M. U. en Química, Universitat de València

44606 - Advanced Organic Chemistry

Prof. Pablo Gaviña

Unit 2

Stereochemistry, stereoselectivity and stereoelectronic effects

Recommended textbooks:

- Francis. A. Carey, Richard J. Sundberg, *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, 5th Edition, Springer.
- F. A. Carroll, *Perspectives on Structure and Mechanism in Organic Chemistry*, 2nd Ed., 2010, Wiley

- Basic concepts of isomerism and stereoisomerism

- Symmetry of organic molecules. Elements of symmetry.

- Reasons of chirality in organic molecules. Stereogenic elements. Nomenclature.

- Diastereoisomerism.

- Prostereoisomerism and prochirality: topicity and its descriptors.

- Conformational analysis. Stereoelectronic effects.

- Influence of configuration and conformation on the reactivity of organic molecules.

- Stereoselectivity and stereospecifity of organic reactions.

General concepts of isomerism and stereoisomerism

Qualitative elementary composition: C, H, O

Quantitative chemical composition: C 66.66%, H 11.11%, O 22.22%

Empirical formula: $(C_4H_8O)_n$

Molecular mass: 72, n = 1

Molecular formula: C_4H_8O

Constitution of the molecule: Nature and bonding of its atoms.

Structure: Constitution and stereochemistry (configuration and conformation)

Isomers:

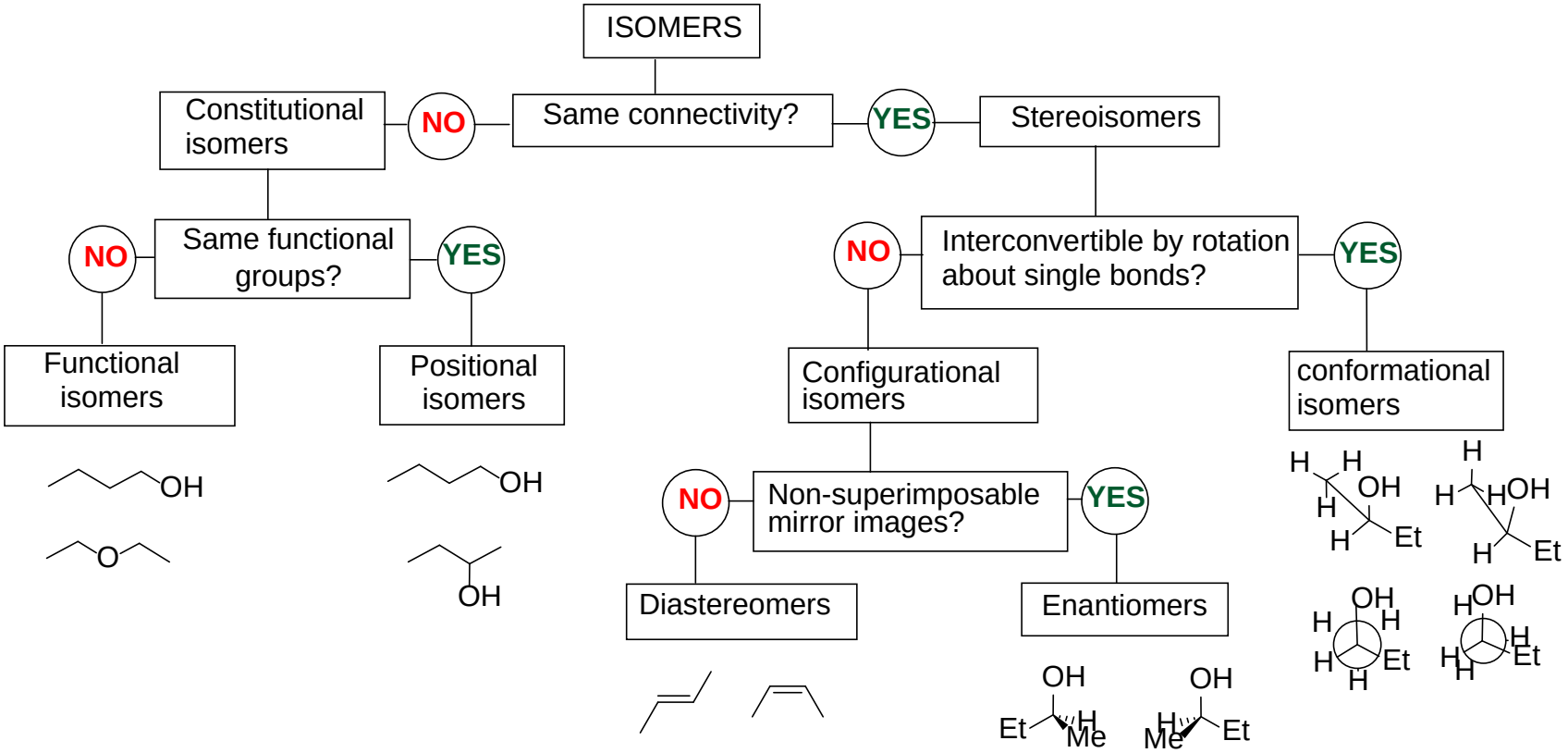
-Constitutional

-Stereoisomerism

- -Configurational isomers
- -Conformers $(C_4H_8O)_n$

CONSTITUTIONAL ISOMERISM AND STEREOISOMERISM

Isomers are chemical compounds that have the same molecular formula but differ in the constitution or arrangement of their atoms in space.



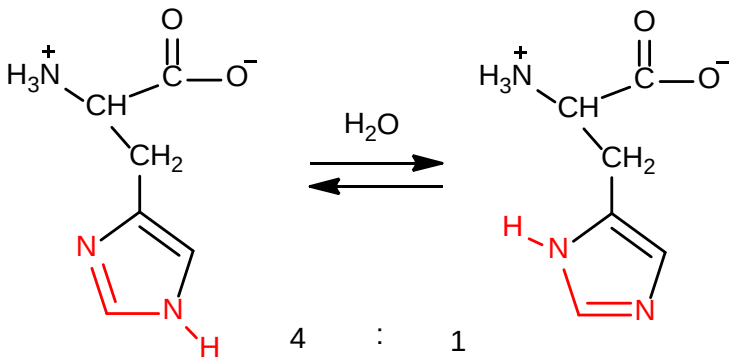
see IUPAC rules on stereochemistry (1974 recommendations)

Equilibrium between constitutional isomers: TAUTOMERISM

There are compounds whose macroscopic behaviour can not be defined in terms of a single constitution.

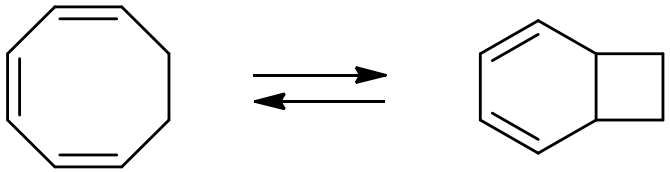
Example: proton tautomerism

L-histidine



Other examples: ketone-enol, enamine-imine,nitroso-oxime tautomerism

Valence tautomerism. Ex: 1,3,5-cyclooctatriene



CONFIGURATIONAL ISOMERISM: ENANTIOMERS

Enantiomers are a pair of stereoisomers in which one is the non-superimposable mirror image of the other.

Compounds that have the property of not being superimposable with their mirror image are called **chirals**. The enantiomers show chirality.

At the EXPERIMENTAL level, the enantiomers show:

Identical chemical composition

Identical physical properties except interaction with polarized light

Identical chemical properties (in an achiral environment)

Optical activity, $\alpha \neq 0$

Identical specific rotation $[\alpha]$, but with opposite signs

RACEMATE OR RACEMIC MIXTURE

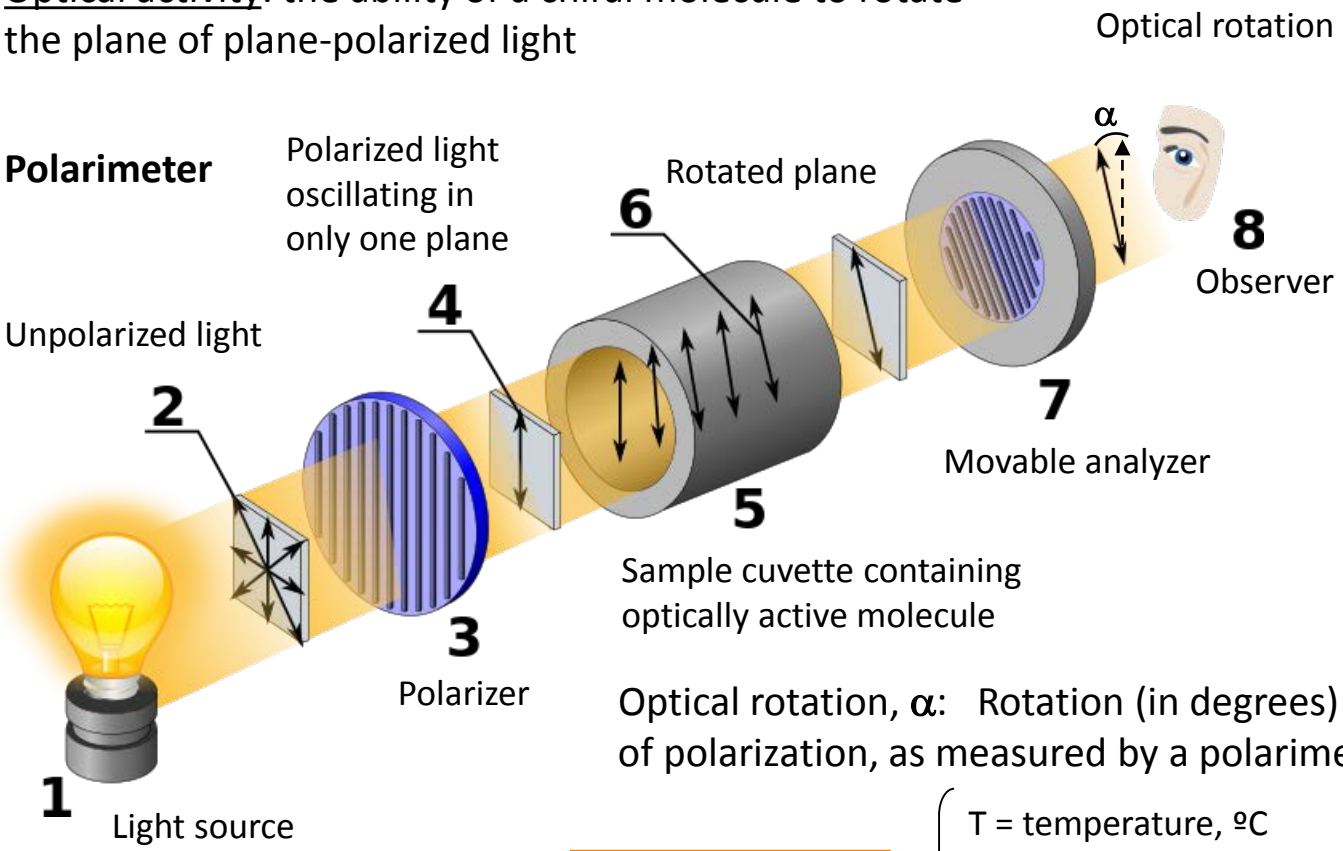
Equimolar mixture of the two enantiomers. $\alpha = 0$

ENANTIOENRICHED MIXTURE

Non-equimolar mixture of the two enantiomers

Enantiomeric excess (ee) = enant. max % - enant. min %

Optical activity: the ability of a chiral molecule to rotate the plane of plane-polarized light



Optical rotation, α: Rotation (in degrees) of the plane of polarization, as measured by a polarimeter.

Specific rotation

(intensive property characteristic of a specific enantiopure chiral compound)

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \cdot c}$$

T = temperature, ºC
λ = wavelength of the light used. Usually the sodium D line (589 nm)
α= Measured rotation in degrees
l= cuvette length (dm)
c= Sample concentration (g /ml)

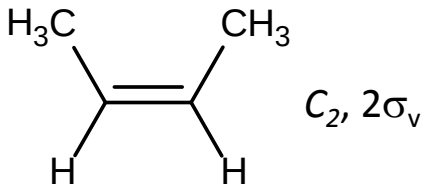
$$\text{Enantiometric excess \% (ee.)} = \frac{[\alpha]_{\text{observed}}}{[\alpha]_{\text{pure enantiomer}}} \cdot 100$$

= % main enant. - % lesser enant

SYMMETRY OF ORGANIC MOLECULES. SYMMETRY ELEMENTS

Proper rotation axis of order n: C_n (rotation)

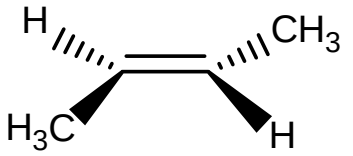
A 360°/ n rotation about the axis produces a structure indistinguishable from the original.



C_2, $2\sigma_v$

Plane of symmetry: σ *(reflection)*

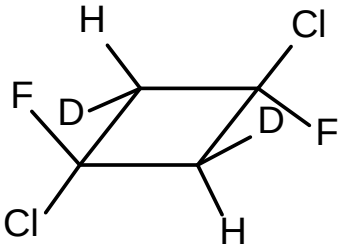
An imaginary plane that divides an object in two halves, so that one half is the mirror image of the other.



C_2, σ_h

Center of symmetry or center of inversion: *i (inversion)*

Point located in the center of the object so that any straight line that passes through it joins two elements of the object equal to each other, opposite and equidistant



i (S_2)

Improper rotation axis: S_n (rotation + reflection)

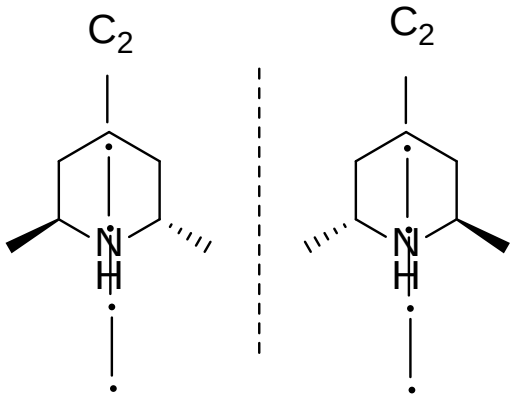
It is equivalent to carrying out two consecutive symmetry operations: a rotation about a C_n axis followed by reflection through a plane perpendicular to that axis. It can be easily demonstrated that $\sigma = S_1$ and $i = S_2$

SYMMETRY AND CHIRALITY

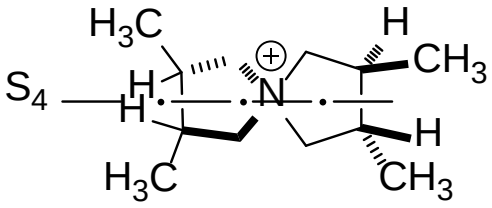
Chirality is a property that depends on symmetry.

Mathematically it can be shown that every object that has an improper rotation axis S_n is **achiral**. Since a center of symmetry (i) and a plane of symmetry (σ) are respectively equivalent to S_2 and S_1, a molecule will be **chiral** **only** when it has no plane or center of symmetry or any improper rotation axis S_n with $n > 2$.

On the other hand, a molecule can have a proper rotation axis (C_n) and be chiral.



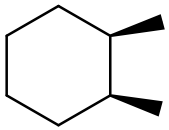
Enantiomers
(chiral)



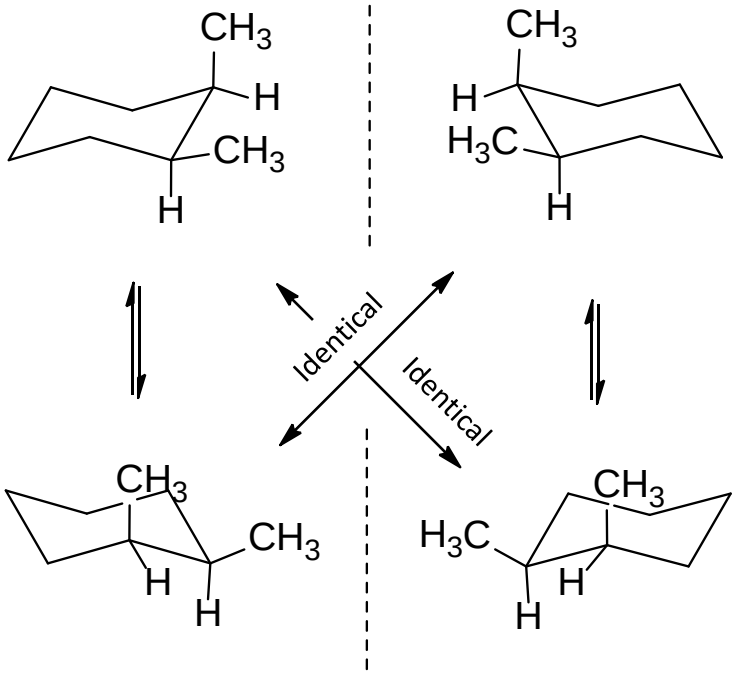
3,4,3',4'-tetramethylspirane-(1,1')-bipyrrolidine ion
Achiral, optically inactive

Conformationally flexible molecules

Example:



cis-1,2-dimethylcyclohexane



In the chair conformation the molecule is chiral and has a non-superimposable mirror image. However, this conformation is in balance with an inverted chair that turns out to be identical to its mirror image (50% of each chair's population, since they are identical in energy). Therefore cis-1,2-dimethylcyclohexane is experimentally an optically inactive substance. In fact, the conformational equilibrium involves going through a highly energetic conformation with a plane of symmetry (achiral). In conformationally fluxional molecules, **if there is one conformation that is achiral, then the molecule as a whole is achiral**.

CAUSES OF CHIRALITY IN ORGANIC MOLECULES: ELEMENTS OF CHIRALITY

The cause of CHIRALITY in a molecule is the presence of one or more CHIRALITY ELEMENTS OR STEREOGENIC ELEMENTS

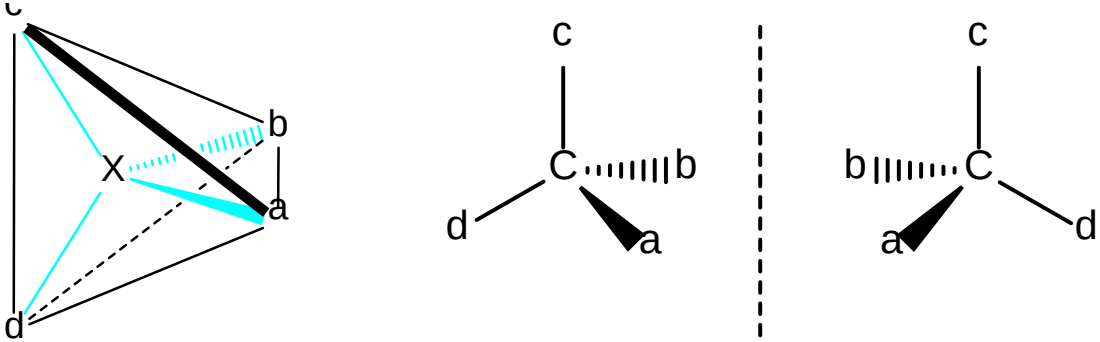
- CHIRALITY CENTER (OR STEREOGENIC CENTER)
- CHIRALITY AXIS
- CHIRALITY PLANE

Molecules with **one** stereogenic element are necessarily CHIRAL

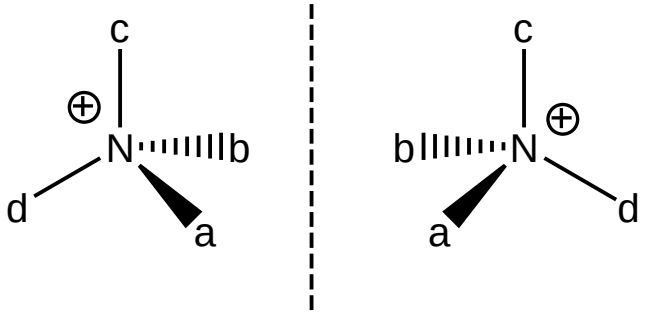
Molecules with **two or more** stereogenic elements can be CHIRAL or ACHIRAL (meso compounds)

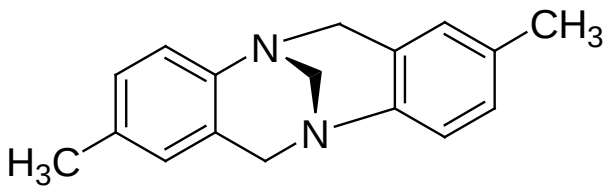
Chirality elements: chirality center (chiral center)

-Tetrahedral carbon. The enantiomers in which the chiral center is a carbon tetrasubstituted with four different substituents are the most numerous.



-Amines and ammonium salts. In principle the amines substituted by three different groups are chiral, but the energies of activation for the inversion are so low that the separation of the enantiomers can not be carried out. The ammonium salts with four different substituents are chiral and resolvable

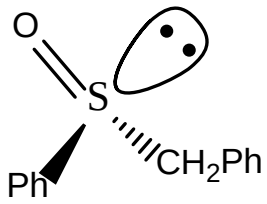


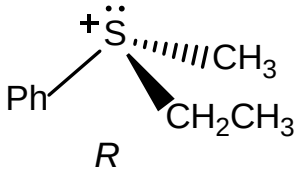


Base of Träger

Sterically hindered inversion → chiral

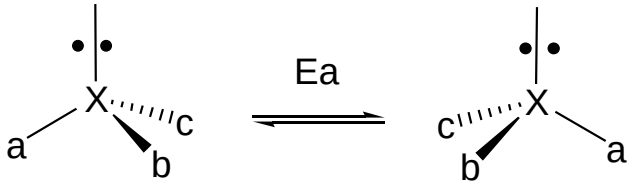
- Sulfoxides and sulfonium salts. The sulfoxides that contain two distinct groups on the S are chiral, as well as the sulfonium salts with three different groups.





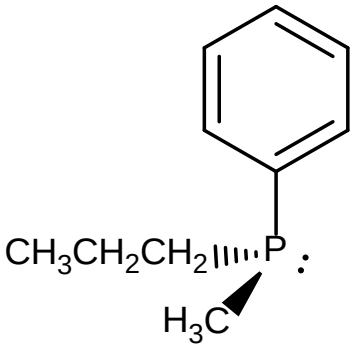
$[\alpha]_D$ = +25.2º

Activation energies for configuration inversion



N 5 Kcal/mol, inversion at r.t.
P 30 Kcal/mol
As 40 Kcal/mol
S 35 Kcal/mol

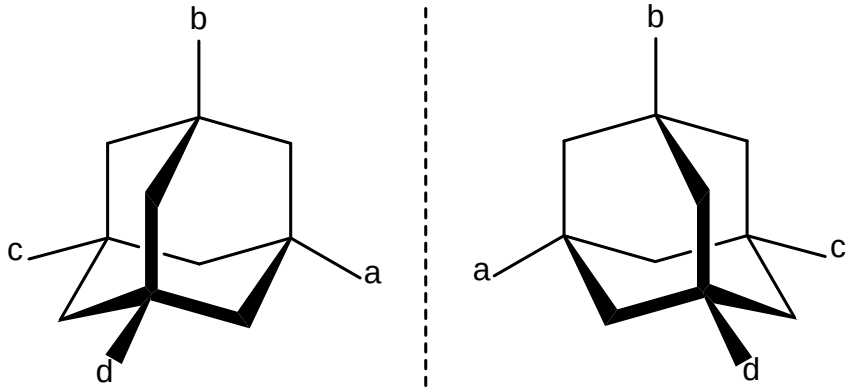
-Phosphines. The activation barriers for the pyramidal inversion of the phosphines are much higher than those of the amines and for this reason numerous chiral phosphines have been prepared.



$[\alpha]_D$ = +35º

-Chiral molecules with a chiral center but without chiral atom.

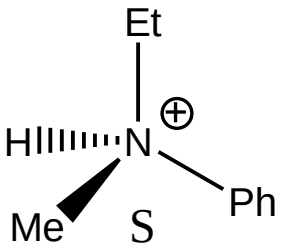
Derivatives of adamantane are among them.

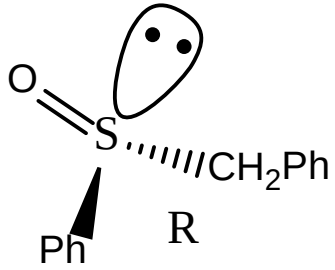


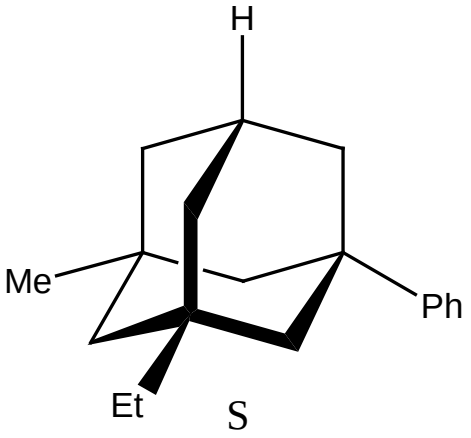
Nomenclature

It uses the descriptors *R* and *S* and follows the Cahn-Ingold-Prelog (CIP) priority rules.

The non-bonded electron pair gets the lowest priority.







CIP rules for assigning priorities

There are 5 rules that are applied hierarchically until a decision is reached. We will only consider the first two.

1.- (a) The higher the atomic number, the higher priority.

(b) A duplicated atom corresponding to an atom closer to the root (the central atom of the hierarchical tree) has a higher priority than a duplicated atom whose original atom is farthest from the root (it is used to prioritize between two cyclic substituents)

2.- When two substituents on the chiral center are identical in everything except for its isotopic distribution**, the isotope of greater mass** has preference over that of smaller mass.

How do these rules apply?

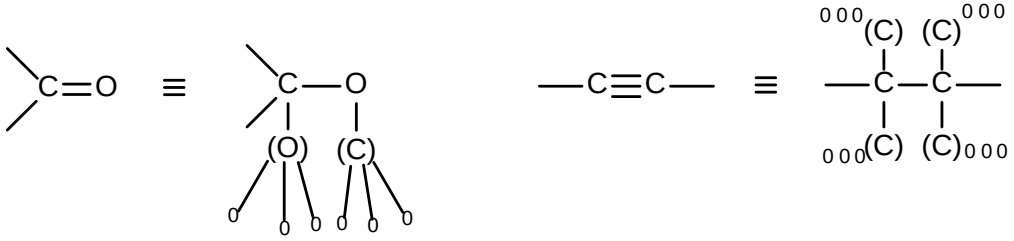
-Each rule is applied exhaustively to all atoms or groups of atoms that are compared.
-Each rule is applied following a hierarchical diagram. The atoms directly attached to the stereogenic center are considered first. If there are two identical atoms attached to the stereocenter, we advance to the next position simultaneously by the two chains, until reaching the first point of difference.
- If branches appear, we will always follow the branch that starts from the highest priority atom.

Duplicated atoms and ghost atoms

They are introduced to be able to apply the CIP rules to molecules with multiple bonds, saturated cycles, aromatic rings or atoms with non-bonded electron pairs.

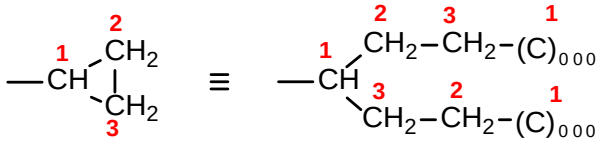
- Double and triple bonds

They are considered as if they were single but doubling or tripling the atoms. Each real atom and "duplicated atom" becomes tetravalent by adding "ghost atoms" (imaginary atoms with atomic number = 0)



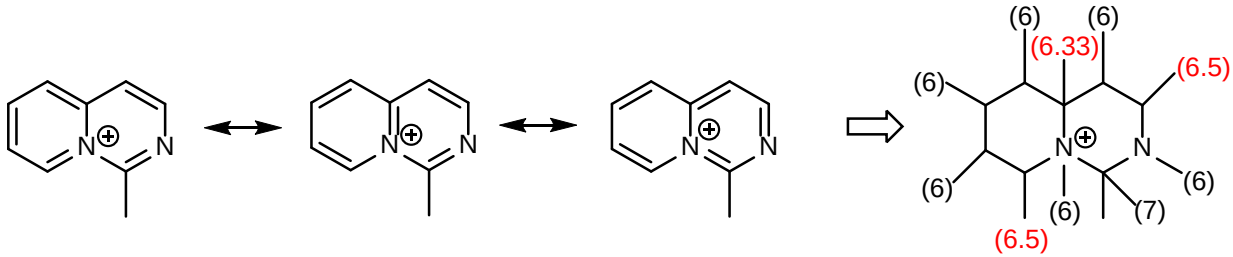
- Saturated cycles

The saturated rings are "opened" and considered as if they were branched chains. The exploration continues until we get back to the starting atom that is considered as a "duplicated atom" to which "ghost atoms" are added to complete the tetravalence.



- Aromatic heterocycles

Each duplicated atom is assigned an average atomic number that it would have if the original atom had double bonds in all possible positions.



- Non-bonded electron pairs

They are assigned an atomic number of zero (less than an atom of H)

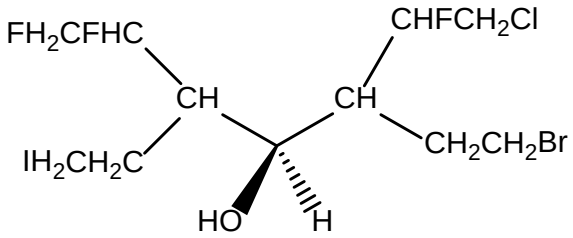
Application of 2nd rule: Only when it isn't possible to get a decision while using rule # 1, what means exhaustively ignoring the isotopic differences, then we can consider the isotopes. The greater atomic mass, the higher priority.

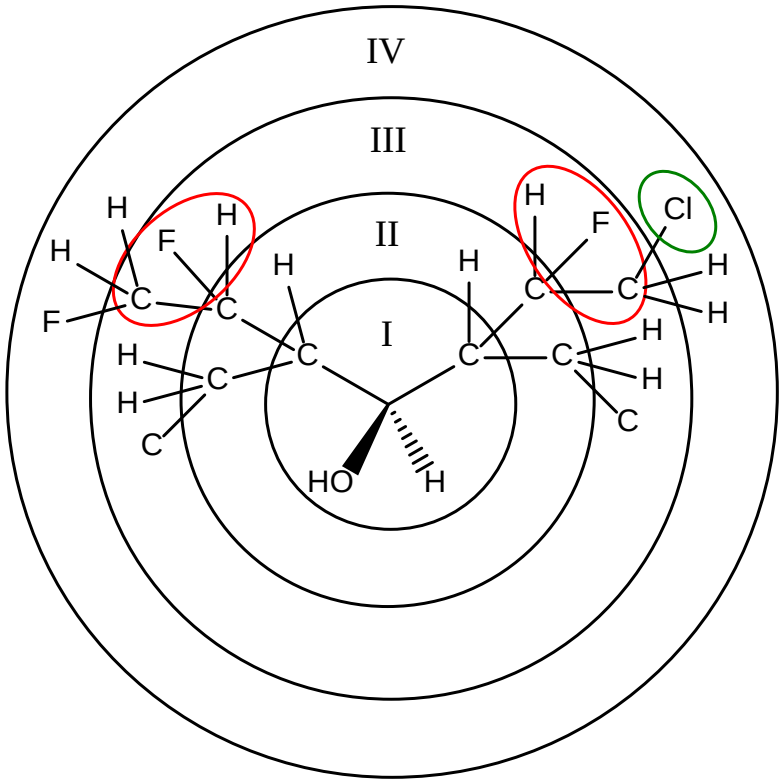
Example: $CH_2CD_2CH_3$ > $CH_2CH_2CH_3$

But…

CH_2CH_2 > CD_2CH_3

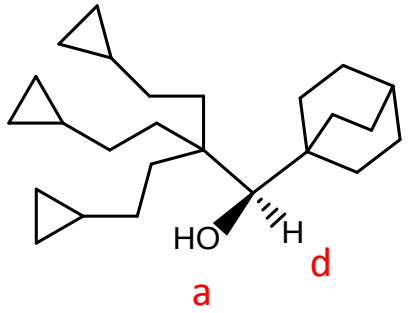
Interesting example of the application of CIP rules via using of a hierarchical tree:





An interesting example of the application of sub-rule 1b: priority in duplicate atoms

Determine the absolute configuration of the following compound:



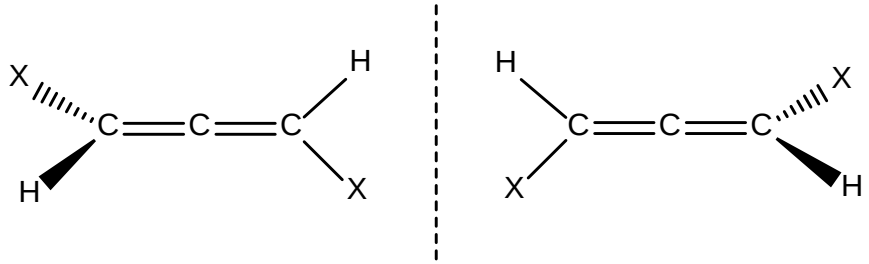
Chirality elements: chirality axis

Allenes.

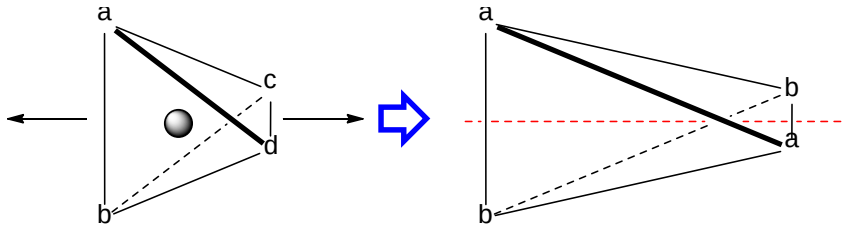
The molecular model of an allene of the type CHX = C = CHX shows that the substituents at the ends are perpendicular to each other.

The allenes of this type lack plane of symmetry, center of inversion or any axis Sn (n> 2), therefore they are chiral and can be resolved in enantiomers.

The allenes do not contain a chiral center and their **chirality comes from a chiral axis** which in this case is the axis C = C = C.



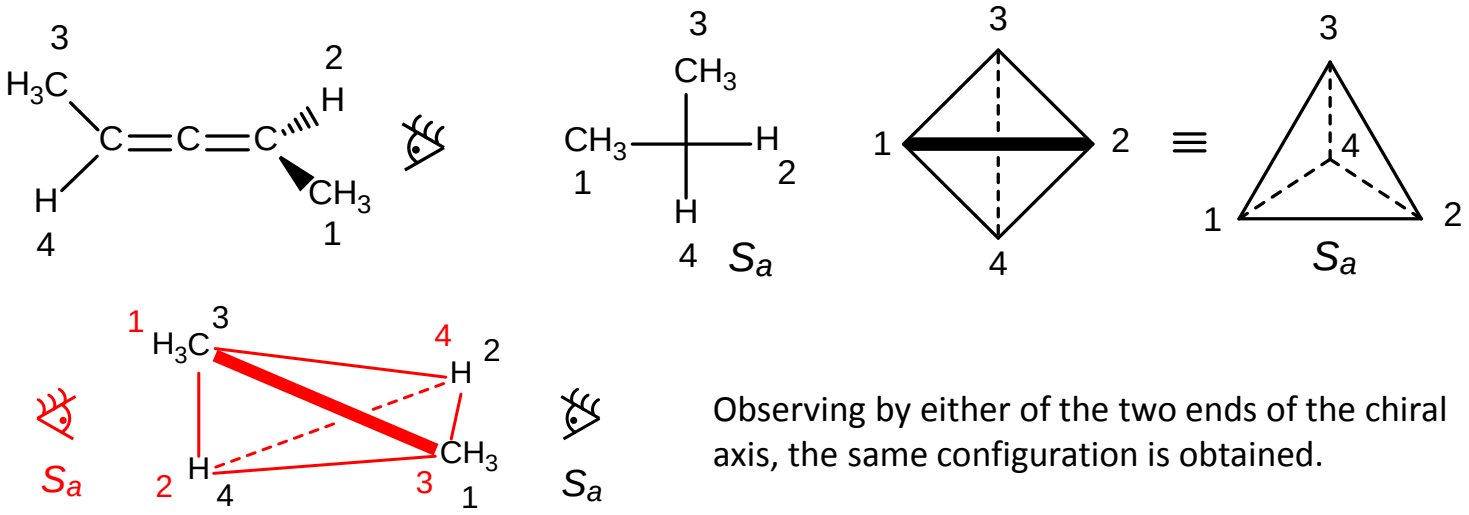
A stereogenic axis can be related to a stereogenic center in which two of the substituents had moved in the direction of the axis.



a,b,c and d are different center of chirality

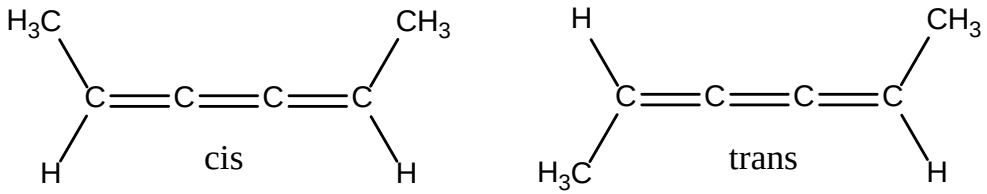
a and b are different axis of chirality

Nomenclature: To use the descriptors ***R_a* and *S_a***. To carry out the assignment, the molecule is observed along the stereo axis. Priorities 1 and 2 are assigned to the two substituents of the carbon closest to the observer following the CIP rules, and then priorities 3 and 4 are assigned to the substituents of the furthest carbon. The substituents ordered 1, 2, 3 and 4 describe the four vertices of a distorted tetrahedron. This tetrahedron is observed by placing substituent 4 away from the observer and sequence 1, 2 and 3 determines whether the system is R or S.

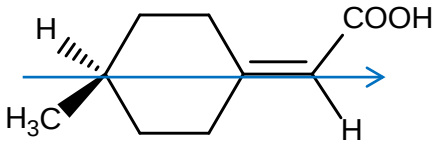


Observing by either of the two ends of the chiral axis, the same configuration is obtained.

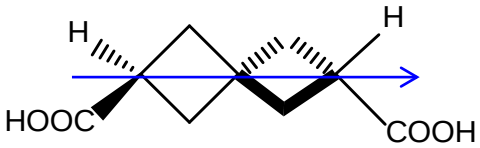
When another double bond is presented, as in the cumulene abC = C = C = Cab, all the substituents are back in the same plane and the molecule only has geometric isomerism (cis / trans)



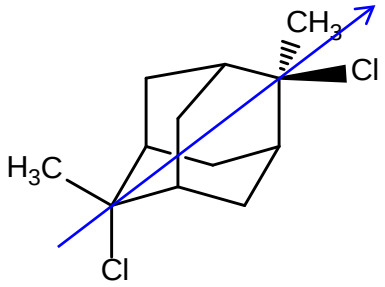
Alkylidene, cycloalkanes, spiranes and other rigid cyclic compounds



alkylidenecyclohexane

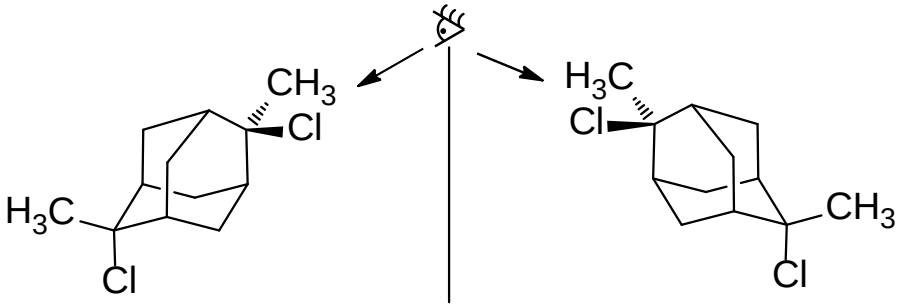


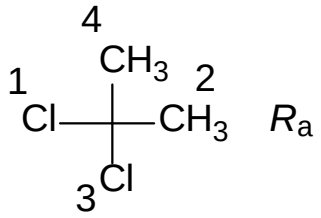
spirane

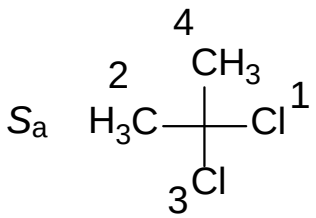


adamantane

Nomenclature. *The R_a and S_a notation for these compounds is determined following the same standards indicated for the allenes.*



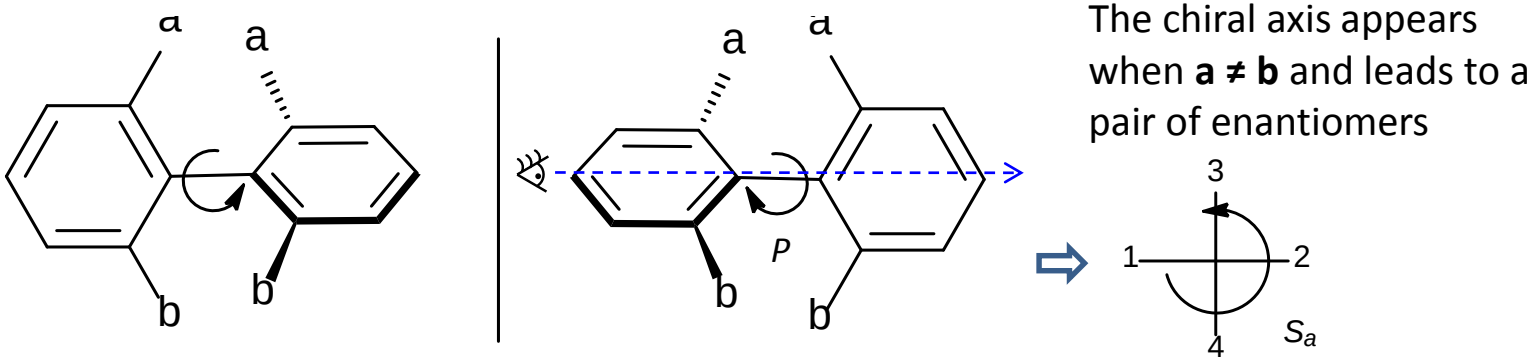




Important: If we use the representation of Fischer to assign the configuration, the substituents closest to the observer (1 and 2) have to be in the horizontal plane

Biphenyls: Atropoisomerism

The biphenyl molecule can rotate around the bond that binds two aromatic rings. This rotation is becoming more difficult when ortho-hydrogens are substituted by other groups. When the substituents at 2.2 'and 6.6' are bulky enough, rotation is impeded and a chiral axis appears. This type of isomerism is called **atropoisomerism** (a = without, tropos = rotation).



Nomenclature. The Ra and Sa notation for these compounds is determined following the same standards indicated for the allenes.

You can also use the nomenclature P (plus) and M (minus) that is used for substances with helical geometry. A molecule will have helicity P if the main groups of both ends of the axis rotate clockwise away from the observer (and M if they rotate in the opposite direction)

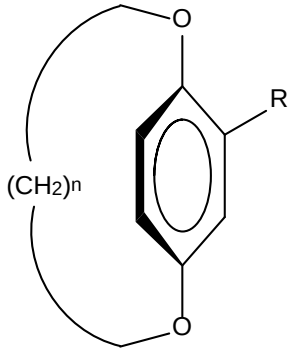
For the molecules with chirality axis, it is:

$R_a = M$
$S_a = P$

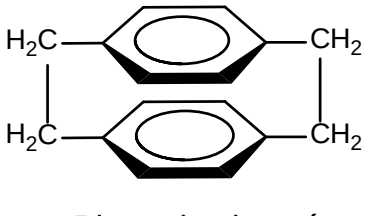
Elements of chirality: plane of chirality

It appears in molecules that contain a group of atoms in a plane, from which the rest of the molecule protrudes, as long as the rotation of the plane is impeded.

Ansa compounds and cyclophane

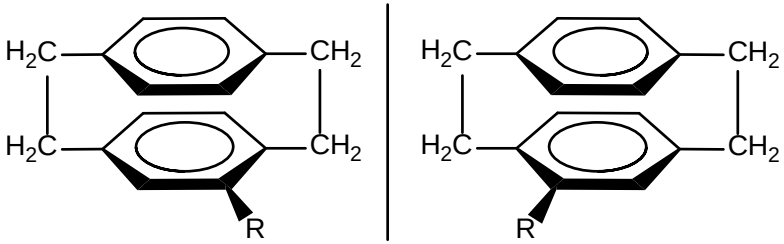


Ansa compound



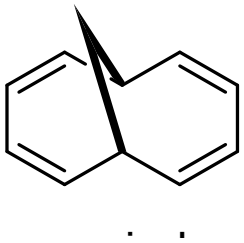
Symmetry plane
Achiral

paracyclophanes

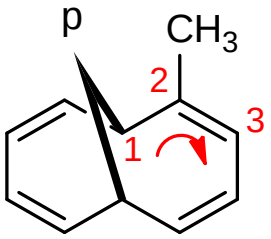


enantiomers

Annulenes

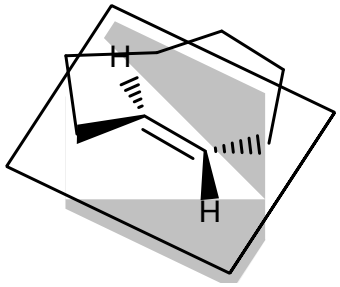


Achiral

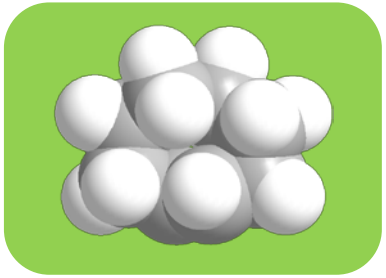


R_p

Trans-Cyclooctene



(E)-cyclooctene

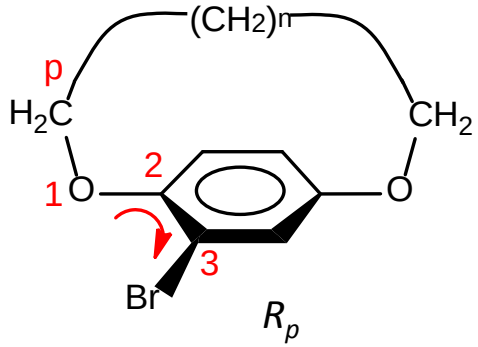


Nomenclature: The descriptors Rp and Sp are used following these rules:

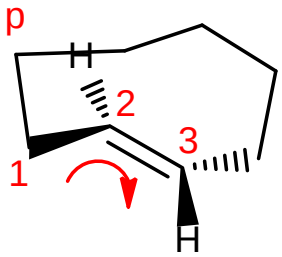
1. Among the atoms directly attached to the chiral plane (but outside the plane), the one with the highest priority (CIP) is selected as the “pilot atom”.

2. From the atom of the chiral plane attached to the pilot atom, a path is traced by the atoms of the chiral plane always following the highest priority atoms.

3. If contemplating from the pilot atom the path 1,2,3 follows a clockwise pattern the chiral plane is designated R. If the pattern is counterclockwise, it is S.



R_p



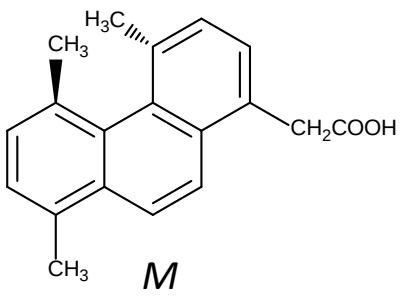
R_p

Elements of chirality: helicity

The existence of enantiomers in some molecules is best defined in terms of helicity. A helix can be right (if its rotation away from the observer is clockwise) or left (anti-clockwise). The right and left helices that have the same shape are mirror images (enantiomers).

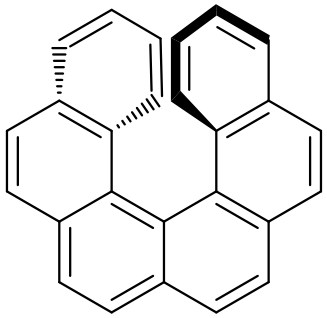
Nomenclature: The chirality of the helixes is denoted by the symbols P for the right helixes (from the Latin plus) and M for the left helixes (from the Latin minus)

4,5-substituted phenanthrene and helicenes. The steric interactions in these systems cause that the aromatic rings are not coplanar. The molecules adopt a helical geometry.



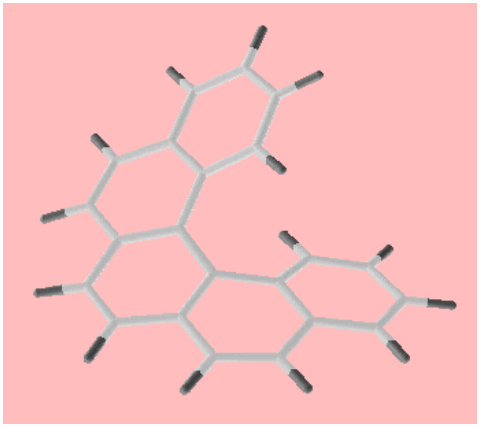
M

Fenanthrene



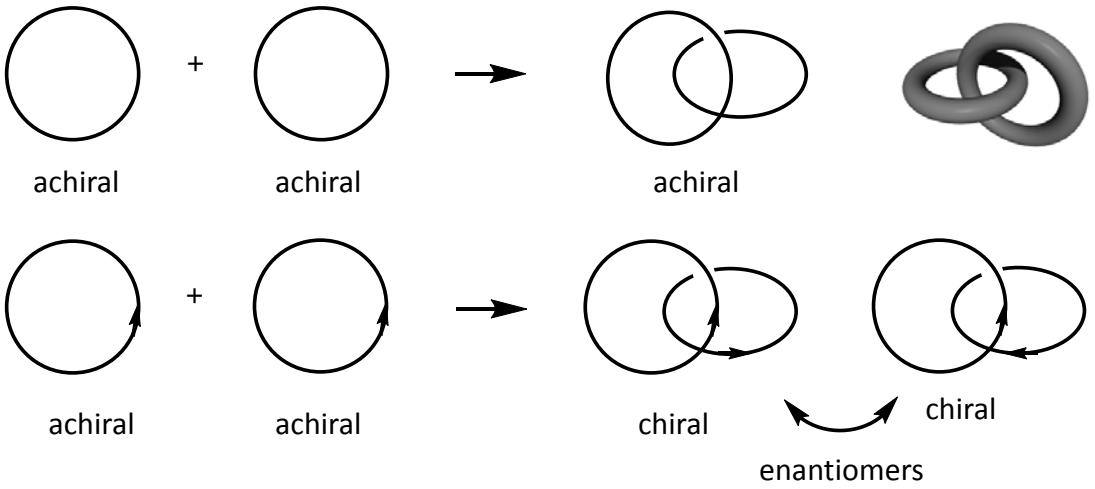
P

Helicene

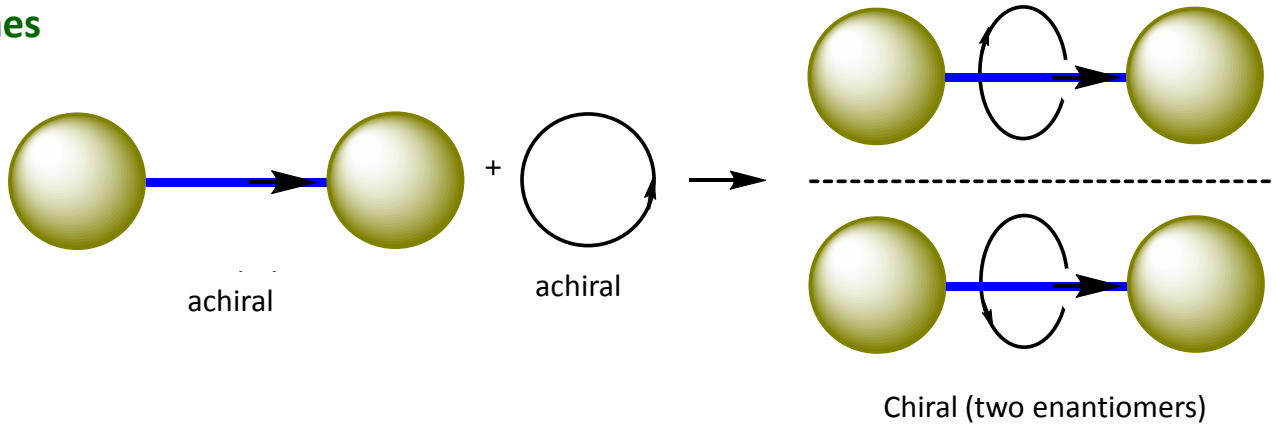


Topological chirality in catenanes and rotaxanes

The introduction of directionality in mechanically interlocked molecules (catenanes and rotaxanes) can generate what is known as topological chirality.

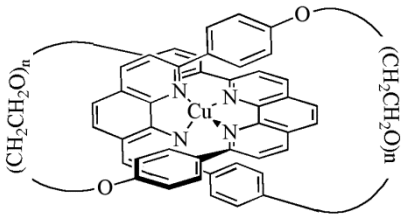


rotaxanes



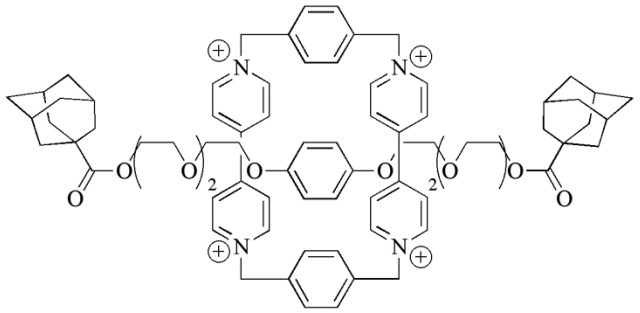
Compounds with topological chirality are chiral, although they may lack classical chirality elements (stereogenic centers, axes or planes). Therefore they can exist as a pair of enantiomers.

Achiral catenane



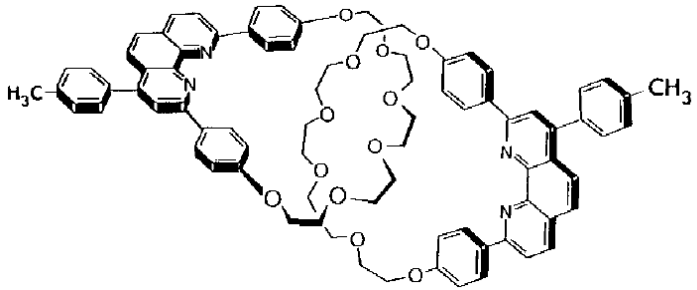
Sauvage, Dietrich-Buchecker,
Tetrahedron Lett. **1983**, *24*, 5091

Achiral rotaxane

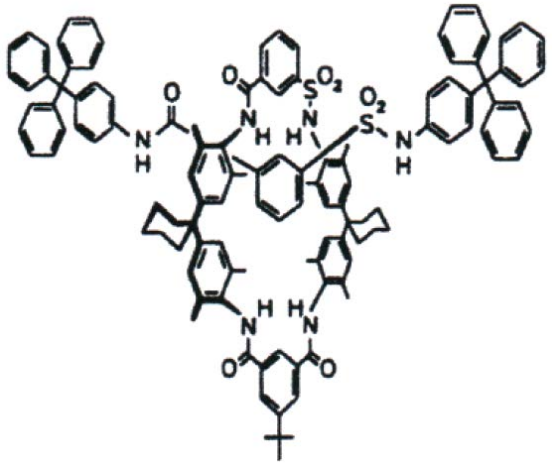


Stoddart et al.
Tetrahedron Lett. **1991**, *32*, 6235

Chiral catenane



Chiral rotaxane



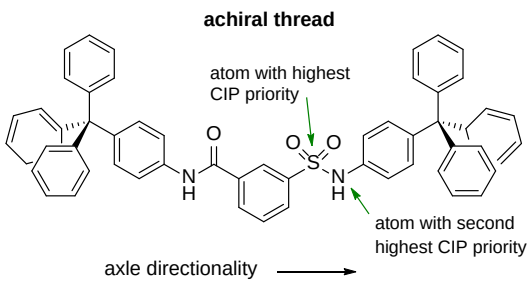
Nomenclature. a) Rotaxanes

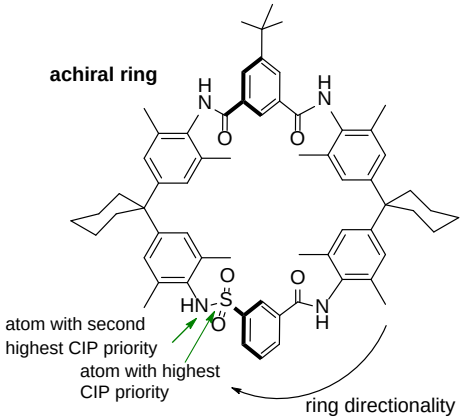
The chirality can be described through the combination of an axial vector and a polar vector that generates a screw movement that turns to the right or to the left

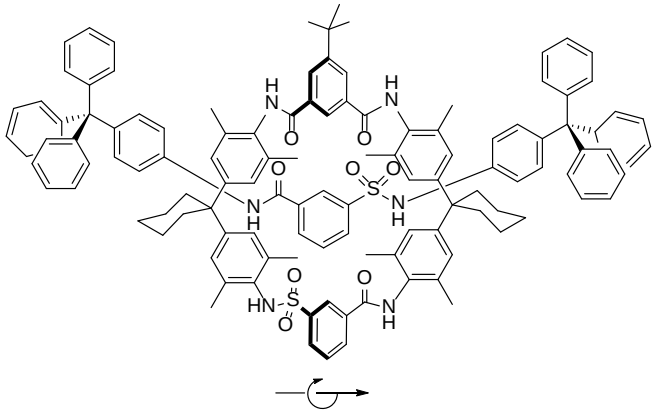
Right
configuration (R)-

Left
configuration (S)-

The directionality (→) of the axial (axis) and polar (ring) vectors is based on the CIP rules and is marked by the direction from the highest priority atom to the next priority (a → b) by the shortest path . If the combination of both vectors results in a "screw" that rotates to the right: (R); if it turns to the left: (S).







Left
configuration (S)-

For catenans, the polar vector of one of the rings is considered, while the other is considered as "open" and assigned an axial vector. And the same rules are applied.

DIASTEREOISOMERS

AT EXPERIMENTAL LEVEL: TWO DIFFERENT SUBSTANCES

- Identical chemical composition
- Different physical and chemical properties
- Optically active or not
- If they are optically active: [α] is different

At MOLECULAR LEVEL: TWO DIFFERENT MOLECULES

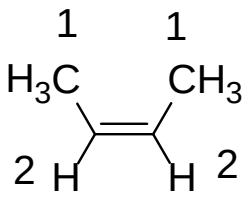
- Identical connectivity
- They are not mirror image

CAUSES OF DIASTEROISOMERISM

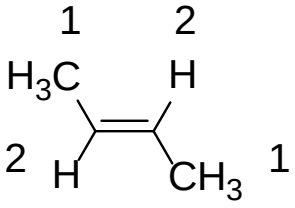
- Restrictions of rotation in unsaturated systems: Alkenes and imines
- Restrictions of rotation in cyclic systems
- Molecules with more than one stereogenic element (center, axis or plane)

DIASTEREOISOMERS: MULTIPLE BONDS

ALKENES

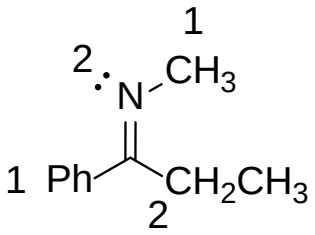


Cis-2-butene
(Z)-2-butene

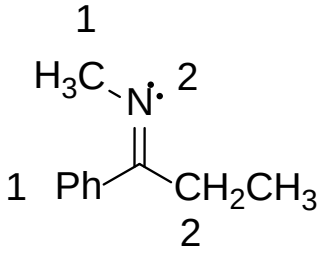


trans-2-butene
(E)-2-butene

IMINES

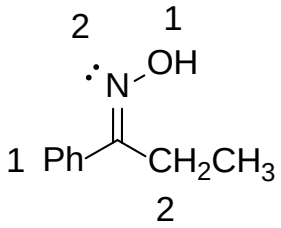


(E)-N-
(1 phenylpropylene)
methylamine

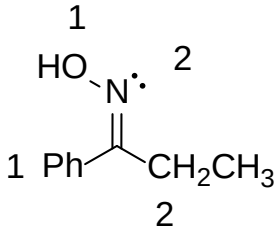


(Z)-N-
(1 phenylpropylene)
methylamine

OXIMES



Propiophenone anti-oxime
Propiophenone (E) - oxime

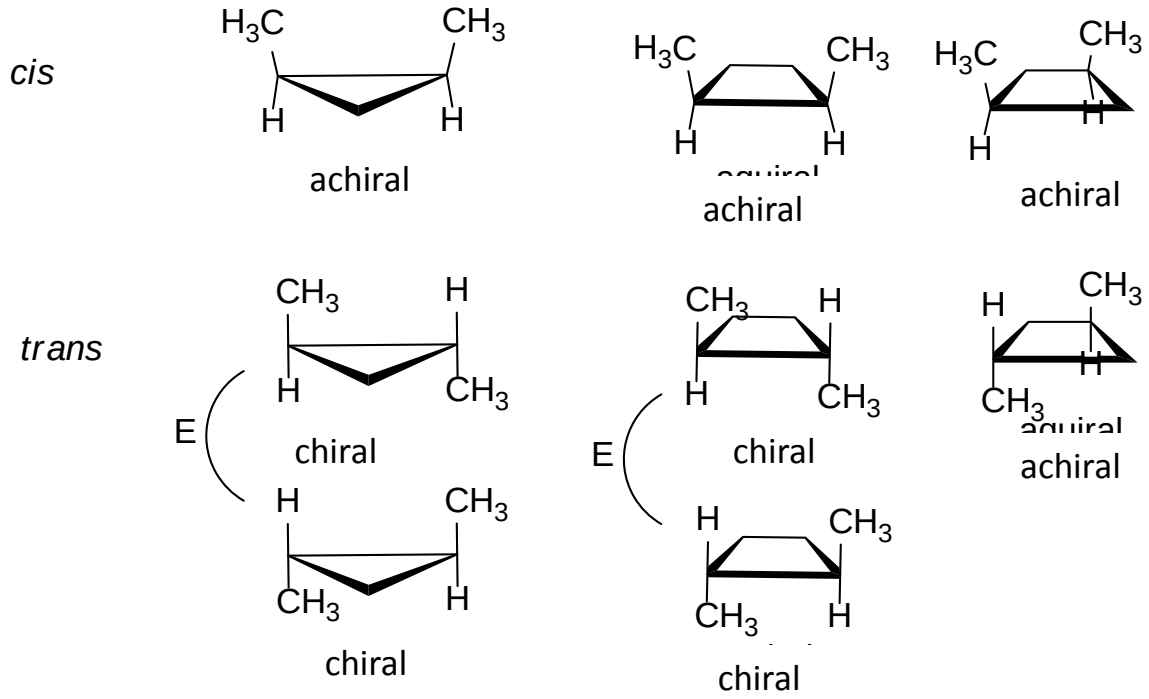


Propiophenone syn-oxime
Propiophenone (Z) - oxime

The twist restrictions of the double bonds C = C and C = N give rise to the appearance of geometric or cis-trans isomerism.

DIASTEREOISOMERS: CYCLIC COMPOUNDS

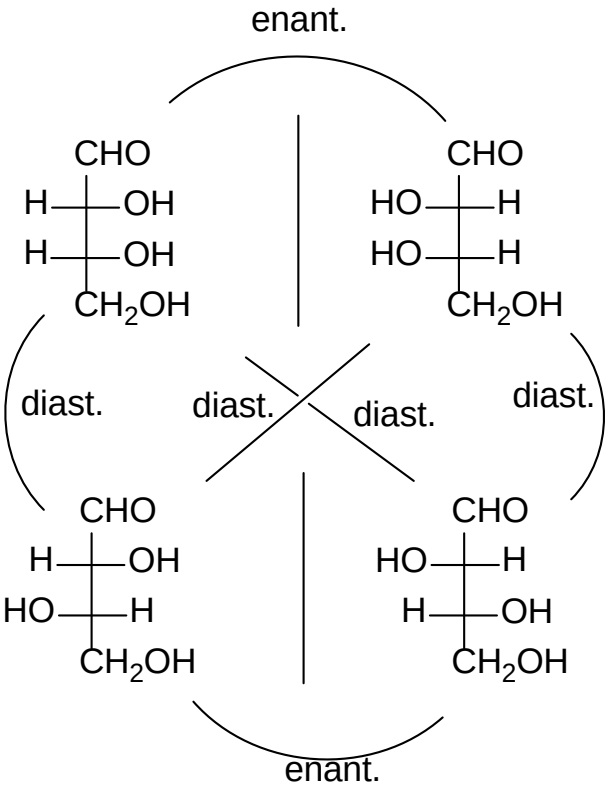
EXAMPLE: dimethylcycloalkanes



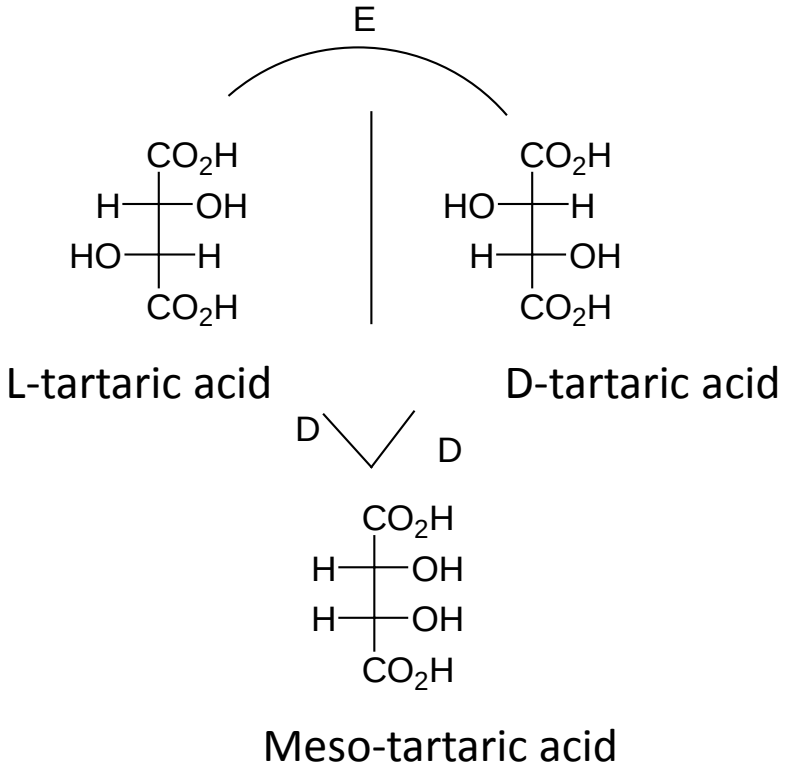
The geometric restrictions of the cyclic compounds favor the appearance of geometric isomerism (cis-trans). The resulting geometric isomers (diastereomers) can be chiral or achiral.

DIASTEREOMERS: COMPOUNDS WITH MORE THAN ONE STEROGENIC ELEMENT

2 stereogenic centers: 2,3,4-dihydroxybutanal



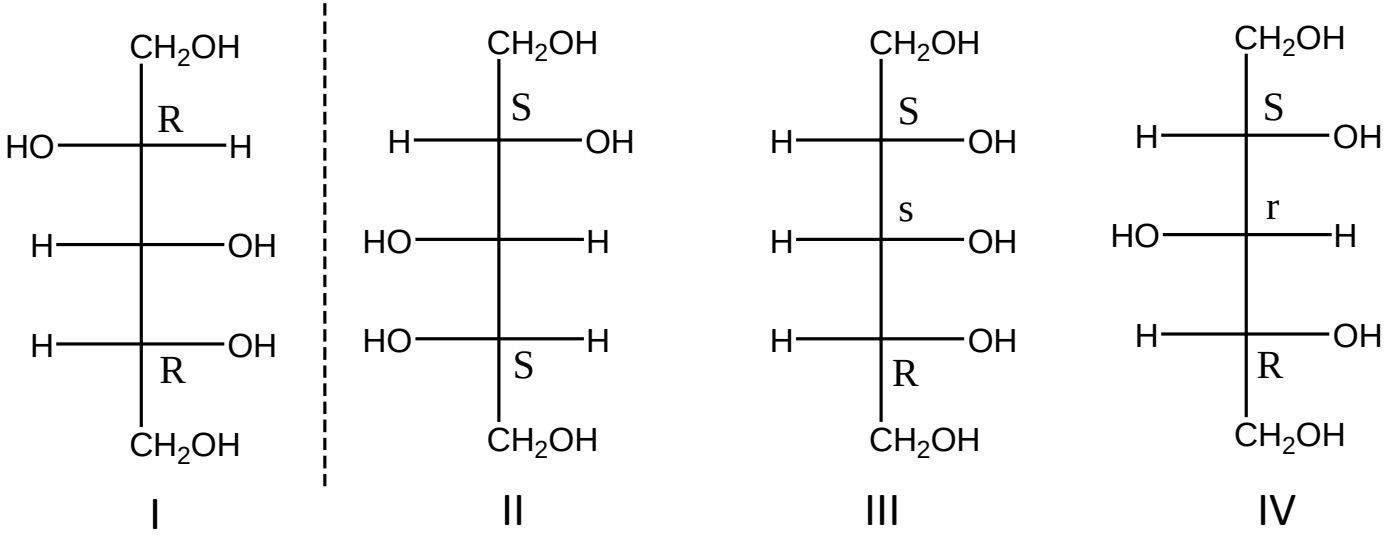
2 stereogenic centers: tartaric acid



The maximum number of possible stereoisomers is equal to 2^n, where n is the number of stereogenic elements (centers, axes, planes). Some stereoisomers are chiral and therefore there are two enantiomers. But there are also molecules that even possessing two or more stereogenic elements are achiral. They are called meso compounds.

OTHER STEREOCHEMICAL NOTATION SYSTEMS

Pseudo-asymmetric carbons



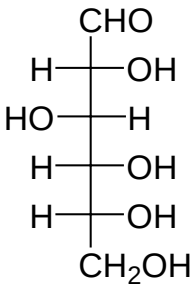
I and II are a pair of enantiomers. Compounds III and IV are meso forms since both have a plane of symmetry. They are a pair of diastereoisomers. The nomenclature of these compounds should reveal the different configuration of carbon 3 (pseudo-asymmetric carbon). For this, the sub-rule is used, which indicates that the chiral groups R have preference over the S, naming the corresponding pseudo-asymmetric carbons as s or r.

III = (*2R, 3s, 4S*)-pentane -1,2,3,4,5- pentaol

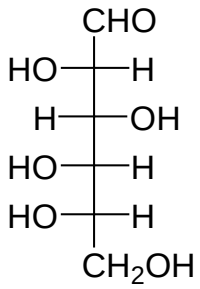
IV = (*2R, 3r, 4S*)-pentane -1,2,3,4,5- pentaol

OTHER STEREOCHEMICAL NOTATION SYSTEMS

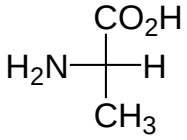
D-L: It is used for sugars and amino acids. In the Fischer projection the substituent of the last stereogenic center is observed. In products D this is to the right, and in the L to the left.



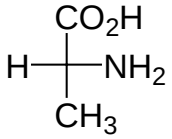
D-(+)-glucose



L-(-)-glucose

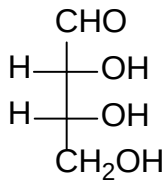


L-(+)-alanine

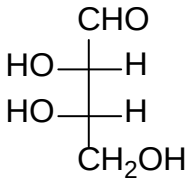


D-(-)-alanine

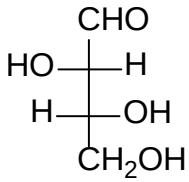
Erythro-threo: Relative stereochemistry. Indicates whether two consecutive substituents are on the same side (erythro) or opposite sides (threo) on a Fischer projection



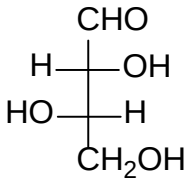
D-erythrose



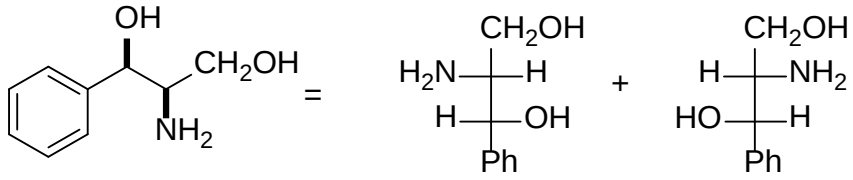
L-erythrose



D-threose



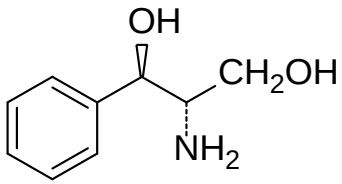
L-threose



(d,l)-threo-1-phenyl-1,3-propanediol

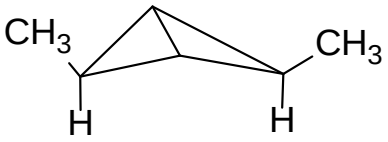
OTHER STEREOCHEMICAL NOTATION SYSTEMS

R*,S*: Relative stereochemistry, when the absolute stereochemistry is not known or is irrelevant.

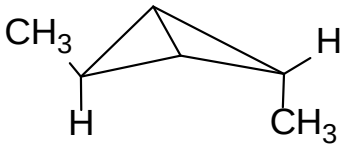


(1R*,2S*-2-amino-1-phenyl-1,3-propanediol.
Rel-(1R,2S)-2-amino-1-phenyl-1,3-propanediol

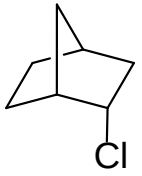
Exo-endo In bicyclic folded systems. The endo substituent is directed towards the interior of the carbon skeleton while the exo is directed towards the outside.



Exo,exo-2,4-dimethylbicyclobutane



Exo,endo-2,4-dimethylbicyclobutane

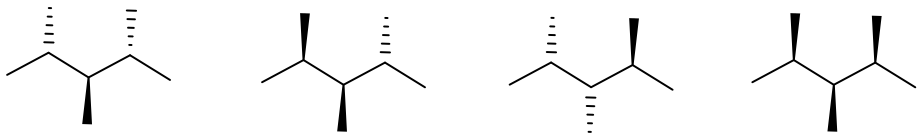


endo-2-chloroborrnane

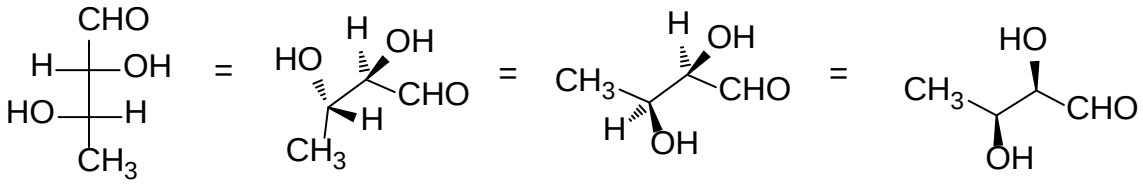
o

OTHER STEREOCHEMICAL NOTATION SYSTEMS

Syn-anti: Indicates the relative orientation of the substituents in a linear chain. The main chain is drawn in a zig-zag pattern.

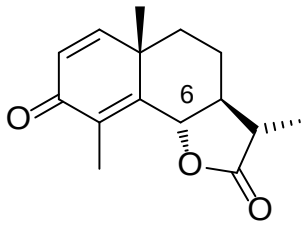


anti,syn Syn,anti Syn,anti Syn,syn

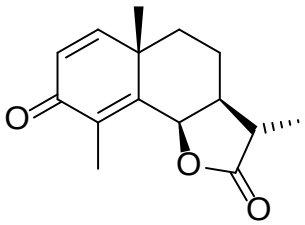


threo syn

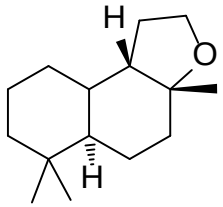
Epi: Epimers are diastereomers that differ in the configuration of a single stereogenic center.



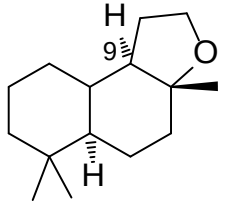
santonin



6-epi-santonin



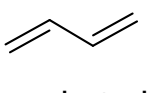
ambrox



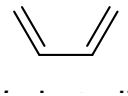
9-epi-ambrox

OTHER STEREOCHEMICAL NOTATION SYSTEMS

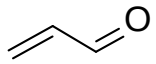
s-cis y s-trans: Indicates the conformation around a single bond that has a certain character of double bond that gives it a torsional barrier.



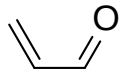
S-trans-butadiene



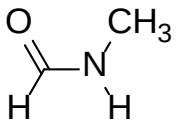
S-cis-butadiene



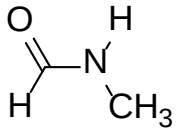
S-trans-propanal



S-cis- propanal



S-cis-N-methylformamide



S-trans-N methylformamide

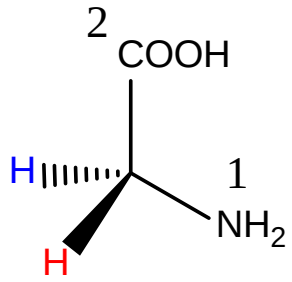
PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

Concept of prochirality

Prochiral center: achiral center that becomes chiral when two identical substituents on noted center (atoms or groups of atoms) become different from each other. The concept also extends to prochiral axes and planes)

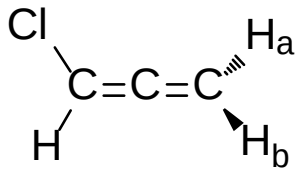
Prochiral groups: The two equal groups attached to a prochiral center (the concept also extends to prochiral axes and planes)

Descriptor pro-R and Pro-S. It is used to differentiate two prochiral groups. To assign a descriptor, the CIP priority rules are applied and arbitrarily assigning a higher priority to the prochiral group that we are considering with respect to its equal.



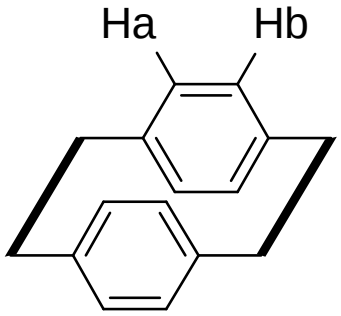
H = pro-*R*
H = pro-*S*

Prochiral carbon



Ha is pro-R
Hb is pro-Sa

Prochiral axis

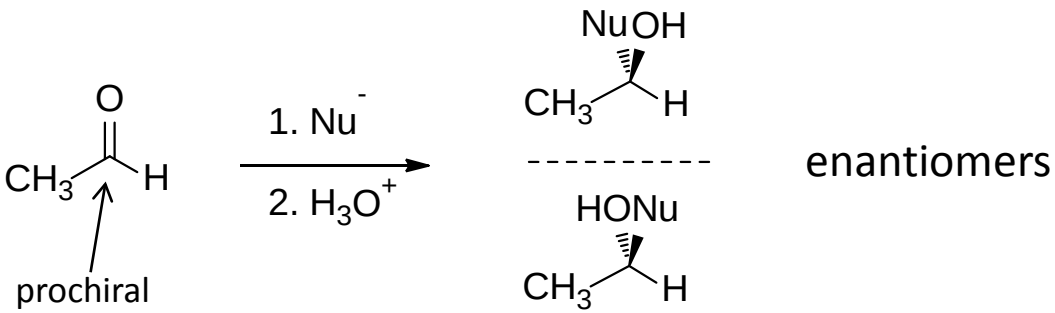


Ha is pro-Sp
Hb is pro-Rp

Prochiral plane

Prochiral sp^2 center

The concept of prochirality can be extended to trigonal carbons (sp^2). Addition reactions to double bonds generate a tetrahedral carbon (sp3). The new carbon can be chiral, and its configuration will depend on the side the reagent approaches. In this case we talk about facial prochirality.



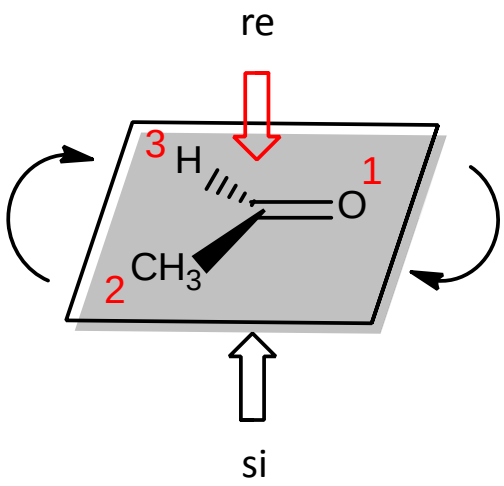
PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

***Re* and *Si* descriptors.** They are used to distinguish the two prochiral faces of a trigonal atom:

1.- The observer is placed in front of one of the faces of the trigonal atom.

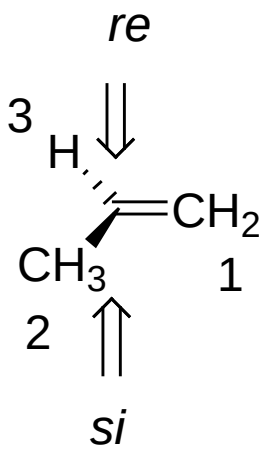
2.- The priority of the bonded groups is established according to the rules of Cahn-Ingold-Prelog, and the direction of rotation is observed.

3.- If the substituents describe a clockwise trajectory, the face is the *Re*-face and if counterclockwise, the *Si*-face.

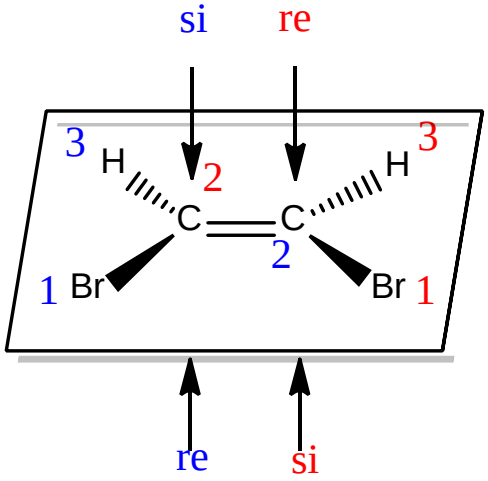


In the case of molecules with carbon-carbon double bonds, the notation must be applied independently for each prochiral carbon.

1 prochiral carbon

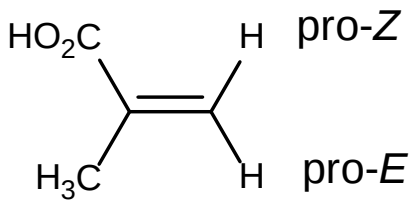


2 prochiral carbons



PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

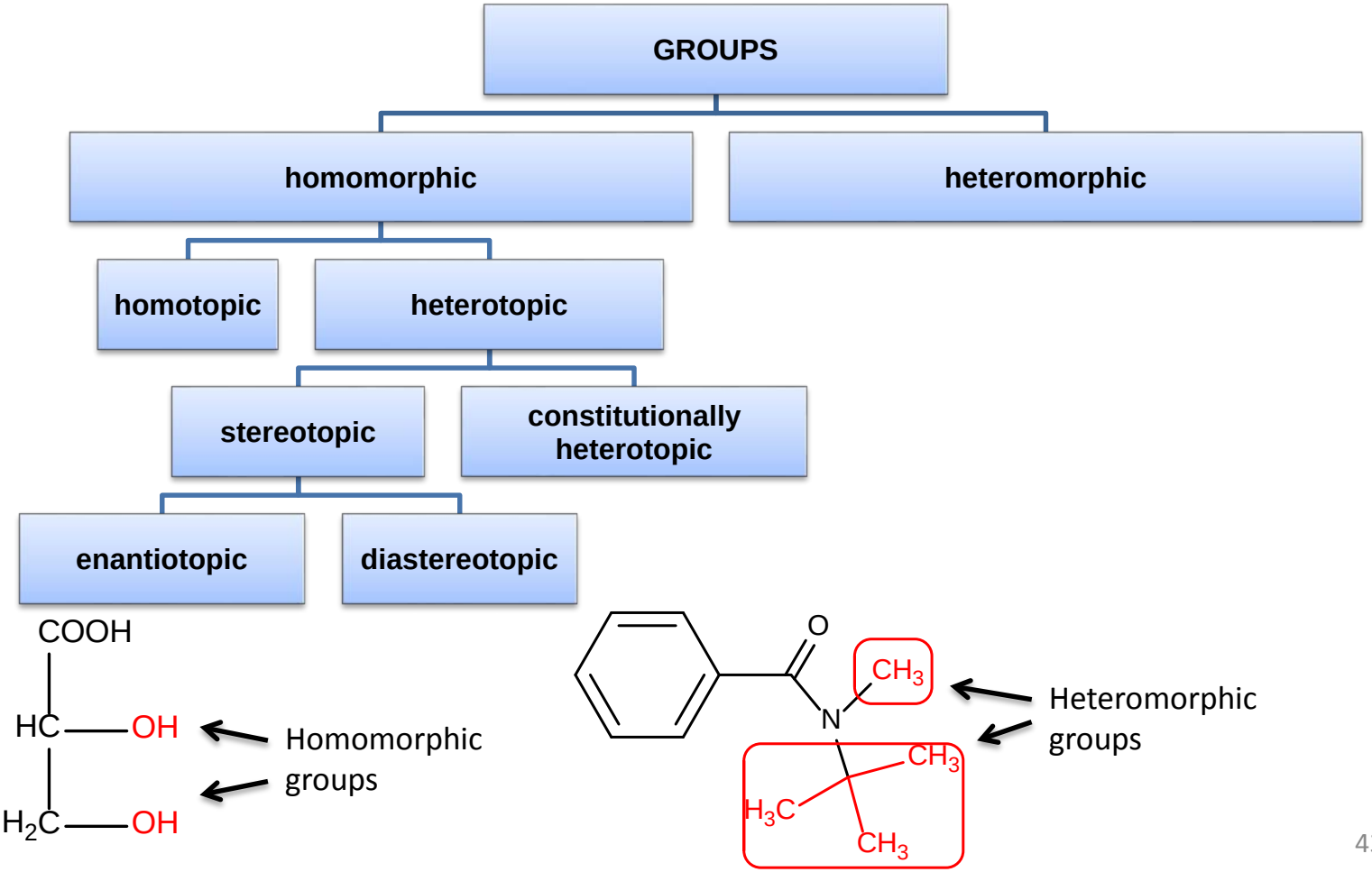
Prostereoisomerism: Descriptor pro-Z and Pro-E. It is used to refer to two pro-stereogenic groups located on a trigonal carbon sp^2. The CIP-sequence rules are applied and of the two equal groups, the highest priority is assigned to the group that we are considering.



ATTENTION: The replacement of a pro-R group by a different group does not necessarily mean that a carbon with an R configuration will be generated. This will depend on whether the new group maintains the same priority as the replaced group. (The same applies to the pro-Z and pro-E groups and the Re and Si faces)

PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

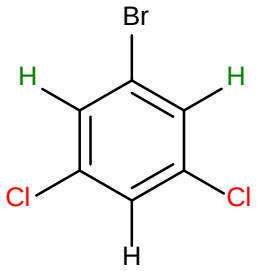
Topocity considers the stereochemical relationships between two identical substituents (atoms or groups of atoms) within a molecule. I.e., it classifies above mentioned substituents according to their symmetry relation. The word "topic" comes from the Greek "topos" which means "place"

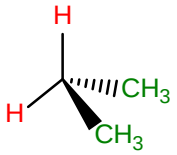


PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

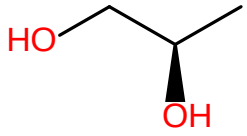
Two identical atoms or two groups of constitutionally identical atoms are called homomorphic. If they are different groups, they are called heteromorphic. The **topicity** considers the relationships between two homomorphic groups of a molecule.

Two identical substituents (homomorphic) that occupy equivalent environments, both in terms of chemical properties and symmetry, are called **homotopic**.

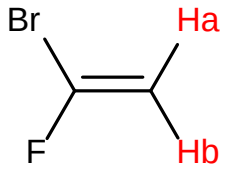




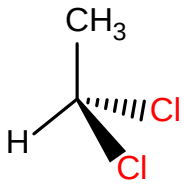
If two identical groups are in different environments (topologically not equivalent) they are called **heterotopic**. These can be constitutionally heterotopic or stereotopic.



Constitutionally heterotopic



stereotopic diastereotopic



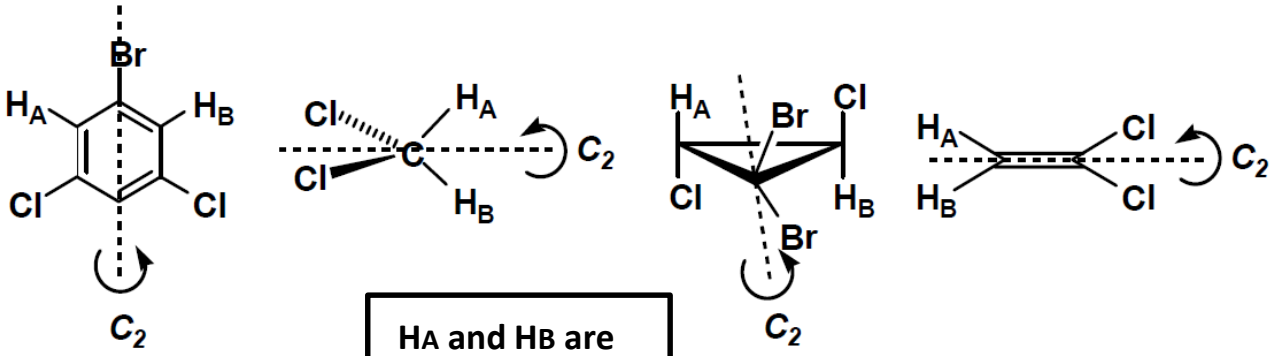
stereotopic enantiotopic

PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

The difference between homotopic, enantiotopic or diastereotopic groups can be made according to two criteria: symmetry and substitution criteria.

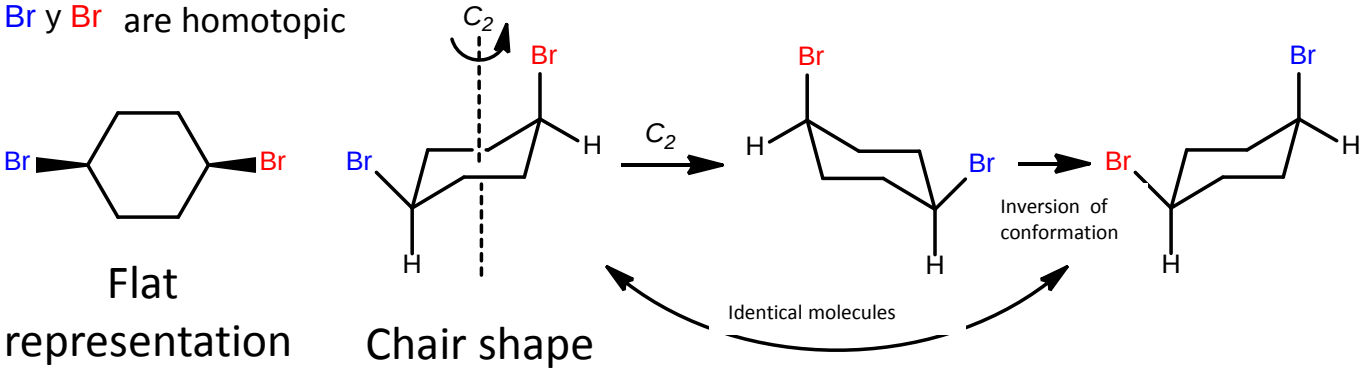
Homotopic groups: They are topologically equivalent homomorphic groups.

Criterion of symmetry: Those groups that can be interchanged by a rotation about a C_n rotation axis giving a structure which is indistinguishable from the original.

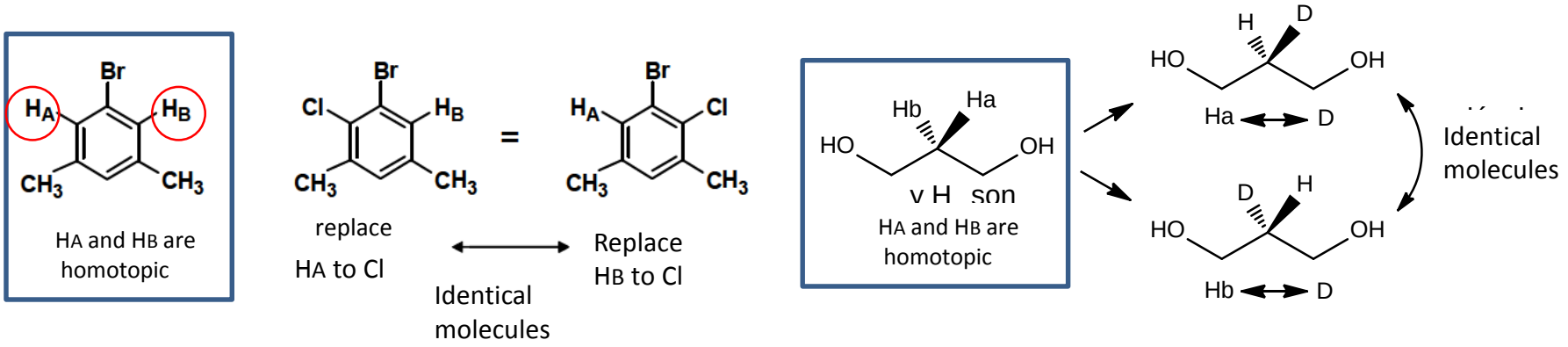


HA and HB are homotopic

Br y Br are homotopic



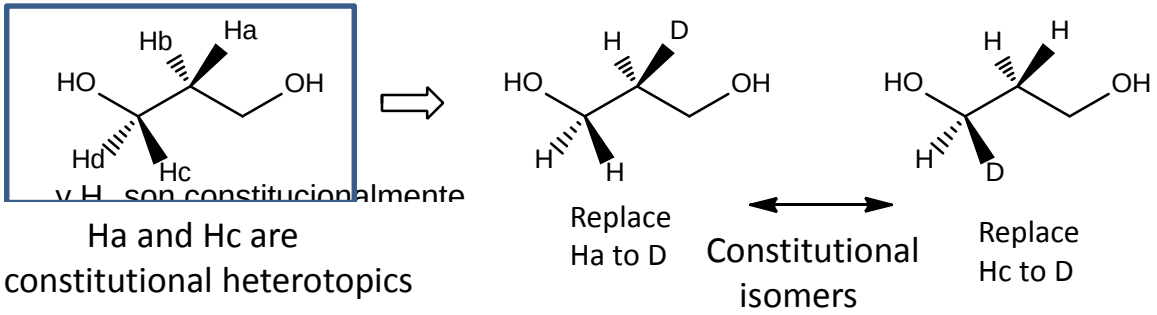
Criterion of substitution: If we alternately replace one and the other group with different atoms, the resulting molecules are identical.



Constitutionally heterotopic groups: They are topologically non-equivalent groups because they present different bonding with the rest of the atoms of the molecule.

Criterion of symmetry: Not related to symmetry.

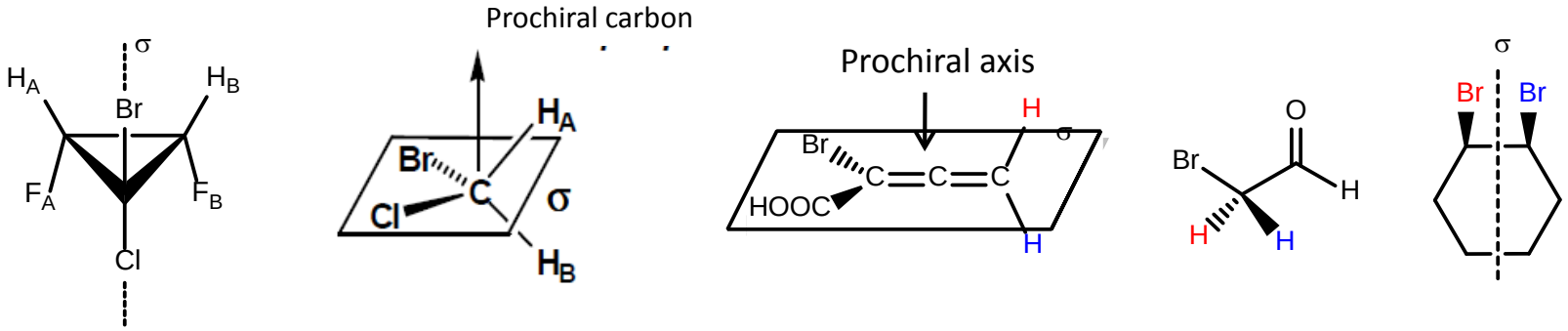
Criterion of substitution: By alternative substitution them with different atoms they give two constitutional isomers.



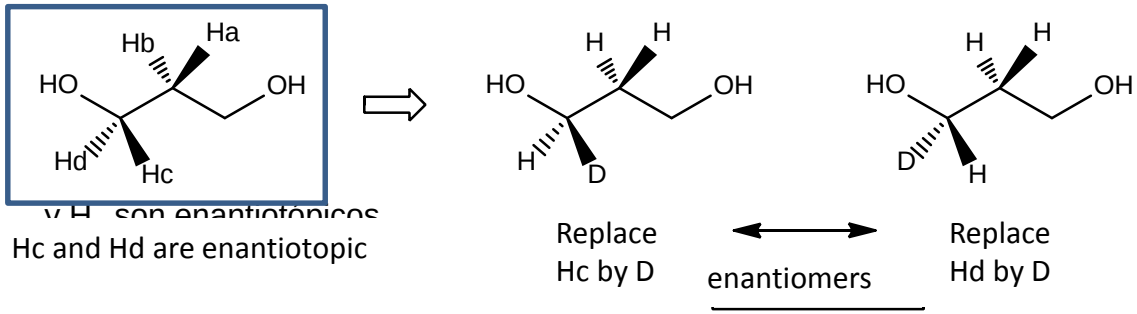
PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

Enantiotopic groups: They are homomorphic groups which are topologically not equivalent.

Criterion of symmetry: They are those that can be exchanged by reflection in a plane of symmetry (σ) giving a structure indistinguishable from the original.



Criterion of substitution: If we alternately replace one and the other group with different atoms, the resulting molecules are enantiomers.



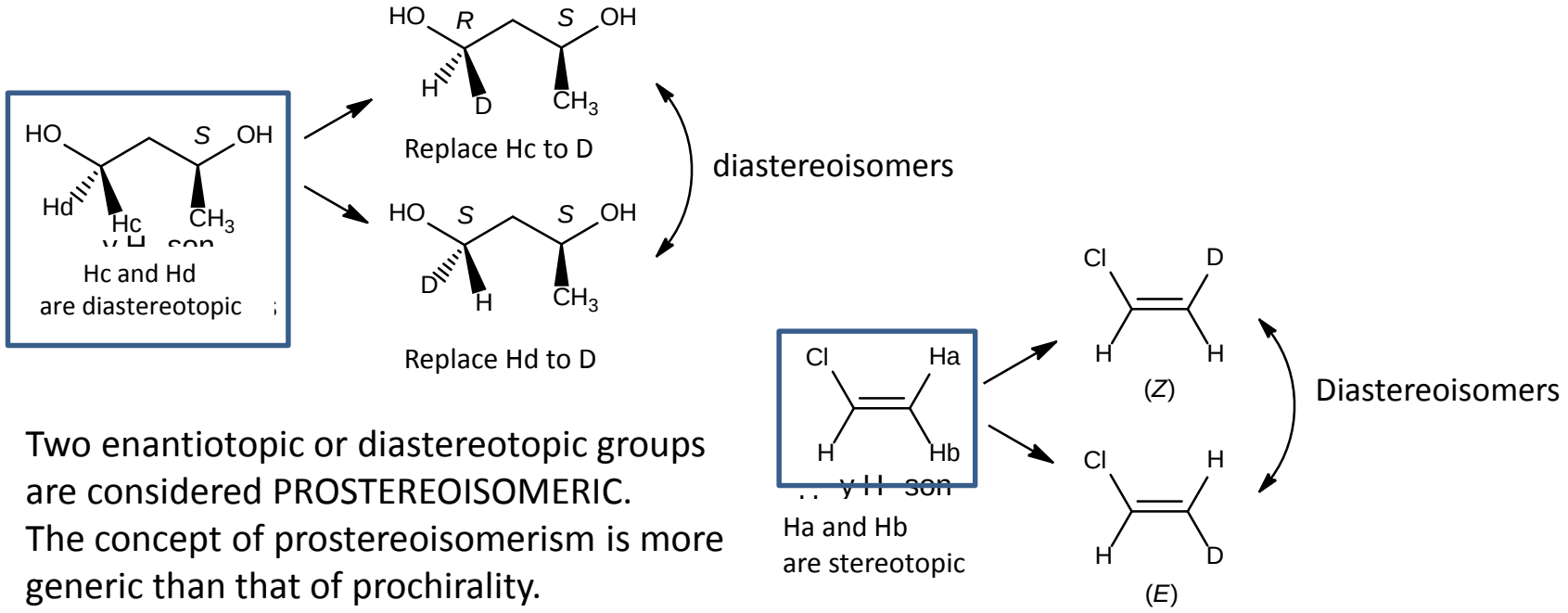
An atom directly bonded to two enantiotopic groups is a PROCHIRAL center (the concept extends to prochiral axes and planes).

PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

Diastereotopic groups: They are topologically non-equivalent homomorphic groups.

Criterion of symmetry: They can not be exchanged via symmetry operations.

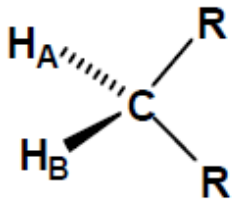
Criterion of substitution: By alternately replacing them with different atoms, two diastereomers are obtained.



Two enantiotopic or diastereotopic groups are considered PROSTEREOISOMERIC.
The concept of prostereoisomerism is more generic than that of prochirality.

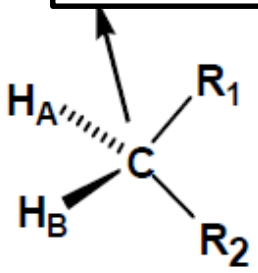
PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

Topicity in methylene groups (-CH2-): Summary



Ha and Hb are homotopic

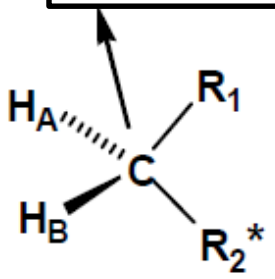
Prochiral carbon



R_1 and R_2 are achiral

Ha and Hb are enantiotopic

Prochiral carbon



R1 is achiral
R2 is chiral

Ha and Hb are diastereotopic

PROCHIRALITY AND PROSTEREOISOMERISM. TOPICITY

BEHAVIOUR OF THE HOMOMORPHIC GROUPS VERSUS CHIRAL OR ACHIRAL REAGENTS AND IN NMR ACCORDING TO THEIR TOPICITY

Indistinguishable

-Homotopic groups

Distinguishable only by chiral reagents (or solvents)

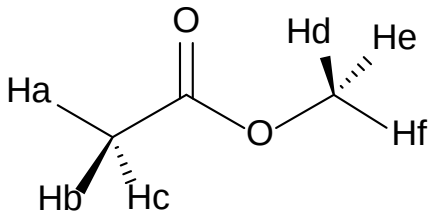
-Enantiotopic groups

Distinguishable by any reagent and by NMR

-Constitutionally heterotopic groups

-Diastereotopic groups

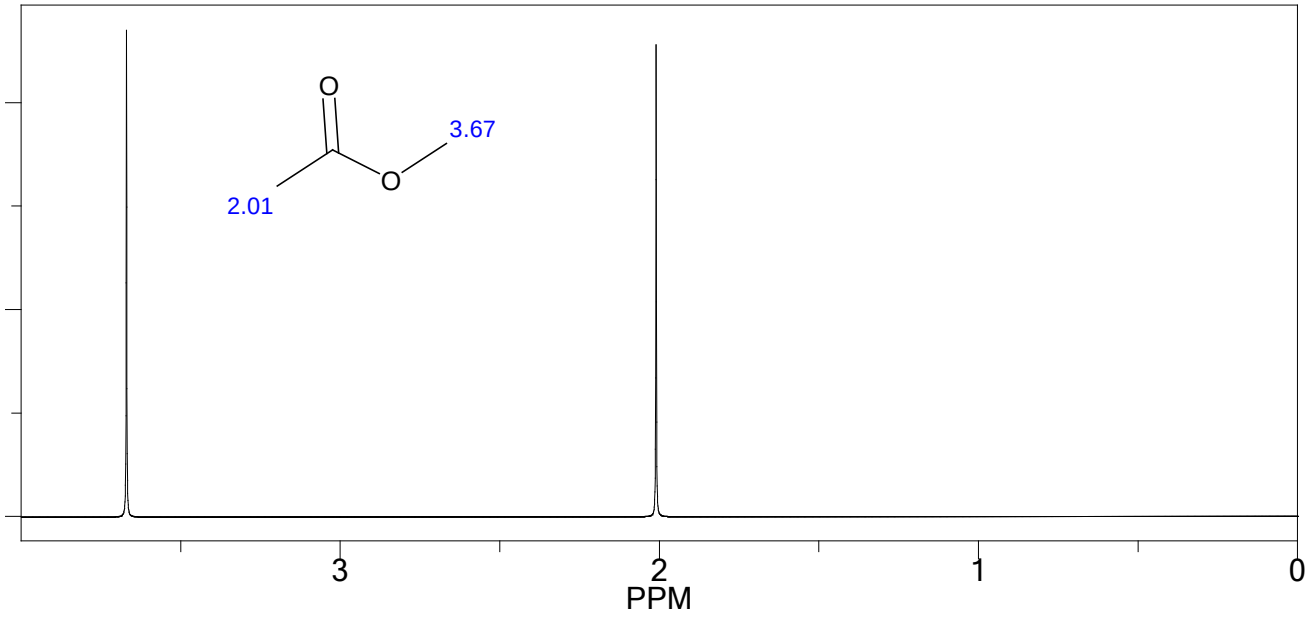
TOPICITY AND NMR: Homotopic and heterotopic constitutional groups



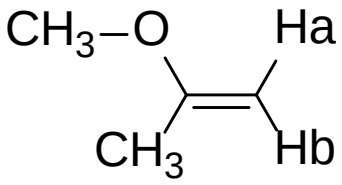
Constitutionally heterotopic

Ha, Hb and Hc are homotopic: 2,01 ppm

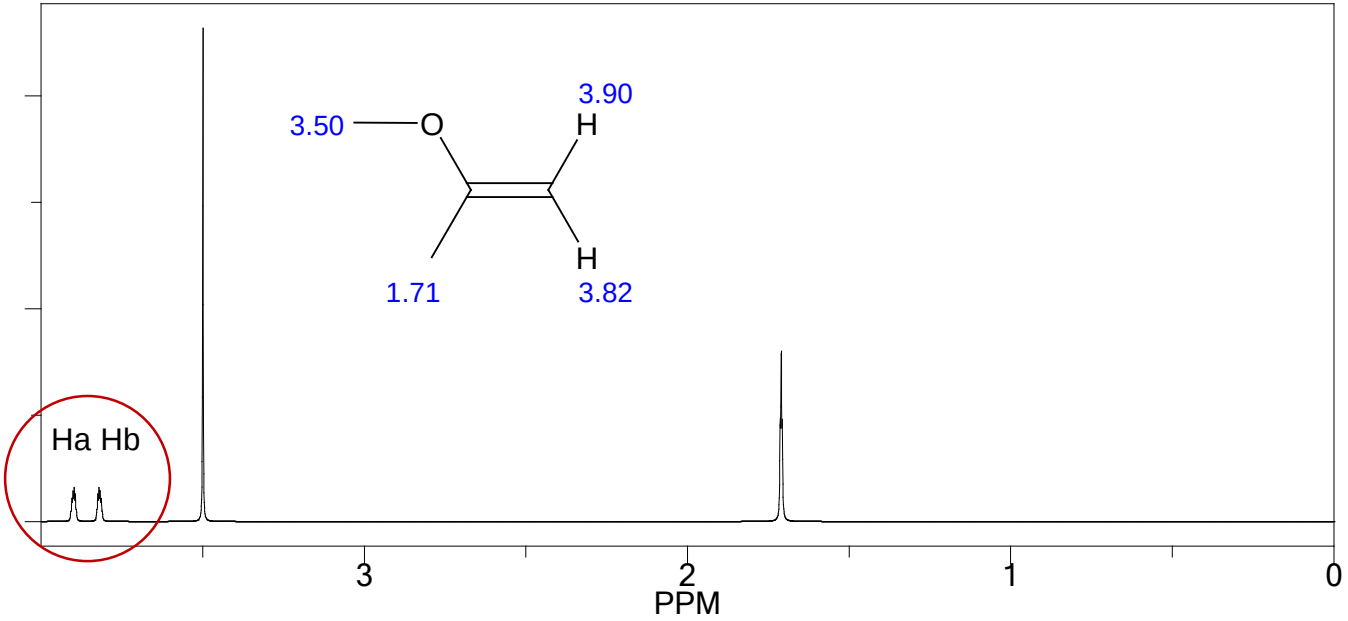
Hd, He and Hf are homotopic: 3,67 ppm



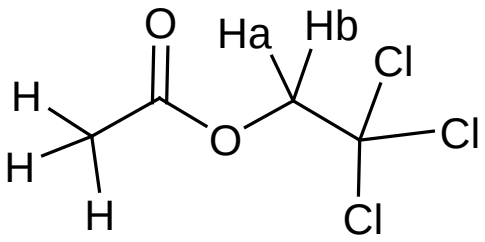
TOPICITY AND NMR: **Diastereotopic groups**



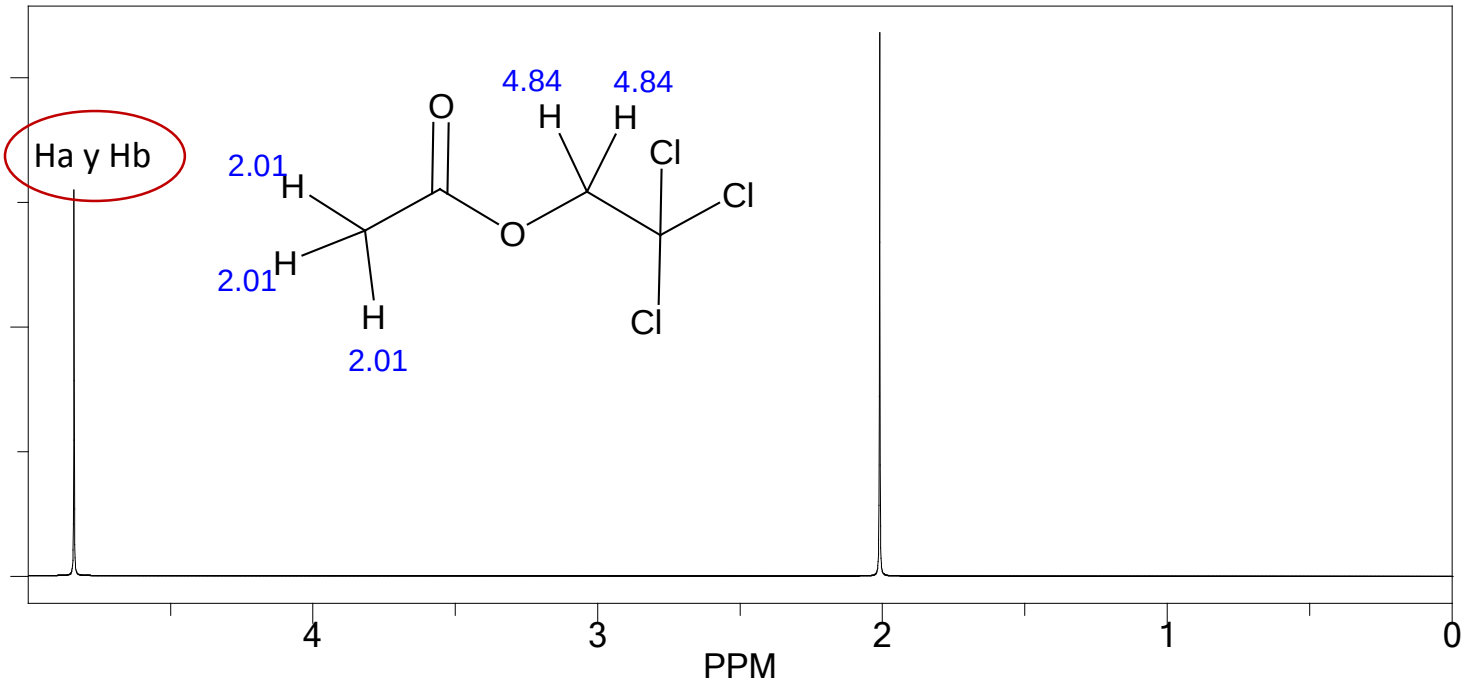
Ha and Hb: diastereotopic, distinguishable



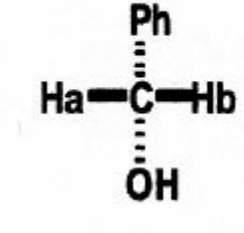
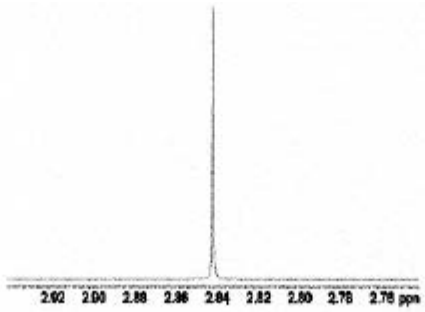
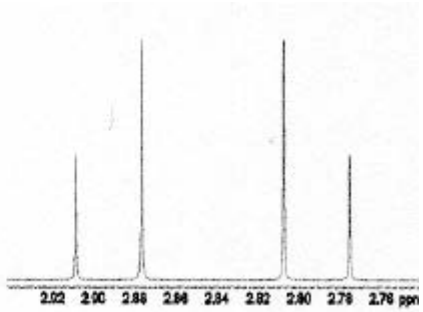
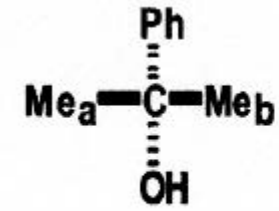
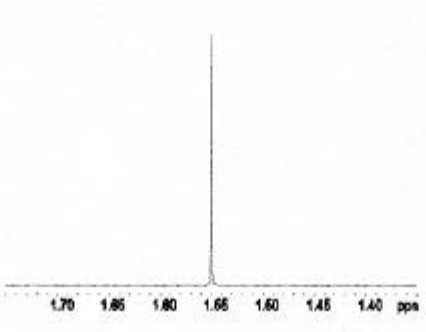
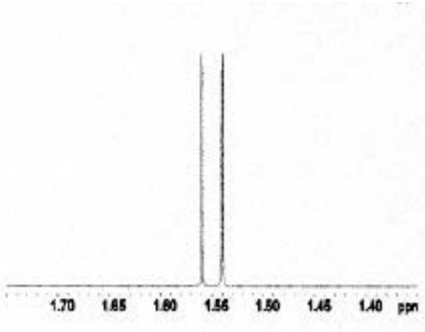
TOPICITY AND NMR: enantiotopic groups in achiral solvent (CDCl3)



H_a and H_b are enantiotopic, not distinguishable by NMR

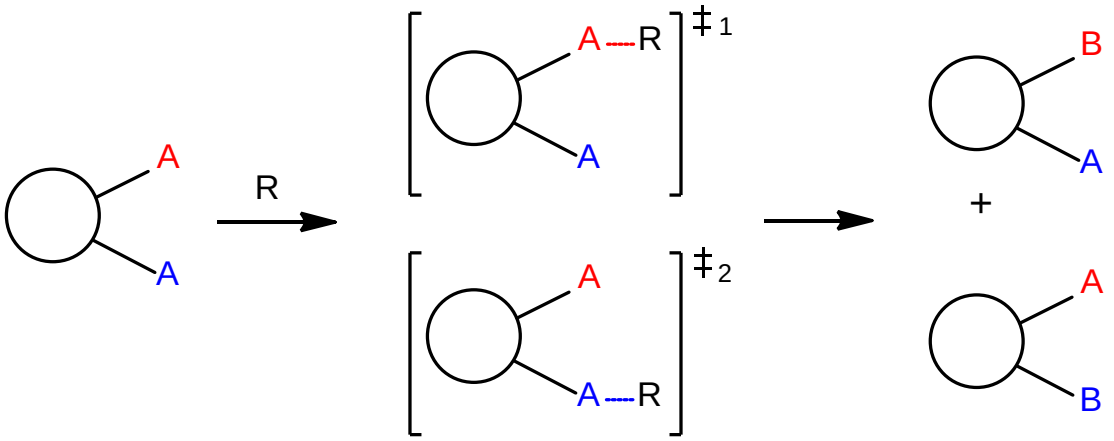


TOPICITY AND NMR: enantiotopic groups in chiral solvent

	Appearance of the spectrum ^{1}H NMR Achiral solvent	Appearance of the spectrum ^{1}H NMR Chiral solvent
		
		

TOPICITY AND REACTIVITY

Let us suppose an achiral reagent R, capable to react with two homomorphic groups of the same molecule according to the following scheme.

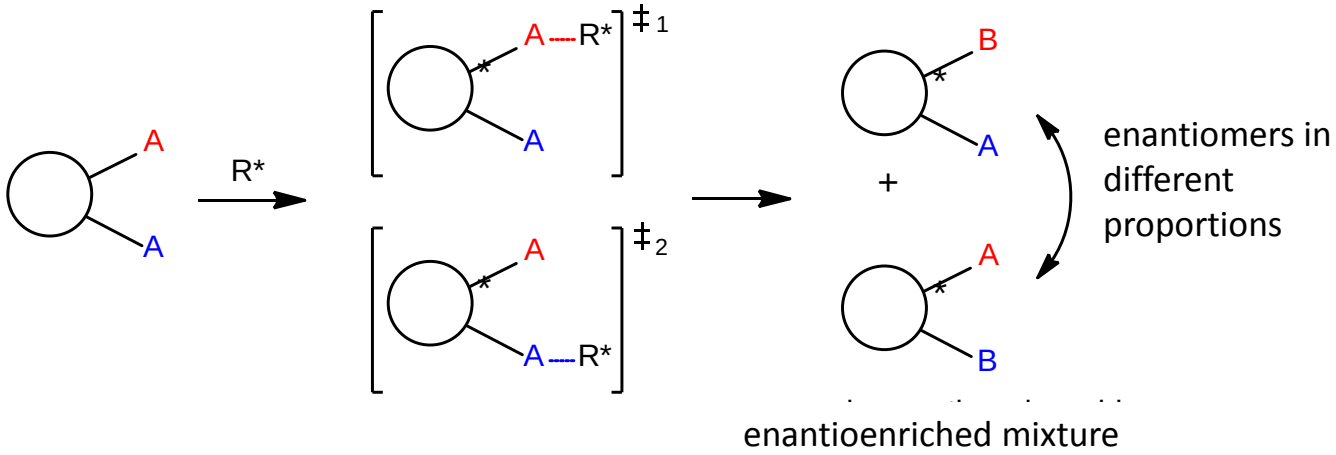


1. If A and A are homotopic, a single reaction product is obtained through a single transition state (the two transition states are identical).
2. If A and A are enantiotopic, both transition states are enantiomers and therefore of equal energy. Two enantiomers are obtained in equal proportions (racemic mixture).
3. If A and A are diastereotopic, both the transition states and the products are diatereoisomers. The final products can be obtained in different proportions.

(see potential E diagrams)

TOPICITY AND REACTIVITY

If **reagent R** is **chiral** , the situation is different for enantiotopic groups

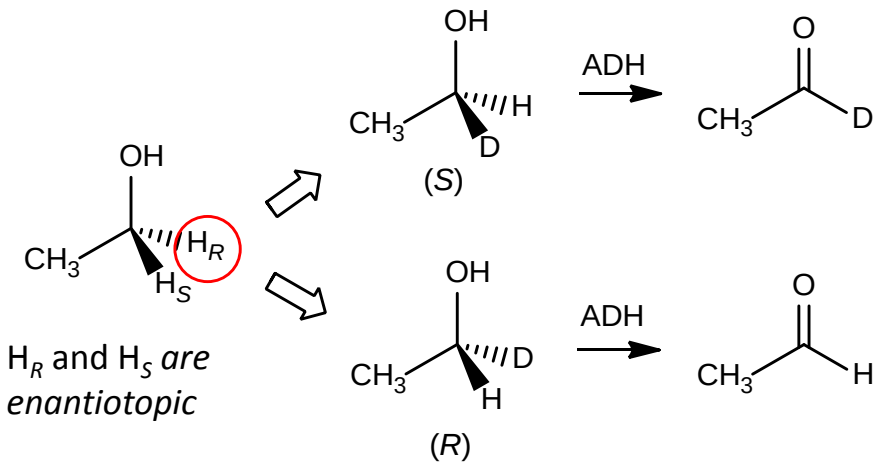


1. If A and A are homotopic , a single reaction product is obtained through a single transition state.
2. If A and A are diastereotopic, both the final products and the transition states are diastereoisomers and different proportions of products are produced.
3. If A and A are **enantiotopic** reactions **proceed** through transition states that are diastereoisomeric (different energy). If the chiral part of the reagent is not incorporated in the final product, the final products obtained are enantiomers but can be formed in different proportions (enantioenriched mixture)

(see potential E diagrams)

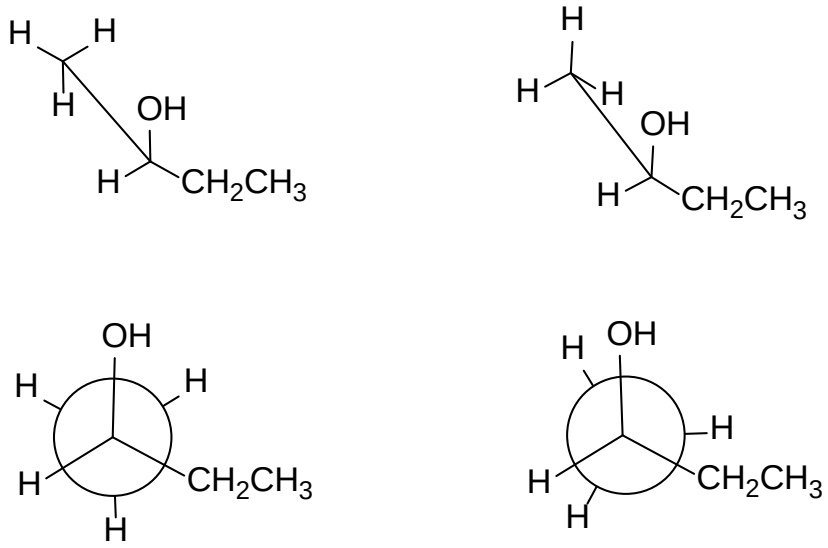
TOPICITY AND REACTIVITY

Example: Oxidation of ethanol to acetaldehyde catalyzed by the enzyme alcohol dehydrogenase (ADH)



Ethanol has two potentially reactive enantiotopic hydrogens. The active center of the ADH enzyme is of chiral nature. By means of deuteration experiments it can be proved that the oxidation of ethanol to acetaldehyde implies the transfer of only the hydrogen *R* to the enzyme.

CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS



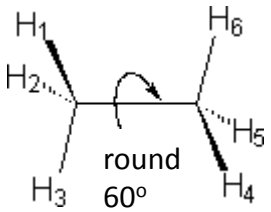
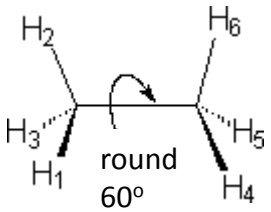
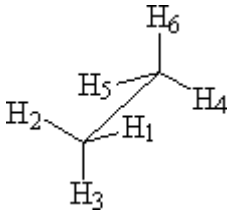
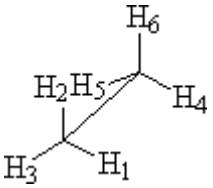
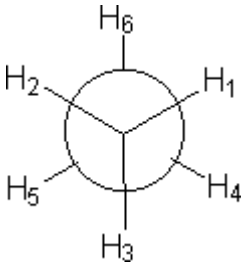
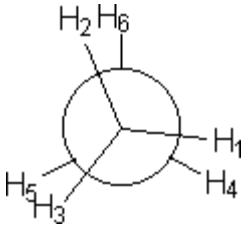
Molecular conformations are the different relative spatial dispositions that the atoms of a molecule can adopt, as a consequence of rotations through simple bonds, at room temperature.

The conformations that correspond to energy minimums are called **conformers** . Normally the conformers are rapidly converted to each other, so that at the equilibrium the lowest energy is the most abundant . This distribution of the conformers can have important repercussions on the *reactivity* of the molecule.

CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

Hydrocarbons . Review the concepts of Organic Chemistry (2nd year)

Representations

	Alternating	**Eclipsed**
Lines and wedges		
Easel		
Newman		

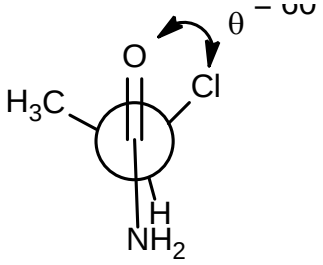
Conformational interconversion in most single molecules occurs rapidly to room T. The isolation of pure conformers is not normally possible.

CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

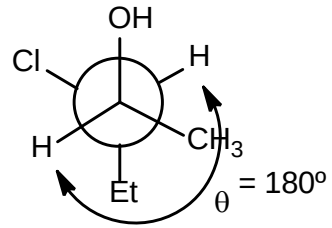
The different conformations around a simple bond can be named according to the dihedral angle θ (theta).

Convention to assign the dihedral angles:

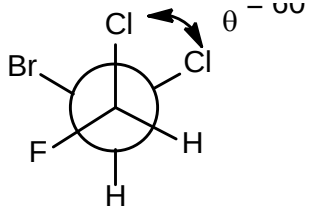
- If the substituents of one end of the single bond are all different from those of the other end, θ is the angle formed by the substituents of higher priority of each end of the bond.



- If there is only one substituent common to both ends of the bond, θ is the angle between both substituents, although their priority was lower than that of the rest of the groups.

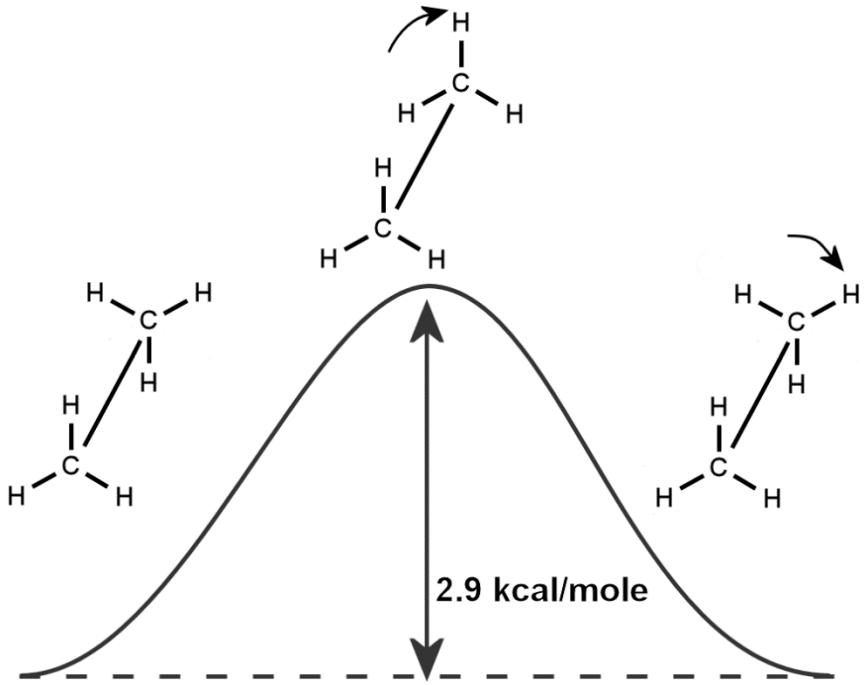


- If there are two or three common substituents, θ is defined by the common substituents of higher priority



CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

Conformations of ethane

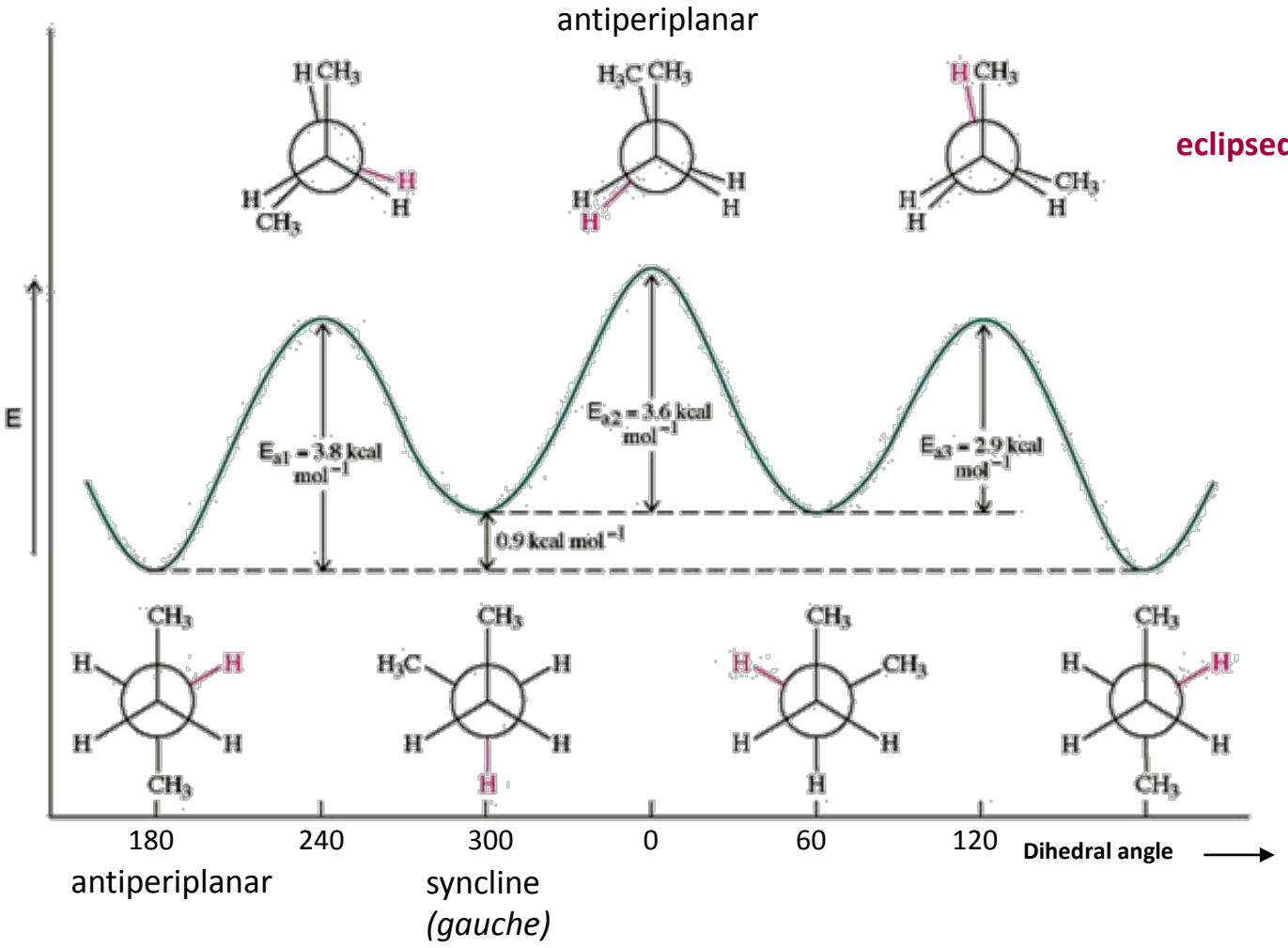


Alternating conformations are more stable than eclipsed ones

Rotation barrier: 3 kcal/mol ⇨ **torsional tension** (1 kcal/mol per interaction)

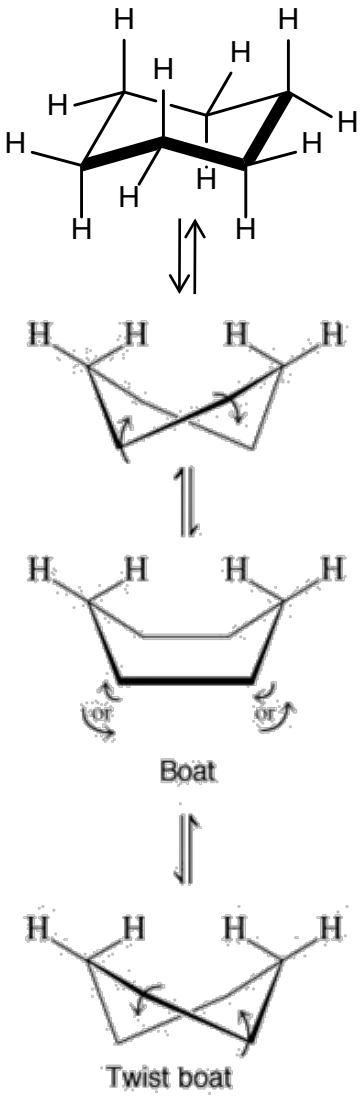
CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

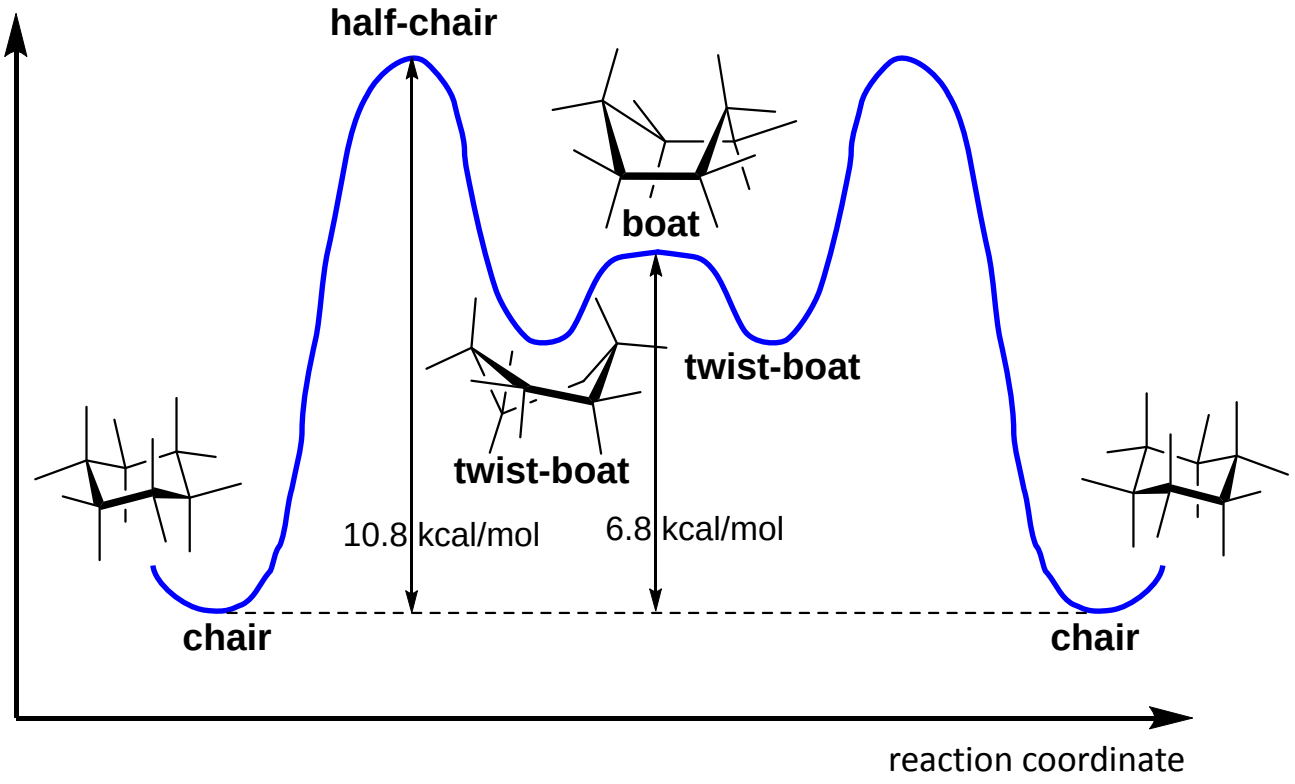
Conformations of butane: anti, gauche and eclipsed



CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

Conformations of cyclohexane: chair, boat and twist-boat

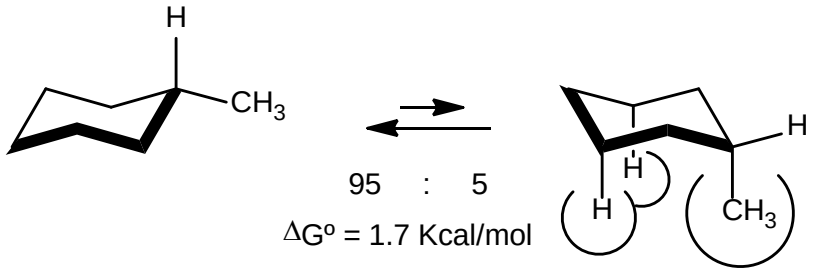




At room temperature, interconversion between conformers occurs about 100,000 times per second!

CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

Unfavorable **1,3-diaxial interactions** shift equilibrium toward equatorial conformers.



Free energy variation for the interconversion between conformers of cyclohexane with an equatorial or axial substitution			
sustituent	**ΔGº(kcal/mol)**	**sustituent**	**ΔGº(kcal/mol)**
H	0	F	0.25
CH_3	1.70	Cl	0.52
CH_3CH_2	1.75	Br	0.55
$(CH_3)_2CH$	2.20	I	0.46
$(CH_3)_3C$	ca. 5	OH	0.94

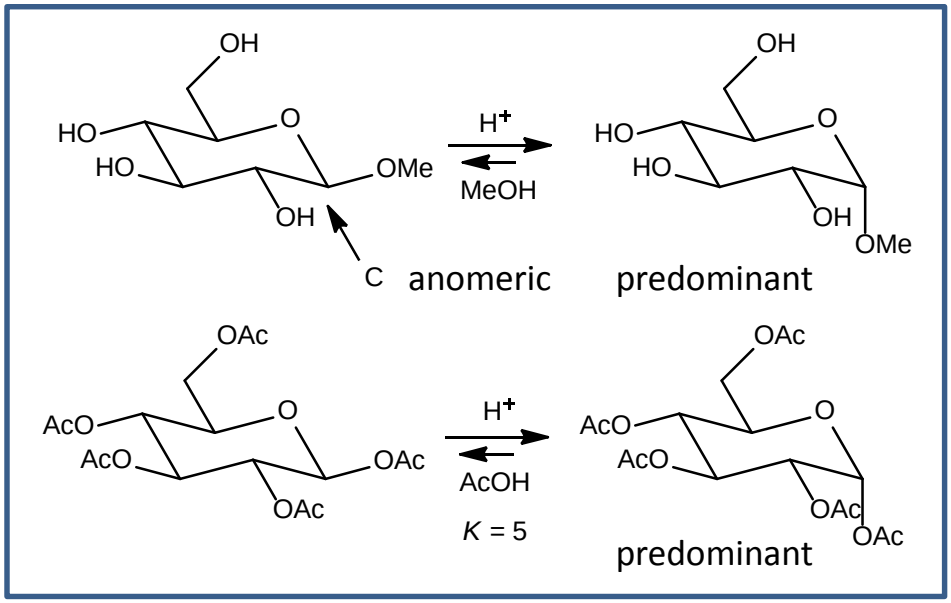
Note: In all the examples the equatorial conformer is the most stable.

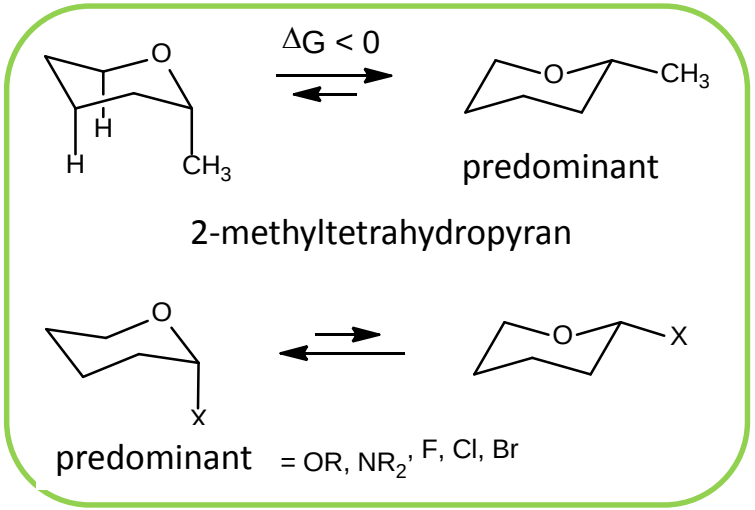
CONFORMATIONAL ANALYSIS. STEREOELECTRONIC EFFECTS

Systems containing heteroatoms. Anomeric effect

Stereoelectronic effects are all those effects on the reactivity of a molecule produced by the particular spatial arrangement of certain pairs of electrons , both bonding and non-bonding. (Deslongchamps)

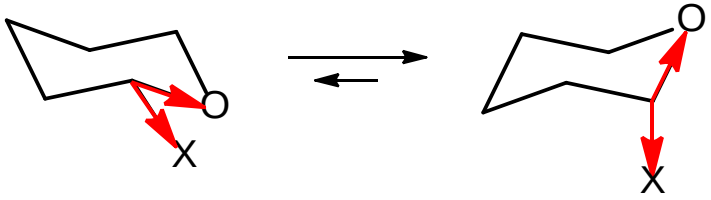
The **anomeric effect** is a type of stereoelectronic effect that is observed in 6-membered heterocyclic rings containing polar substituents on the carbon next to the heteroatom, and manifests itself in the preference of the polar group to adopt an axial arrangement, as opposed to what is normally observed for substituted cyclohexanes. The term "anomeric effect" is because this effect was observed initially in the anomeric carbon of the hemiacetal form of sugars.

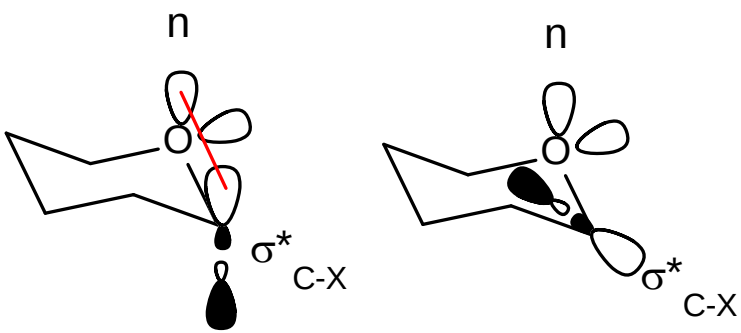




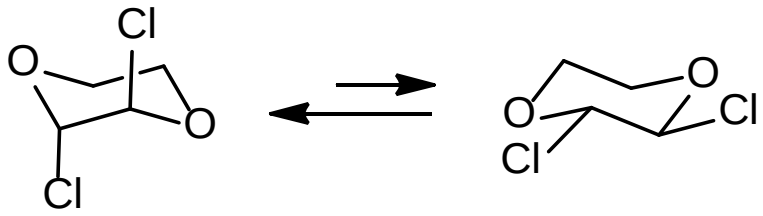
STEREOELECTRONIC EFFECTS

Anomeric effect





(hyperconjugation)



trans – 2,3 – dichloro- 1,4 - dioxane

Lemieux (1950) considers that it is a destabilizing effect of electrostatic origin. In favor of this interpretation is the fact that the equatorial form is predominant in polar solvents.

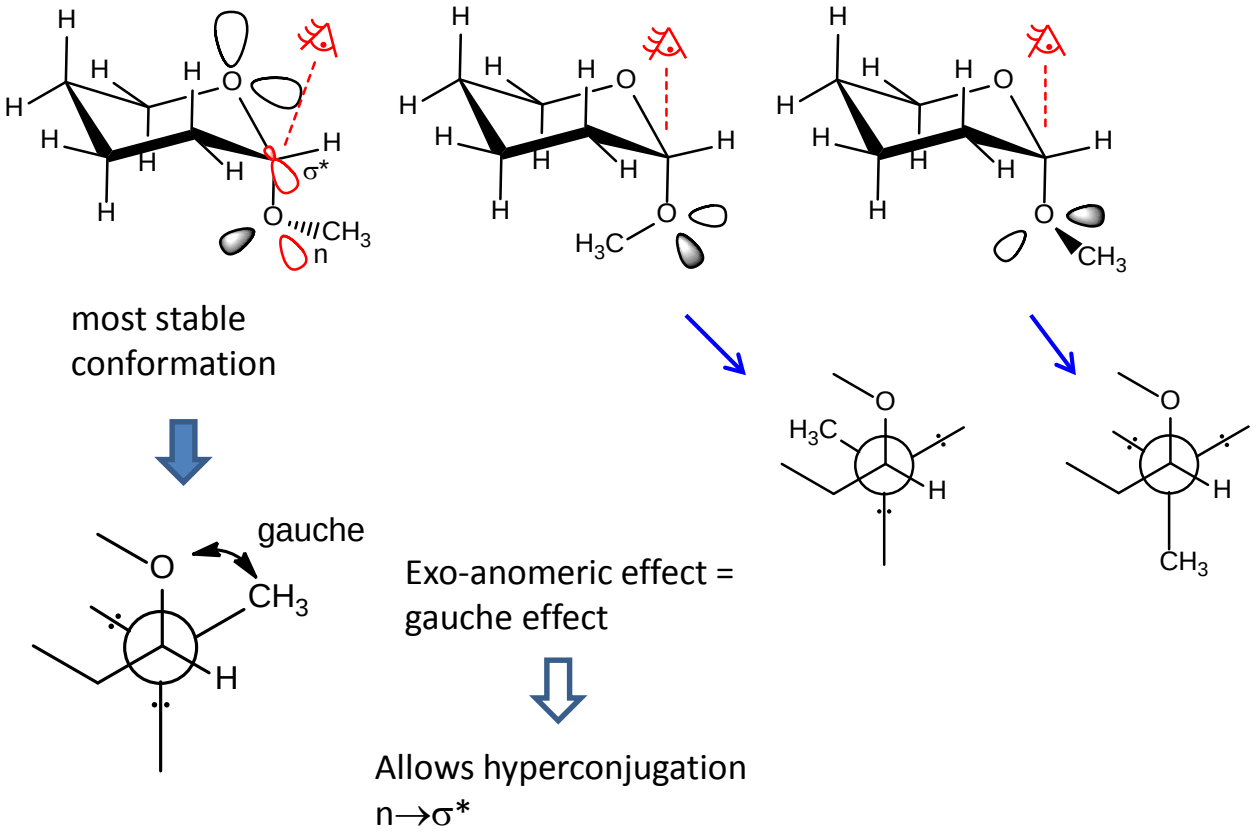
Deslongchamps (1980) maintains the electrostatic component, but gives greater importance to the orbitals. The origin of the effect would be in a binding (stabilizing) interaction between a n orbital of the heteroatom and the orbital σ * of the C-X bond, which occurs only if X is axial (coplanar orbitals). With non-polar groups (alkyl) this interaction is not very effective due to the difference of E between the orbitals involved.

In the trans-2,3-dichloro-1,4-dioxane, conformation with the axial Cl also predominates. Measurements indicate that the C-Cl bond is longer and the CO bond is shorter than in other molecules.

STEREOELECTRONIC EFFECTS

Exo-anomeric effect

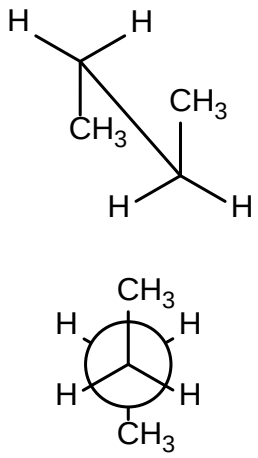
The exo-anomeric effect refers to the conformation of the O-glycosidic bond (gauche effect)



STEREOELECTRONIC EFFECTS

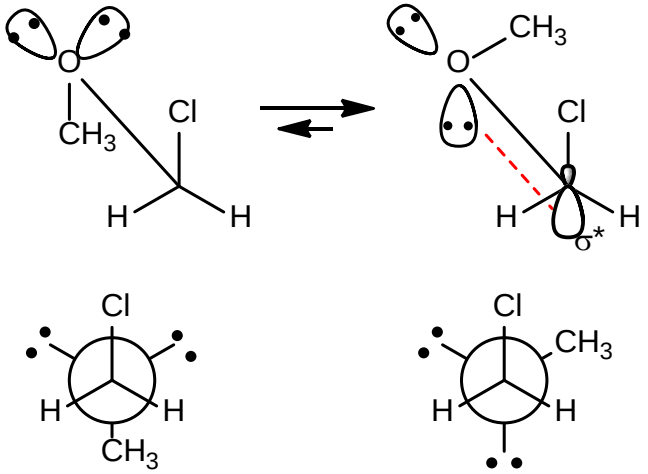
Anomeric effect in acyclic systems

CH_3-CH_2-CH_2-CH_3



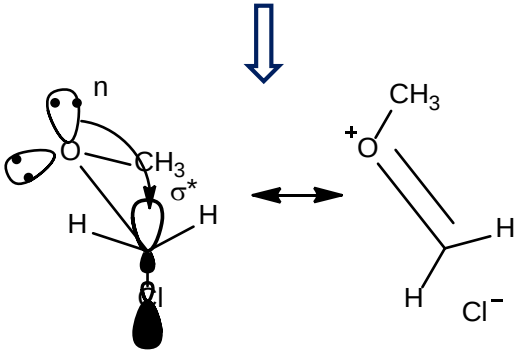
most stable conformation

CH_3-O-CH_2Cl



most stable conformation

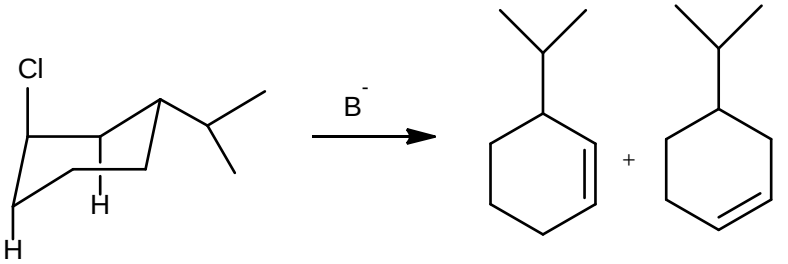
Another way to see it: resonance limits



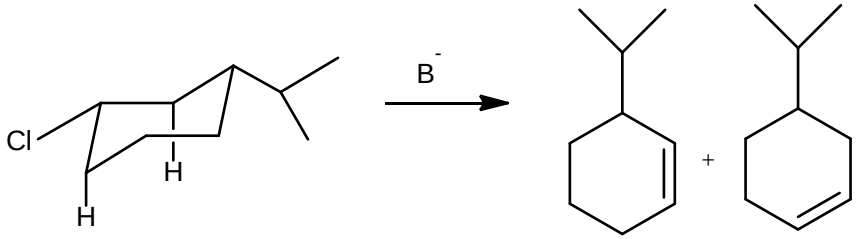
pair of lonely electrons antiperiplanar with respect to the polar link.

INFLUENCE OF CONFORMATION ON REACTIVITY

E_2 Reaction

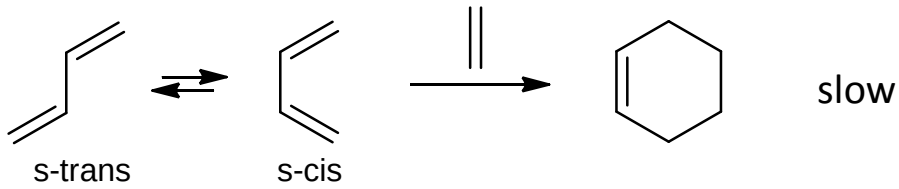


fast reaction

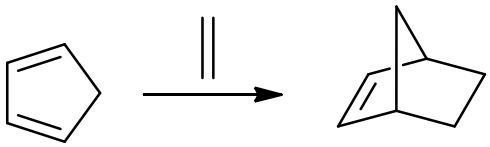


slow reaction

Diels-Alder reaction



slow



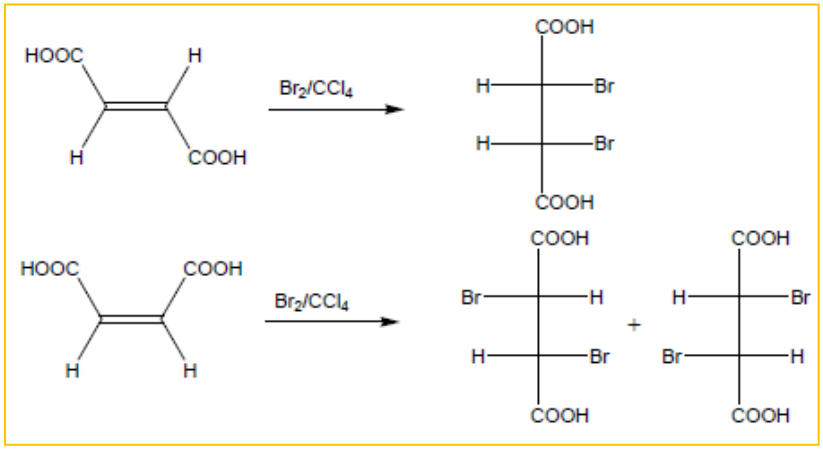
fast

cyclopentadiene has
fixed cis-conformation

STEREOSELECTIVITY AND STEREOSPECIFICITY IN ORGANIC REACTIONS

Stereospecific reaction: the reaction in which different stereoisomerically starting compounds lead to stereoisomerically different products under the same reaction conditions.

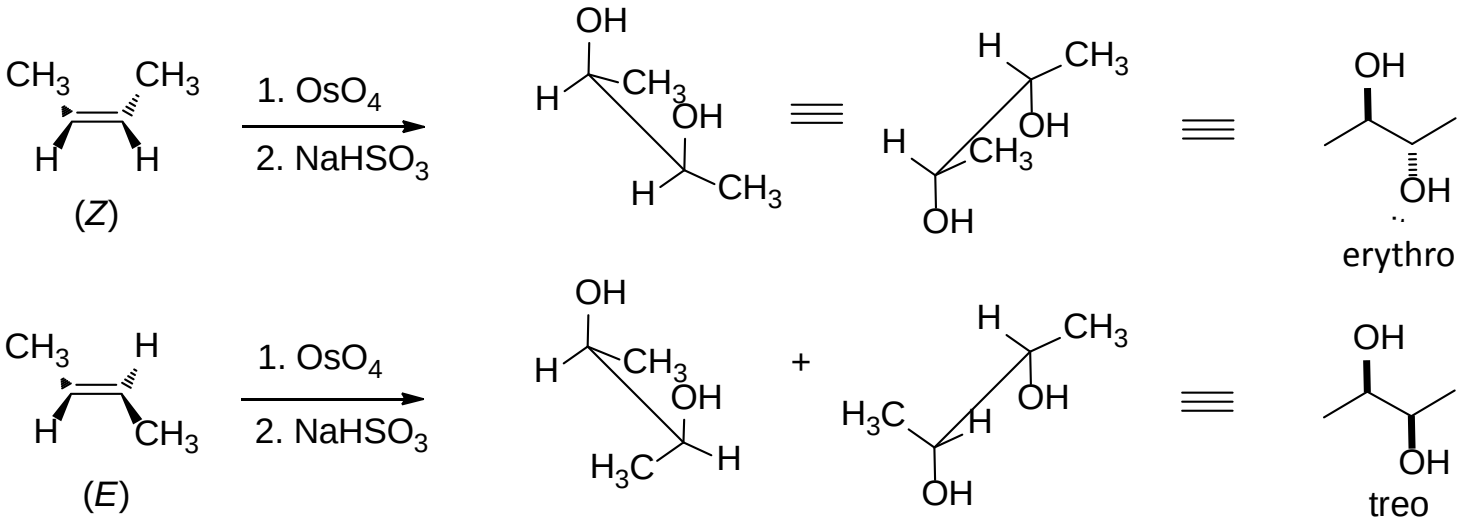
More precisely: A reaction is stereospecific when the configuration of the product is determined by that of the reactant, and when such configuration is a consequence of a particular reaction mechanism with a very precise stereochemistry (eg. S_N2 reaction, hydroboration or epoxidation of alkenes).



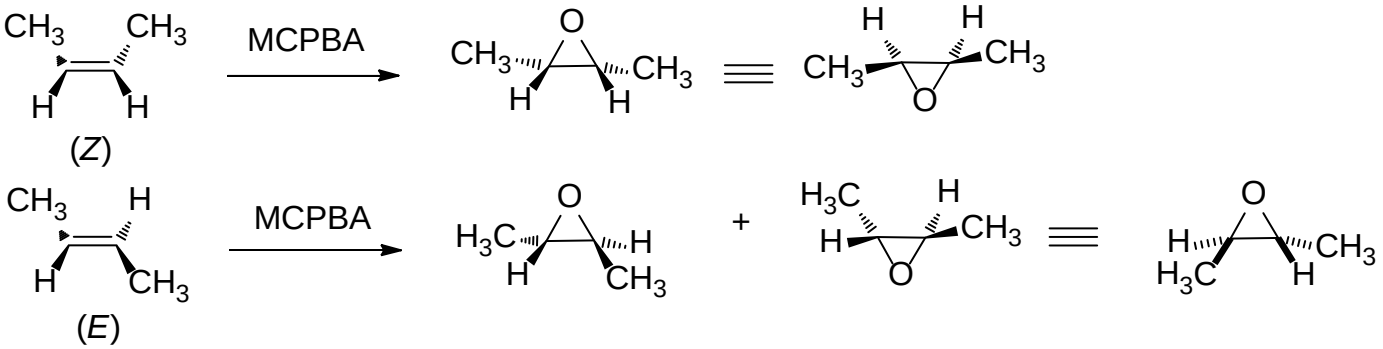
Stereoselective reaction: Those reactions that mechanistically could lead to two or more stereoisomers but one of them predominates (or is exclusively formed) over the others.

Examples of STEREOSPECIFIC reactions

Hydroxylation with OsO_4: Stereospecific *syn*, two OH groups are introduced by the same side of the double bond.

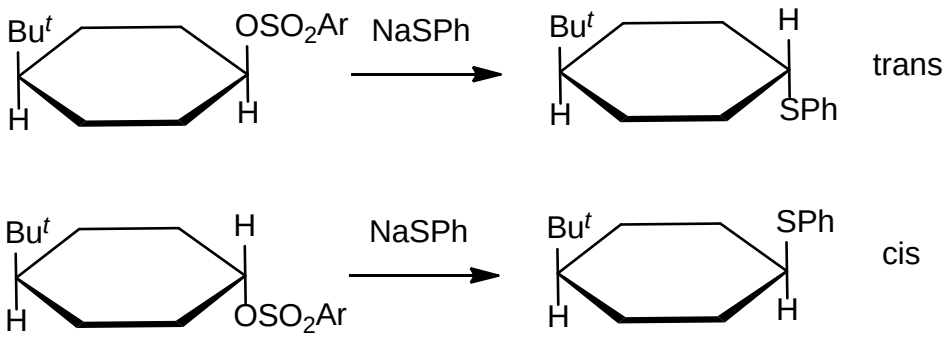


Epoxidation with peracids: Stereospecific *syn*. The stereochemistry of the double bond is maintained in the epoxide.

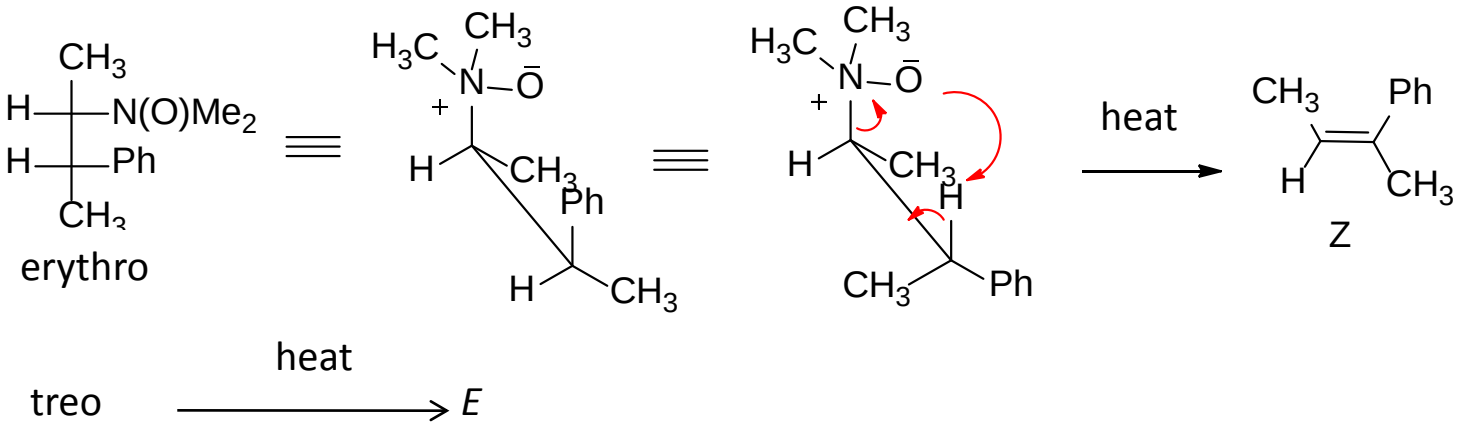


Examples of STEREOSPECIFIC reactions

Substitution reactions S_N2: Occur stereospecifically with inversion of configuration.

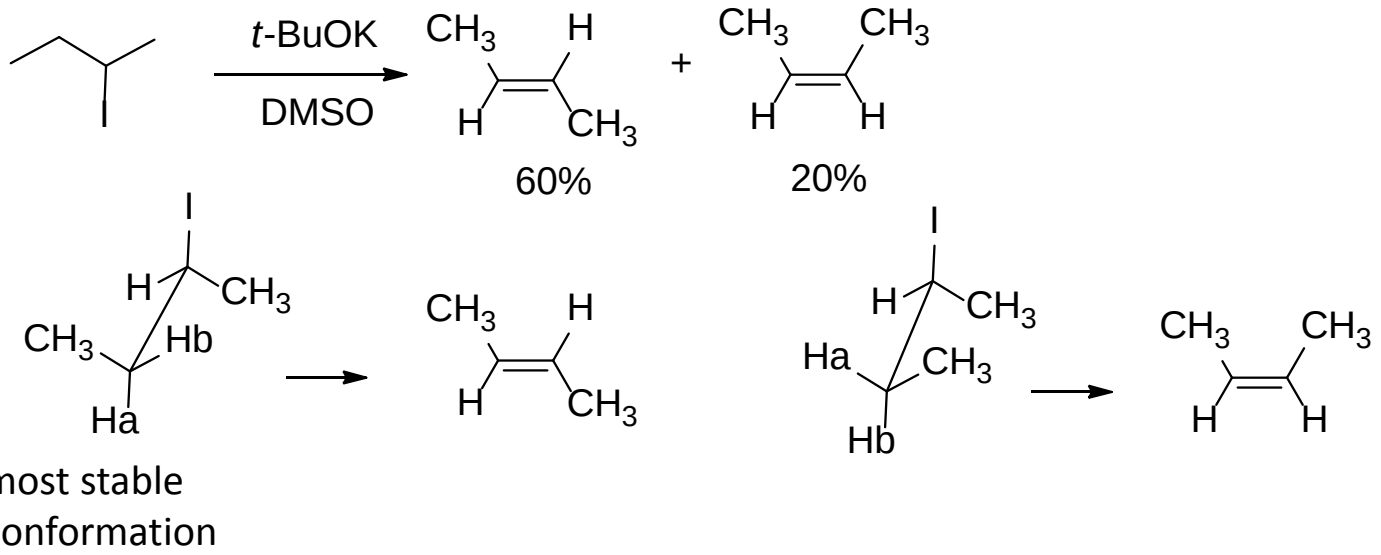


Pyrolysis of amine oxides : Require a *syn*-coplanar arrangement of the proton and the N-oxide group.

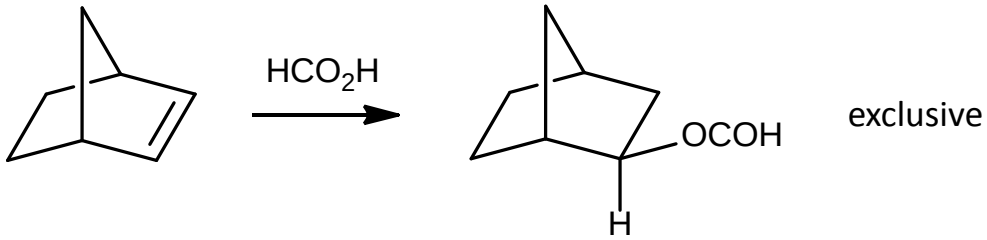


Examples of DIASTEREOSELECTIVE reactions

Dehydrohalogenation : the most stable olefin is formed mostly.

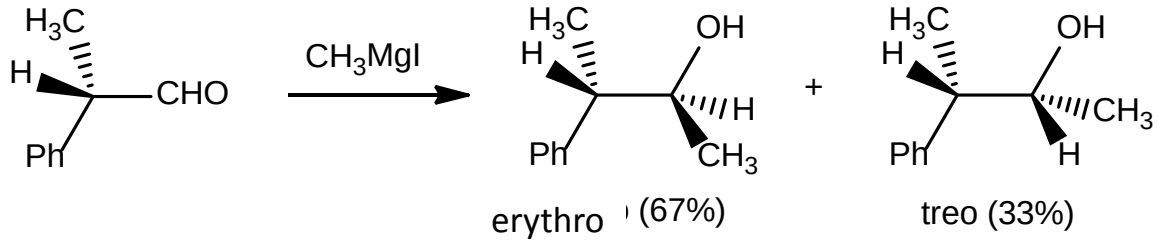


Addition to alkenes : the addition of formic acid to norbornene produces a single stereoisomer (exo)



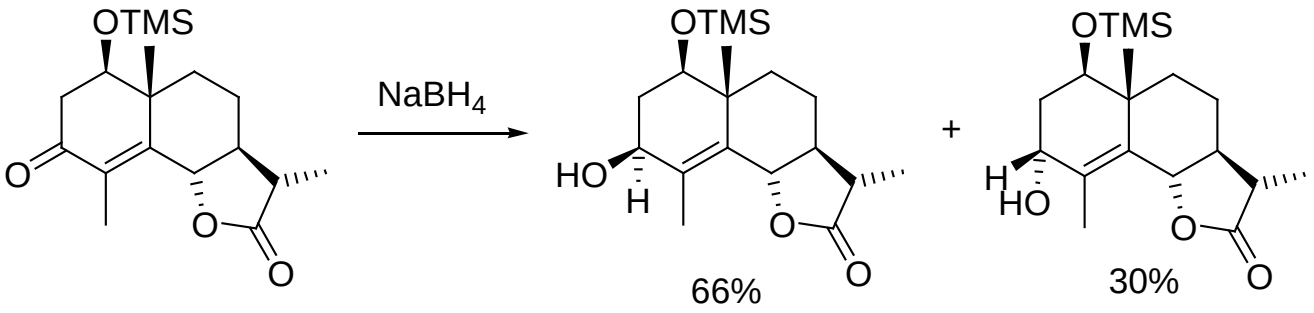
Examples of DIASTEREOSELECTIVE reactions

Addition to carbonyl (alkylation) : The addition of methylmagnesium iodide to 2-phenylpropanal produces twice as much erythro as treo.



The selective formation of a particular configuration by generating a new chiral center in an already chiral molecule is an example of asymmetric induction. The corresponding transition states are diastereomeric.

Addition to carbonyl (reduction)



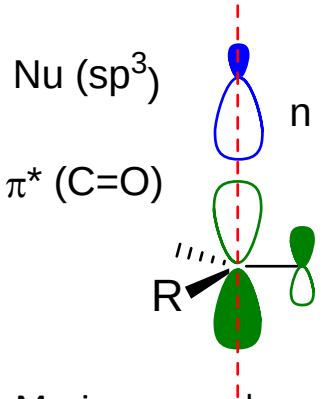
Examples of DIASTEREOSELECTIVE reactions

DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

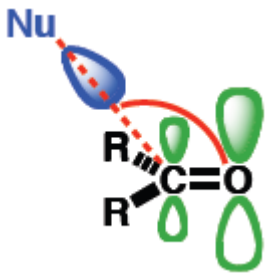
The carbonyl group reacts with a large number of nucleophiles giving addition reactions in which the trigonal carbon sp^2 is transformed into a tetrahedral sp^3 carbon. The process involves the interaction between the HOMO of the nucleophile and the LUMO of the carbonyl group.

This interaction requires a very specific approach angle of approx. 107º, which is known as the Bürgi-Dunitz angle.

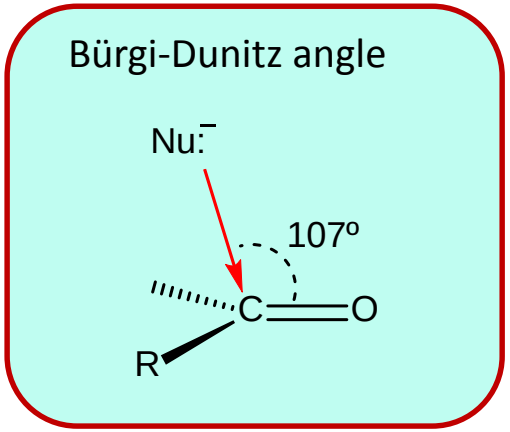
This angle is a compromise between the orthogonal approach to maximize the HOMO and LUMO interaction, and the angular approach to minimize the repulsion exerted by the electrons of the carbonyl p-system (carbonyl HOMO)



Maximum overlap between n and π*(C=O)



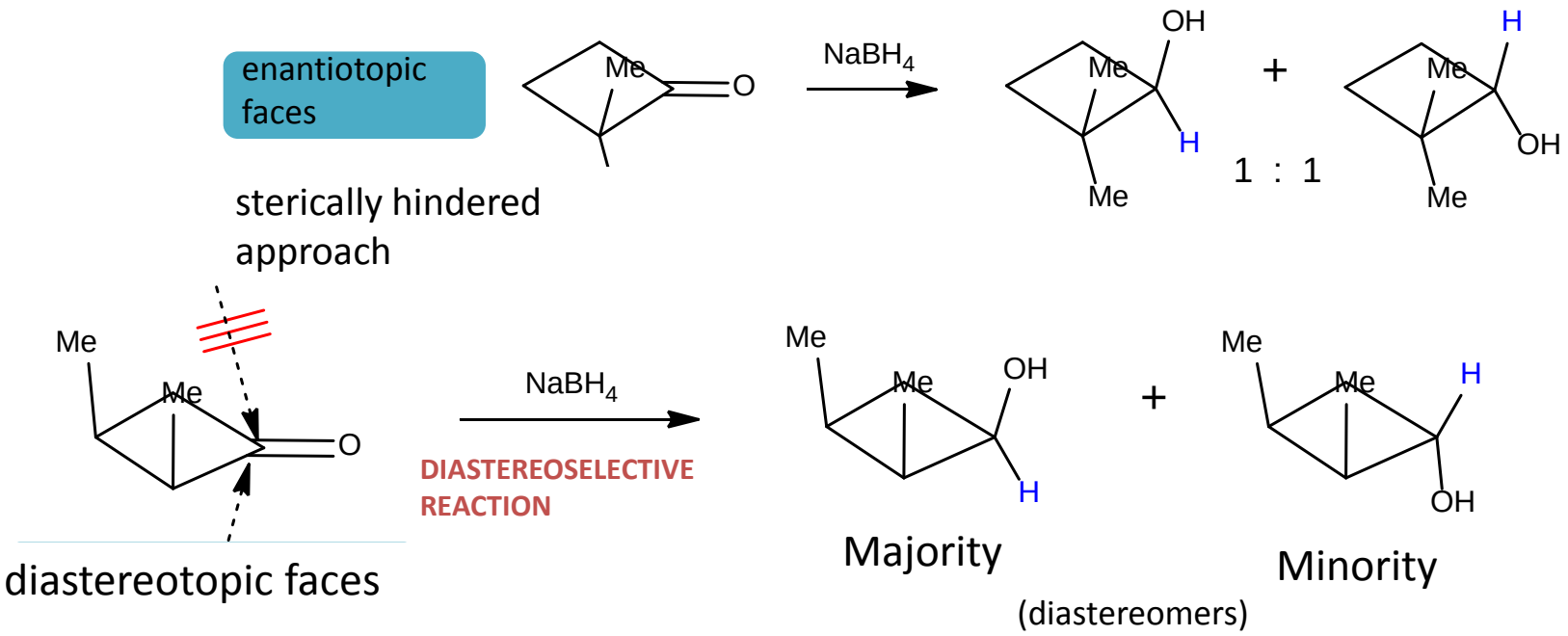
Repulsion between π (C=O) and nucleophile



Examples of DIASTEREOSELECTIVE reactions

DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

If the two faces of the carbonyl group are not homotopic, the addition of the nucleophile results in a new center of chirality. The configuration of this new center will depend on the face of the carbonyl group by which the nucleophile approaches. More specifically, if the two faces are diastereotopic (differentiable) the attack by one of them may be favored with respect to the other, giving rise to diastereoselectivity.
There are different factors that control the organic reactions (electrostatic, orbital and steric), and the steric factors are usually control the stereoselectivity of the carbonyl additions.

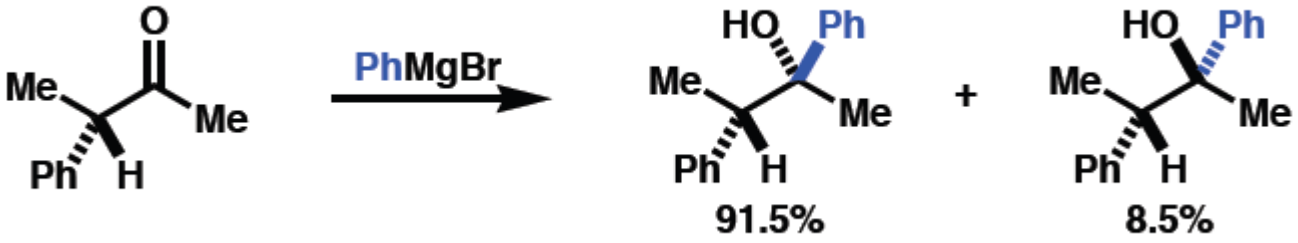


Examples of DIASTEREOSELECTIVE reactions

DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

In **conformationally flexible molecules** (acyclic ketones and aldehydes), diastereoselectivity can also be observed in the nucleophilic addition, especially when a stereogenic center exists close to the carbonyl group.
Most studies have focused on the case in which there is a **stereogenic center in position α to the carbonyl group** . In these cases it is not so obvious to predict which face of the carbonyl is less sterically hindered. Two models have been proposed that explain the diastereoselectivity of the reaction:

Felkin-Anh model
Cram chelate model

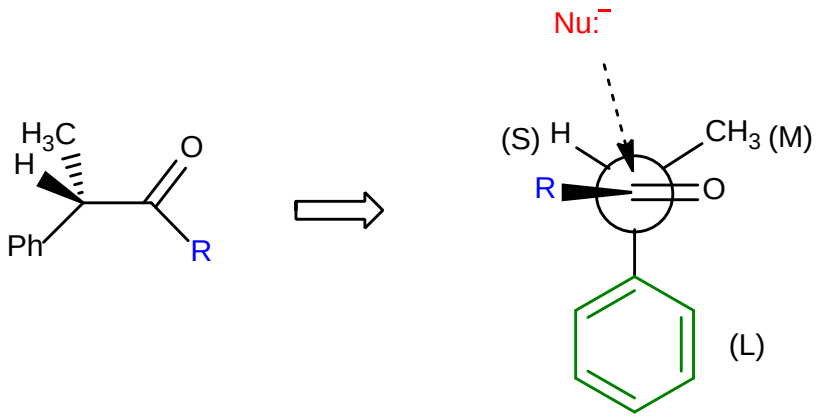


DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

Felkin-Anh model

The main key of this model is to avoid the eclipsed conformation between the R substituent of the carbonyl and the larger (L) substituent in the α carbon in the ET:
Felkin rules:

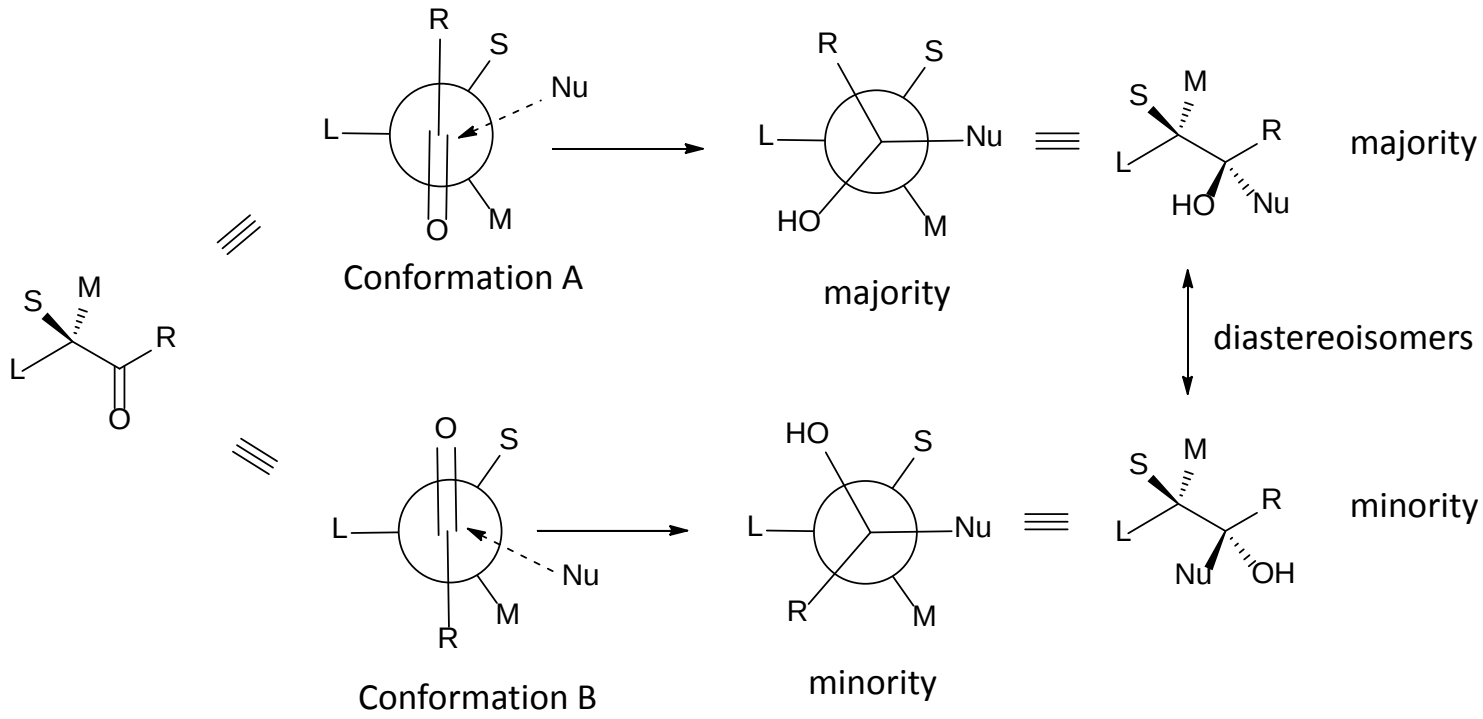
- ET similar to the reactants.
- Alternating conformations, not eclipsed, to minimize steric interactions.
- The main steric interactions involve the nucleophile, the R group and the large (L) and medium (M) groups, but not the carbonyl oxygen.



DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

Felkin-Anh model

1. Draw the Newman projection with the most voluminous group (**L**) perpendicular to the carbonyl group (two possible conformations A and B).
2. Nu^- is approached following the Bürgi-Dunitz angle in *anti* to the **L** group, and close to the smaller substituent (**S**) to minimize steric interactions.

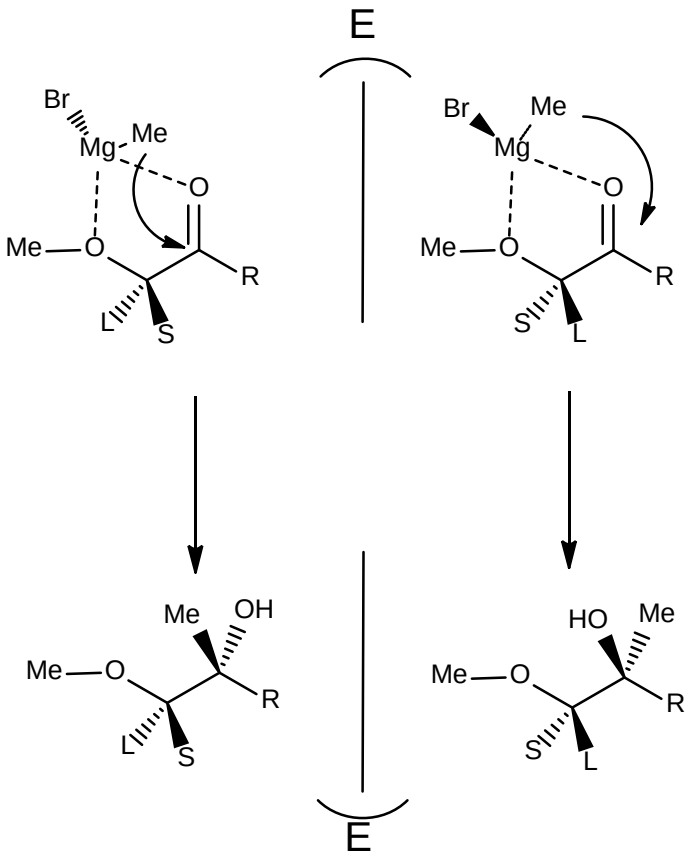


DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

Cram chelate model

Requirements:

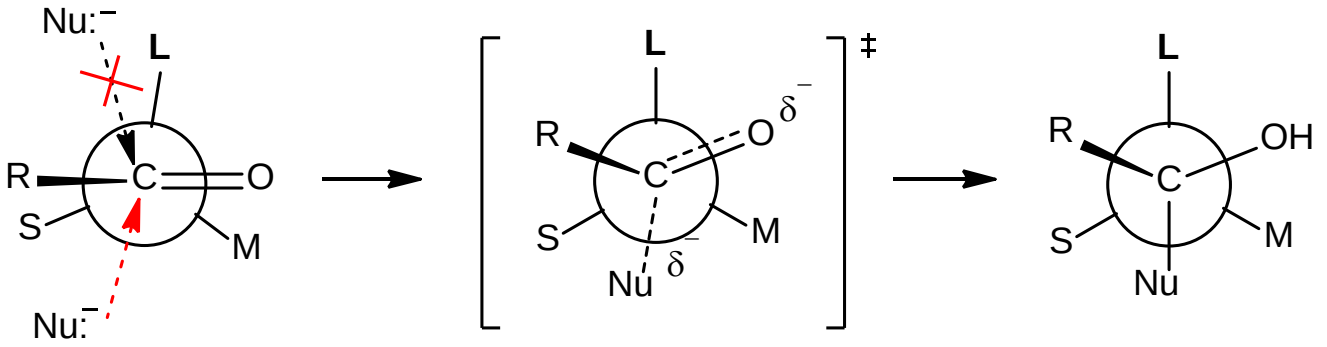
- Carbon α asymmetric
- Coordinating substituent (O, N)
- Presence of metals in the reaction medium capable of being coordinated.



If the carbon α has coordinating substituents and there are metals in the reaction medium, a **chelate** is formed between the metal, the coordinating atom and the carbonyl oxygen so that the attack of the nucleophile is produced by the less sterically hindered face (cyclic model) .

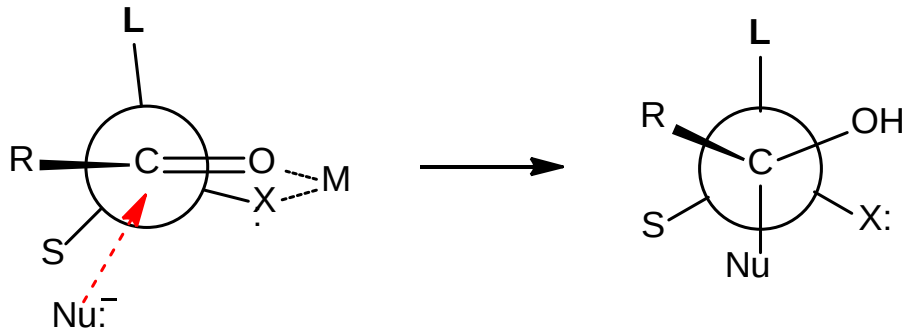
DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

Model of Felkin-Anh



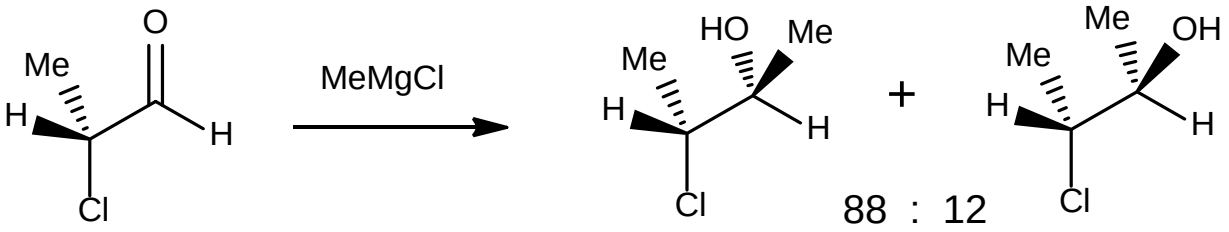
(L= large; M= medium; S= small)

Cram chelate model

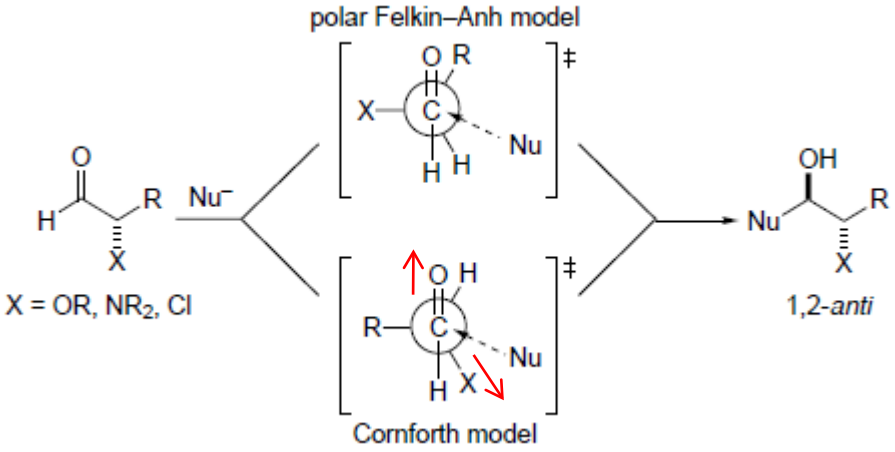


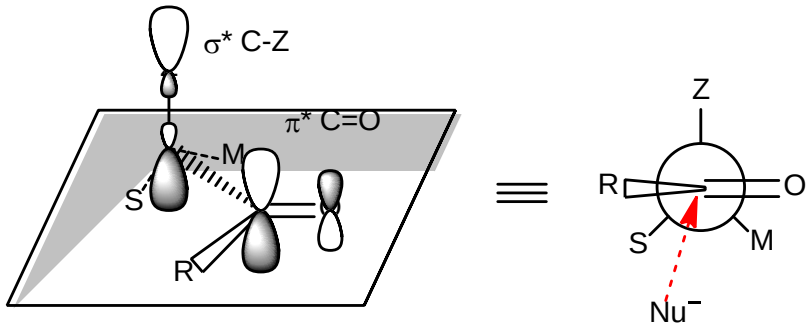
DIASTEREOSELECTIVITY IN THE ADDITIONS TO CARBONYL GROUP

Cornforth model / Felkin-Anh polar model: Halogens in carbon α



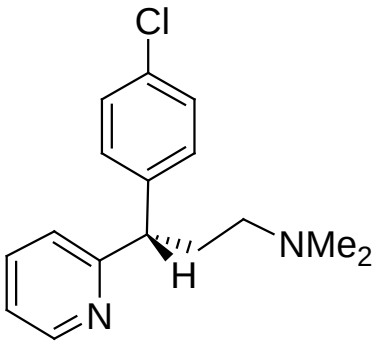
If the carbon α has a halogen, it behaves as if it were the most voluminous group in the polar Felkin-Anh model , standing perpendicular to the carbonyl (stabilization of the transition state by hyperconjugation), or it is located in *anti* carbonyl in the model of Conforth , to minimize dipolar repulsions between C-X and C = O. In both cases the result is the same (debate)





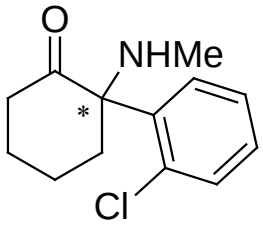
polar Felkin-Anh model

EXAMPLE OF ENANTIOMERICALLY PURE COMPOUNDS



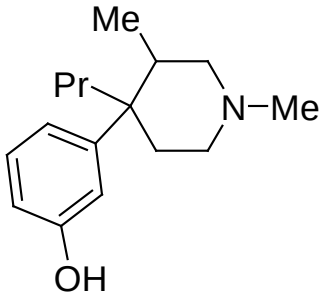
feniramine dexchloro

S is 200 times more powerful than *R*



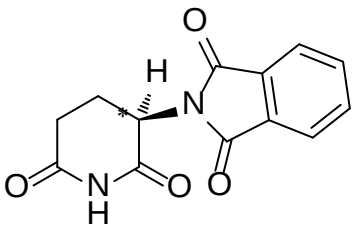
C etamine

Hypnotic and analgesic
d is active
l is toxic



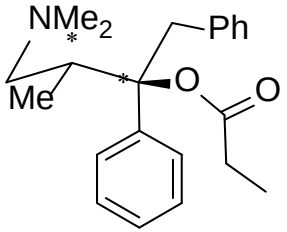
Picenadol

Analgesic
d is opiate agonist
l is antagonistic



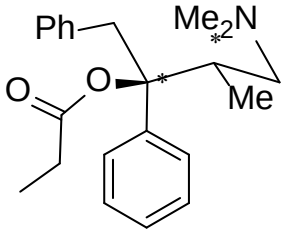
thalidomide

R - (+) Analgesic and antiemetic.
S- (-) teratogenic



DARVON

(2*S*, 3*R*)-(+)-dextropropoxifeno



NOVRAD

(2*R*, 3*S*)-(-)-dextropropoxifeno

DARVON analgesic
NOVRAD antitussive

At the biological level, bioactive substances exert their action by interacting with receptors present in cells. These receptors (proteins, sugars or nucleic acids) are CHIRAL so the activity of the two enantiomers of a drug can be different.

OBTAINING ENANTIOMICALLY PURE COMPOUNDS (OR ENANTIOMERICALLY ENRICHED)

SYNTHESIS OF ENANTIOMERICALLY PURE COMPOUNDS

Natural products

ENANTIOSELECTIVE REACTIONS

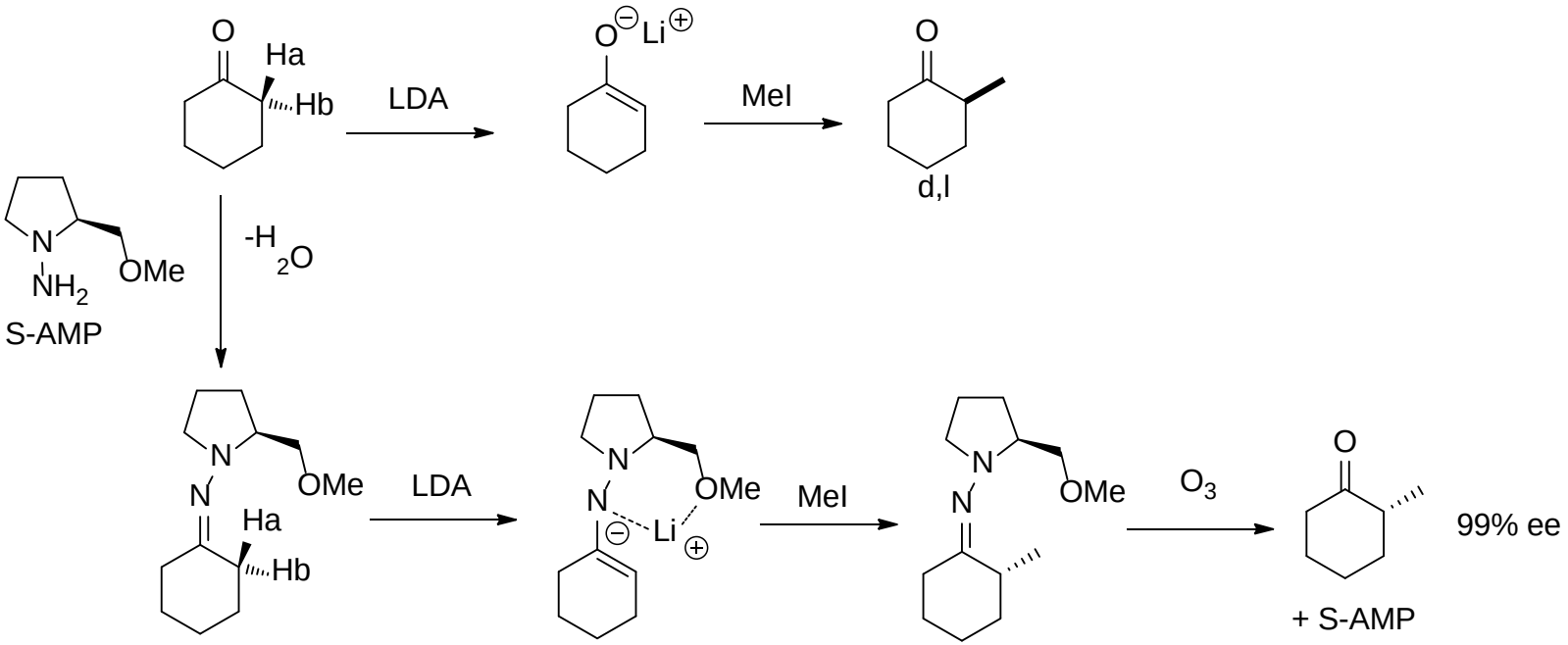
Chiral auxiliaries
Chiral reagents
Chiral catalysts

RESOLUTION OF RACEMATES

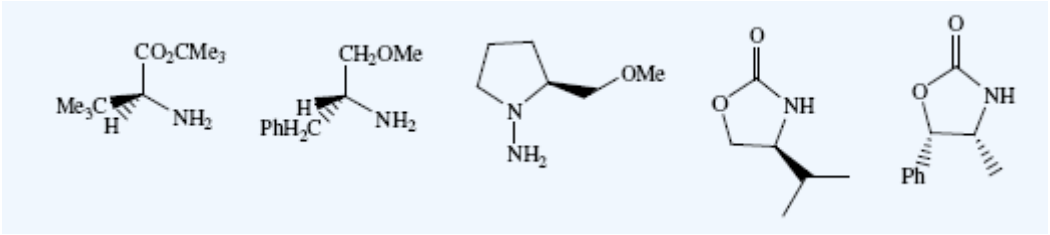
Formation of derivatives
Kinetic resolution
Chiral chromatography

ENANTIOSELECTIVE REACTIONS

Chiral auxiliary : An enantiomerically pure substance that covalently bonds to the substrate and separates from the product after the reaction. By joining the auxiliary to the substrate, the enantiotopic groups are transformed into diastereotopic and can be differentiated by conventional achiral reagents.

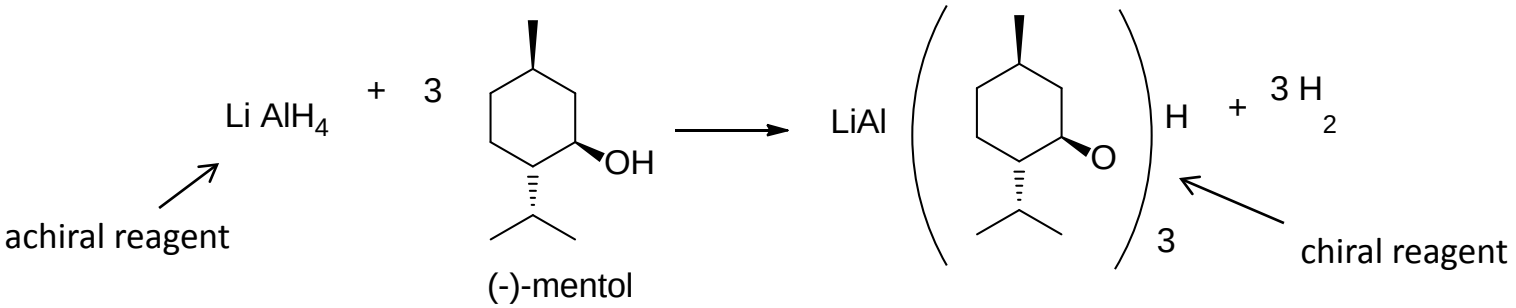


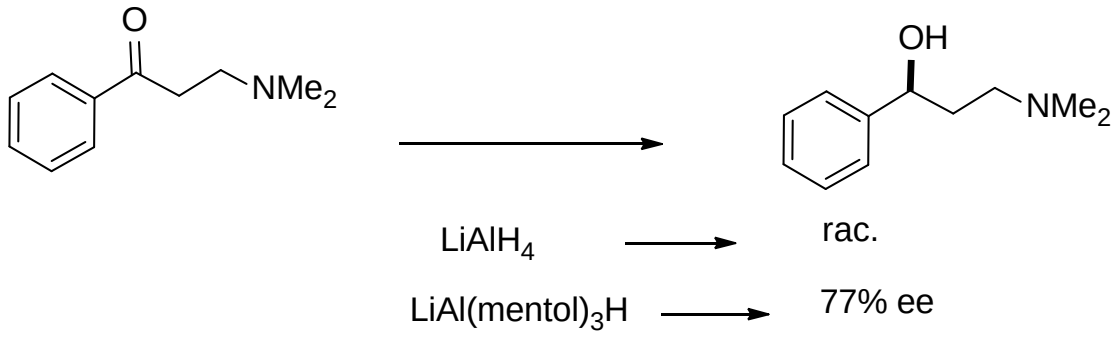
Some chiral auxiliaries used for the alkylation of ketones



ENANTIOSELECTIVE REACTIONS

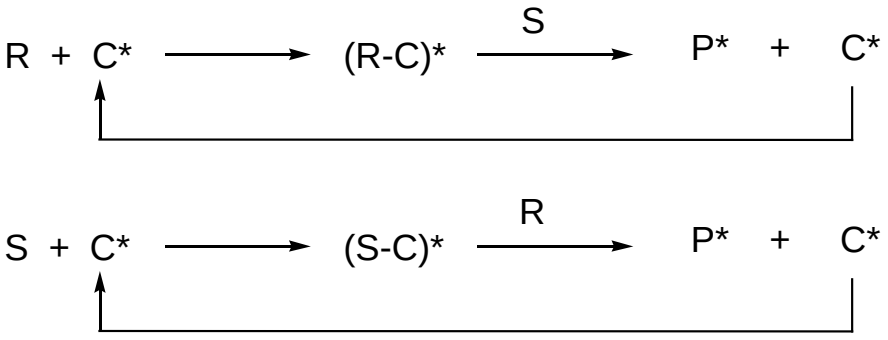
Chiral reagent. A conventional reagent can be reacted with an enantiomerically pure substance to give a chiral reagent. This chiral reagent is able to differentiate groups or enantiotopic faces.

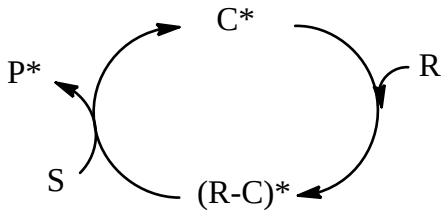




ENANTIOSELECTIVE REACTIONS

Chiral catalyst : The enantiomerically pure substance is used in a catalytic amount accompanied by a conventional reagent in a stoichiometric amount.

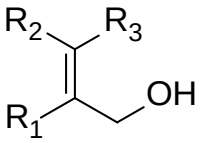




C* = chiral catalyst, R= reagent S = substrate, P* = chiral product

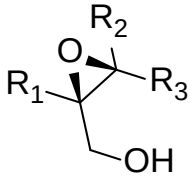
Example: enantioselective epoxidation of sharpless allylic alcohols

$Ti(O^iPr)_4$/ DET system catalyzes the enantioselective epoxidation of allylic alcohols

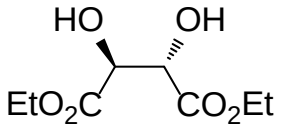


t-BuOOH / CH_2Cl_2

$Ti(O^iPr)_4$ / (-)-DET cat.



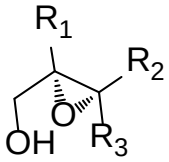
ee> 90%



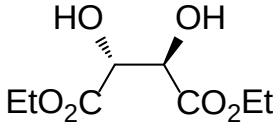
(-)-DET

t-BuOOH / CH_2Cl_2

$Ti(O^iPr)_4$ / (+)-DET cat.



ee> 90%



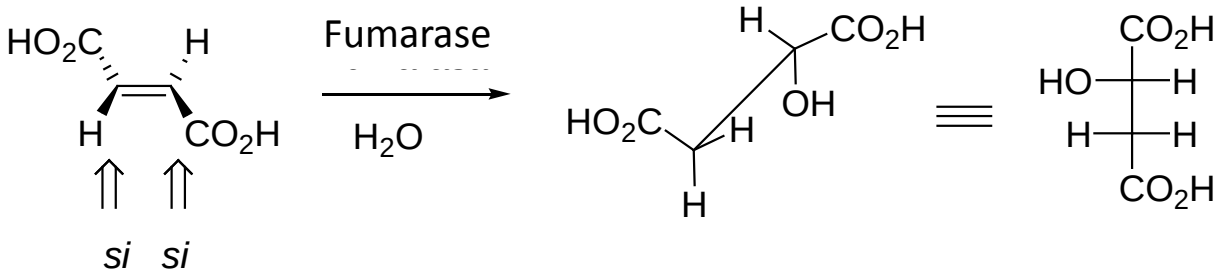
(+)-DET

(diethyl tartrate)

ENANTIOSELECTIVE REACTIONS

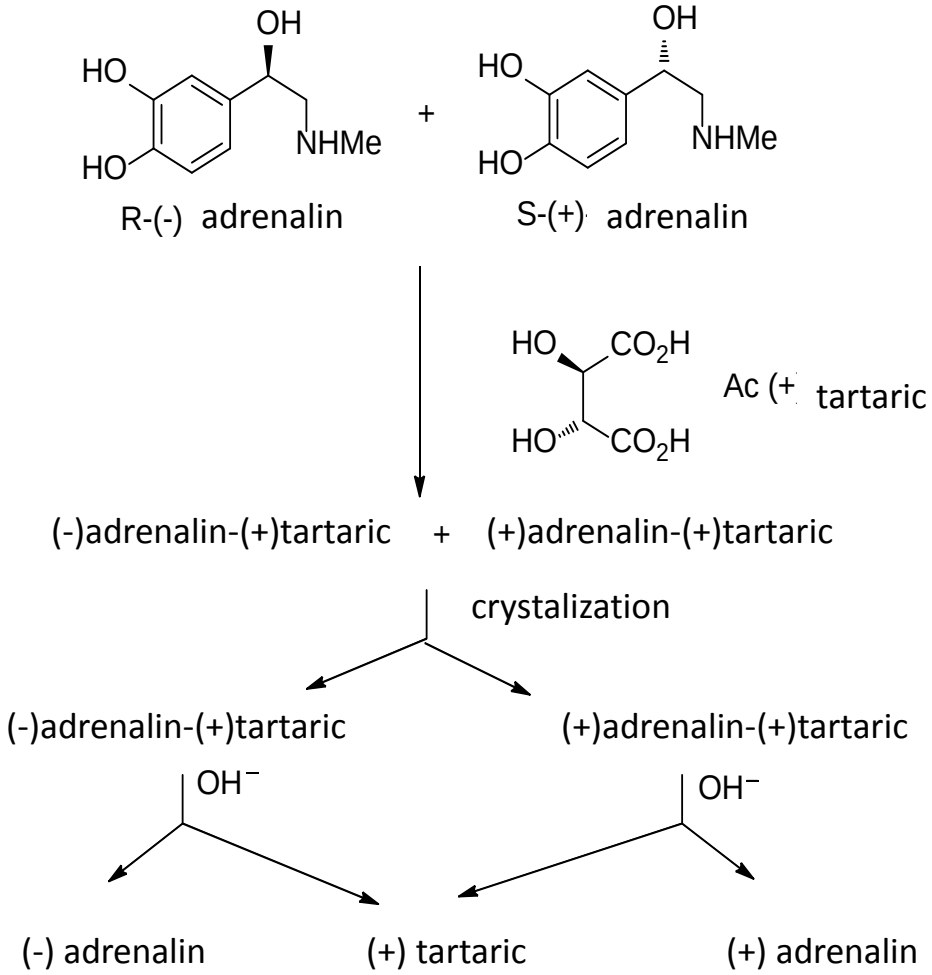
Example: reaction with enzymes

The enzyme fumarase catalyzes the addition of water to the face *si*, *si* the fumaric acid leading exclusively to the L-malic acid.



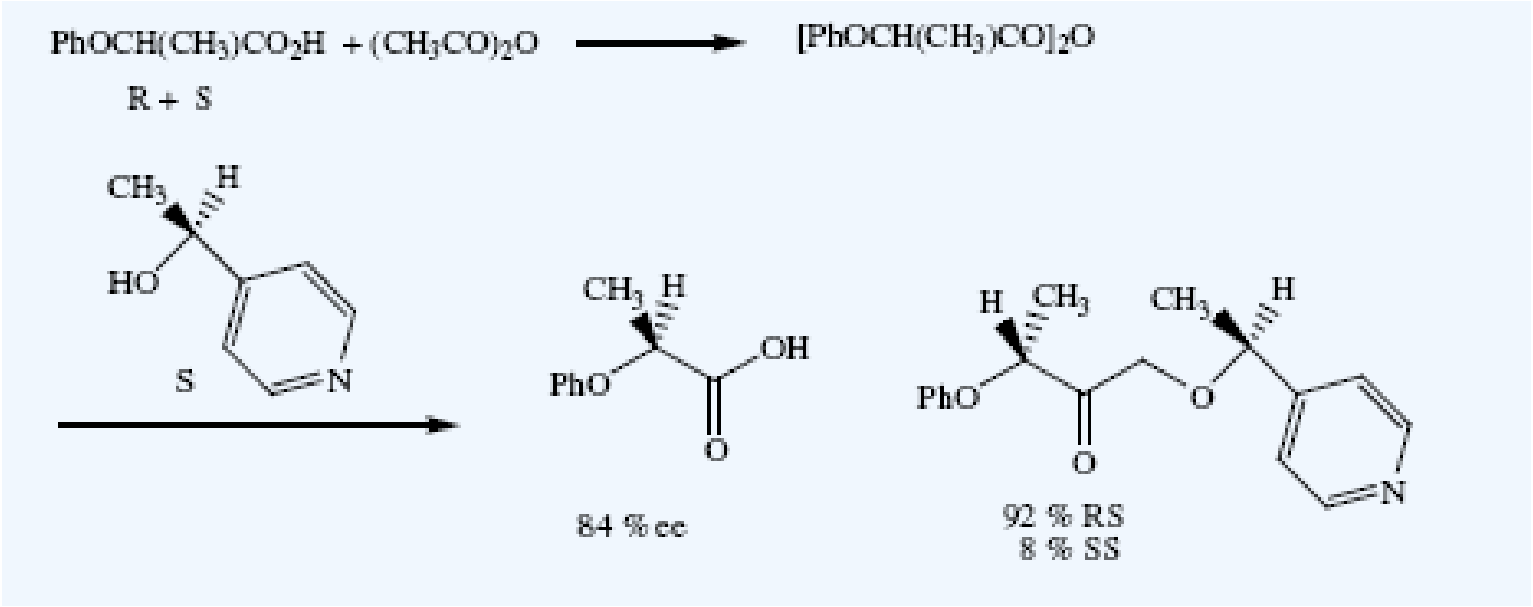
RESOLUTION OF RACEMATES. REVERSIBLE TRAINING OF DERIVATIVES

The racemic mixture is reacted with an enantiomerically pure substance by transforming into a diastereomer mixture separable by physical methods. Once separated, the reaction is reversed to obtain each pure enantiomer.



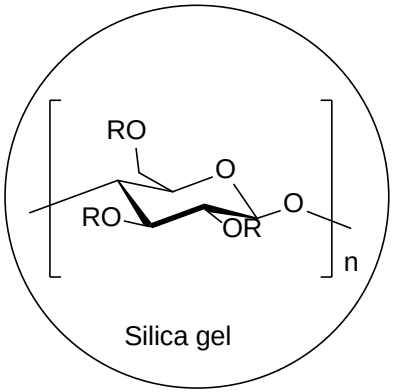
KINETIC RESOLUTION OF RACEMATES

The **kinetic resolution** is based on the fact that the reaction rate of two enantiomers versus a chiral agent is different. In the most favorable case one of the enantiomers reacts completely while the other does not at all.

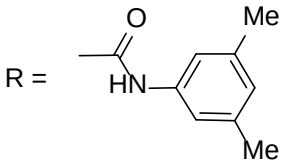


RESOLUTION OF RACEMATES. QUIRAL CHROMATOGRAPHY

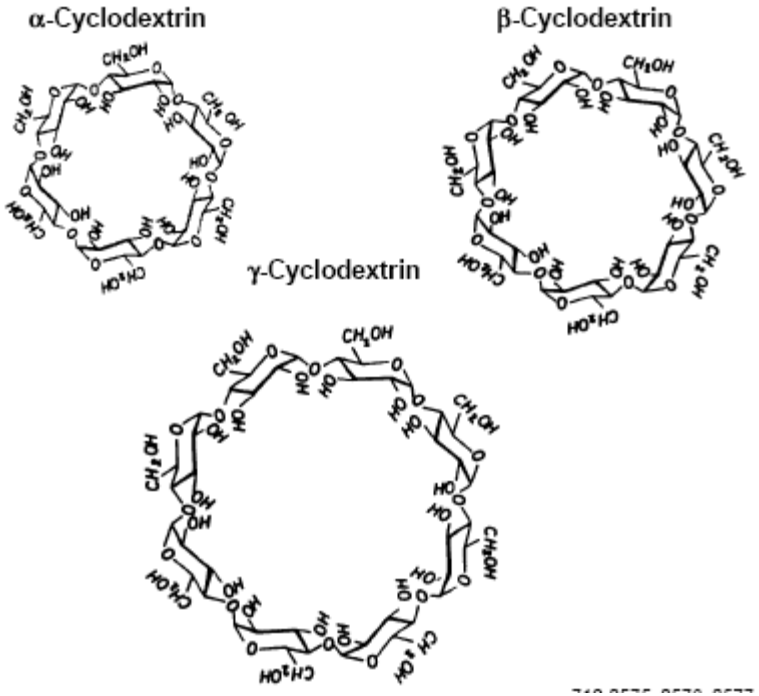
Chiral chromatography uses a chiral stationary phase. Generally, silica gel functionalized with cellulose or amylose derivatives is used for HPLC or with cyclodextrins for GC. Each enantiomer is retained with a different force and therefore elutes at different times.



Tris (3,5-dimetilfenilcarbamat) de cel·lulosa



CHIRALCEL OD (DAICEL)



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Estas diapositivas forman una parte del contenido docente de la asignatura "Química Orgánica Avanzada" del Máster Universitario en Química.