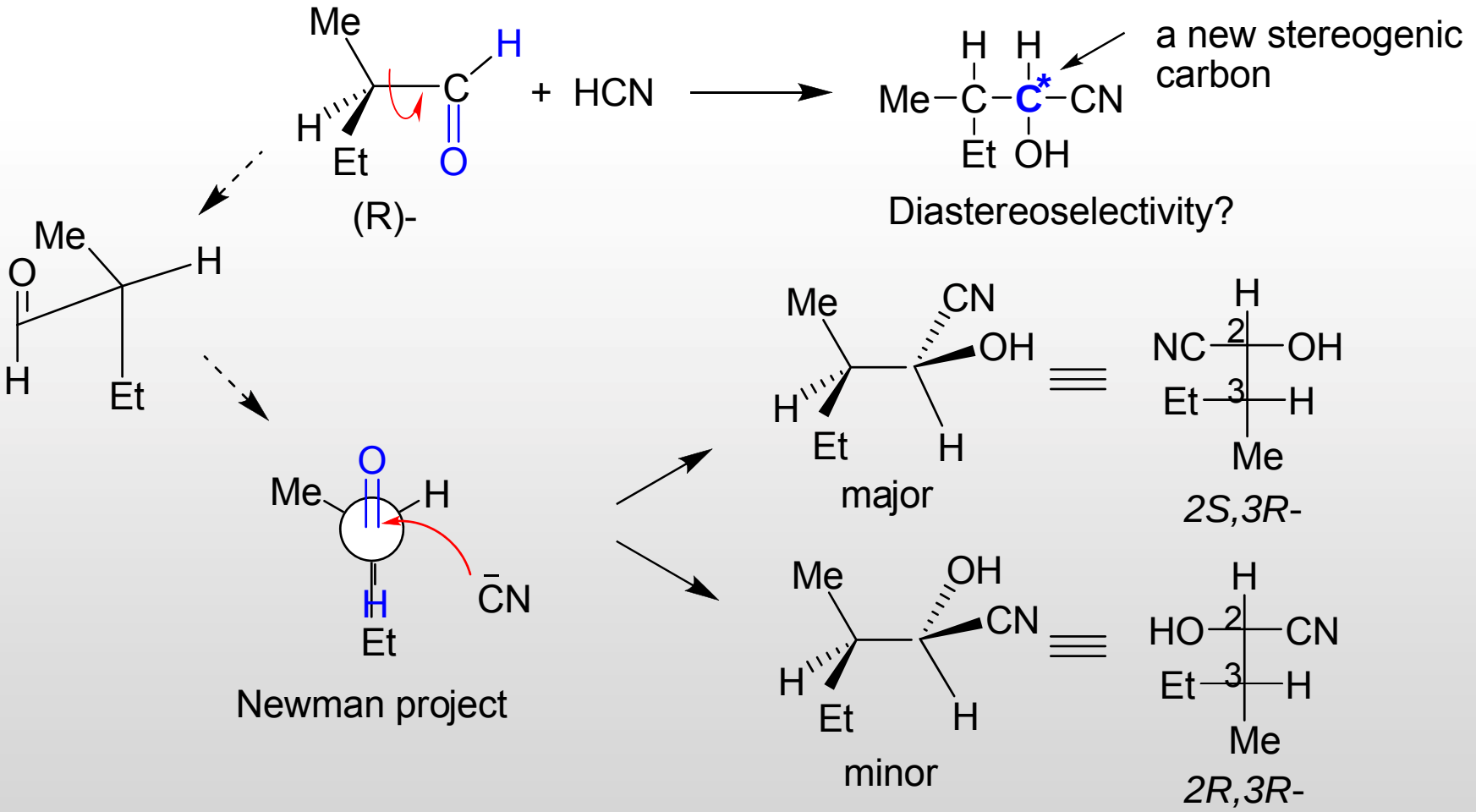


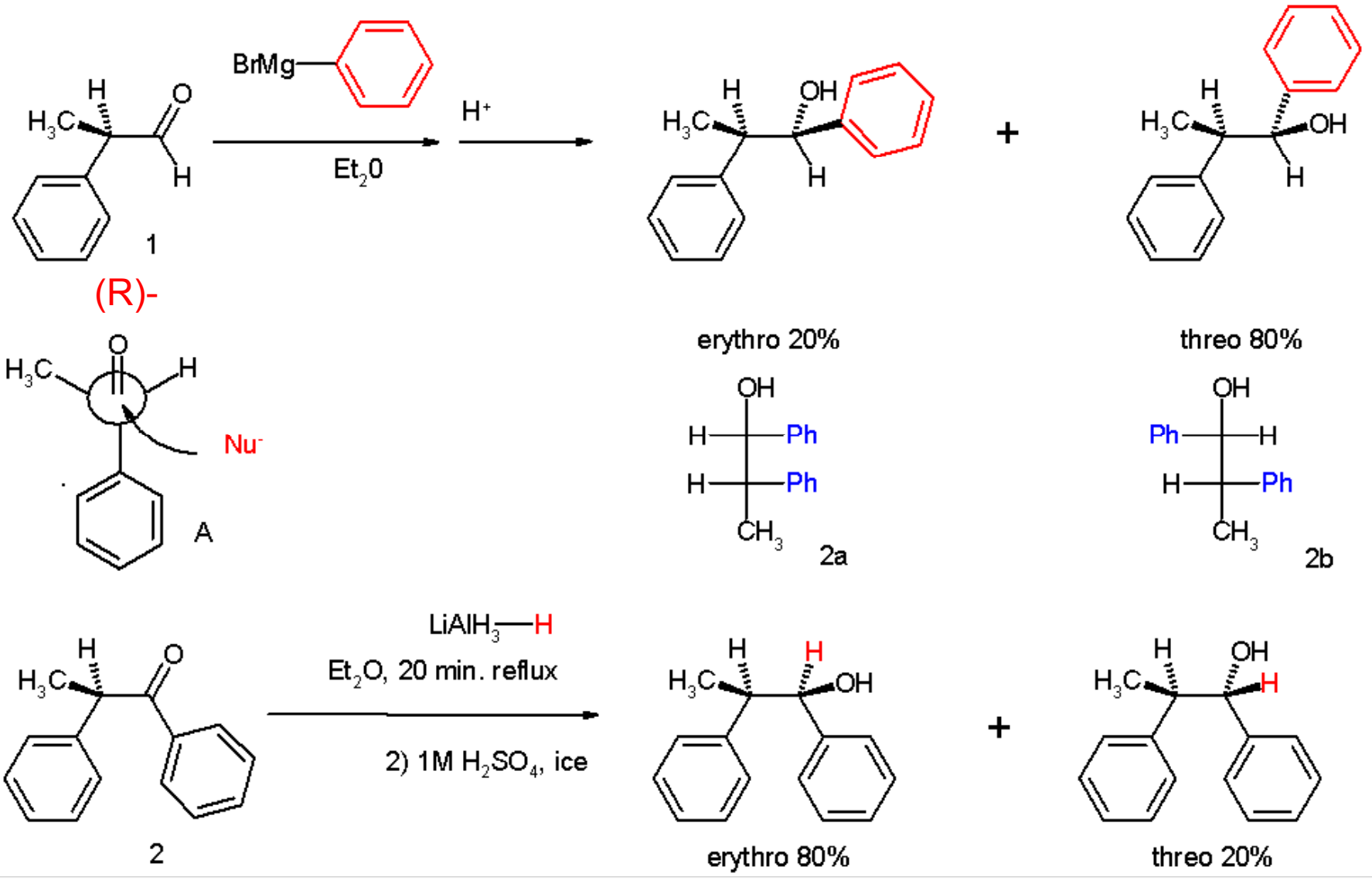
Carbonyl 1,2-asymmetric induction → Cram's rule
Diastereoselectivity 非对映选择性

In certain non-catalytic reactions that diastereomer will predominate which could be formed by the approach of the entering group from the least hindered side when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center.

The rule indicates that the presence of an asymmetric center in a molecule induces the formation of an asymmetric center adjacent to it based on steric hindrance.



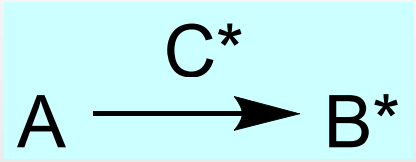


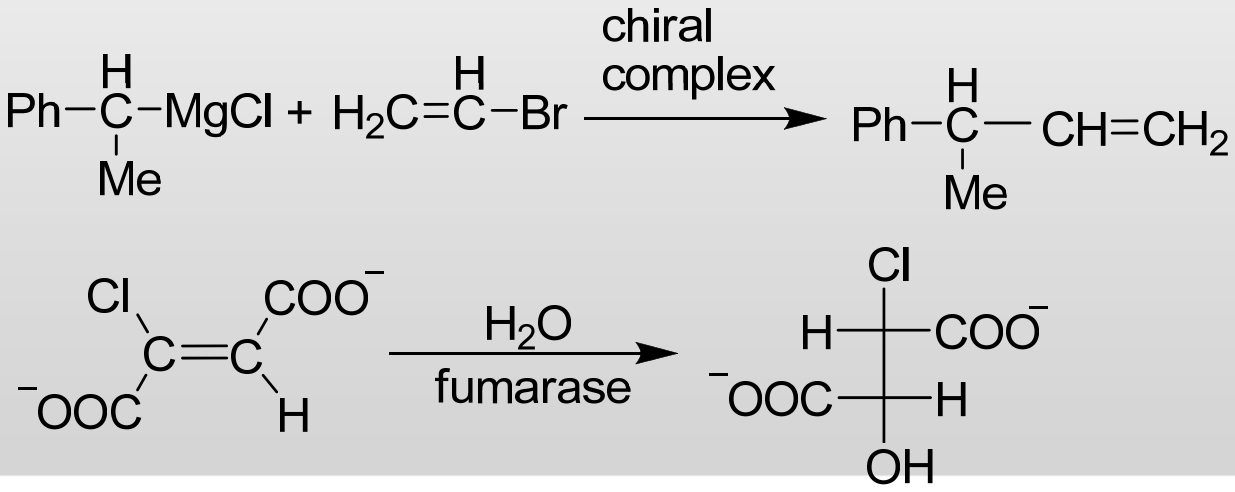


Asymmetric catalysis

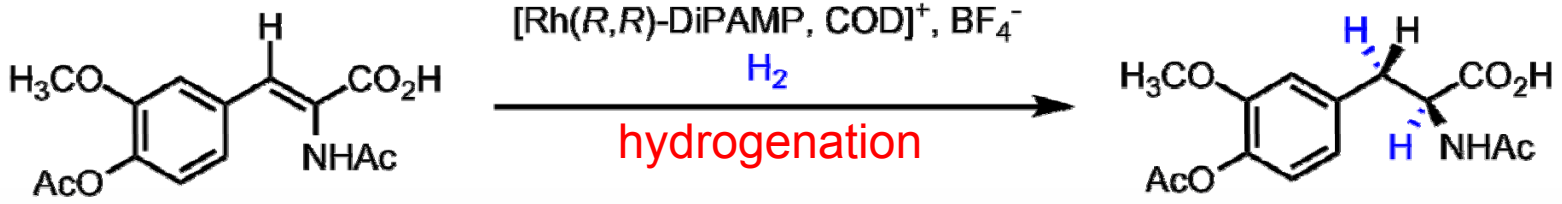
Small amounts of chiral, enantiomerically pure (or enriched) catalysts promote reactions and lead to the formation of large amounts of enantiomerically pure or enriched products. Mostly, three different kinds of chiral catalysts are employed:

- Metal complexes derived from chiral ligands
- Chiral organocatalysts (asymmetric organocatalysis, enantioselective organocatalysis)
- Biocatalysts

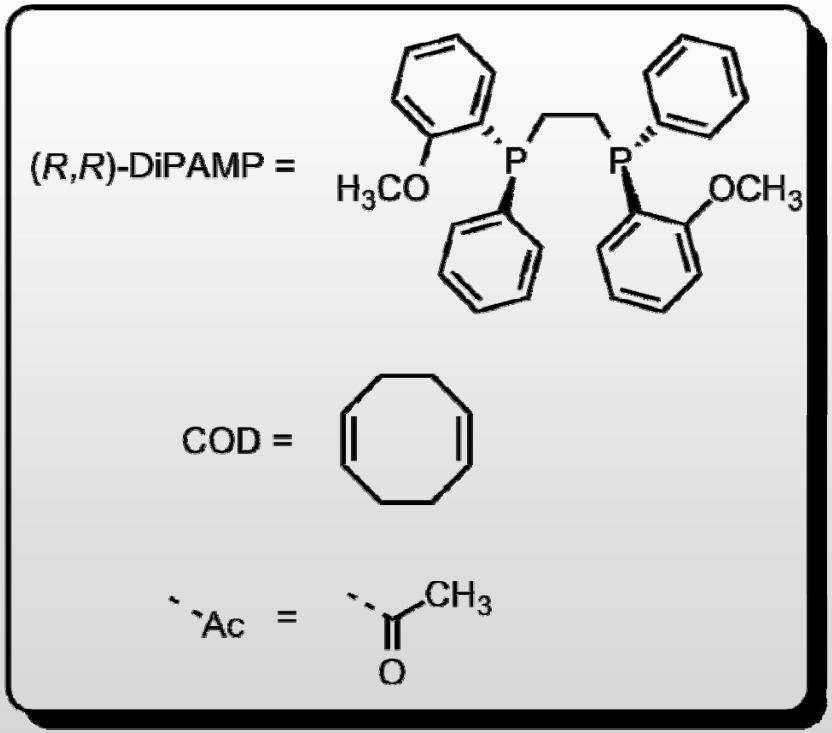




William S. Knowles (1968):

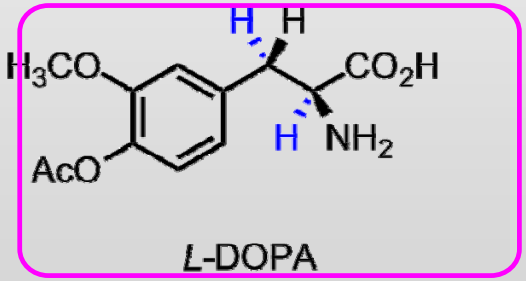


15%ee



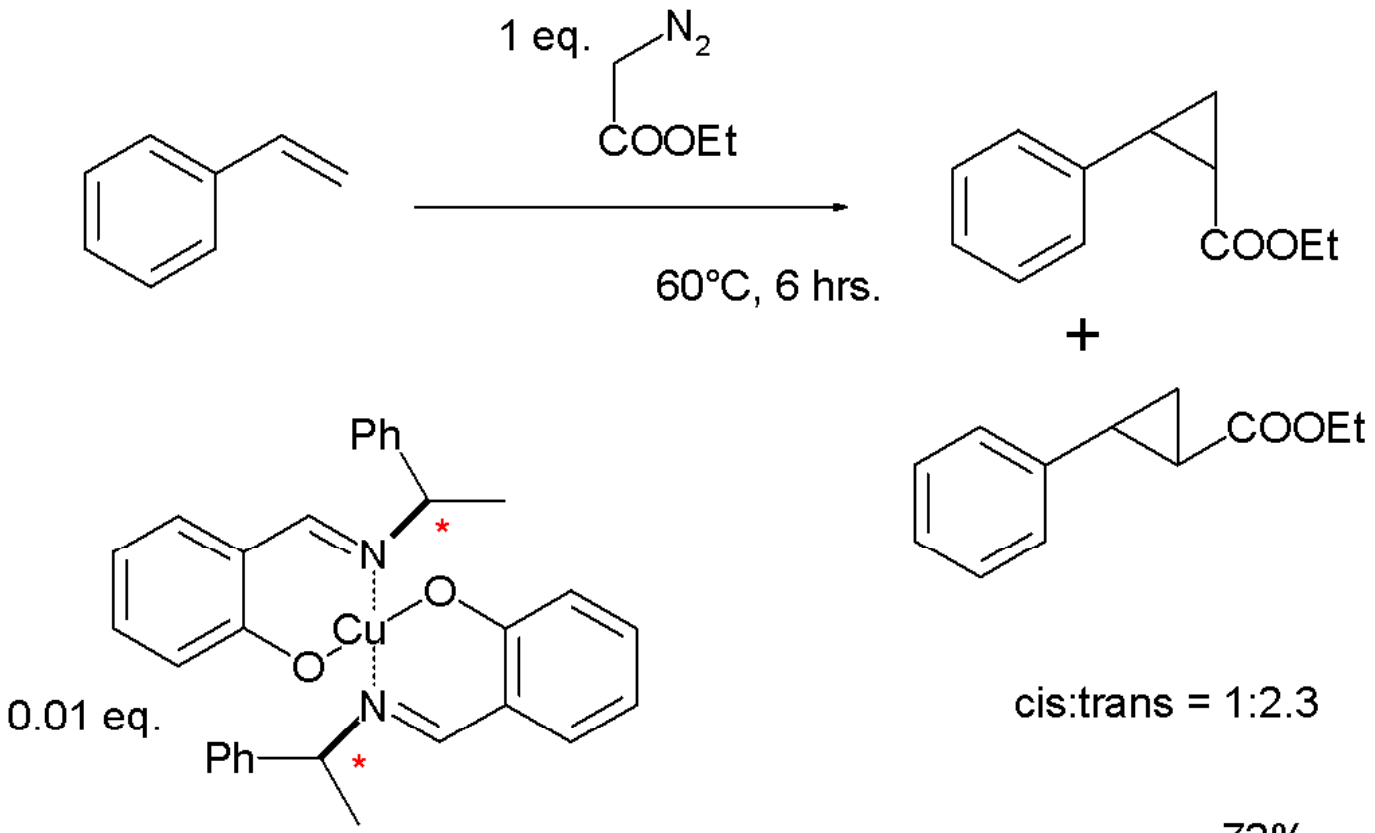
Used for the clinical treatment of Parkinson's disease (PD) and dopamine-responsive dystonia (DRD)

H_3O^+

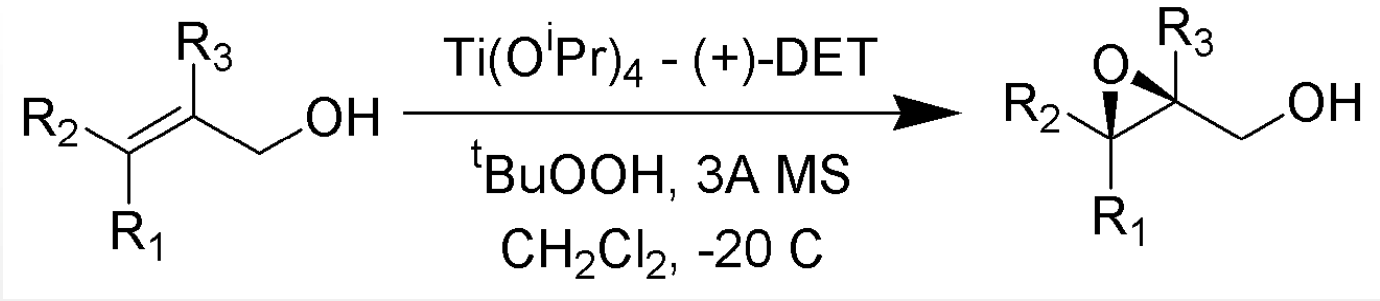


治疗帕金森症、多巴反应性肌张力失常

Ryoji Noyori (1968), independently published his chiral ligand for a cyclopropanation reaction of styrene.



Sharpless epoxidation reaction: an enantioselective chemical reaction to prepare 2,3-epoxyalcohols from primary and secondary allylic alcohols.

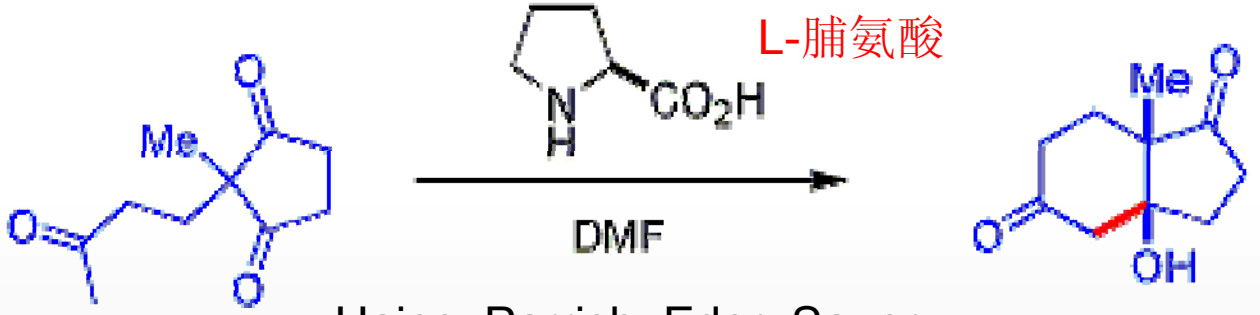


The oxidizing agent is *tert*-buty hydroperoxide. Enantioselectivity is achieved by a catalyst formed from titanium tetra(isopropoxide) and diethyl tartrate (DET). Only 5-10 mol% of the catalyst in the presence of 3Å molecular sieves (3Å MS) is necessary.

Epoxides can be easily converted into dialcohols, aminoalcohols or ethers.

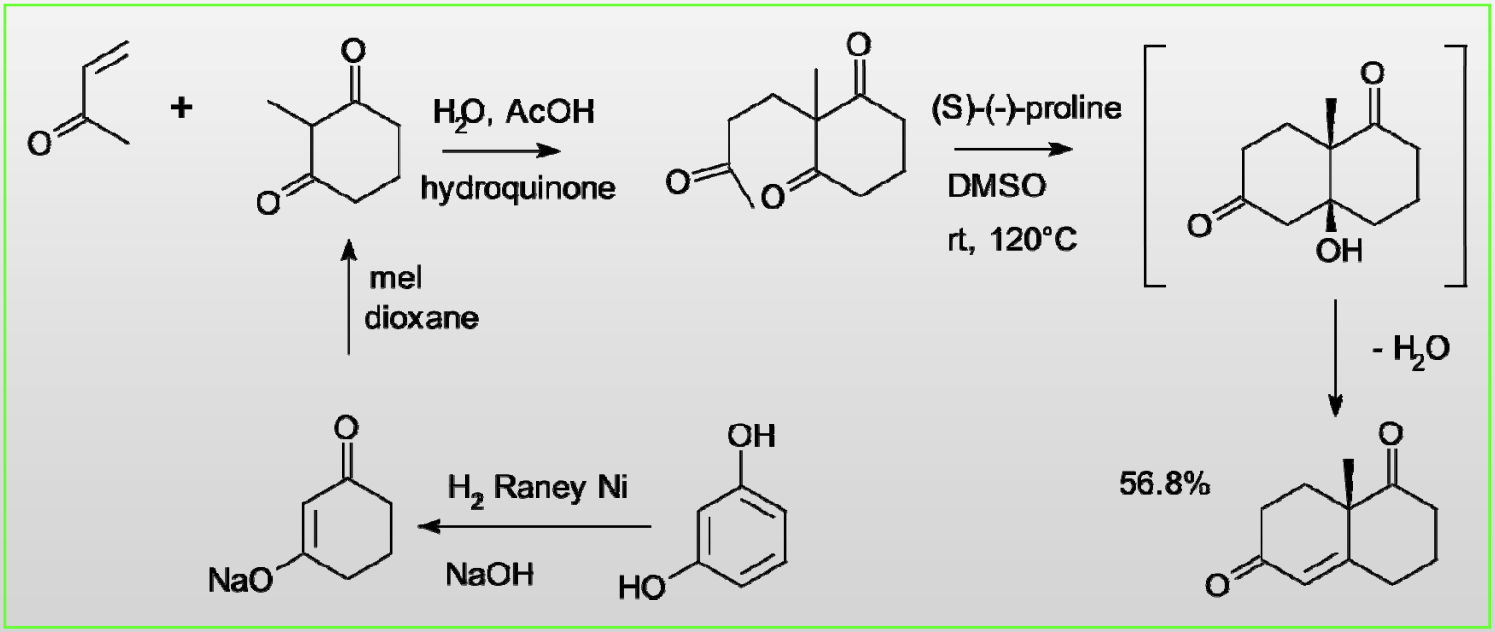
W.S. Knowles, R. Noyori, Sharpless: Nobel Prize in Chemistry(2001)

Asymmetric Organocatalysis



Hajos–Parrish–Eder–Sauer–Wiechert reaction (1970s)

99%, 93% ee

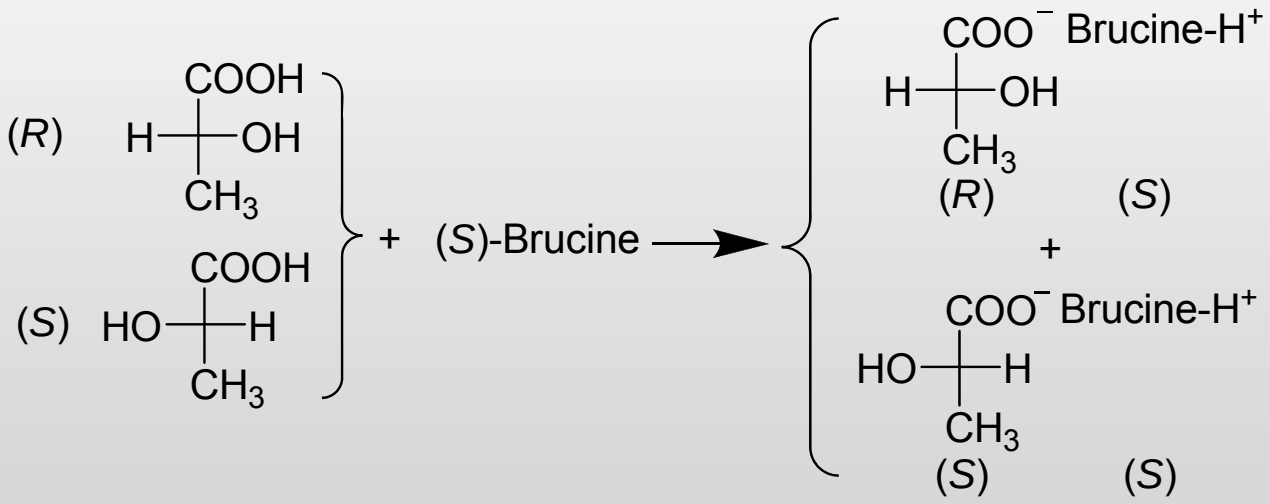


II. The resolution of enantiomers (optical resolution)

a. Resolution by crystallization

Pasteur (1849): the manual separation of left-handed and right-handed tartaric acid crystals

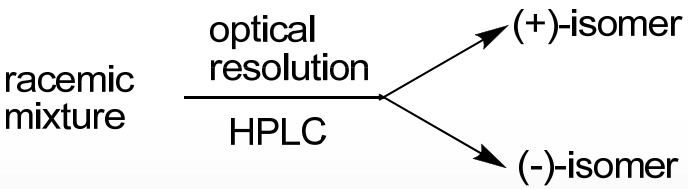
b. Using chiral resolving agents

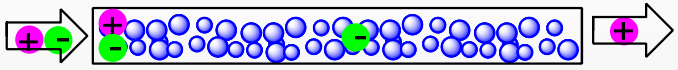


Brucine 二甲马钱子碱

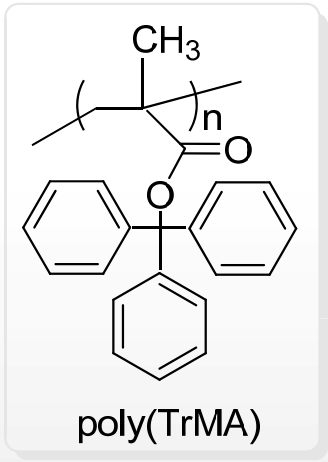
Louis Pasteur (27 Dec.1822–28 Sep. 1895)

c. Optical resolution based on HPLC

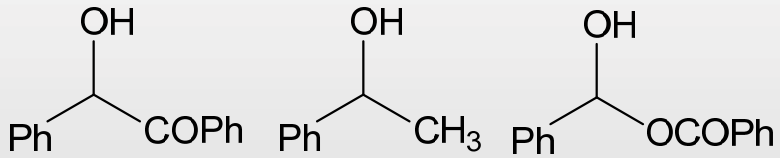


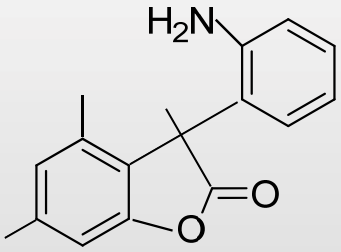


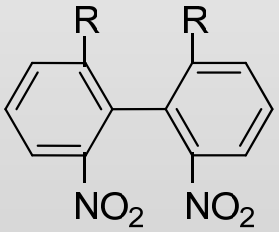
Chiral Stationary Phases
(CSPs)

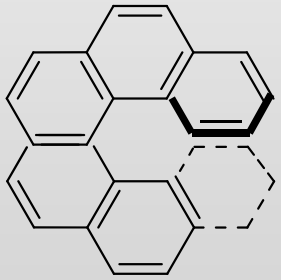


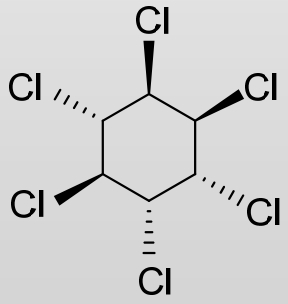
poly(TrMA)











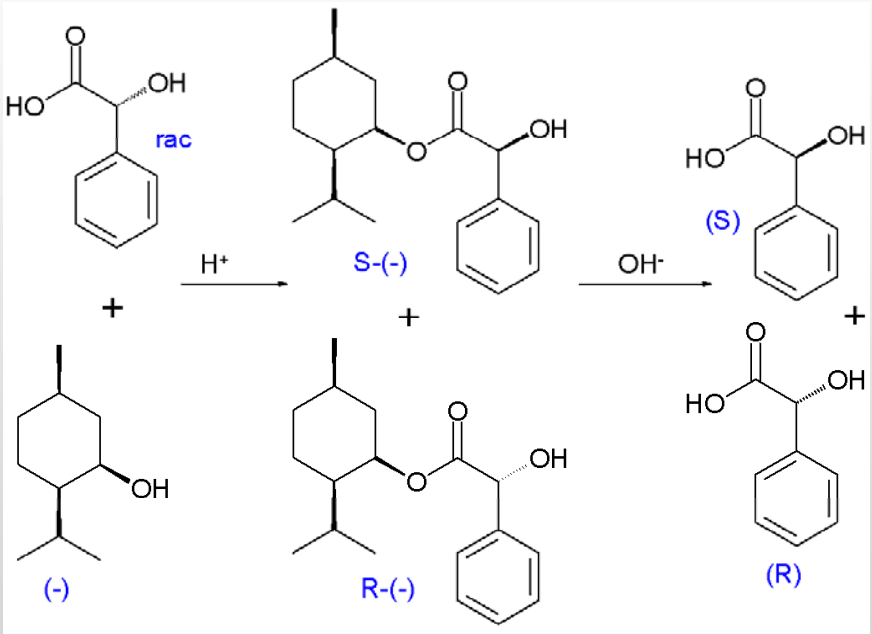
d. Kinetic resolution 动力学拆分

In **kinetic resolution** two enantiomers show different reaction rates in a chemical reaction thereby creating an excess of the less reactive enantiomer. This excess goes through a maximum and disappears on full completion of the reaction.

Marckwald and McKenzie (1899):

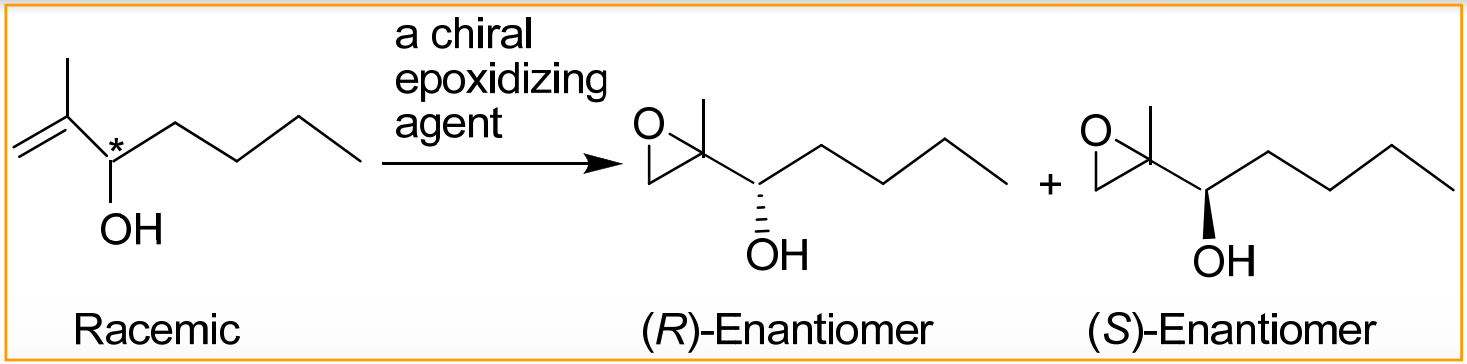
mandelic acid

(-)-menthol
薄荷醇

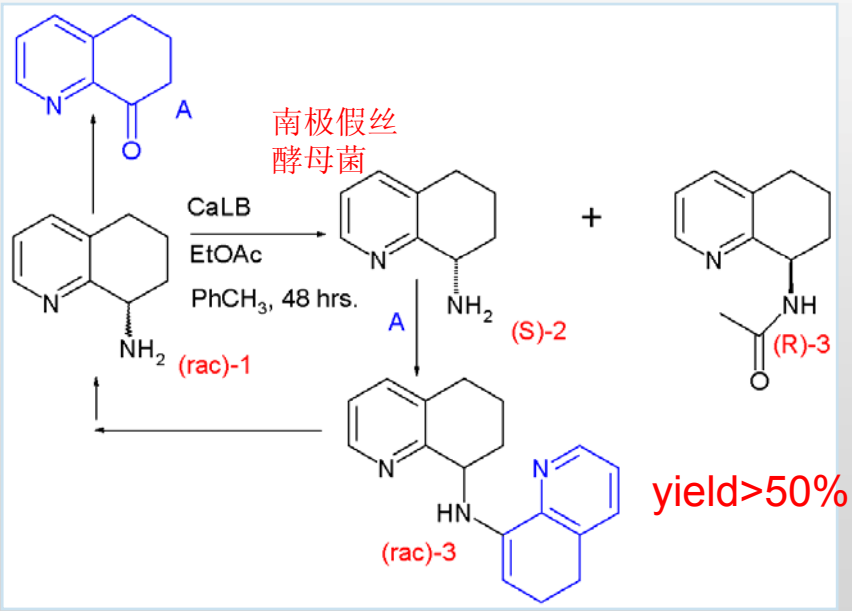


Diastereomeric esters

The (R)-mandelic acid displays the higher reaction rate and, with incomplete conversion, the reaction mixture becomes enriched in (S)-mandelic acid. Full hydrolysis of the incomplete esterification mixture gives an excess of (R)-mandelic acid.



One enantiomer was converted to the epoxide and the other was not, the rate ratio being more than 100.



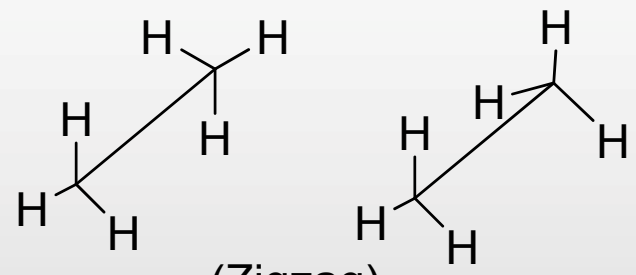
The biocatalytic acetylation of a racemic 8-amino-tetrahydroquinoline (1) with Candida antarctica Lipase B: *The enzyme only converts the R-enantiomer and in regular kinetic resolution a 50:50 mixture of (S)-amine (2) is retained and (R)-acetamide (3) obtained.*

3.10 Conformational analysis

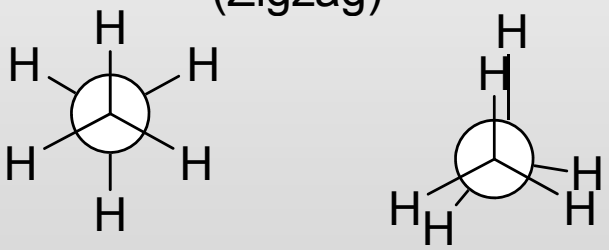
I. Linear alkane conformation

- **Conformational isomerism** is a form of stereoisomerism in which molecules with the same configuration exist as different conformational isomers or conformers in 3-D due to rotations about one or more σ bonds.

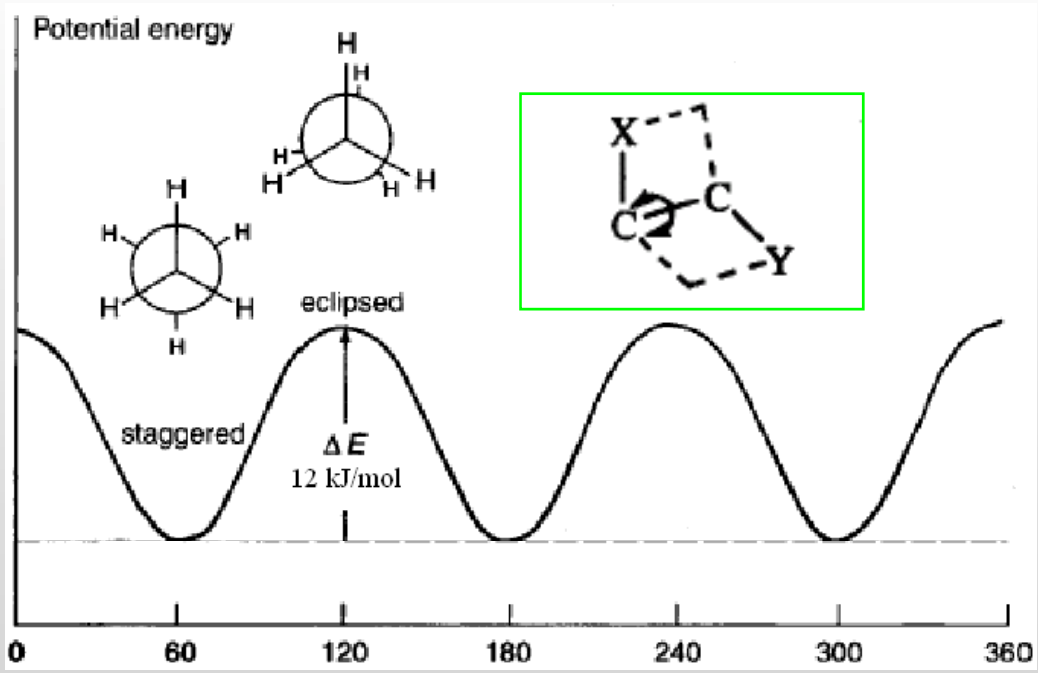
staggered eclipsed



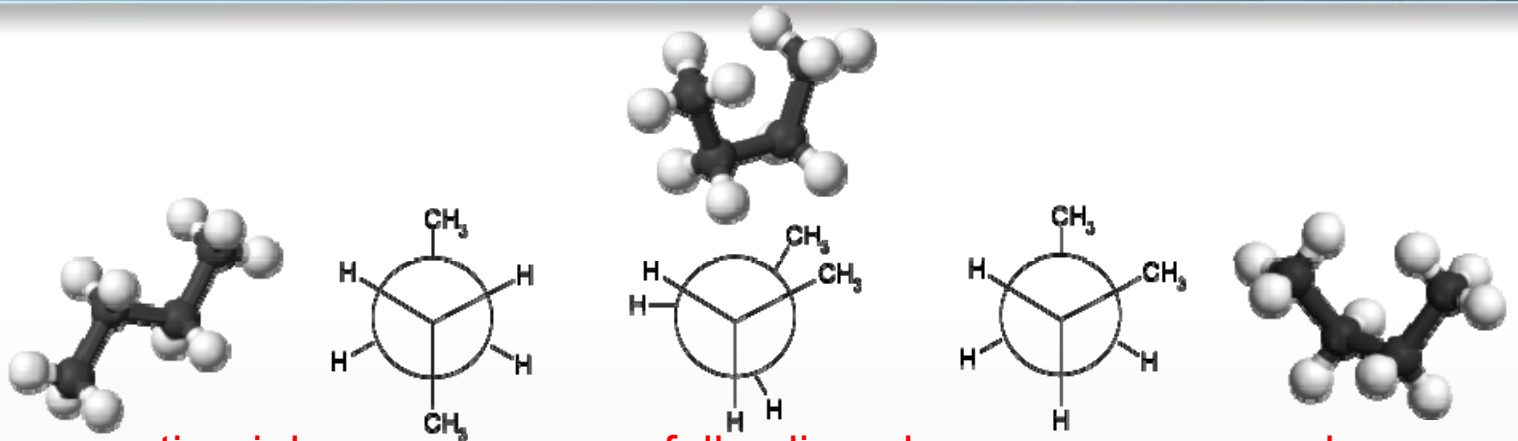
(Zigzag)



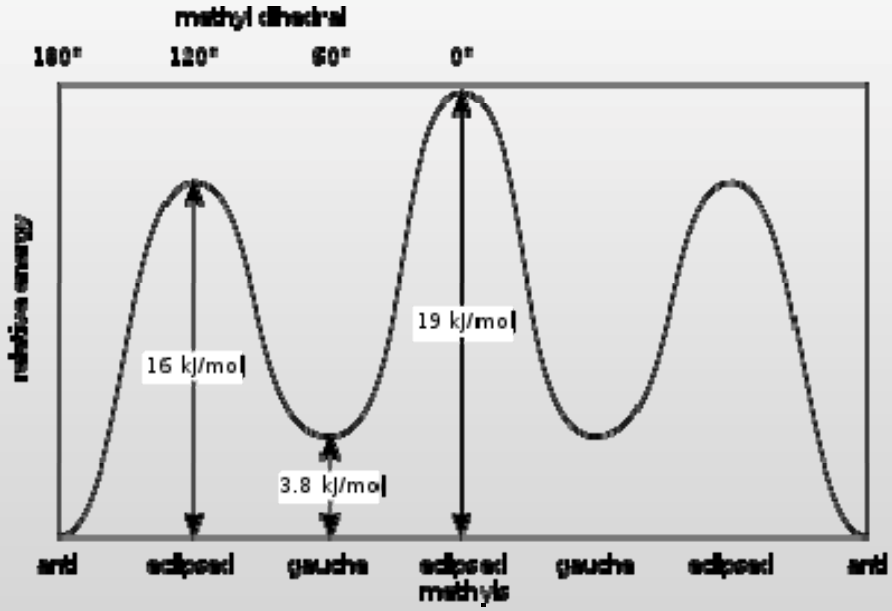
(Newman projection formulas)



Conformational energy diagram for ethane



antiperiplanar full eclipsed gauche



Relative energies of conformations of butane with respect to rotation of the central C-C bond.

Energy barrier

- **MO calculations**: The torsion barrier is caused by repulsion between overlapping filled molecular orbitals. That is, the ethane molecule has its lowest energy in the staggered conformation because in this conformation the orbitals of the C-H bonds have the least amount of overlap with the C-H orbitals of the adjacent carbon.
- Groups larger than hydrogen cause larger barriers. When the barrier is enough high (as in the case of suitably substituted biphenyls), rotation at room temperature is completely prevented and we speak of configurations, not conformations.
- Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.
- *Hyperconjugation not steric repulsion leads to the staggered structure of ethane.* Pophristic, V. & Goodman, L. Nature **411**, 565–568 (2001)

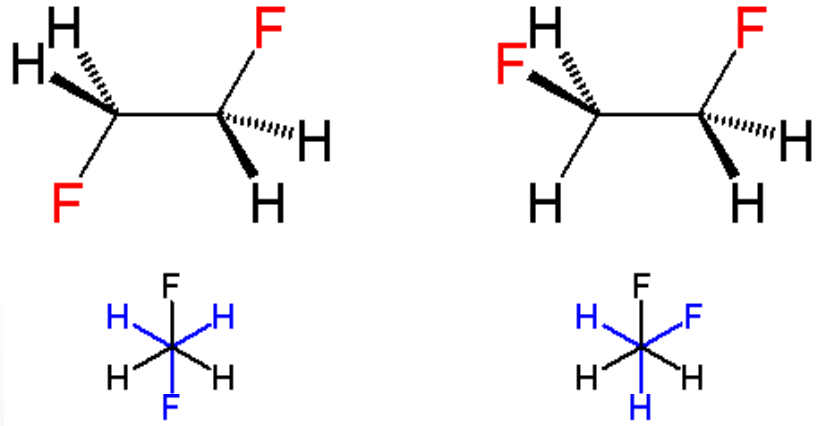
Conformational stability: influencing factors

	antiperiplanar	gauche
$ClCH_2CH_2Cl$ (CCl_4, 25˚C)	70%	30%
$BrCH_2CH_2Br$ (CCl_4, 25˚C)	89%	11%

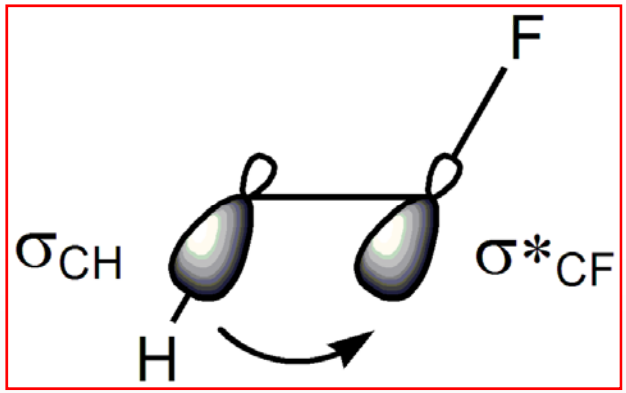
Usually, for butane and for most other molecules of the forms YCH_2-CH_2Y and YCH_2-CH_2X, the anti-conformer is the most stable.

- **Gauche Effect 歪扭效应**

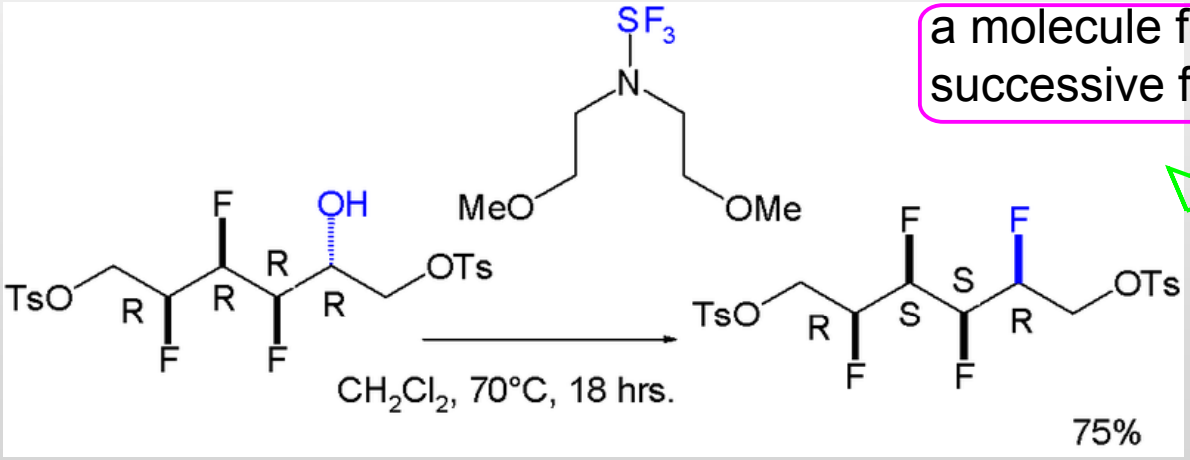
Compounds	Preferential conformation
FCH_2- CH_2OH	*gauche*
FCH_2 - $CH_2OCOCCl_3$	*gauche*
$ClCH_2$ - CH_2OH	*gauche*



The gauche conformation is more stable by 2.4 to 3.4 kJ/mole in the gas phase.



Hyperconjugation model for explaining the gauche effect in 1,2-difluoroethane



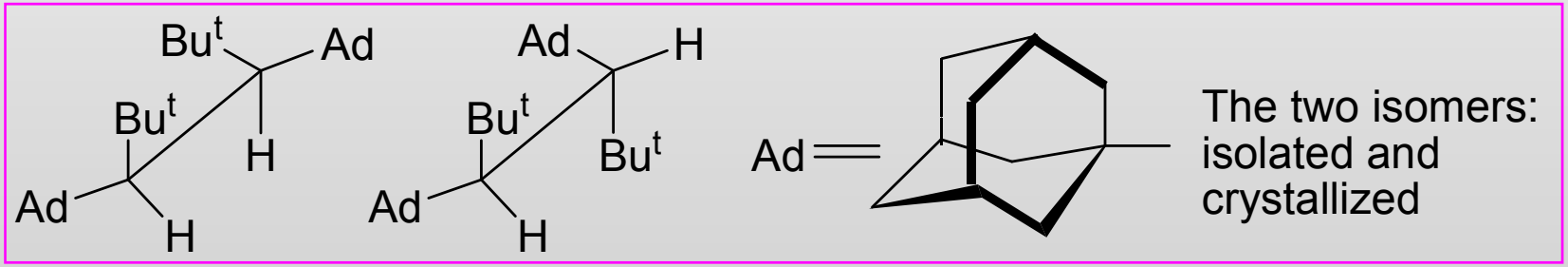
a molecule featuring 4 successive fluor syn substituents

Hunter, L. Et al, J. Am. Chem. Soc.; **2006**; 128(51), 16422-16423

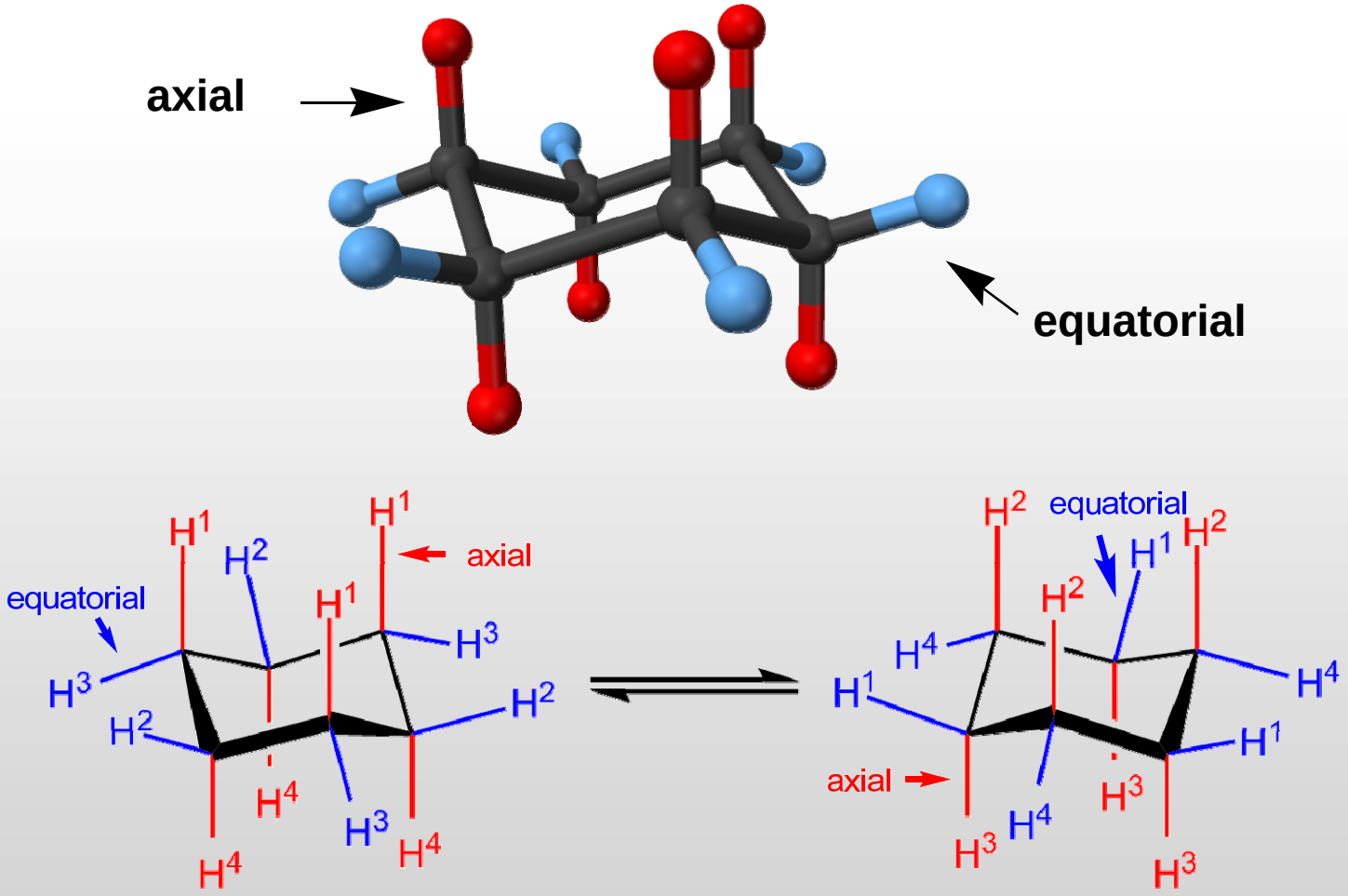
The gauche effect is very sensitive to solvent effects, due to the large difference in polarity of the two conformers.

$(CH_3)_2C(NO_2)–C(NO_2)(CH_3)_2$

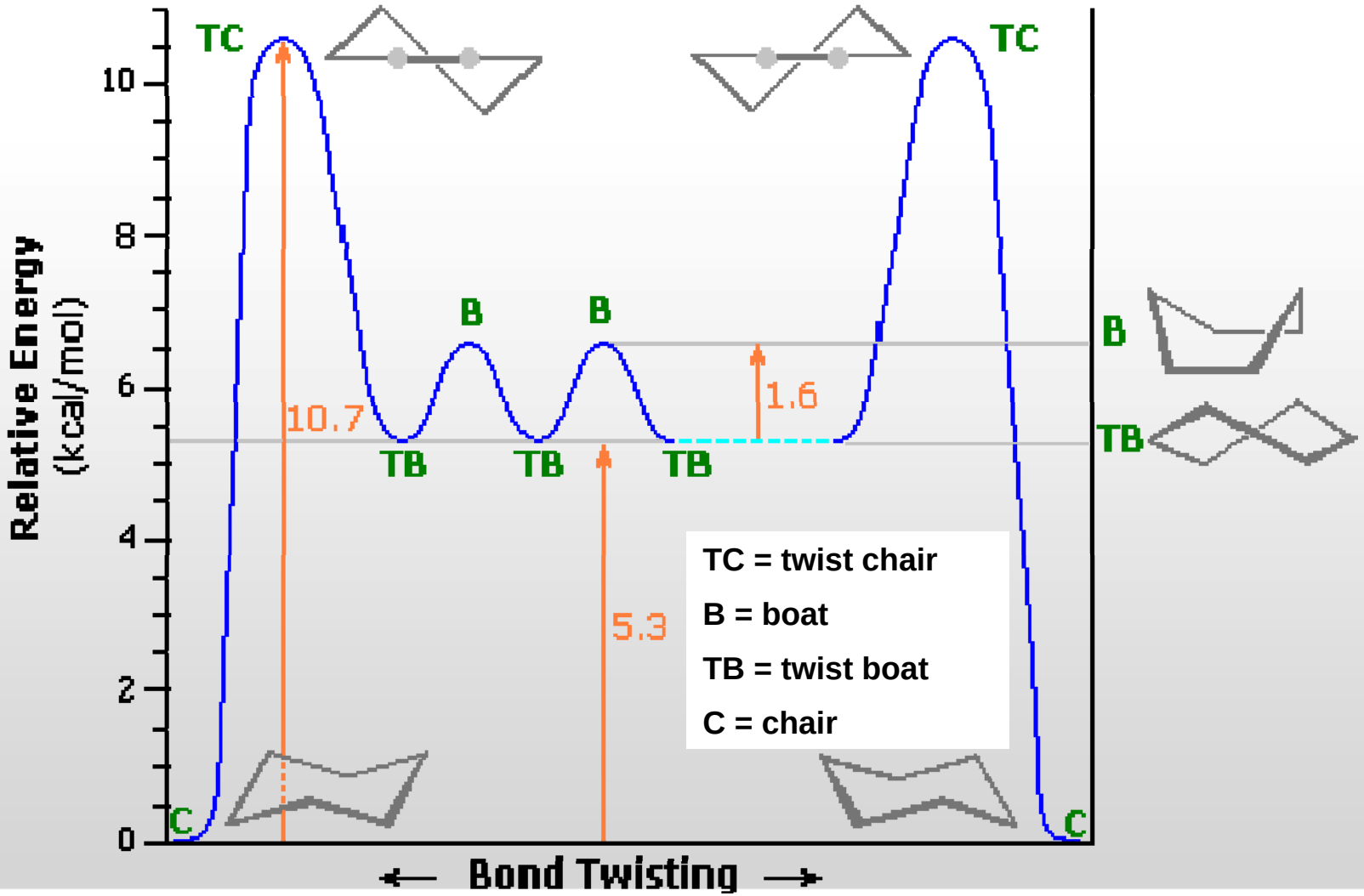
Solvent	Gauche / Anti
None (solid)	100 / 0
C_6H_6	79 / 21
CCl_4	42 / 58



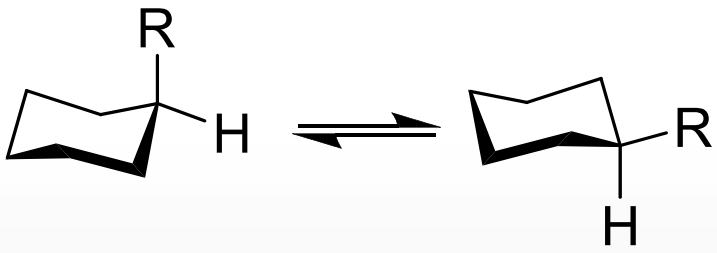
II. Ring conformation



Conformational Energy Profile of Cyclohexane



What happens if we introduce substituents?



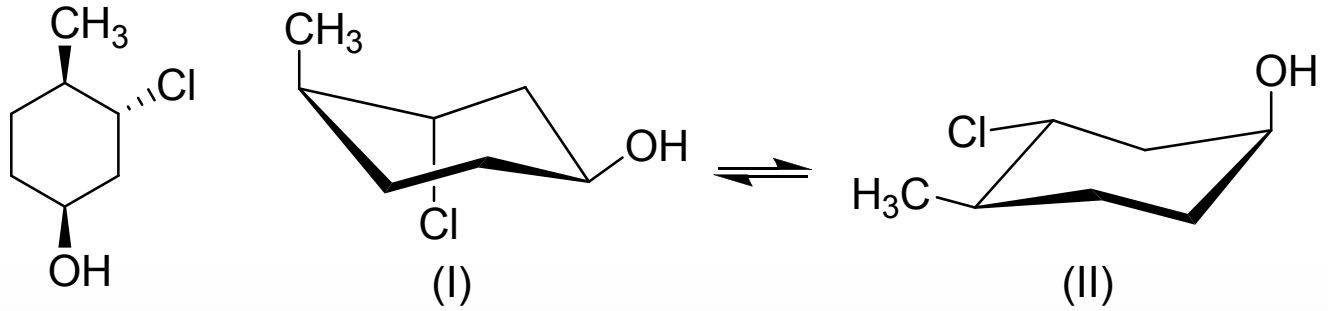
Molecule	Energy difference, *A* value (axial–equatorial) in kJ/mol
methylcyclohexane	6.17
ethylcyclohexane	6.11
isopropylcyclohexane	7.65
Tert-butylcyclohexane	19.55

What is the reason for the big increase in A value at tert-butylcyclohexane?

TABLE. Energy difference between axial and equatorial for cyclohexane derivatives (*A* value)

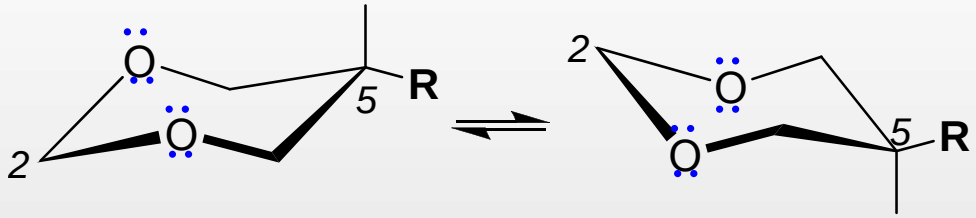
Group	kJ/mol	Group	kJ/mol	Group	kJ/mol
D	0.03	OAc	3.0	$CH{=}CH_2$	7.1
CN	0.6~1.0	OMe	3.1	CH_3	6.17
F	1.0	OH	3.8~4.1	CH_2CH_3	6.11
$C{\equiv}CH$	1.7	NO_2	4.6	*i*-Pr	7.65
I	1.9	COOEt	4.6~5.0	C_6H_{11}	9.0
Br	2.0~2.6	COOMe	5.3~5.5	$SiMe_3$	10~11
Ots	2.15	COOH	5.7~6.1	$C6H_5$	11
Cl	2.2	NH_2	5.9	*t*-Bu	**19.52**

Note: Alkyl groups have a greater preference than polar groups, and for alkyl groups the preference increases with size.



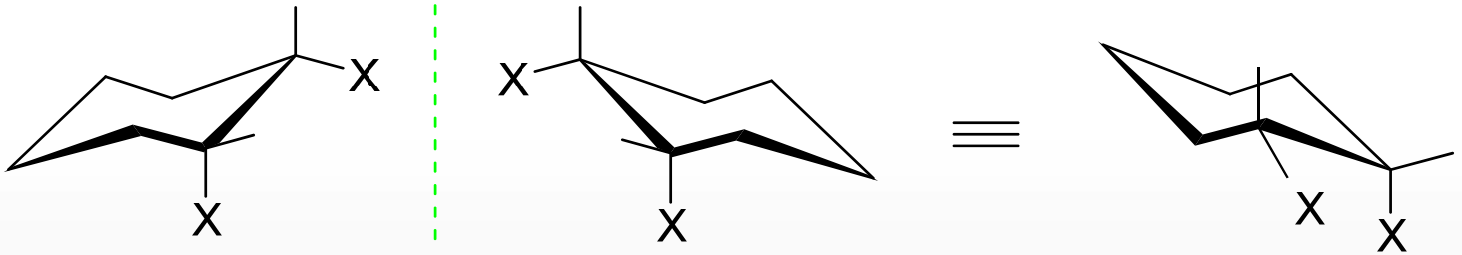
(I) (II)

A value: **8.37**(6.17+2.2) **3.8**



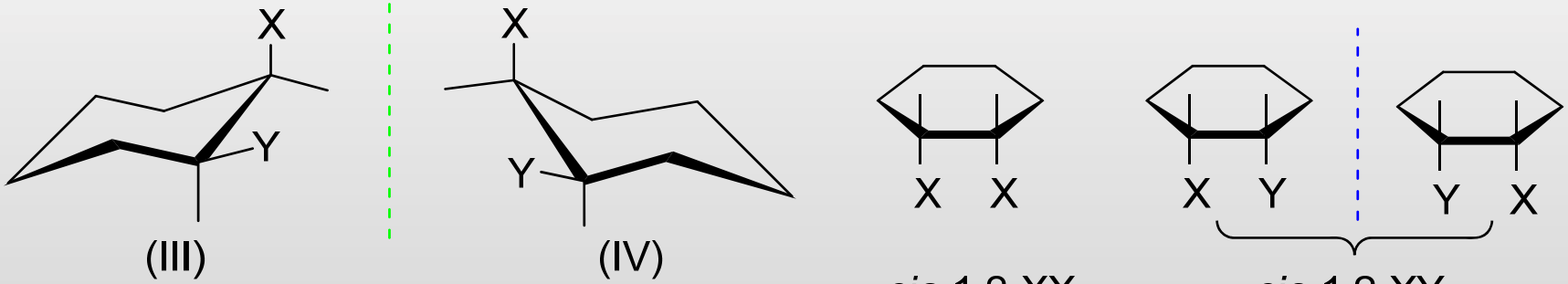
5-alkyl-substituted 1,3-dioxane

The 5-substituent in the 1,3-dioxane derivative has a much smaller preference for the equatorial position than in cyclohexane derivatives, the *A* values are much lower. This indicates that the lone pairs on the oxygens have a smaller steric requirement than the C-H bonds in the corresponding cyclohexane derivatives.



(I) (II) (V)

cis-1,2-X,X-disubstituted cyclohexane
optically inactive

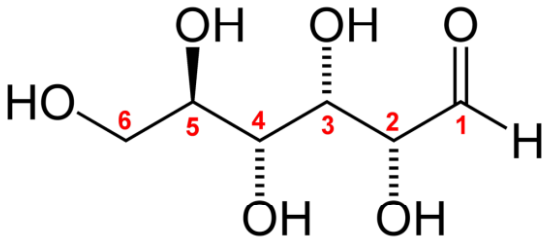


(III) (IV)

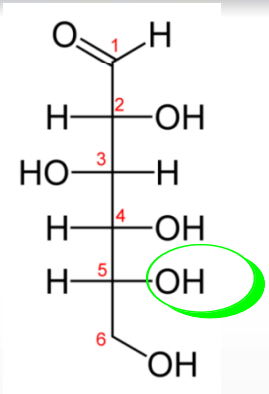
cis-1,2-X,Y-disubstituted cyclohexane
optically active

cis-1,2-XX
optically inactive

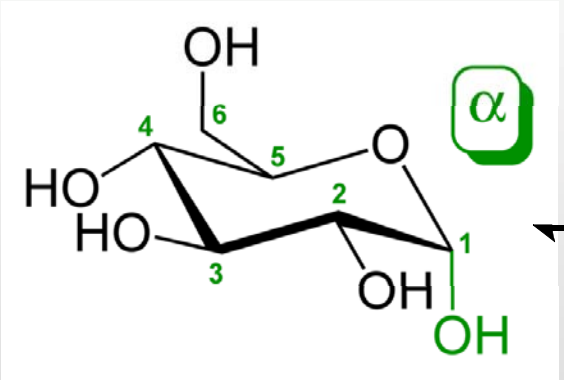
cis-1,2-XY
optically active



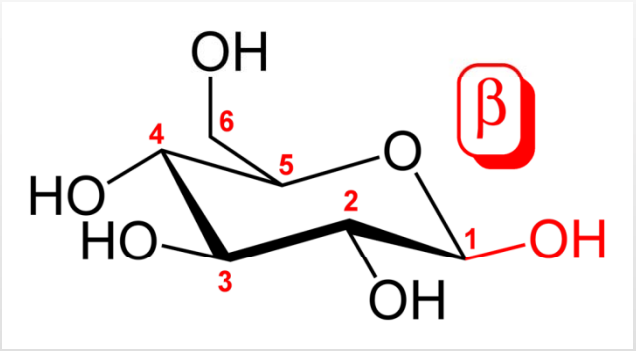
The chain form of D-glucose



The Fischer projection of the chain form of D-glucose



α-D-glucopyranose

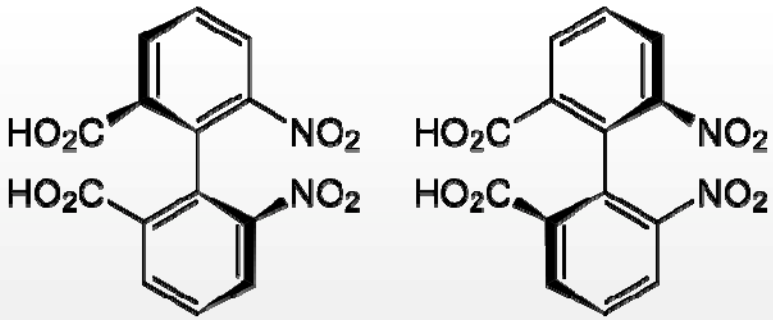


β-D-glucopyranose

Anomeric effect: the heteroatomic substituents adjacent to a heteroatom within a cyclohexane ring tend to prefer the *axial* orientation instead of the less hindered *equatorial* orientation that would be expected from steric considerations. 异头效应

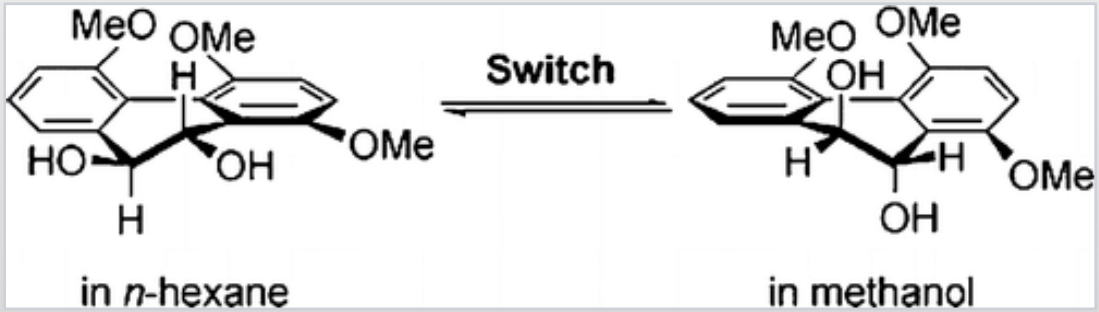
III. Atropisomerism

Atropisomers, the word atropisomer is derived from the Greek **a**, meaning *not*, and **tropos**, meaning *turn*. 阻转异构体



S_a R_a

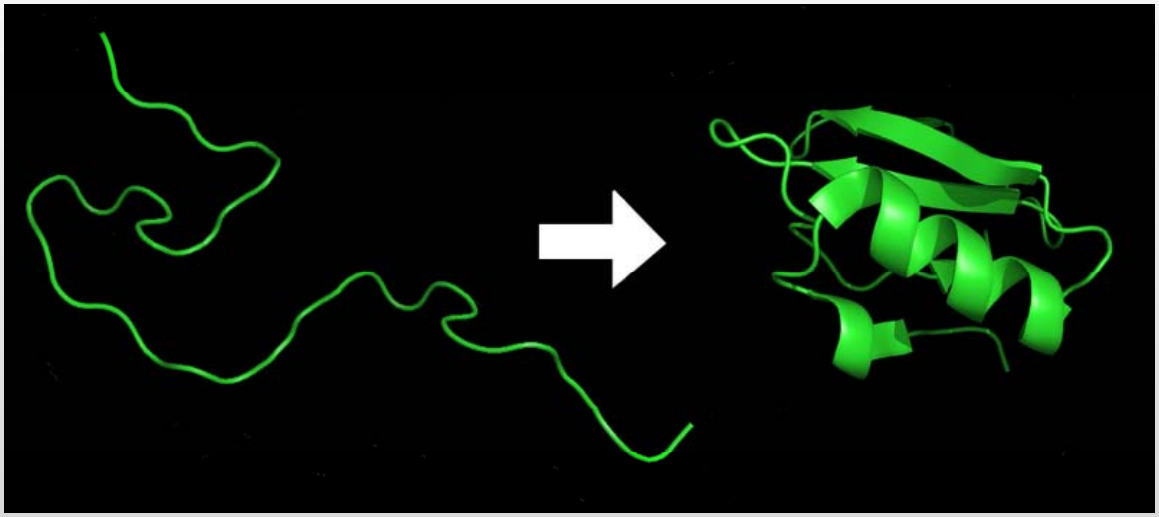
An **axial chirality switch** : In methanol this compound has the two alcohol groups in equatorial positions; in hexane, however, helicity is reversed, with both groups in axial positions.



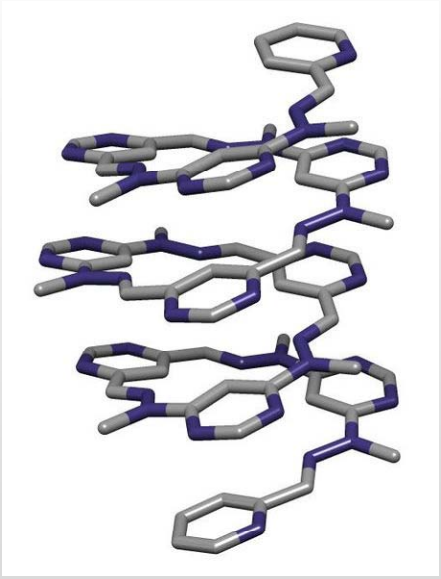
Org. Lett.; 2007; **9**(5), 899 - 902

IV. Folding, foldamers

In chemistry, **folding** is the process by which a molecule assumes its shape or conformation. The process can also be described as **intramolecular self-assembly**, a type of molecular self-assembly, where the molecule is directed to form a specific shape through noncovalent interactions, such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi interactions, and/or electrostatic effects.

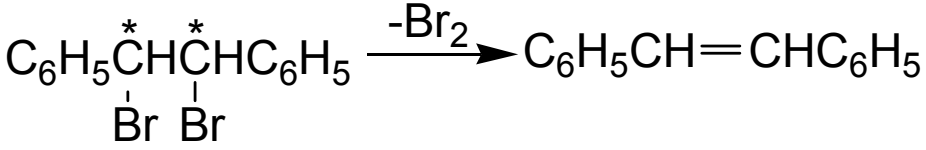


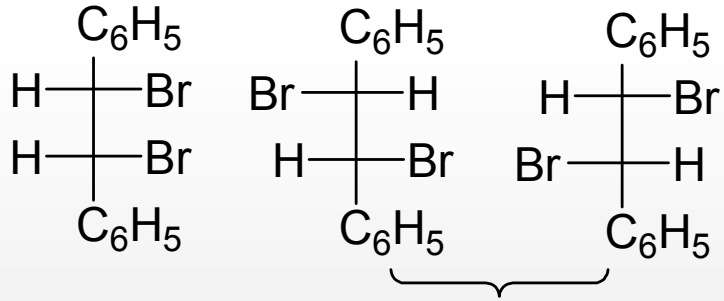
Protein before and after folding

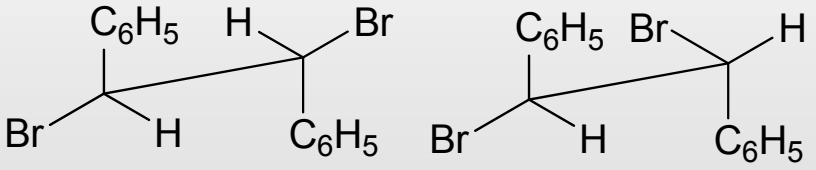


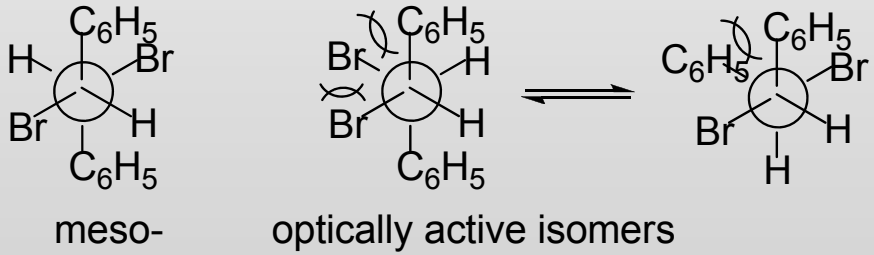
Lehn, et al. Helv. Chim. Acta. 2003, 86, 1598-1624

V. Conformation-dependent reactions: conformation effect







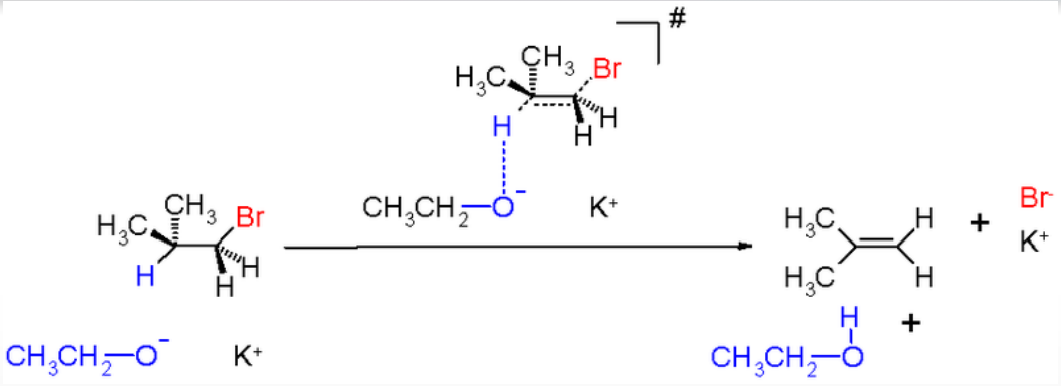


E_2 elimination	Relative rate
meso-isomer	100
Optically active isomers	1

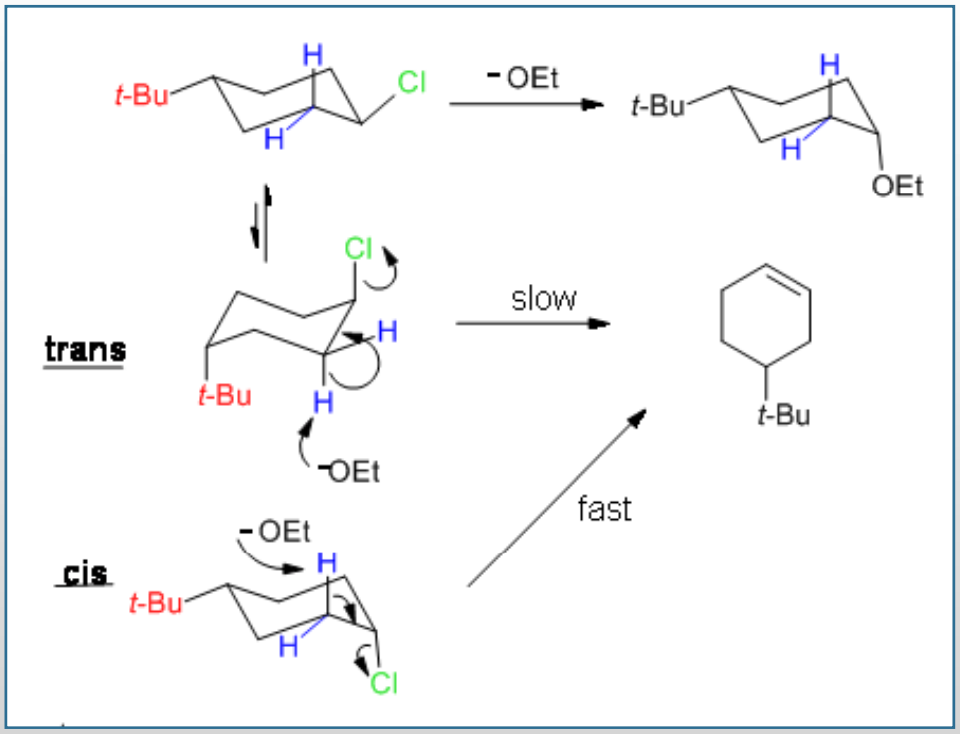
Conformational analysis

i. Conformation effect ~ reaction mechanism

ii. Stereo relation of groups and the strain changes



E2: the optimum geometry for the transition state requires the breaking bonds to be antiperiplanar, as they are in the appropriate staggered conformation.

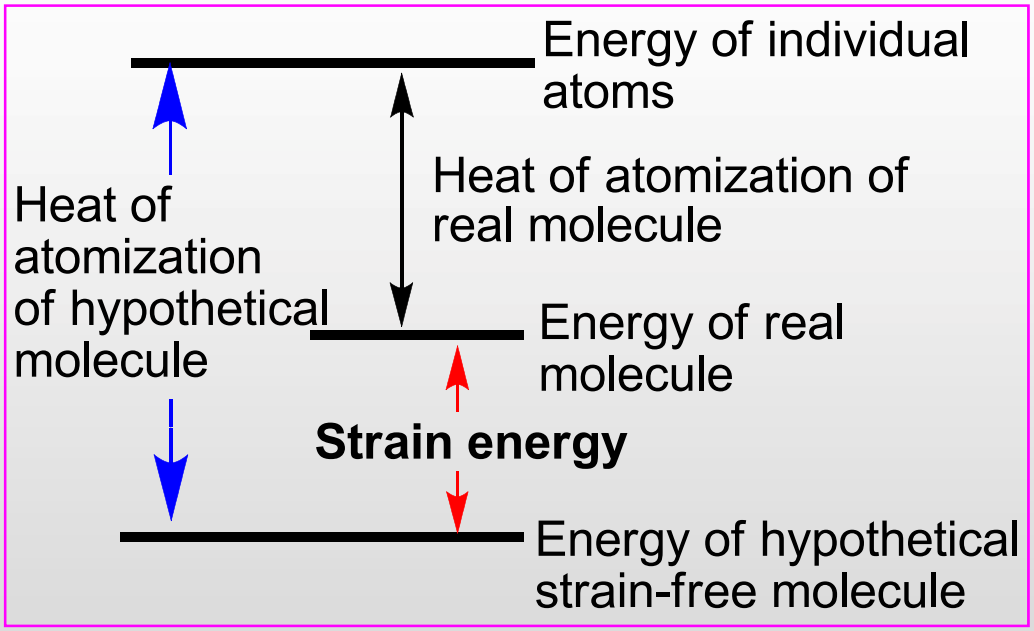


The trans isomer can attain antiperiplanarity only via the unfavored axial conformer and therefore it does not eliminate. The cis isomer is already in the correct geometry in its most stable conformation and therefor it eliminates easily.

Question: *trans*-4-tert-butylcyclohexyl chloride cannot easily eliminate but instead undergoes substitution.

3.11 Strain

- Steric strain exists in a molecule when bonds are forced to make abnormal angles. This results in a higher energy than would be the case in the absence of angle distortions.



Strain energy calculation

Several types of strain exist:

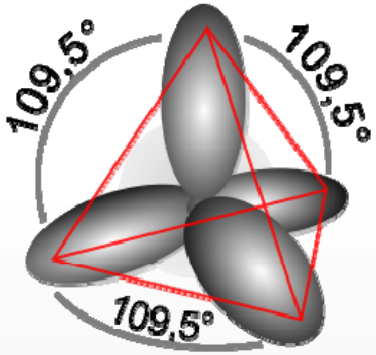
- **Angle strain**
- **Torsional strain**
- **van der Waals strain**

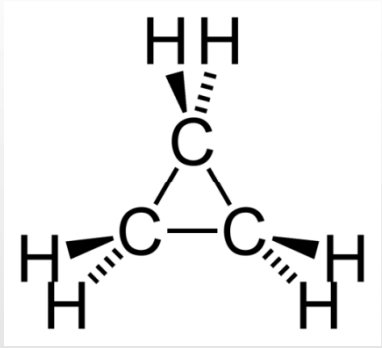
A quantitative measure for angle strain is strain energy. Having higher angle strain makes a molecule more unstable and reactive.

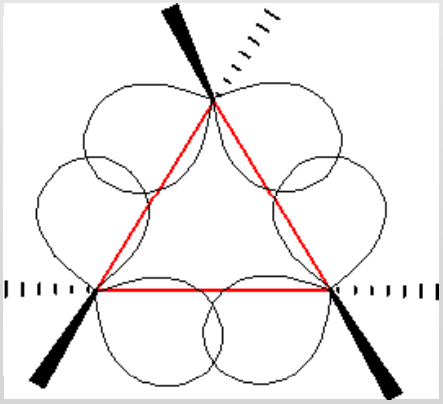
Angle strain and torsional strain combine to create ring strain that affects cyclic molecules.

Strain in small rings

- For a normal carbon atom — equivalent sp^3 orbitals: ~25% *s* character + ~75% *p* character







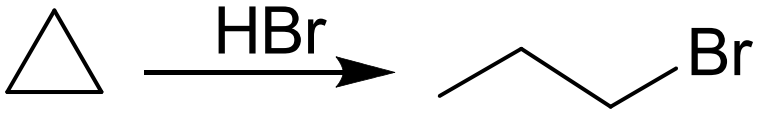
For a cyclopropane carbon atom — nonequivalent hybrid orbitals: two orbitals involved in ring bonding have more *p* character (less *s* character), while the two orbitals directed to the outside bonds have less.

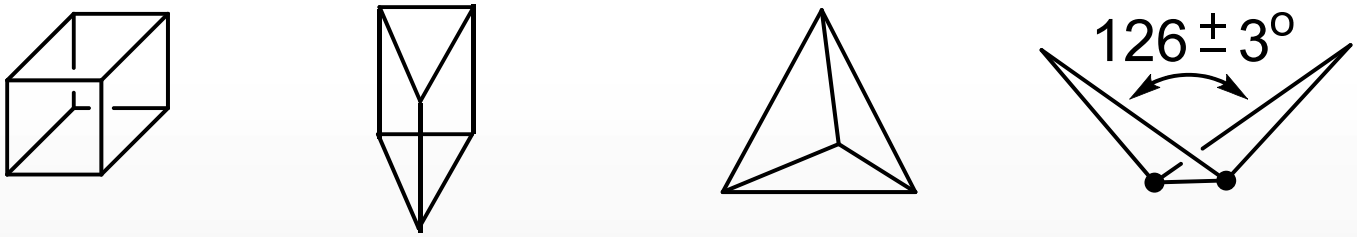
- ♦ the external orbitals: ~33% *s* character (sp^2)
- ♦ the internal orbitals: ~17% *s* character (sp^5)

Table. Heats of combustion in the gas phase for cycloalkanes, per CH_2 group

Size of ring	ΔHc (kJ/mol)	Size of ring	ΔHc (kJ/mol)
3	695.8	10	663.6
4	685.8	11	662.7
5	664.0	12	660.2
6	658.6	13	659.8
7	662.3	14	658.6
8	663.6	15	659.0
9	664.6	16	659.0

i. Small rings (3- and 4-membered): Small-angle strain predominates.
ii. Common rings (5-, 6-, and 7-embered): Largely unstrained.
iii. Medium rings (8- to 11-membered): Considerable strain.
iv. Large rings (12-membered and larger): Little or no strain.





cubane prismane tetrahedrane bicyclobuane

Cubane is actually quite kinetically stable due to a lack of readily available decomposition paths.

Prismane is similar to that of cyclopropane with a high ring strain. Due to this ring strain, the bonds have a low bond energy and break at a low activation energy, which makes synthesis of the molecule difficult.

Tetrahedrane is a platonic hydrocarbon with a tetrahedral structure. Extreme angle strain (carbon bond angles deviate considerably from the tetrahedral bond angle of 109.5) prevents this molecule from forming outside of man-made production.

Overview of Chapter 3

- 结构异构、立体异构、构型异构、构象异构
- 光学活性 、手性、（非）对映异构体、**ee**
- 对映异构体性质几乎相同；非对映异构体性质差别较大
- 非对映异构体：多个手性中心；顺反异构（烯烃、环）
- 产生手性的原因：手性中心；位阻（旋转受阻、π- π、螺旋 ）
- **D, L; (+), (-); R, S; erythro, threo; endo, exo; axial, equatorial; trans, cis; E, Z**
- 基团大小判断：**RS**构型、顺反构型
- **Fisher**投影式、**Newman**投影式
- 前手性：（非）对映异位（面）
- 立体选择性、立体专一性、非立体选择性
- 不对称合成：反应物具有（前）手性，与手性助剂催化剂作用，放大差别
- 手性拆分：同上