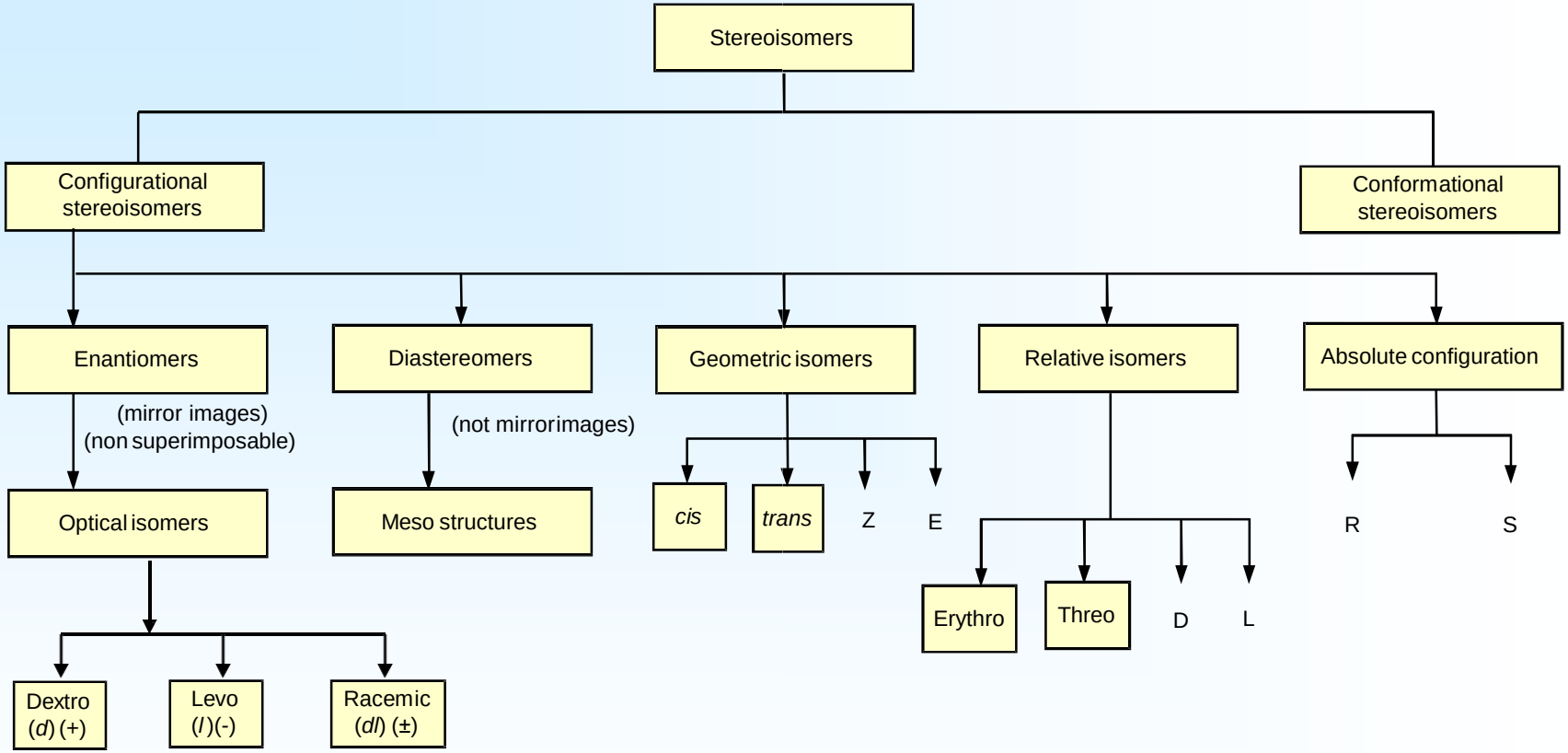
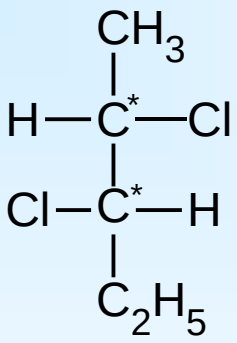
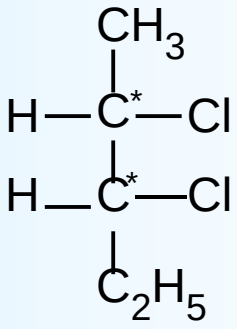
CLASSIFICATION OF STEREOISOMERS



DIASTEREOMERS





2,3-Dichlc ropentane

(**not mirror image**)

* chiral carbon atom

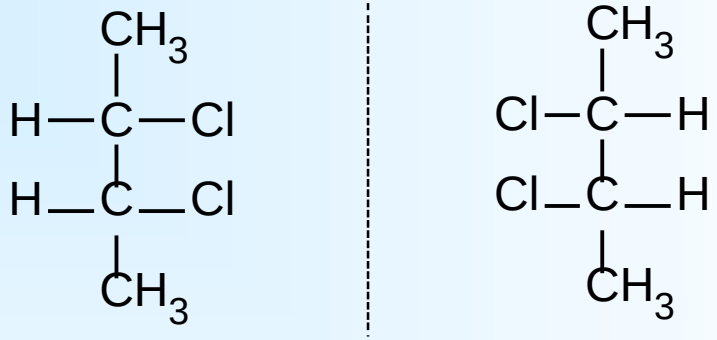
DIASTEREOMERS

- Diastereomers have different physical properties.
- Chemical properties are not identical.
- May be optically inactive.
- The phenomenon of formation of diastereomers is called **diastereoisomerism**.

MESO STRUCTURES

- Molecules have symmetric end – the term ***Meso*** is used.
- ***Meso*** means combining form middle, intermediate.
- A ***Meso*** compound is one whose molecules are supeimposable or their mirror images even though they contain chiral centers.
- A ***Meso*** compound is optically inactive.

MESO STRUC TURES

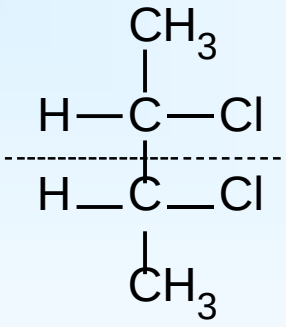


2,3-Dichlorobutane

- Superimposable; **turned end-for-end** a *Meso* compound (in same plane).

MESO STRUCTURES

- In *meso* structure one half of the molecule is the mirror image of the other half.



2,3-Dicholorobutane

- In *meso* compounds two chiral centers have opposite configuration.

GEOMETRIC ISOMERISM

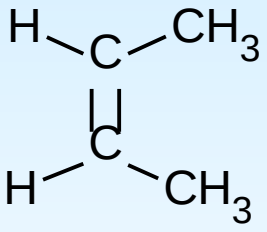
- The phenomenon of forming geometric isomers is called **geometric isomerism**.
- A pair of **geometric isomers**, are, then **diastereomers,** as they are **not mirror images**.
- **Geometric isomers**, interconverted – in principle – by rotation about a double bond.
- **Geometric isomers** have **different** physical and frequently different chemical reactivities.

GEOMETRIC ISOMERS

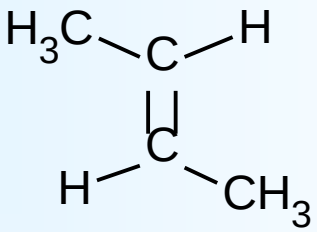
- Science of properties and relations of lines (bond).
- **Not** require chiral carbon atom.
- The particular kind of **diastereomers** that owe their existence to hindered rotation about double bonds are called **geometric isomers**.

GEOMETRIC ISOMERS

- The **configurations** of the **isomeric 2-butenes**



***cis*-2-Butene**



***trans*-2-Butene**

(**not mirror image**)

- ***cis*** – (*Latin*: on this side or same side or identical groups)
- ***trans*** – (*Latin*: across or opposite)

Cis-Trans Isomers

In **cis-trans isomers**

- there is no rotation around the double bond in alkenes.
- groups attached to the double bond are fixed relative to each other.

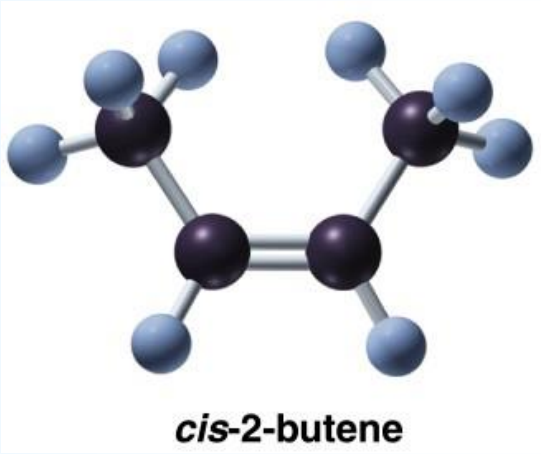
You can make a "double bond" with your fingers with both

***Cis*-hands (*cis*-thumbs/fingers)**

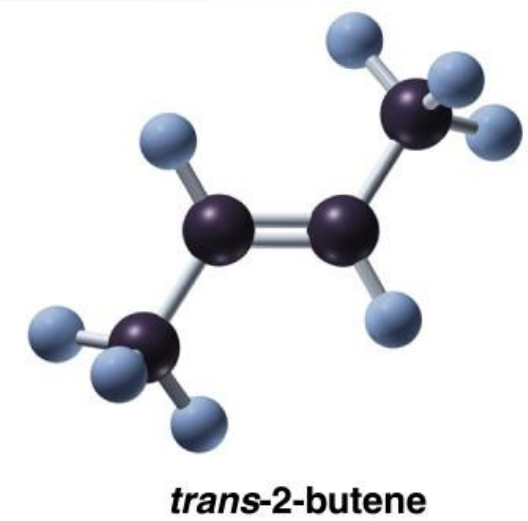
***Trans*-hands (*trans*-thumbs/fingers)**

Cis-Trans Isomers

Two isomers are possible when groups are attached to the double bond are different.

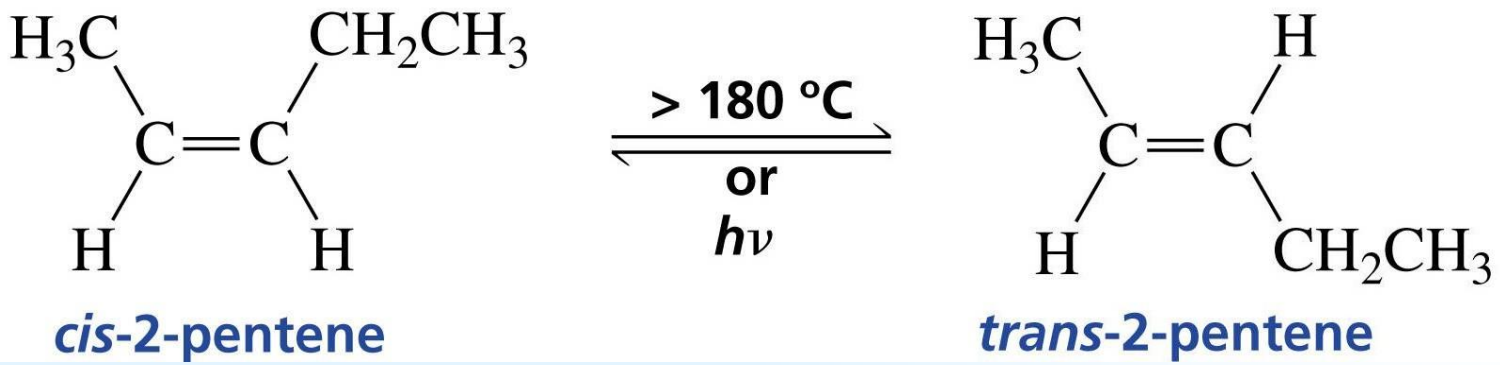


- In a **cis isomer**, groups are attached on the same side of the double bond.



- In the **trans isomer**, the

Example

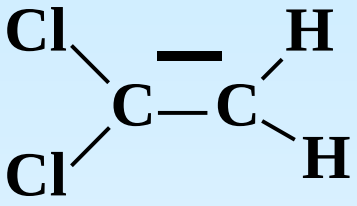


cis-trans isomerism: (Geometrical)

Like atoms/groups on the same side of the double bond: cis

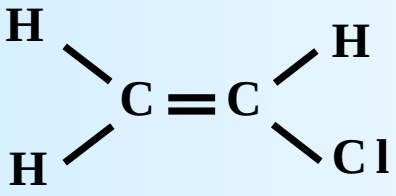
like atoms/groups on the opposite side of the double bond: trans

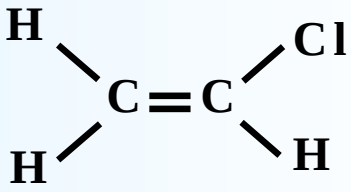
As expected, if one C atom that contributes to the double bond bears 2 identical atoms / groups, no cis or trans isomerism



1,1-Dichloroethene

NO cis- OR trans-

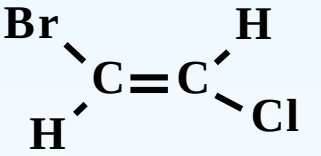




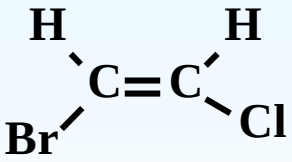
Chloroethene

NO cis- OR trans-

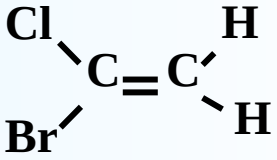
is it trans- , cis- or neither?



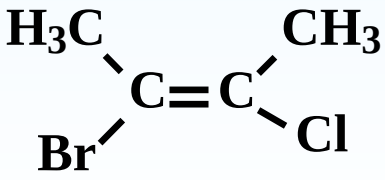
trans-



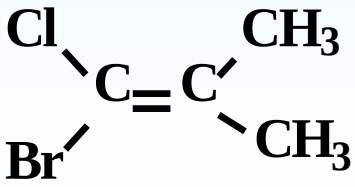
cis-



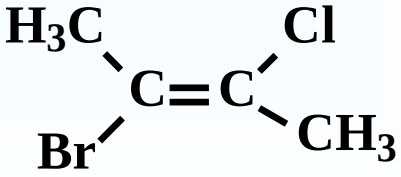
neither



cis-



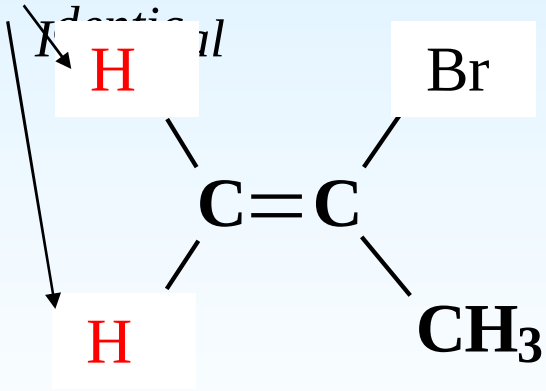
neither



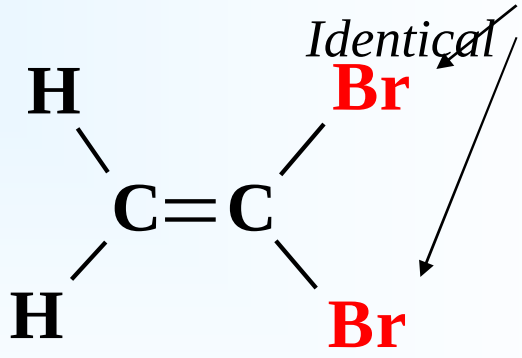
trans-

Cis-Trans Isomerism

- Alkenes cannot have cis-trans isomers if a carbon atom in the double bond is attached to *identical groups*.



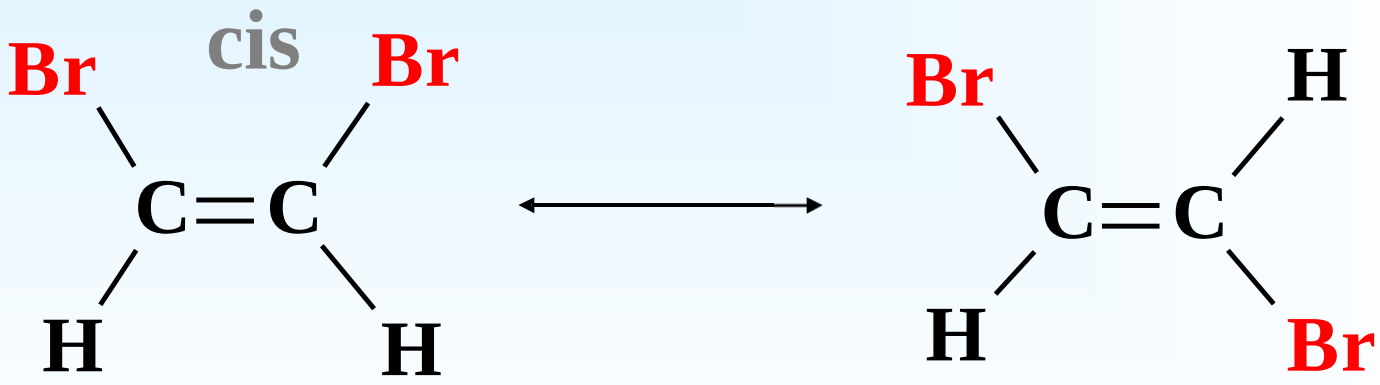
2-bromopropene
(not cis or trans)



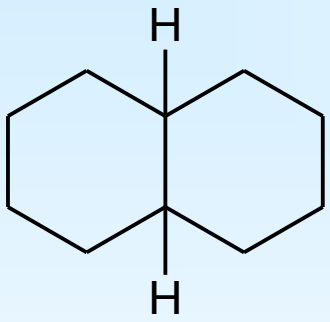
1,1-dibromoethene
(not cis or trans)

Naming *Cis-Trans* Isomers

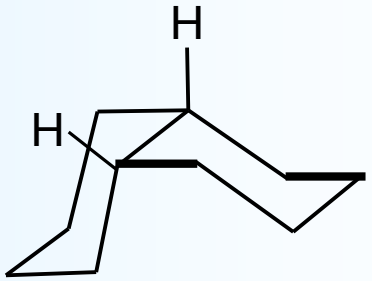
The prefixes cis or trans are placed in front of the alkene name when there are *cis-trans* isomers.



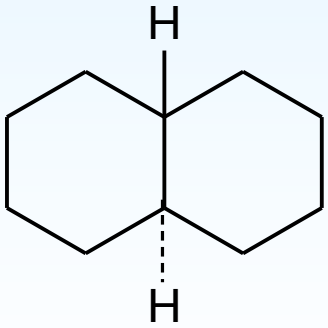
Naming *Cis-Trans* Isomers



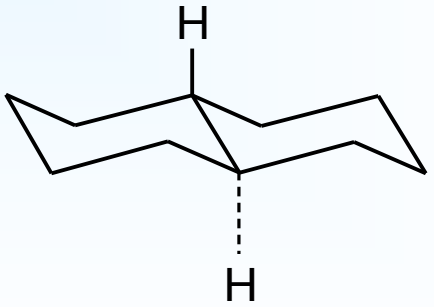
***cis*-Decalin**



***cis*-Decalin**



***trans*-Decalin**

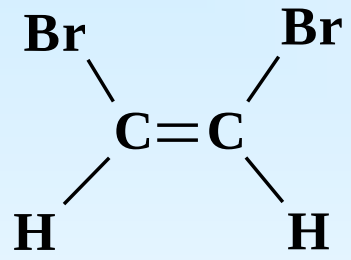


***trans*-Decalin**

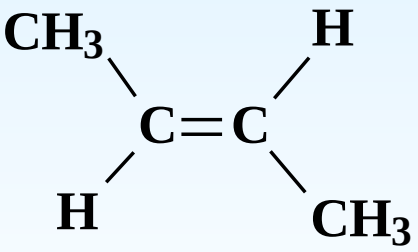
Learning Check

Name each, using *cis*-*trans* prefixes when needed.

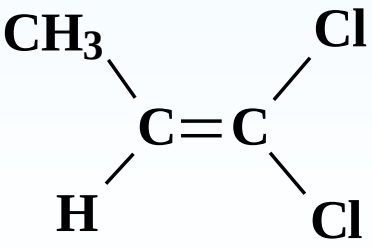
A.



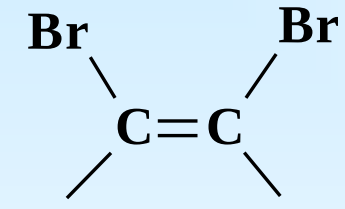
B.



C.

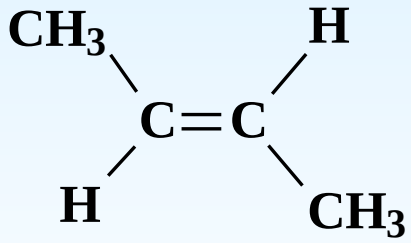


Solution

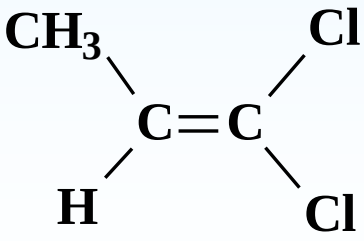
A. 

dibromoethene

cis-1,2-

B. 

trans-2-butene

C. 

1,1-dichloropropene

RELATIVE CONFIGURATION

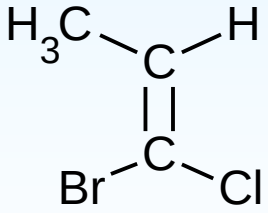
Erythro and Threo isomers

- Used for molecules having non-symmetric ends.
- Generally used in **Fischer** projection.
- **Not mirror images**.
- Resembles with **diastereomers.**

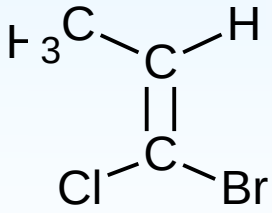
GEOMETRIC ISOMERS

Z AND *E*

- ***Z*** German : *Zusammen* = together, same side
- ***E*** German : *entgegen* = opposite, opposite side



(*Z*)-1-Bromo-1-chloropropene



(*E*)-1-Bromo-1-chloropropene

Priority

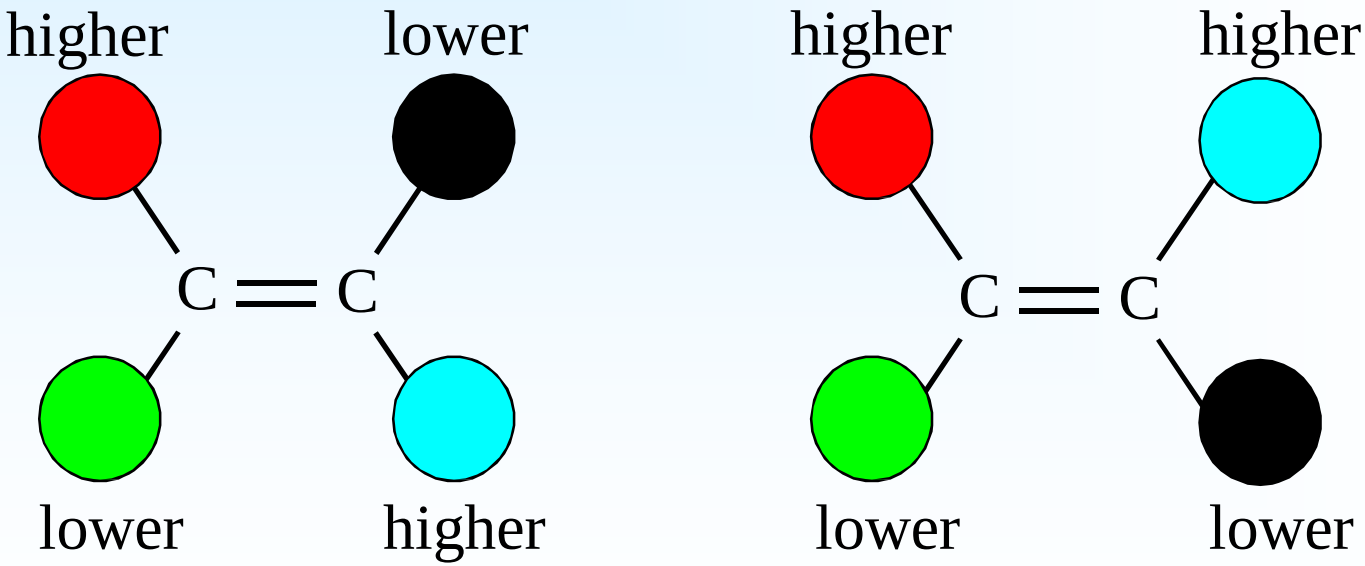
CH_3 > H

Br > Cl

The E-Z Notational System

Question: How are substituents ranked?

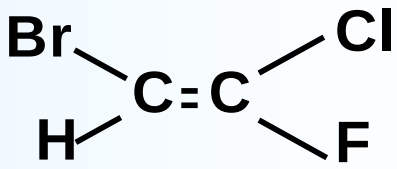
- Answer: They are ranked in order of decreasing atomic number.



Entgegen *Zusammen*

If the alkene has 4 <u>different</u> substituents attached to the unsaturated carbon atoms,

e.g.

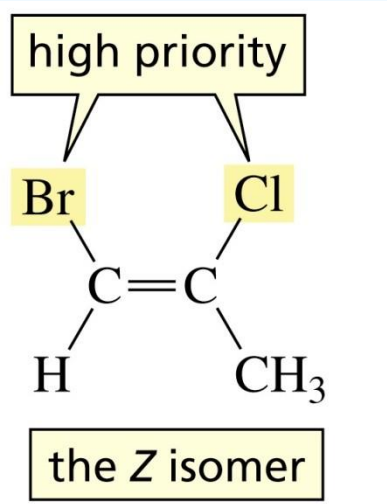


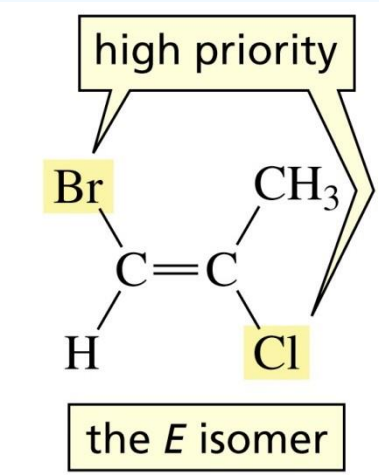
It is impossible to decide whether this compound is cis or trans

(E) / (Z) system:

Rule 1: Examine the 2 atoms bonded directly to a specific sp^2 carbon & decide which has a higher priority (atomic number) .

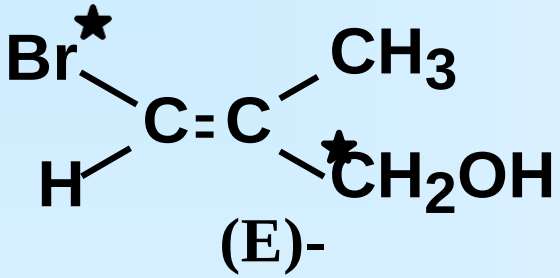
If the two atoms of higher priority are on opposite sides, the alkene is designated (E) (from the German word Entgegen, meaning opposite)





If the two atoms of higher priority are on the same side of the double bond, the alkene is designated (Z) (from the German word Zusammen, meaning together).

Rule 2: If there is a tie, consider the atoms attached to the tie. e.g



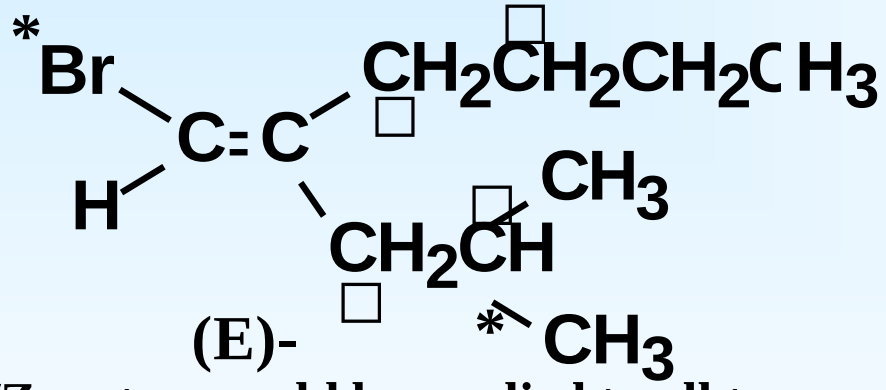
(E)-

3H □ 3X1 = 3

2H,O □ 2+8 = 10

If needed, go to the second atom…etc.

e.g.

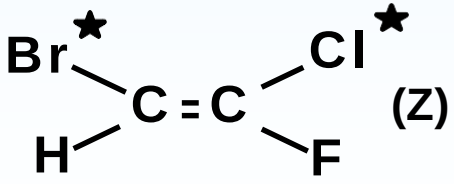


(E)-

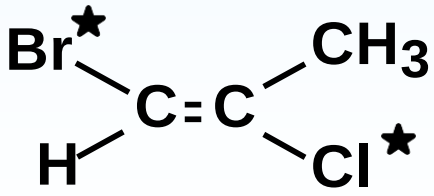
□ 2H,C = 2X1 + 1X6 = 8

□ H,2C = 1X1 + 2X6 = 13

E/Z system could be applied to all types of alkenes i.e. it may replace cis/trans system. However, the latter does not always replace the former.



(Z)



(E)

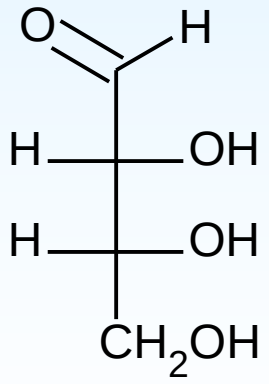
Z or E ?

Erythro and Threo isomers

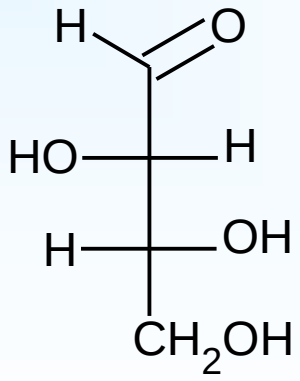
- **Two like functional groups**

Same side (**Erythro**)

Opposite side (**Threo**)



Erythrose



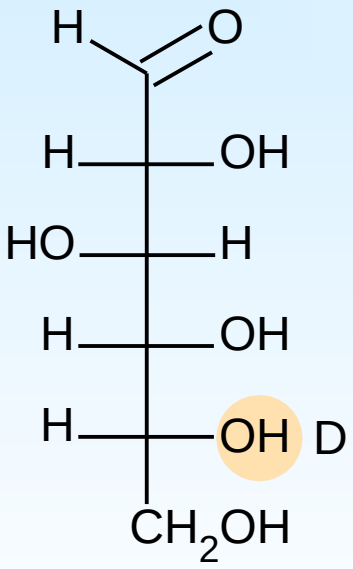
Threose

RELATIVE CONFIGURATION

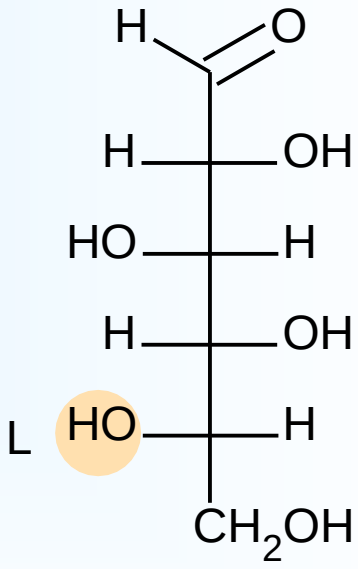
D and L isomers

- Used for molecules having non symmetric ends.
- Orientation of –H and –OH on chiral carbon which is farther most from the primary chiral carbon.
- Generally used in Fischer projection.

D and L isomers



D-Glucose



L-Glucose

ABSOLUTE CONFIGURATION

R and *S* isomers

- Suggested by **Cahn**, **Ingold** and **Prelog** (**CIP**).
- ***R*** Latin : ***rectus*** = riǥht
- ***S*** Latin : ***sinister*** = left

R.S. Cahn (The Chemical Society, London)

Sir Christopher Ingold (University College, London)

R and S isomers

- **V. Prelog** (Eidgenossiche Technische Hochschule, Zurich)
- **CIP** system most frequently used for designating absolute configurations of **chiral** compounds.

R and *S* isomers

- **Sequence rules**

1) Arrange the ligands associated with an element of chirality into order of **priority**.

Priority Rules

- Higher atomic number is given higher priority.
- Higher atomic mass is given higher priority.

***R* and *S* isomers**

cis* > *trans

[(*R*, *R*)] or (*S*, *S*)] > [(*R*, *S*) or (*S*, *S*)].

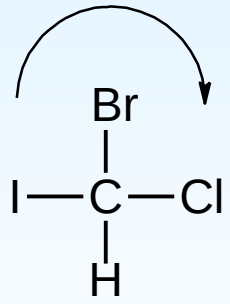
I > Br > Cl

2) View the molecule with the lowest priority group pointing away from the viewer.

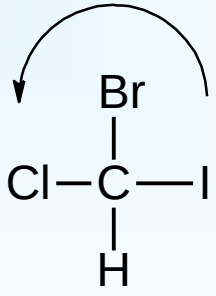
3) Count the remaining ligands **in order of decreasing priority**.

R and *S* isomers

- If the path traced is clockwise, the **(*R*)** absolute configuration is assigned.
- If the path traced is cc unterclockwise, the **(*S*)** absolute configuratior is assigned.



R



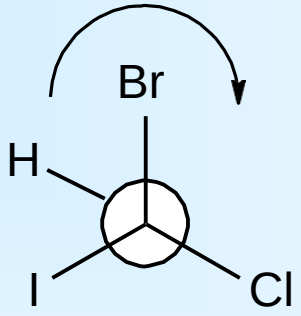
S

Priority

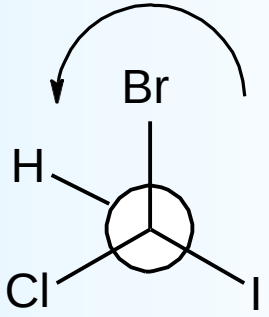
I > Br > Cl > H

Bromochloroiodomethane

R and *S* isomers



R



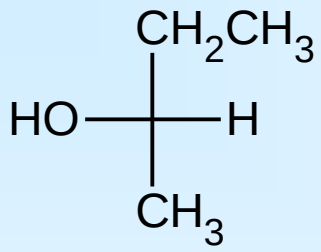
S

Priority

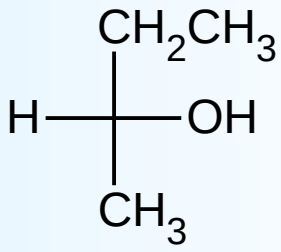
I > Br > Cl > H

Atoms priority	I > Br > Cl > H			
At. No.	53	35	17	1
At. Wt.	126.91	79.91	35.06	1.008

R and *S* isomers

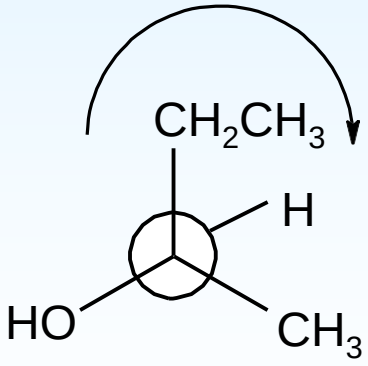


(-)-2-Butanol

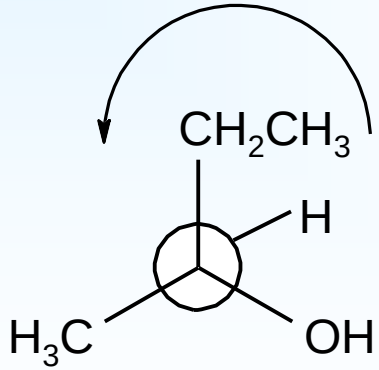


(+)-2-Butanol

Relative configuration



(*R*)-2-Butanol

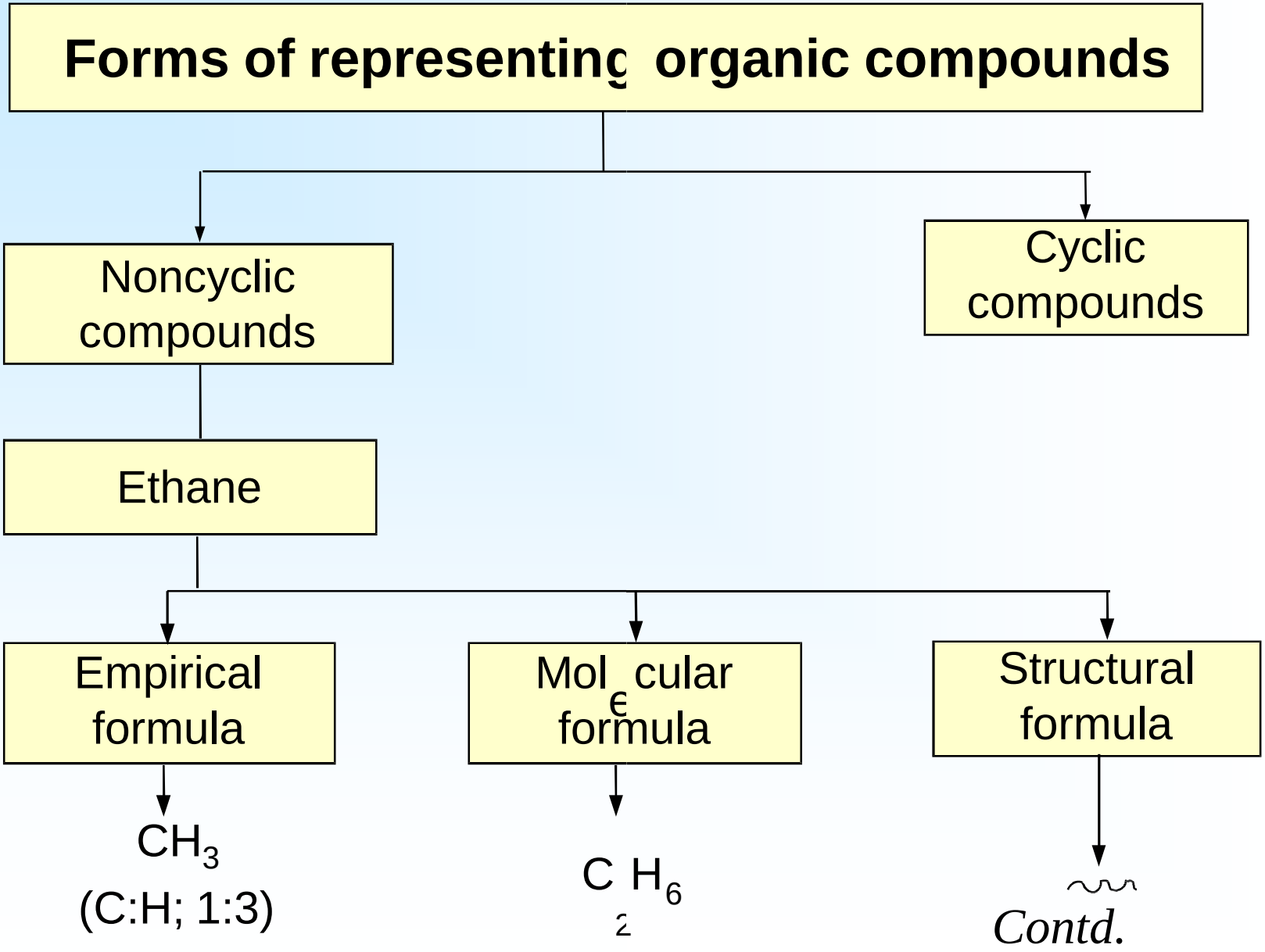


(*S*)-2-Butanol

Priority

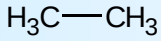
HO > CH_3CH_2 > CH_3

Absolute configuration

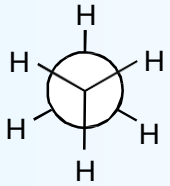

Forms of representing organic compounds
Noncyclic compounds
Cyclic compounds
Ethane
Empirical formula
Molecular formula
Structural formula
CH_3
(C:H; 1:3)
C_2H_6
Contd.

Ethane Structural formula

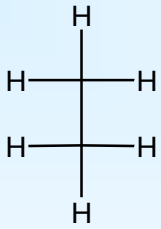
Chain formula (normal chain)



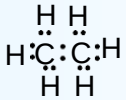
Newman projection



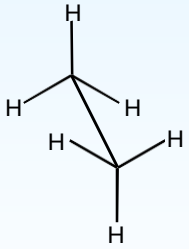
Fischer formula

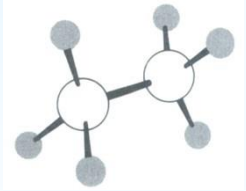


Electronic formula



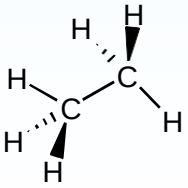
Andiron formula (Sawhorse drawing)

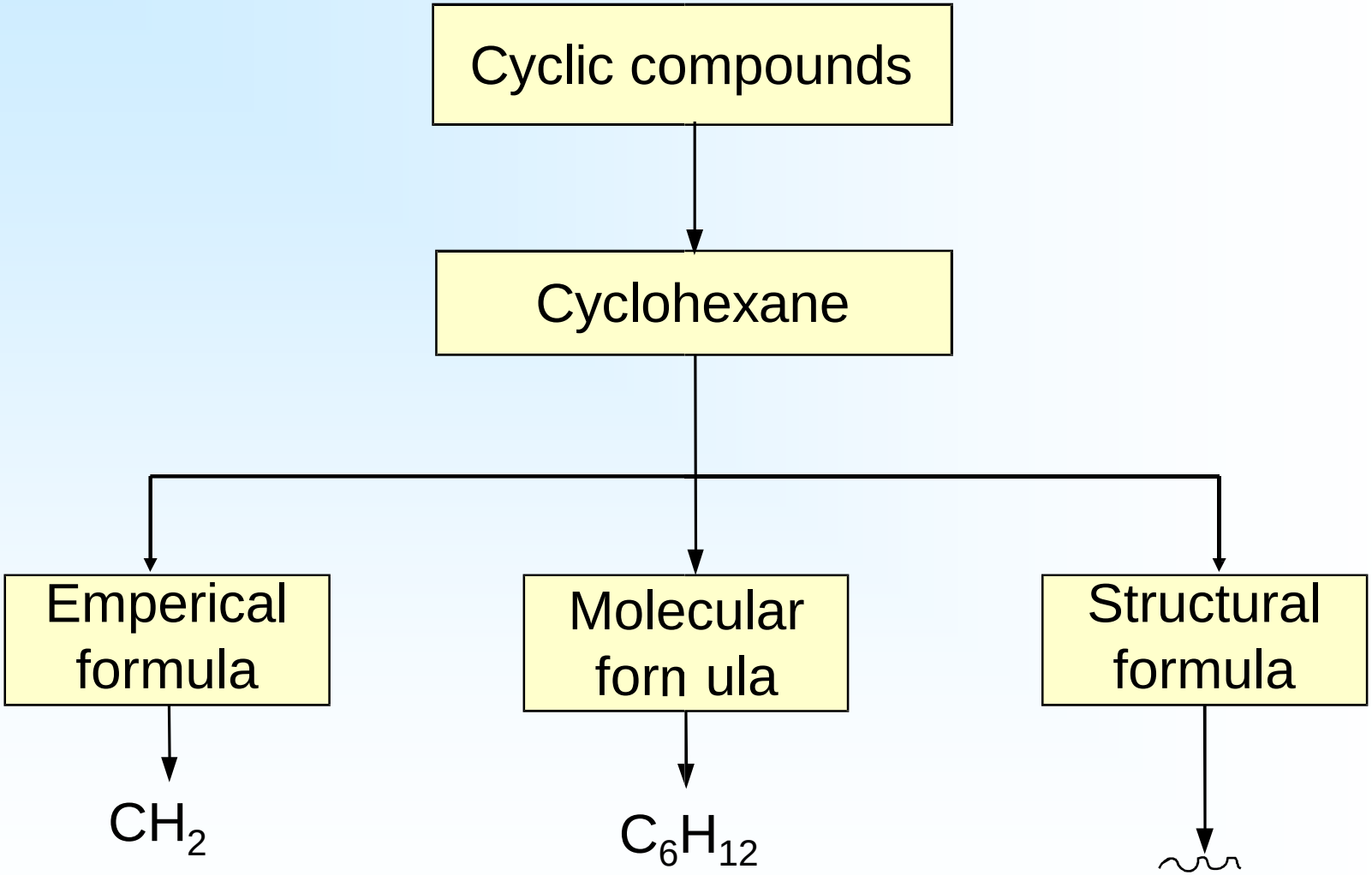




Ball & Stick formula

Dimensional formula (Wedge-and-dash drawing)



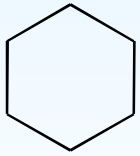

Cyclic compounds
Cyclohexane
Emperical formula
Molecular forn ula
Structural formula
CH_2
C_6H_{12}

Contd.

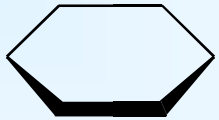
Cyclohexane structural formula

Chain formula

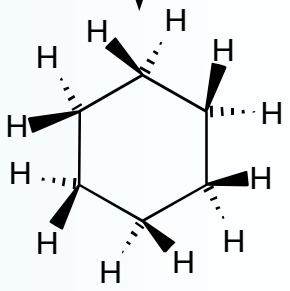
Polygon formula



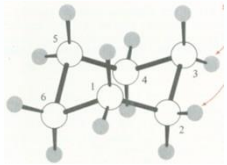
Haworth projection



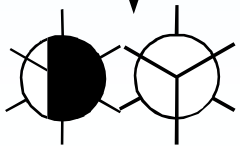
Wedge-and-dash drawing



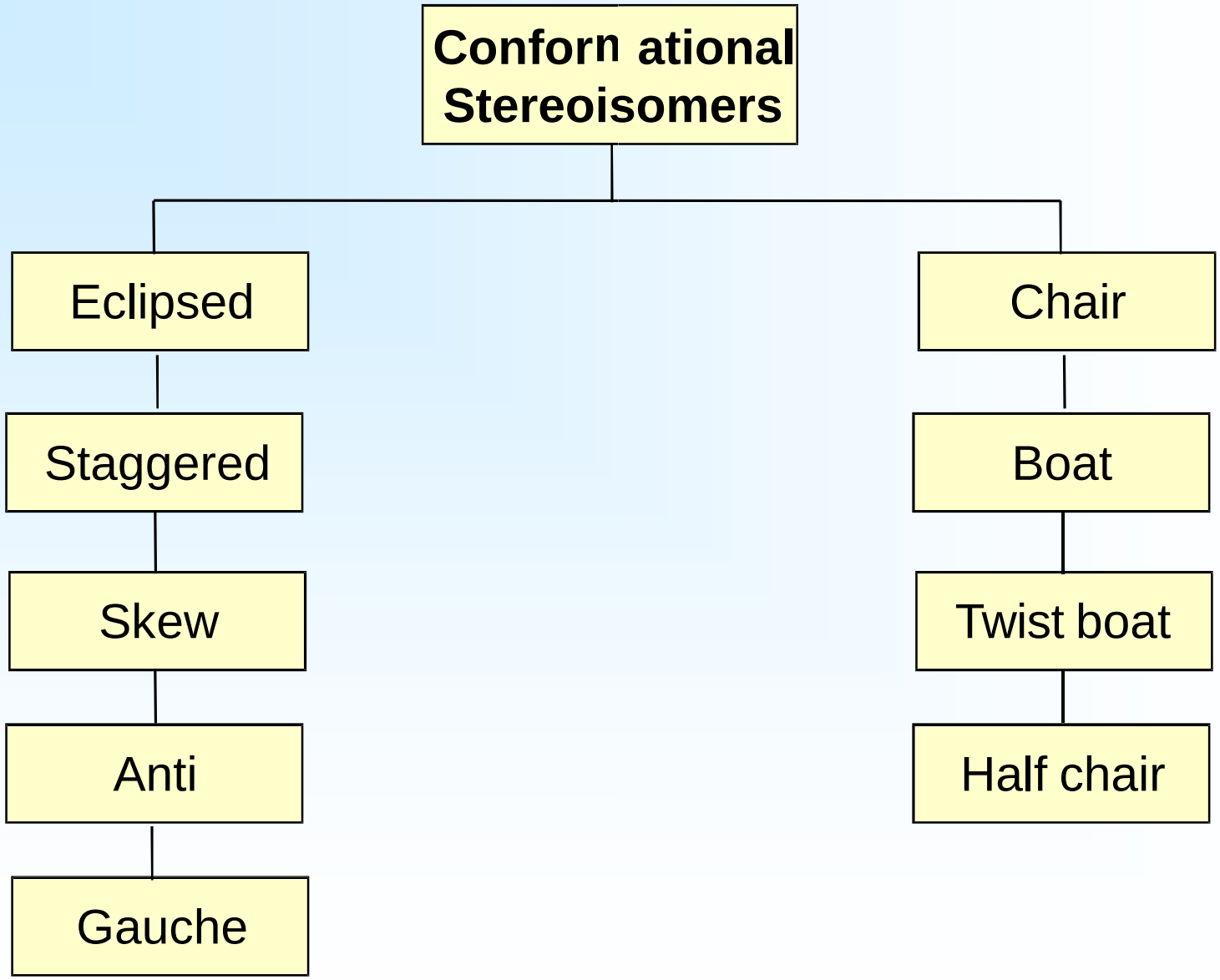
Ball and Stick formula



Newman projection

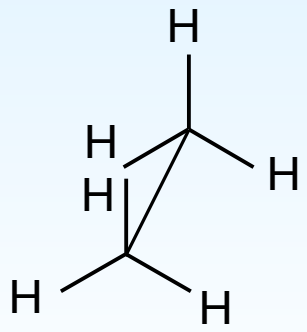


Chair formula

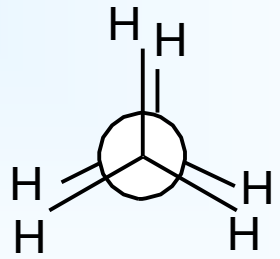

Conforn ational Stereoisomers
Eclipsed
Staggered
Skew
Anti
Gauche
Chair
Boat
Twist boat
Half chair

CONFORMATIONS

- Different arrangements of atoms that can be converted into one another by rotation about single bonds are called **conformations.**



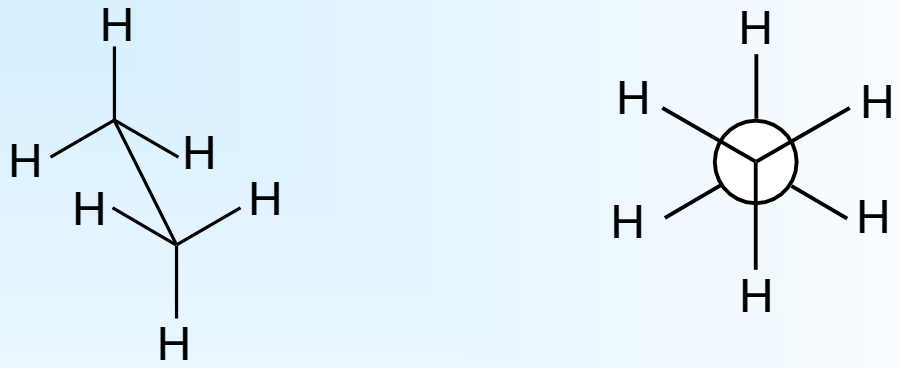
Andiron formula



Newman projection

Eclipsed conformation ethane

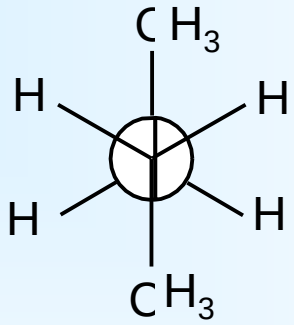
CONFORMATIONS



Staggered conf rmation Ethane

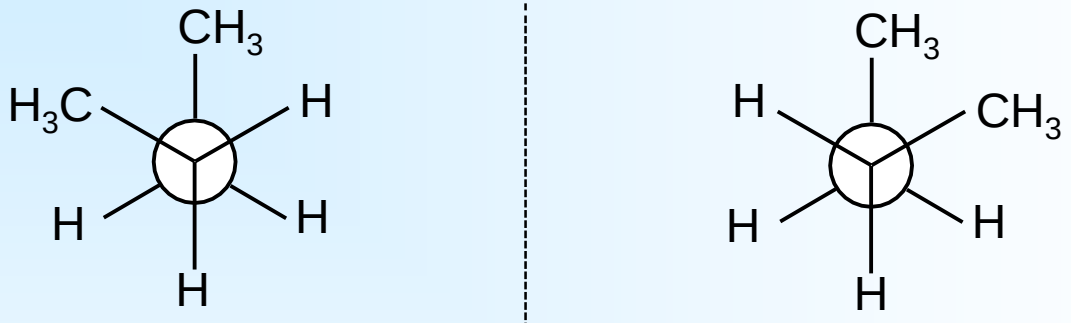
- The infinity of interm ediate conformations are called **skew conformations.**

CONFORMATIONS



Anti conformation n-Butane

CONFORMATIONS

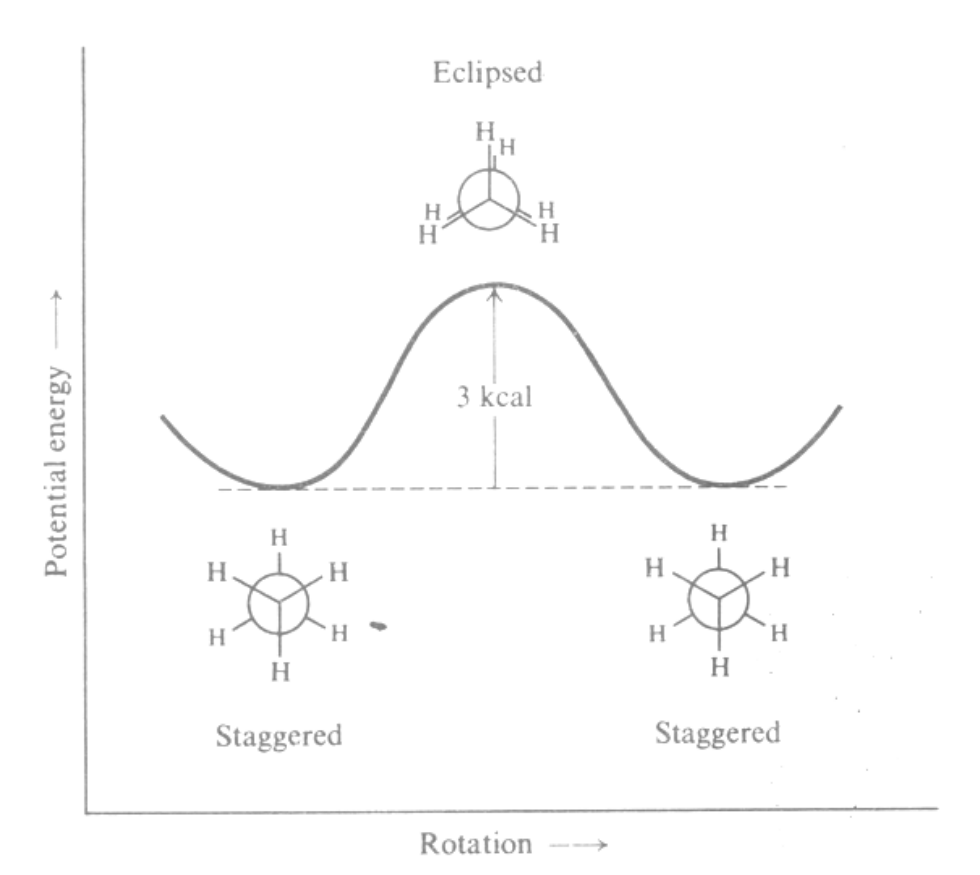


Gauche conformation n-Butane

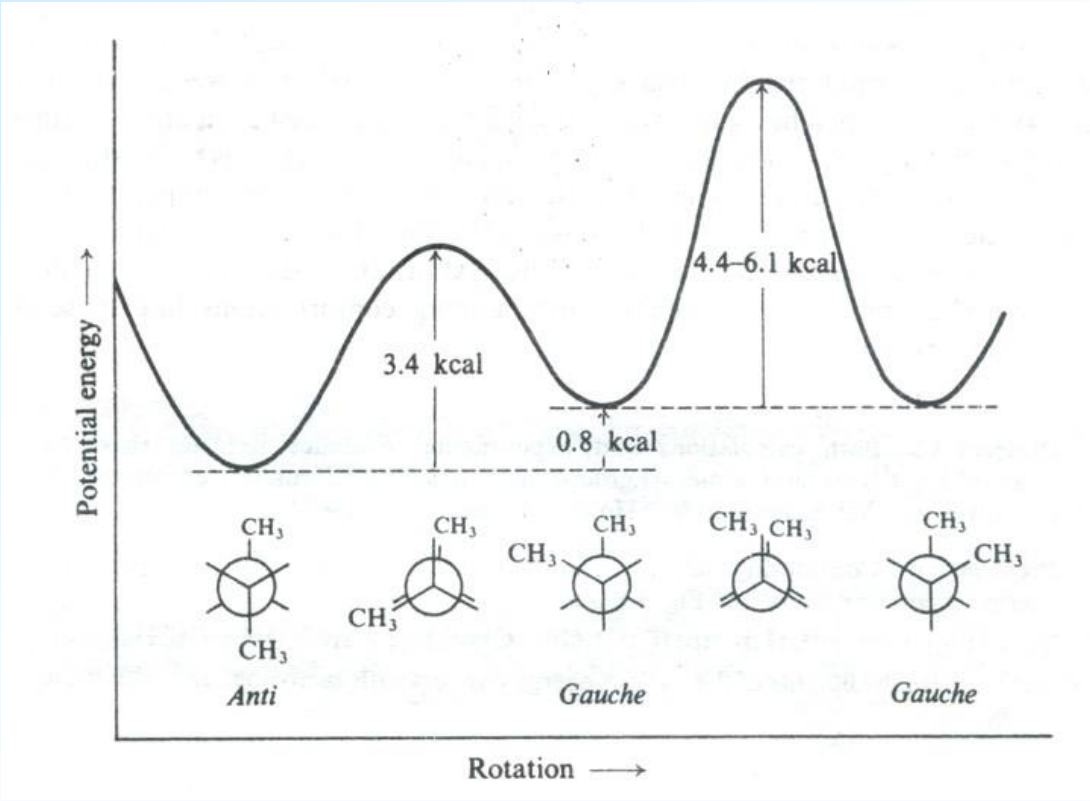
- Van der Waals forces
- Repulsive (Steric repulsion)
- Strain (Steric strain)
- Strain (Torsional strain)
- Shielding / Crowding of CH_3 groups.
- Mirror images **(Conformational) enantiomers**
- Anti and Gauche are not mirror images **(conformational) diastereomers**

CONFORMATIONAL ISOMERS / CONFORMERS

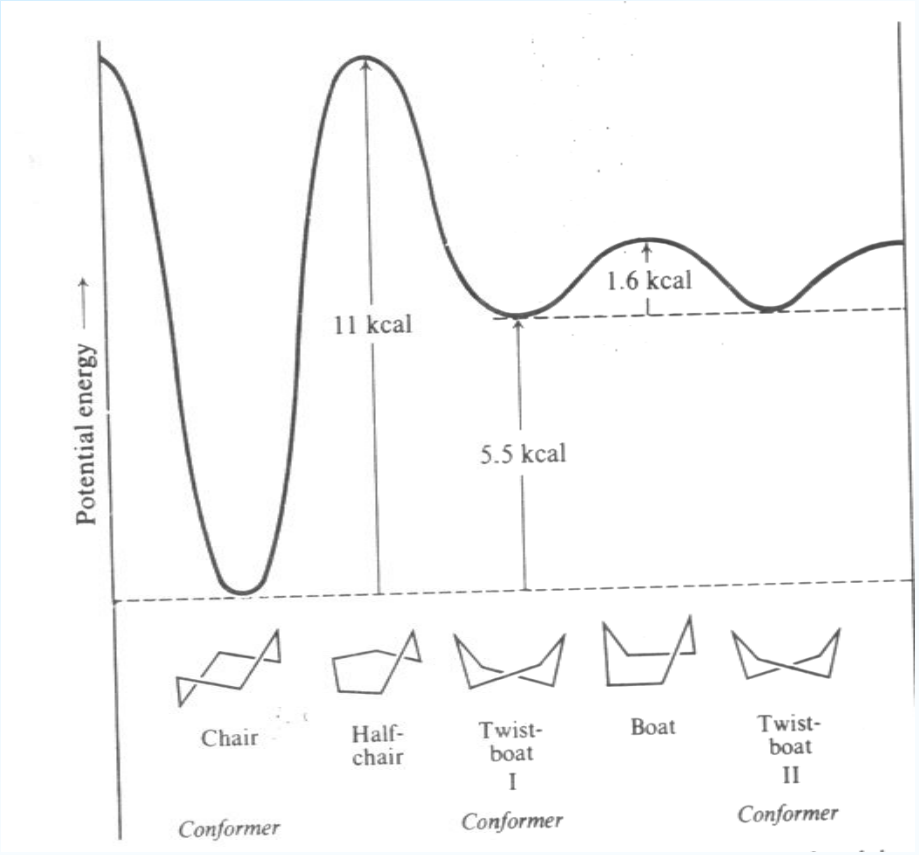
- Different conformations corresponding to **energy minima** are called **conformational isomers** or **conformers**.
- Conformational isomers are interconvertable by rapid rotations about one or more single bonds (C-C).



Potential energy changes during rotation about the carbon-carbon single bond of ethane.

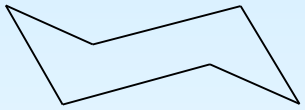


Potential energy changes during rotation about the C(2)-C(3) bond of *n*-butane.

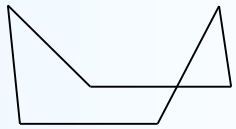


Potential energy relationships among conformations of cyclohexane.

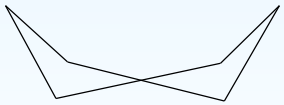
CONFORMATIONS OF CYCLOHEXANE



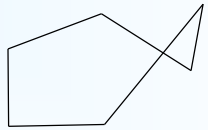
Chair



Boat

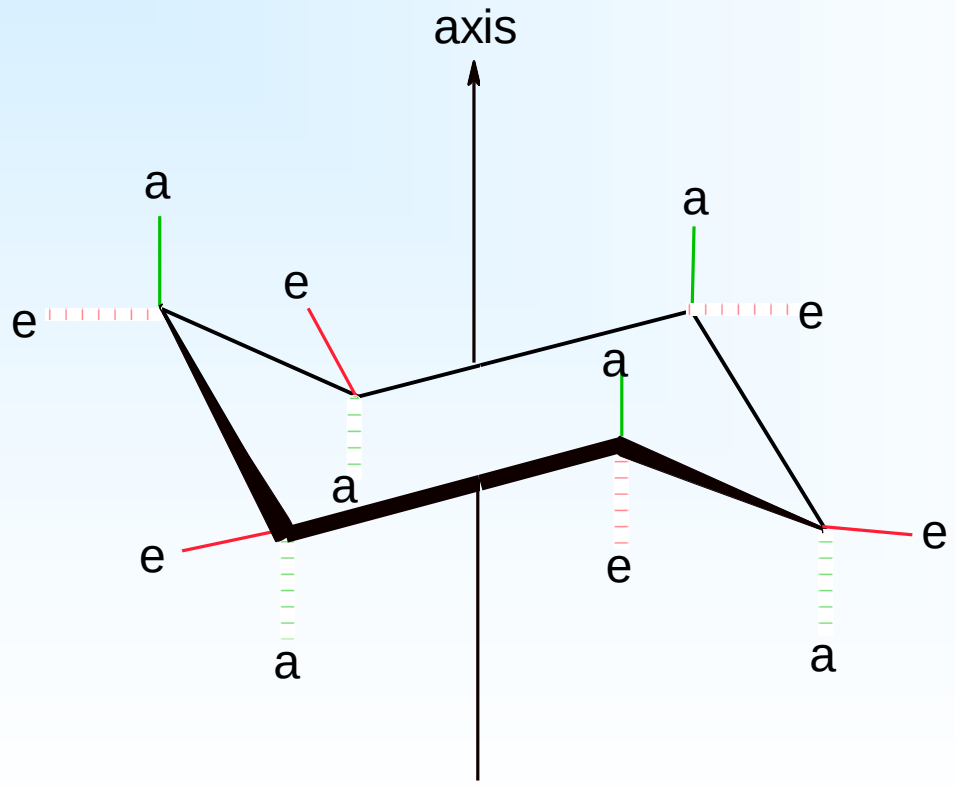


Twist-boat



Half-chair

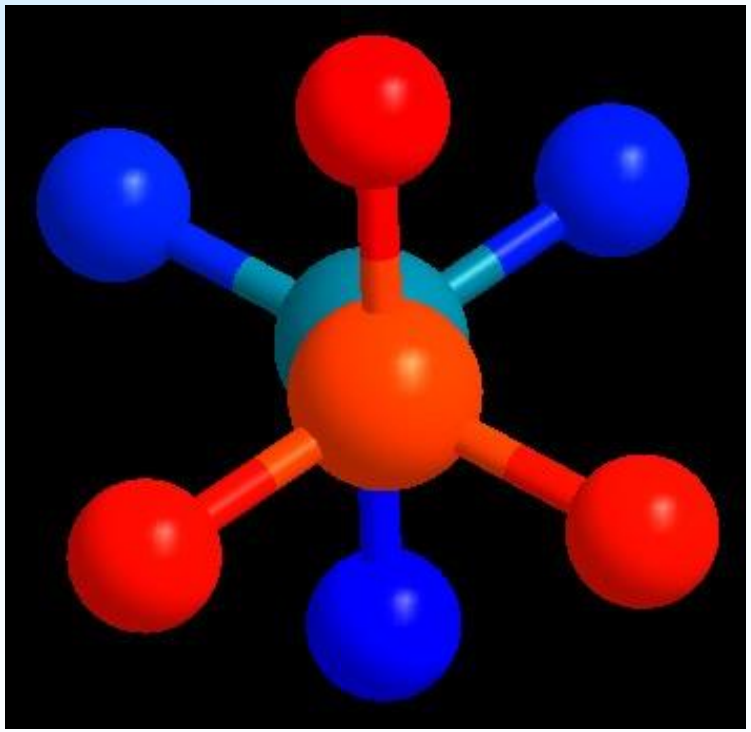
CHAIR CONFORMER OF CYCLOHEXANE



CHAIR FORM MOST STABLE CONFORMATION

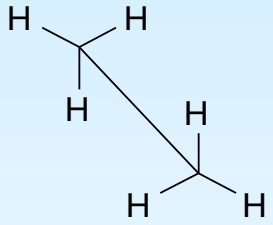
- Symmetrical
- Compact
- Completely free of strain-angle/torsional/ Van der Waals forces (strain/torsion/repulsion).
- Every angle is the tetrahedral angle.
- Every C-C bond precise staggering.
- Energy minima
- No crowding of hydrogen atoms.

Newman projection formula: Ethane(Staggered)

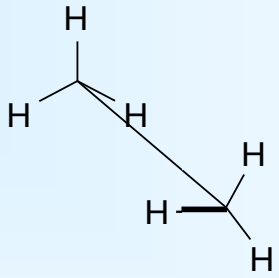


Anti conformation; 180 ^{o} tortional angle

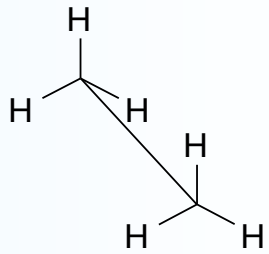
Sawhorse &Newman projection formula: Ethane



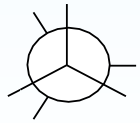
Staggerd
(Most stable)
180o



Gauch Conformation
60 o



Eclipsed
Least stable
0 o



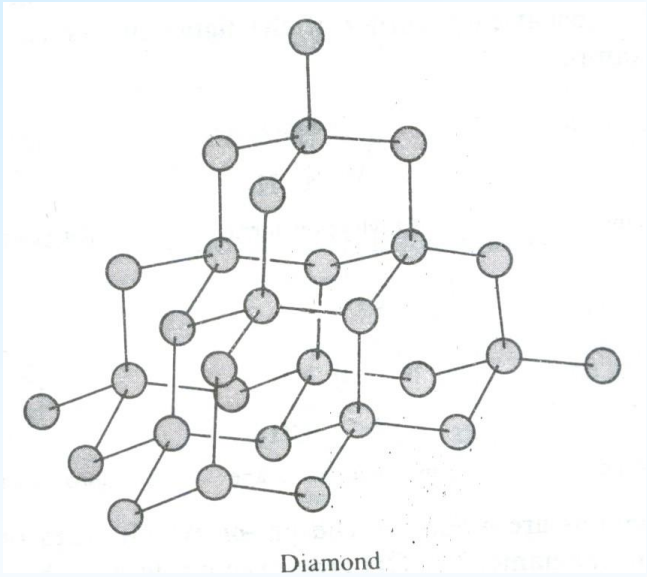
Conformational Isomerism in Cyclohexane:

Cyclohexane exists in two puckered conformations, the **boat and chair forms**, that have tetrahedral bond angles. The boat form is less stable and not preferred because of interactions between the two end or **flagpole** carbons and because the hydrogens on the other adjacent carbons are eclipsed. In the preferred chair form, atoms on adjacent carbons are staggered and there are no flagpole type interactions. There are two orientations of hydrogens in the chair conformation. **Axial hydrogens** are oriented directly above or below the "plane" of the ring in an alternating arrangement. **Equatorial hydrogens** protrude out along the perimeter of the ring.

CHAIR FORM MOST STABLE CONFORMATION

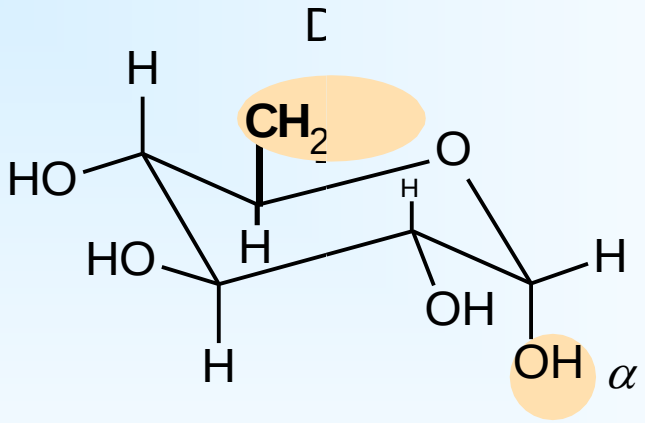
- **Everything just fits** (geometrical demands).
- Architectural perfection.
- Cyclohexane chairs in the structure of diamond.
- Diamond most stable form of carbon and the hardest substance known.
- Replacing one methylene group with oxygen make up the most abundant building block of the organic world, D-glucose.

CHAIR FORM MOST STABLE CONFORMATION


Diamond

- Appearance of chair form in diamond

CHAIR FORM MOST STABLE CONFORMATION

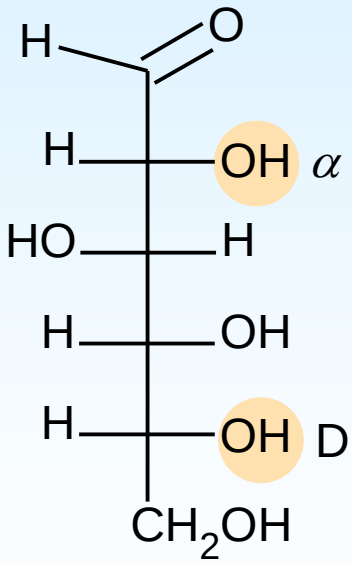


α-D-(+)-Glucopyranose

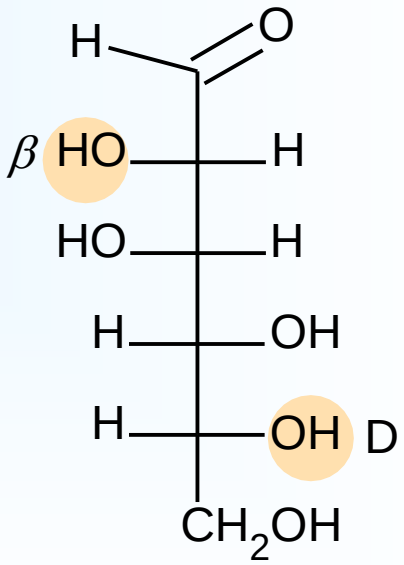
- Appearance of chair form in α-D-(+)-Glucopyranose

GLUCOSE NOMENCLATURE

FISCHER PROJECTIC N

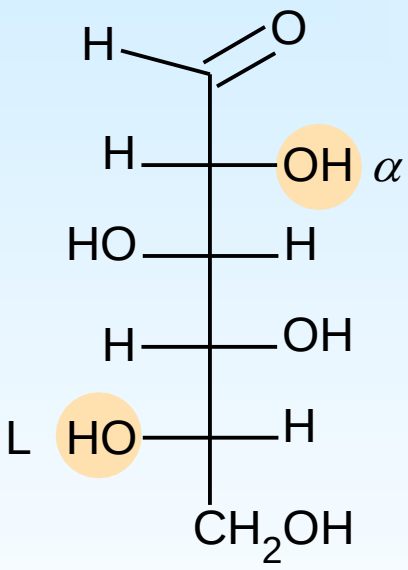


α-D-(+)-Glucose

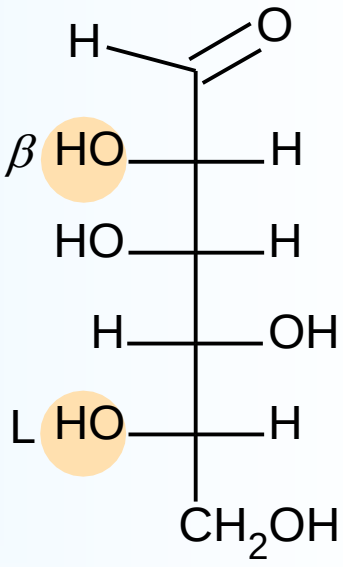


β-D-(+)-Glucose

FISCHER PROJECTIC N

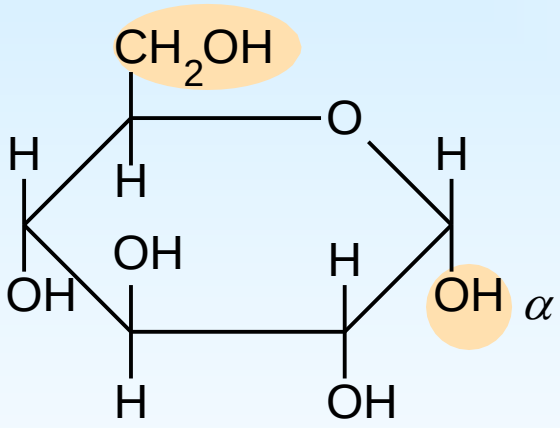


α-L-(+)-Glucose



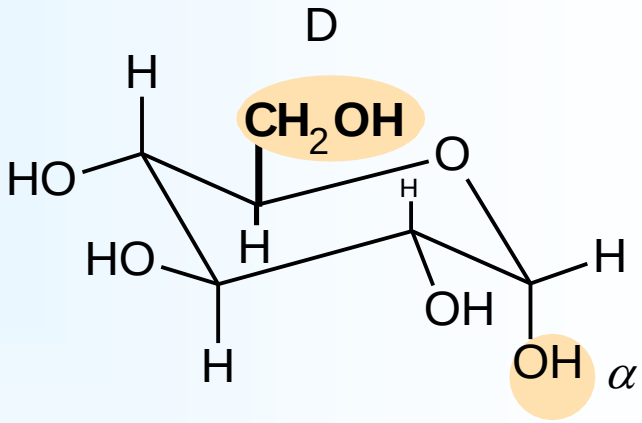
β-L-(+)-Glucose

HAWORTH PROJECTION



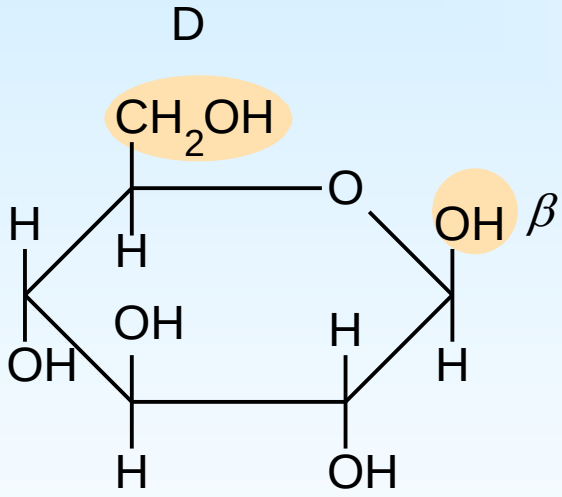
α-D-(+)-Glucopyranose

CHAIR CONFORMER



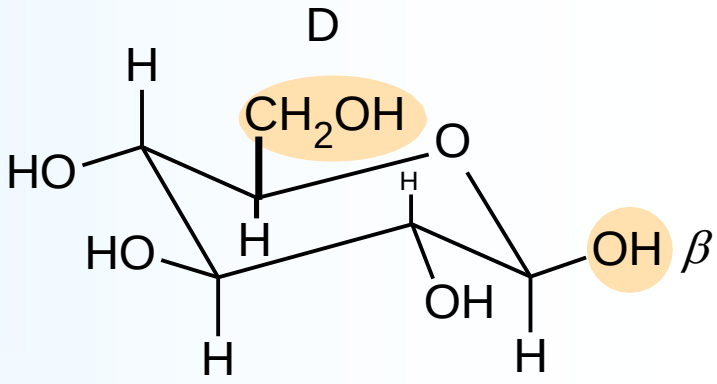
α-D-(+)-Glucopyranose

HAWORTH PROJECTION



β-D-(+)-Glucopyranose

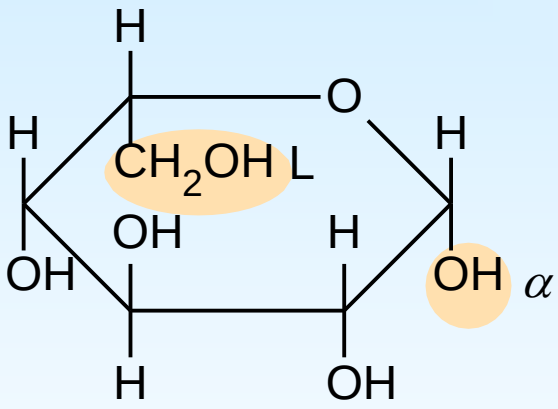
CHAIR CONFORMER

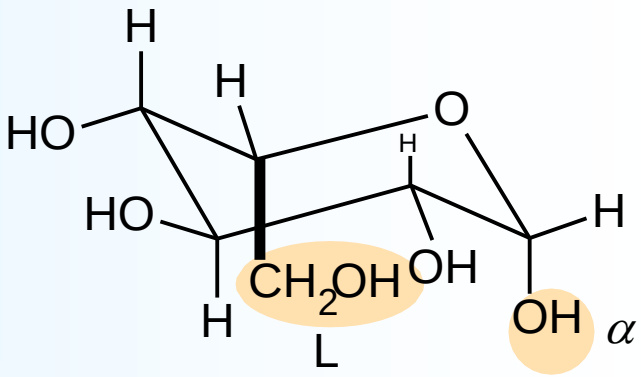


β-D-(+)-Glucopyranose

HAWORTH PROJECTION

CHAIR CONFORMER



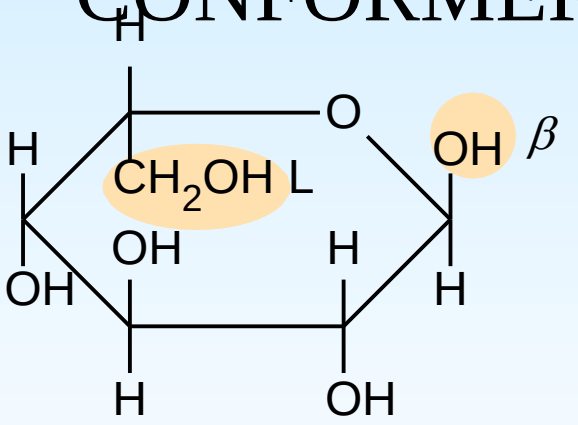


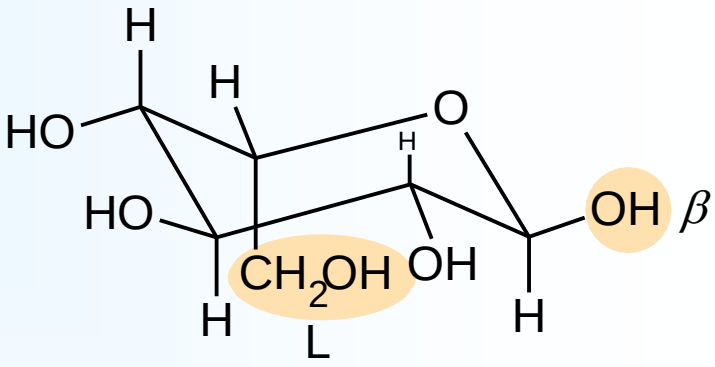
α-L-(+)-Glucopyranose

α-L-(+)-Glucopyranose

HAWORTH PROJECTION CONFORMER

CHAIR





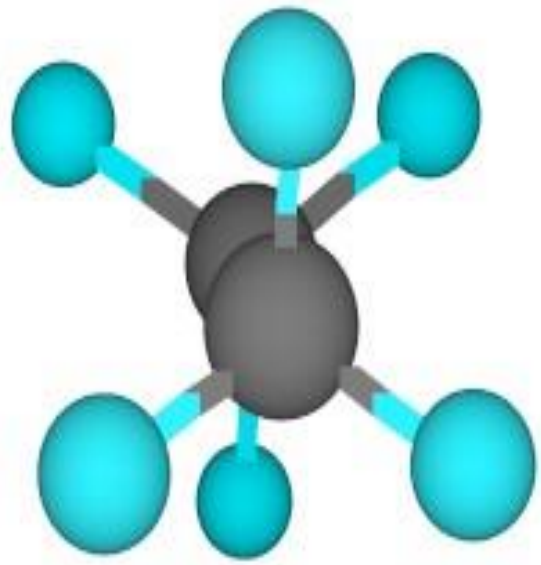
β-L-(+)-Glucopyranose

β-L-(+)-Glucopyranose

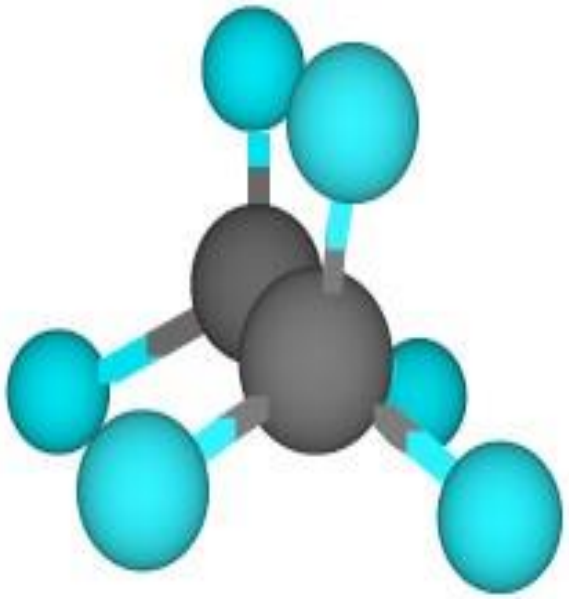
Ethane

Make a model of ethane, C2H6. Rotate the two carbons relative to each other around the carbon-carbon bond. Make the staggered and eclipsed conformations.

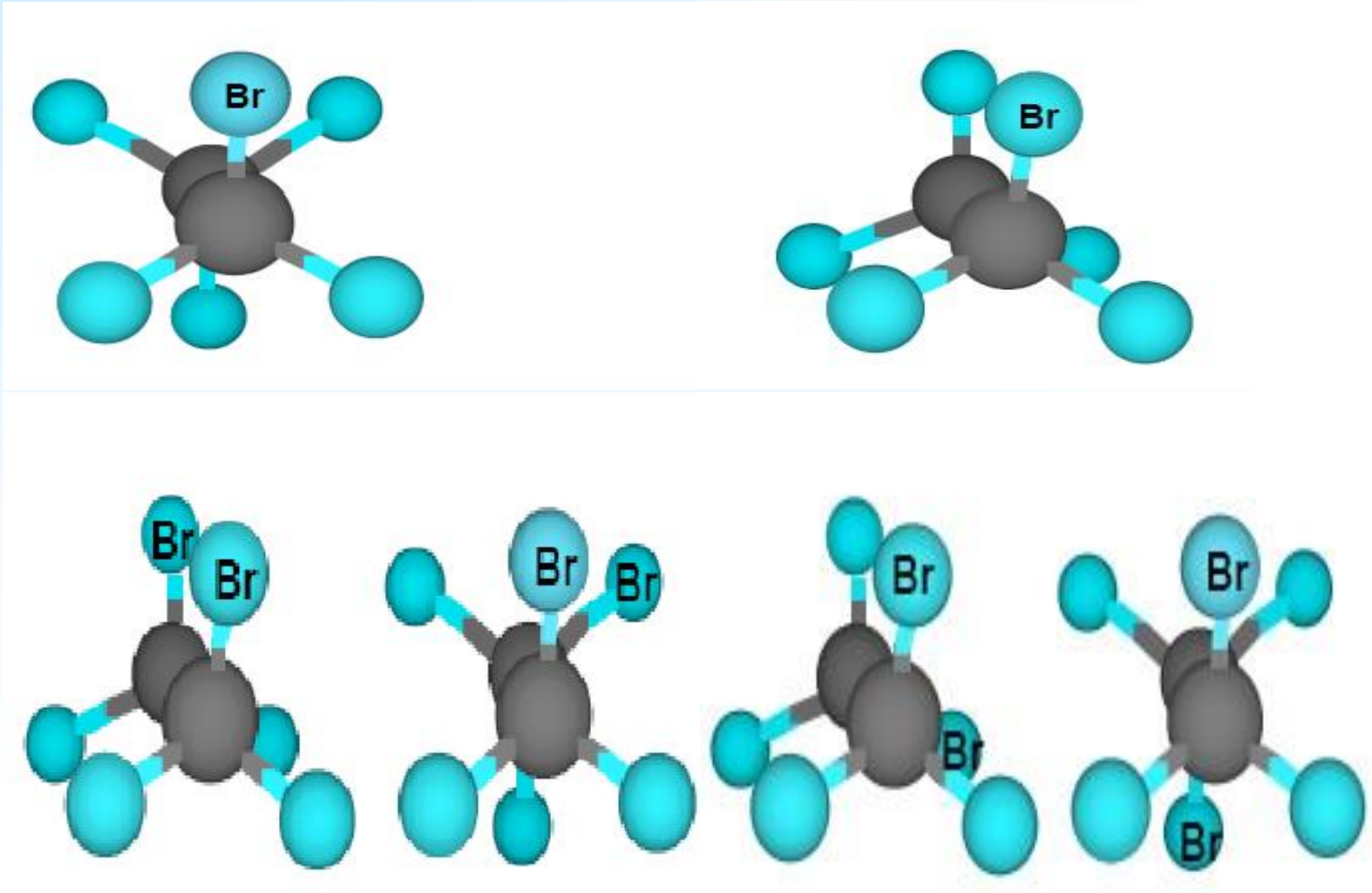
staggered



eclipsed



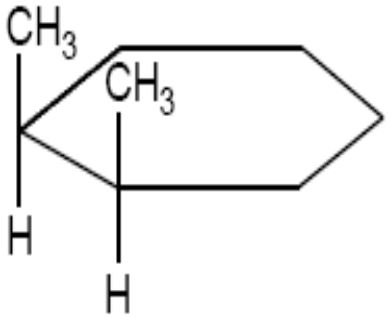
Bromoethane

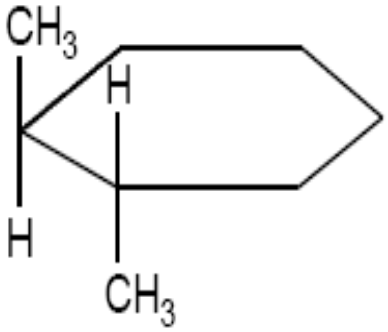


Geometric Isomerism:

(a) 1,2-dimethylcyclohexane

cis

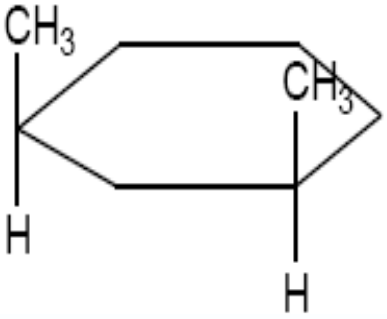


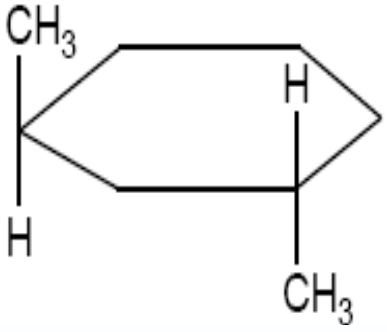


trans

(b) 1,3-dimethylcyclohexane

cis

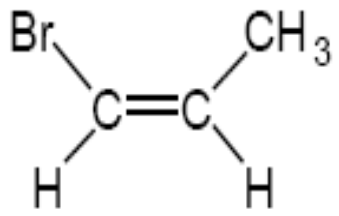




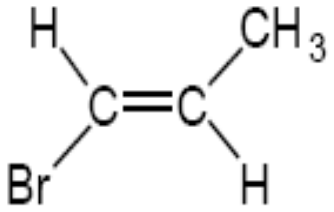
trans

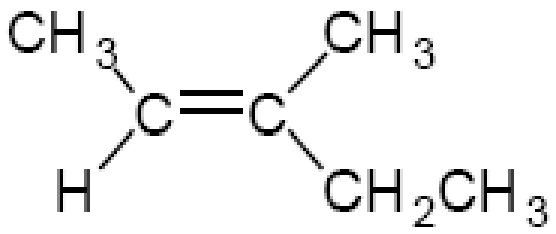
(a) 1-bromopropene has two different groups on each carbon involved in the double bond and exhibits geometric isomerism.

cis

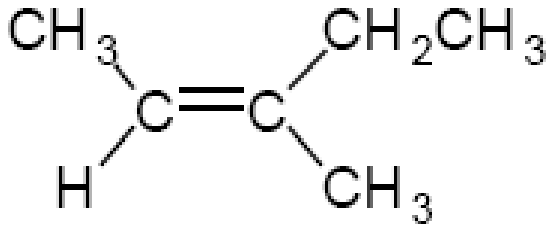


trans

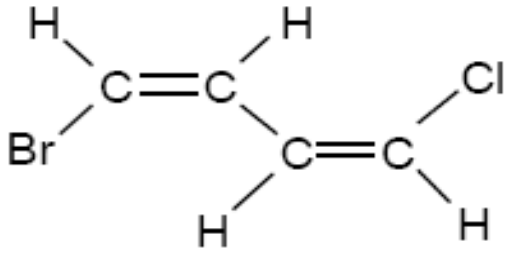




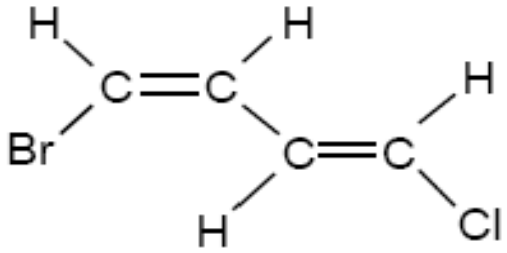
trans or E



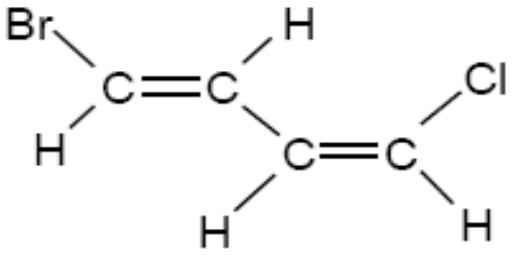
cis or Z



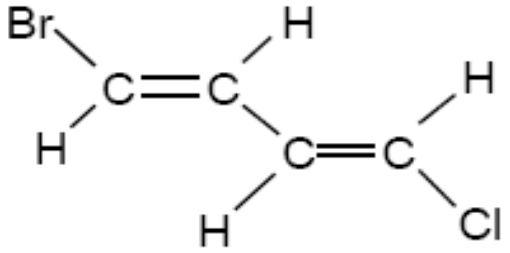
cis-cis



cis-trans



trans-cis

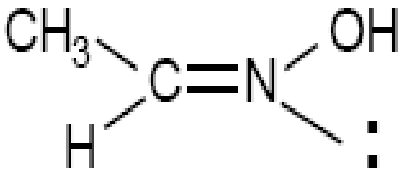


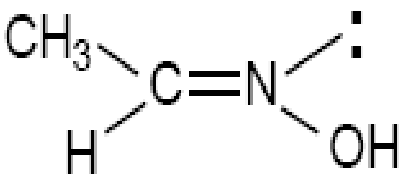
trans-trans

(a) This molecule is capable of exhibiting four geometric isomers since each double bond shows geometric isomerism and the molecule is not symmetrical.

Geometrical isomerism in oximes

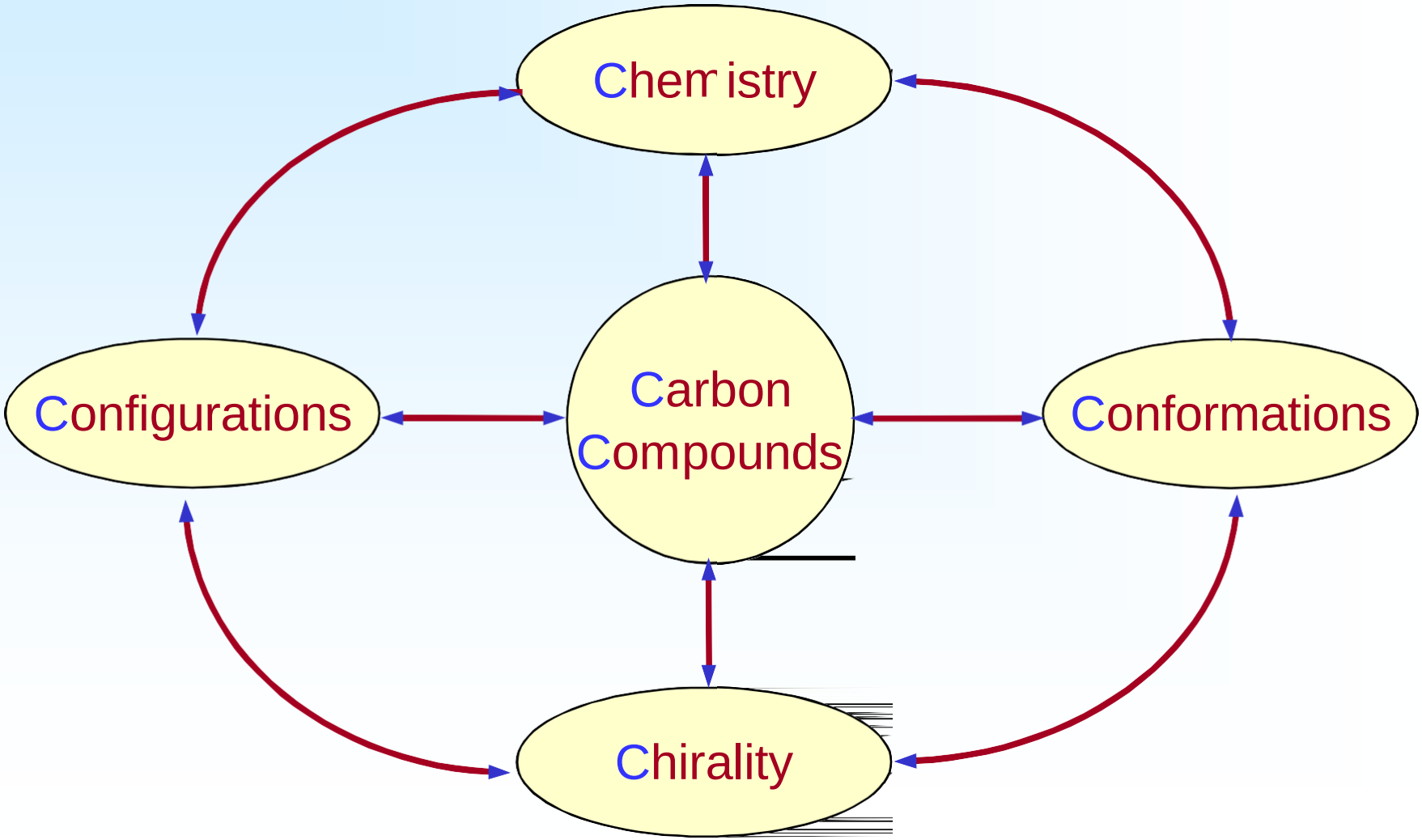
This compound can exhibit geometric isomerism because the nitrogen is sp^2 hybridized and trigonal. The carbon has a methyl and a hydrogen and the nitrogen has an OH and an electron-pair.





STEREO CHEMISTRY OF SOME DRUG MOLECULES

CONFUSING ‘C’


Chemistry
Configurations
Carbon Compounds
Conformations
Chirality

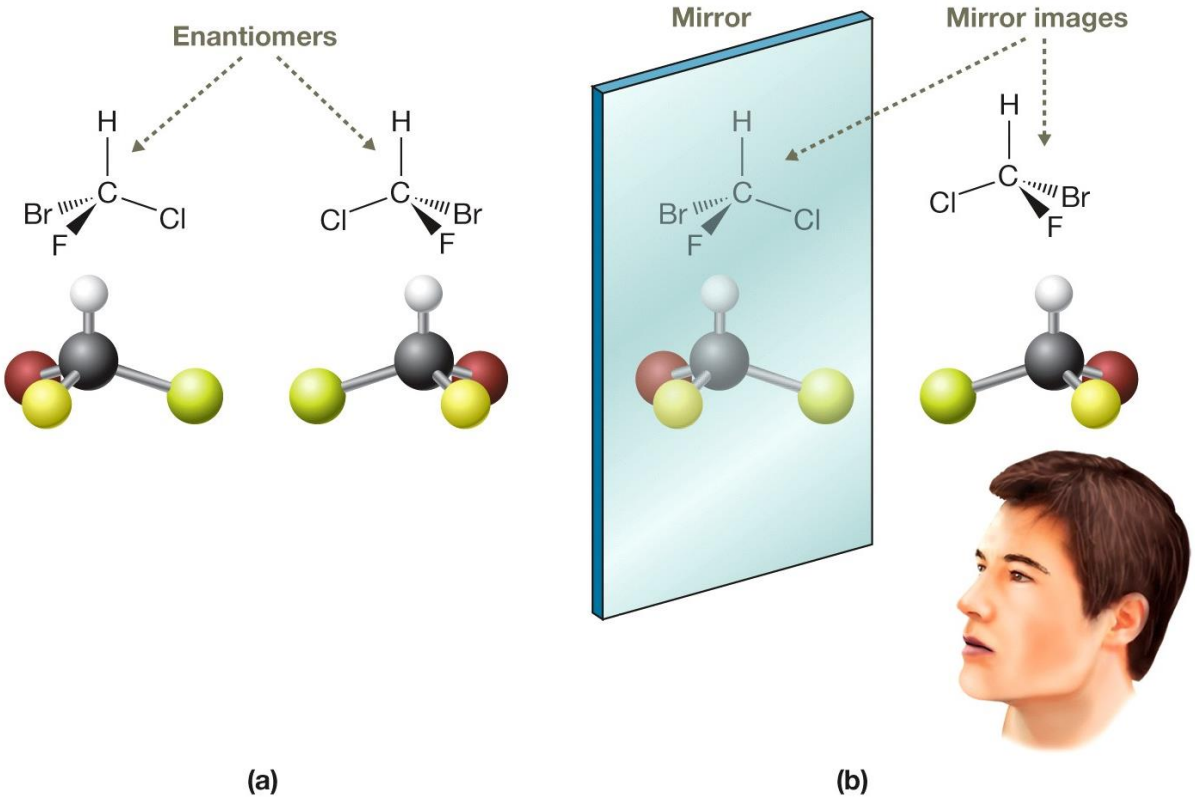
- Stereoisomers
- Chirality
- (R) and (S) Nomenclature
- Depicting Asymmetric Carbons
- Diastereomers
- Fischer Projections
- Stereochemical Relationships
- Optical Activity
- Resolution of Enantiomers

Types of Stereoisomers

- Two types of stereoisomers:
  - enantiomers
    - two compounds that are nonsuperimposable mirror images of each other
  - diastereomers
    - Two stereoisomers that are not mirror images of each other
    - Geometric isomers (cis-trans isomers) are one type of diastereomer.

Enantiomers

- Enantiomers are *nonsuperimposable* mirror images.
- Molecules are nonsuperimposable if there is no orientation in which all atoms of both molecules can be superimposed.



All Isomers

Stereoisomers

Identical	*Enantiomers*	*Diastereomers*
Superimposable	Non-superimposable	Non-superimposable
Same spatial arrangement	Same spatial arrangement	Different spatial arrangement
Same atom connectivity	Same atom connectivity	Same atom connectivity

Chiral

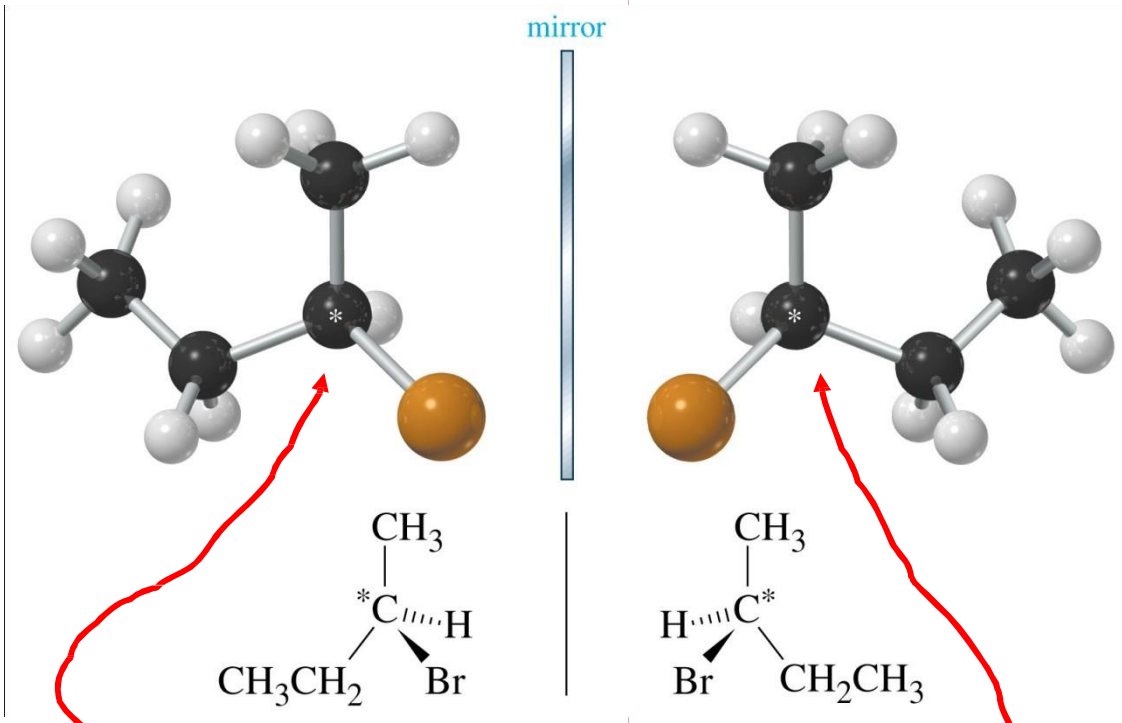
- Enantiomers are chiral:
  - Chiral:
    - Not superimposable on its mirror image

- Many natural and man-made objects are chiral:
  - hands
  - scissors
  - screws (left-handed vs. right-handed threads)

Right hand threads slope up to the right.

Chiral

- Some molecules are chiral:



Asymmetric (chiral) carbon

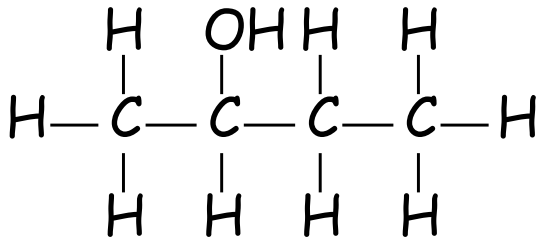
Asymmetric Carbons

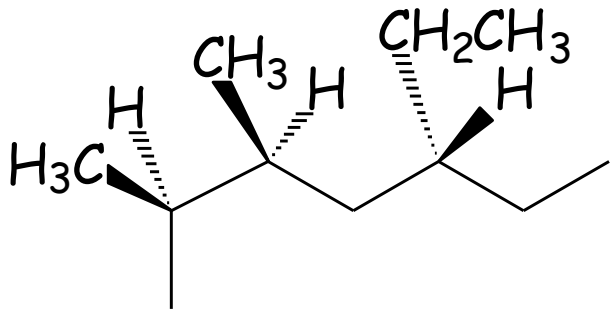
- The most common feature that leads to chirality in organic compounds is the presence of an asymmetric (or chiral) carbon atom.
  - A carbon atom that is bonded to four different groups

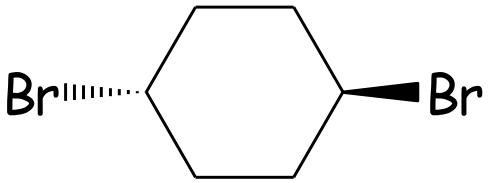
- In general:
  - no asymmetric C → usually achiral
  - 1 asymmetric C → always chiral
  - ≥ 2 asymmetric C → may or may not be chiral

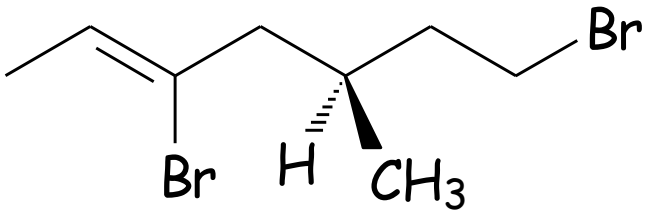
Asymmetric Carbons

Example: Identify all asymmetric carbons present in the following compounds.



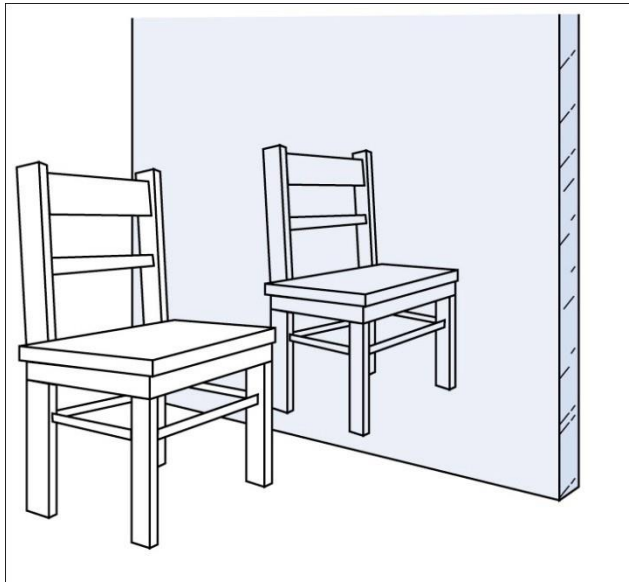


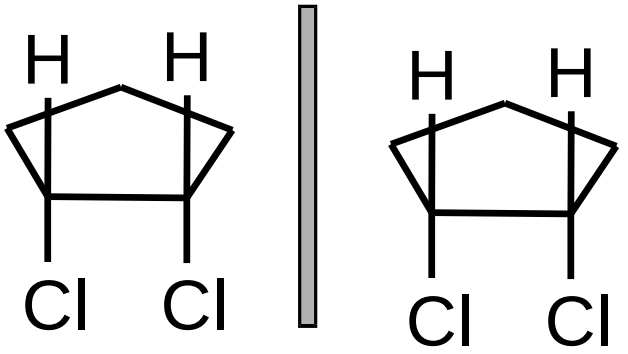




Achiral

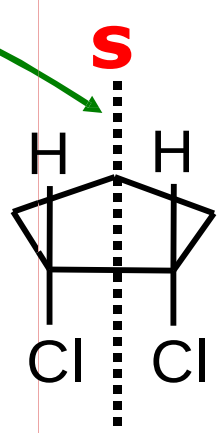
- Many molecules and objects are achiral:
  - identical to its mirror image
  - not chiral





Internal Plane of Symmetry

- Cis-1,2-dichlorocyclopentane contains two asymmetric carbons but is achiral.
  - contains an internal mirror plane of symmetry



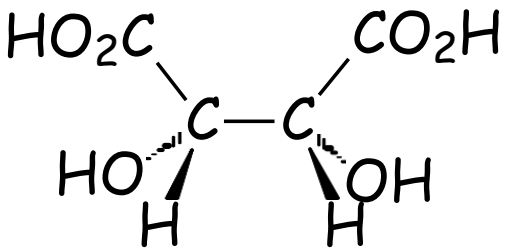
- Any molecule that has an internal mirror plane of symmetry is achiral even if it contains asymmetric carbon atoms.

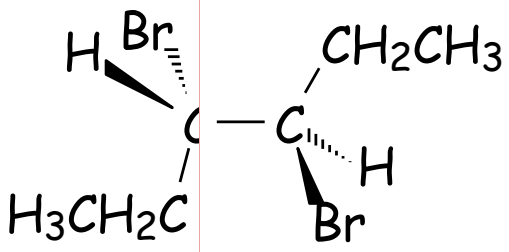
Internal Plane of Symmetry

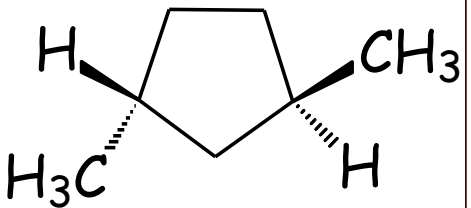
- Cis-1,2-dichlorocyclopentane is a meso compound:
  - an achiral compound that contains chiral centers
  - often contains an internal mirror plane of symmetry

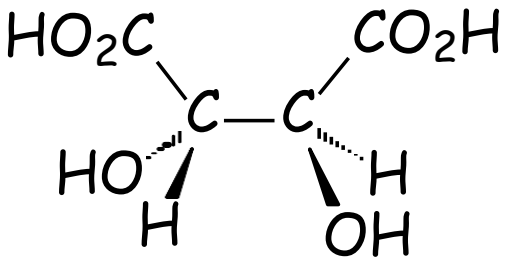
Internal Plane of Symmetry

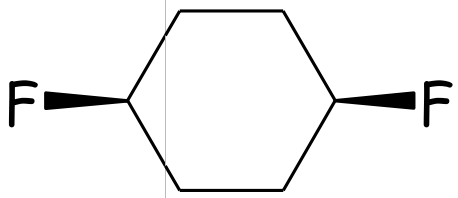
Example: **Which of the following compounds contain an internal mirror plane of symmetry?**

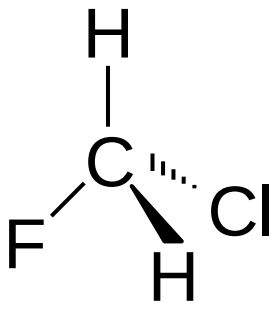












Chiral vs. Achiral

- To determine if a compound is chiral:
  - 0 asymmetric carbons: → Usually achiral
  - 1 asymmetric carbon: → Always chiral
  - 2 asymmetric carbons: → Chiral or achiral
    - Does the compound have an internal plane of symmetry?
      - Yes: → achiral
      - No:
        - If mirror image is non-superimposable, then it's chiral.
        - If mirror image is superimposable, then it's achiral.

4.5 Isomerism in Organic Compounds

Identifying Chiral Carbons in a Molecule

- Step 1: Locate the tetrahedral carbons (carbons with four atoms bonded to them).
- Step 2: Inspect the tetrahedral carbons. Determine if the four groups attached to the tetrahedral carbons are different.
- Step 3: Assign the chiral centers. Typically, an asterisk is drawn next to the chiral carbon.

4.5 Isomerism in Organic Compounds

The Consequences of Chirality

- Biological receptors are "handed."
- A chiral molecule can fit only into a complementary receptor.
- In many pharmaceuticals, only a single enantiomer has biological activity.
- In some cases, one enantiomer of a drug can be beneficial and the other harmful.

4.5 Isomerism in Organic Compounds

The Consequences of Chirality

- This was the case with thalidomide.
- One enantiomer was effective in alleviating the symptoms of morning sickness.
- The mirror image was teratogenic.
- The drug was initially sold as a 50:50 mixture of the enantiomers; many mothers who took it later gave birth to babies with severe birth defects.

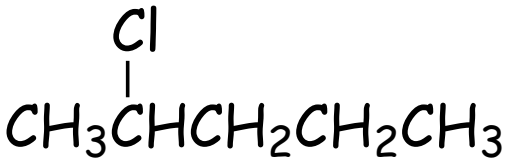
Conformationally Mobile Systems

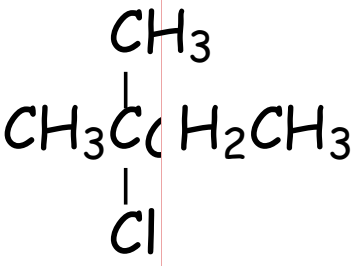
- Alkanes and cycloalkanes are conformationally mobile.
  - rapidly converting from one conformation to another

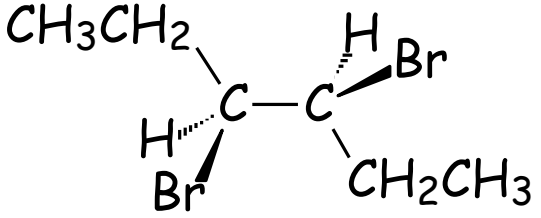
- In order to determine whether a cycloalkane is chiral, draw its most symmetrical conformation (a flat ring).

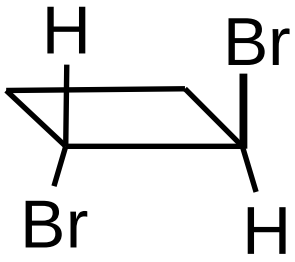
Chiral vs. Achiral

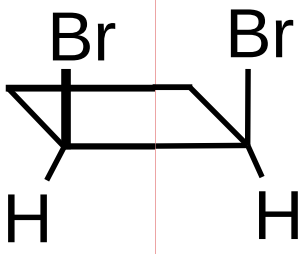
Example: **Identify the following molecules as chiral or achiral.**











trans-1,3-dibromocyclohexane

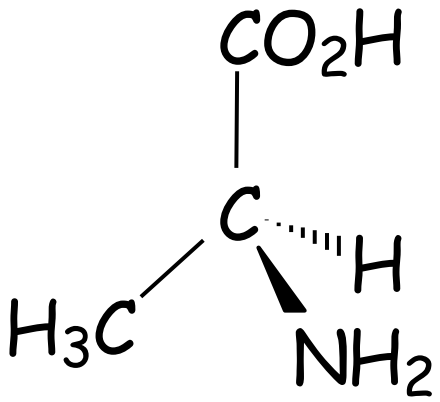
ethylcyclohexane

(R) And (S) Nomenclature

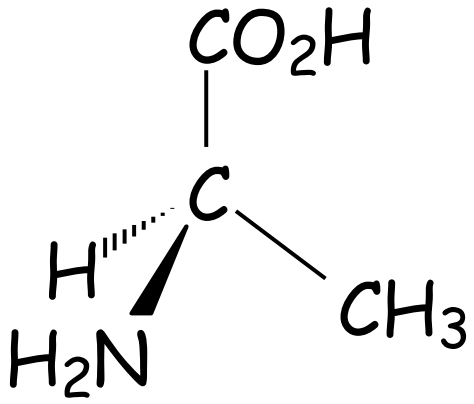
- Stereoisomers are different compounds and often have different properties.
- Each stereoisomer must have a unique name.
- The Cahn-Ingold-Prelog convention is used to identify the configuration of each asymmetric carbon atom present in a stereoisomer.
  - (R) and (S) configuration

(R) and (S) Nomenclature

- The two enantiomers of alanine are:



Natural alanine
(S)-alanine



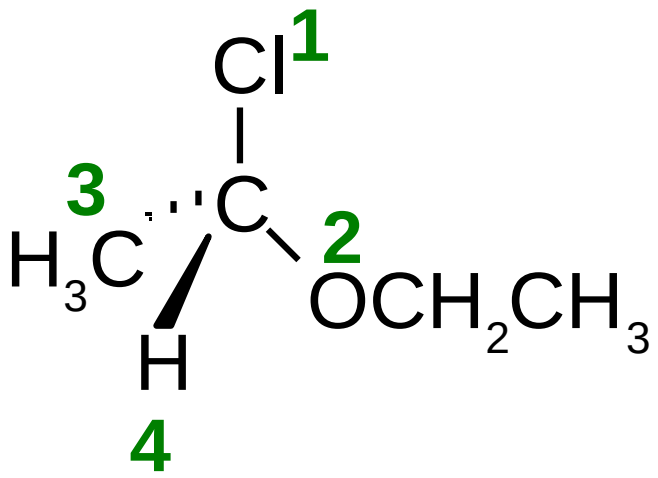
Unnatural alanine
(R)-alanine

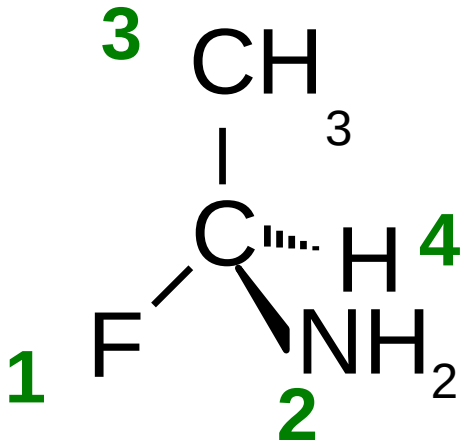
(R) and (S) Nomenclature

- Assign a numerical priority to each group bonded to the asymmetric carbon:
  - group 1 = highest priority
  - group 4 = lowest priority

- Rules for assigning priorities:
  - Compare the first atom in each group (i.e. the atom directly bonded to the asymmetric carbon)
    - Atoms with higher atomic numbers have higher priority

(R) and (S) Nomenclature



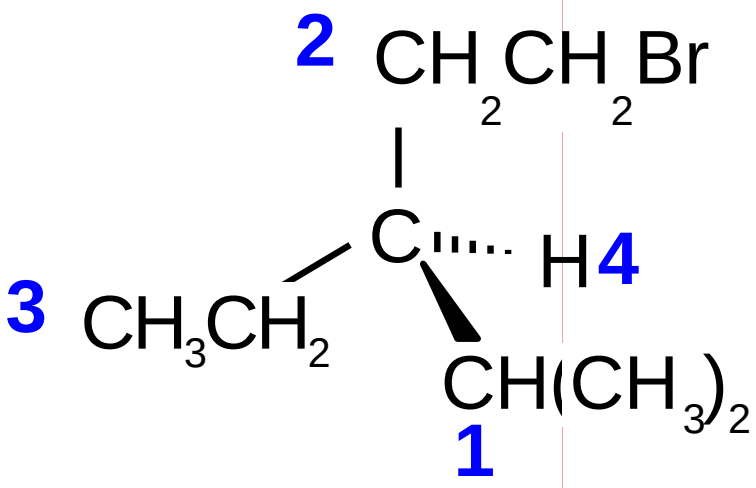


Example priorities:

I > Br > Cl > S > F > O > N > ^{13}C > ^{12}C > ^{3}H > ^{2}H > ^{1}H

(R) and (S) Nomenclature

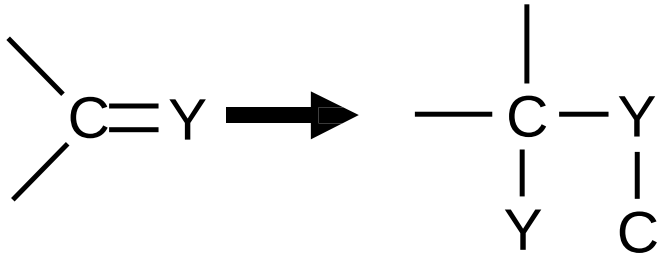
- In case of ties, use the next atoms along the chain as tiebreakers.

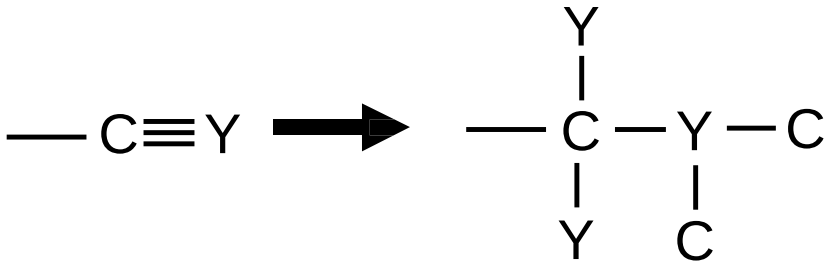


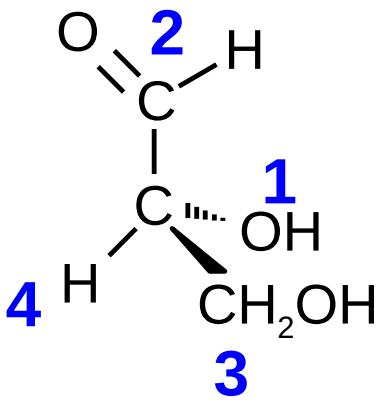
$CH(CH_3)_2 > CH_2CH_2Br > CH_3CH_2$

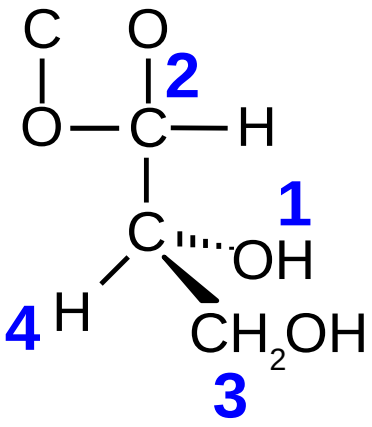
(R) and (S) Nomenclature

- Treat double and triple bonds as if both atoms in the bond were duplicated or triplicated:





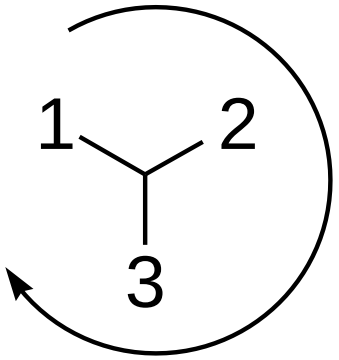




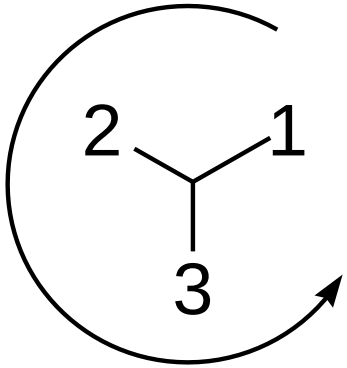
(R) and (S) Nomenclature

- Using a 3-D drawing or model, put the 4th priority group in back.
- Look at the molecule along the bond between the asymmetric carbon and the 4th priority group.
- Draw an arrow from the 1st priority group to the 2nd group to the 3rd group.
  - Clockwise arrow → (R) configuration
  - Counterclockwise arrow → (S) configuration

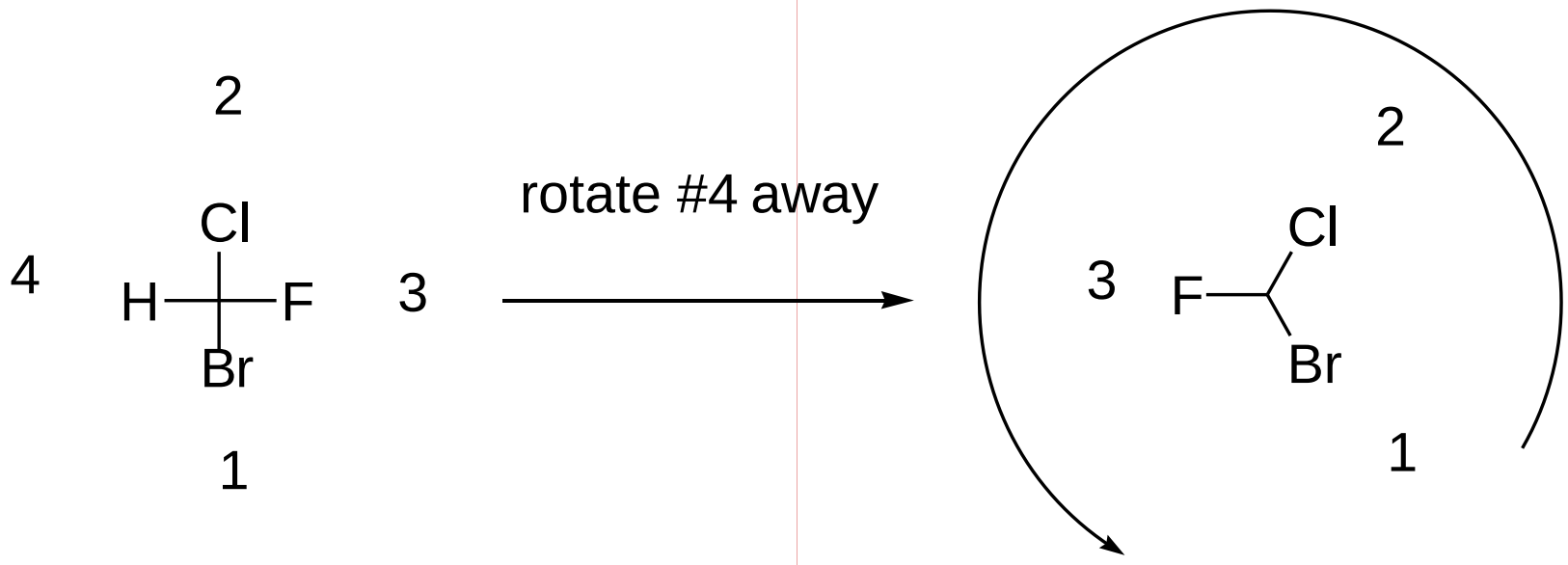
With group #4 rotated away:



R



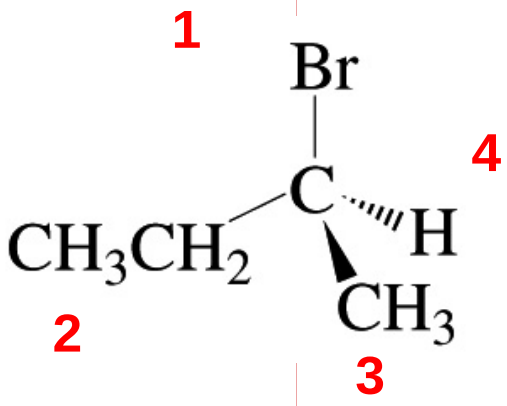
S



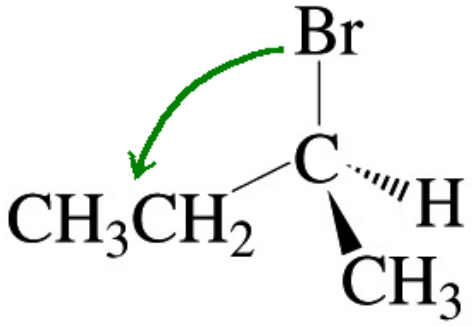
(*S*)-configuration

Naming from the Perspective Formula

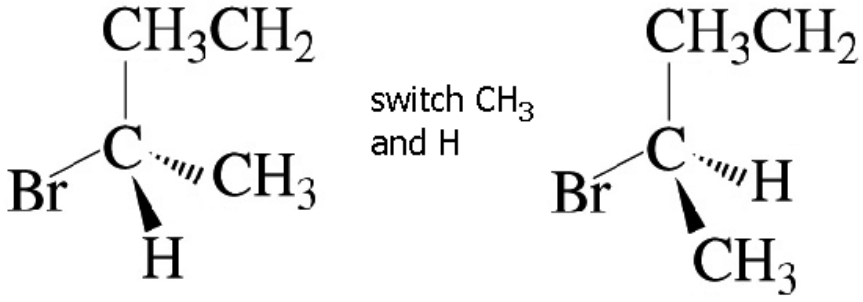
1. **Rank the groups bonded to the asymmetric carbon**



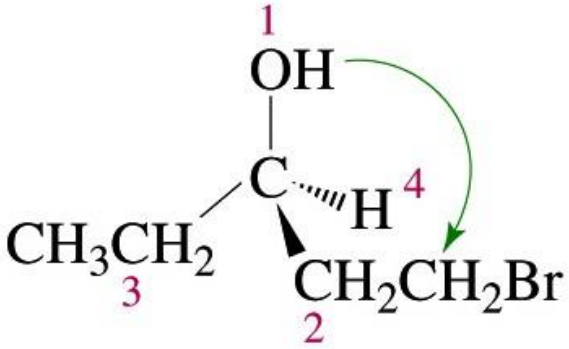
2. **If the group (or atom) with the lowest priority is bonded by hatched wedge,**



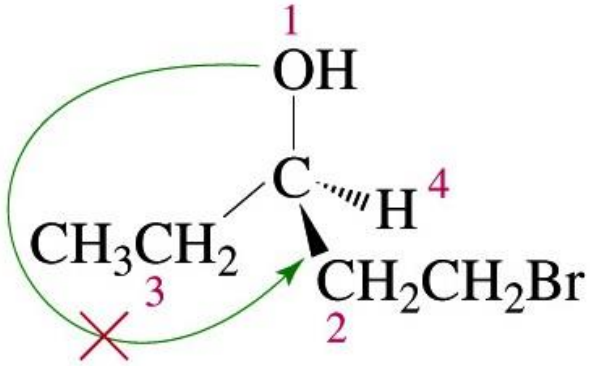
3. If necessary, rotate the molecule so that the lowest priority group (or atom) is bonded by a hatched wedge



4. You can draw group 1 to group 2, passing group 4, but never 3

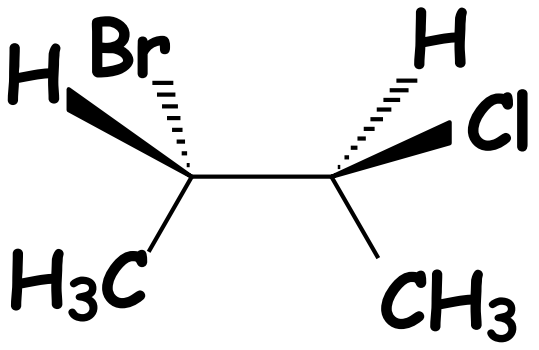


(*R*)-1-bromo-3-pentanol



(R) and (S) Nomenclature

- When naming compounds containing multiple chiral atoms, you must give the configuration around each chiral atom:
  - position number and configuration of each chiral atom in numerical order, separated by commas, all in ( ) at the start of the compound name

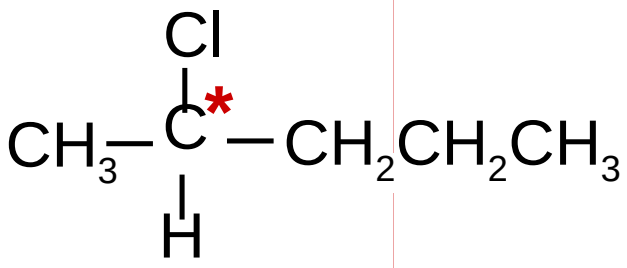


(2S, 3S)-2-bromo-3-chlorobutane

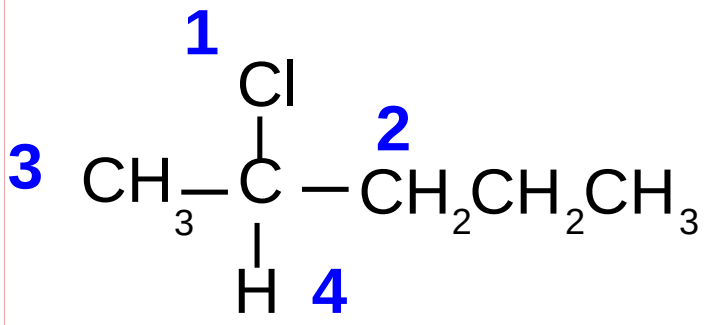
Depicting Structures with Asymmetric Carbons

Example: Draw a 3-dimensional formula for (R)-2-chloropentane.

Step 1: Identify the asymmetric carbon.

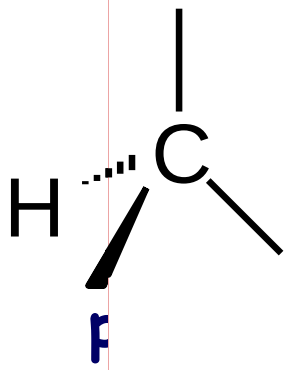


Step 2: Assign priorities to each group attached to the asymmetric carbon.

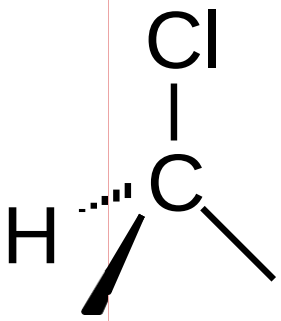


Depicting Structures with Asymmetric Carbons

Step 3: Draw a "skeleton" with the asymmetric carbon in the center and the lowest priority group attached to the "dashed" wedge (i.e. pointing away from you).

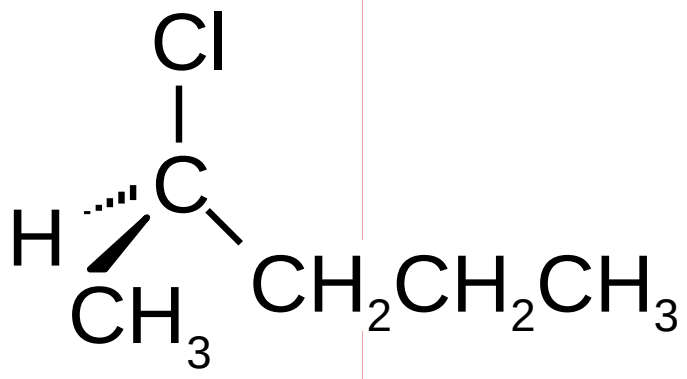


Step 4: Place the highest riority group at the top.



Depicting Structures with Asymmetric Carbons

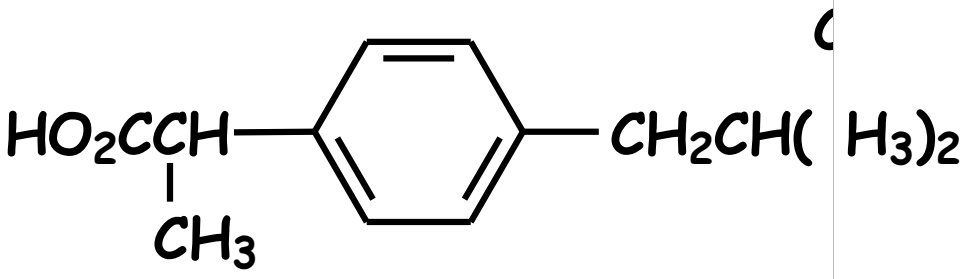
Step 5: For (R) configuration, place the 2nd and 3rd priority groups around the asymmetric carbon in a clockwise direction.



Step 6: Double-check your structure to make sure that it has the right groups and the right configuration.

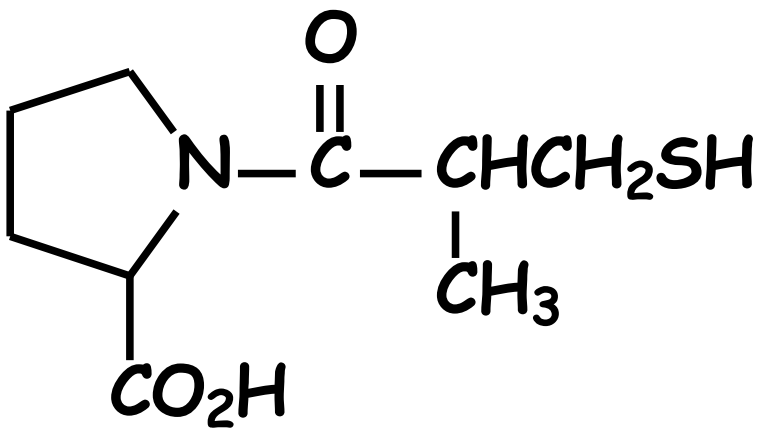
Depicting Structures with Asymmetric Carbons

Example: The R-enantiomer of ibuprofen is not biologically active but is rapidly converted to the active (S) enantiomer by the body. Draw the structure of the R-enantiomer.



Depicting Structures with Asymmetric Carbons

Example: Captopril, used to treat high blood pressure, has two asymmetric carbons, both with the S configuration. Draw its structure.

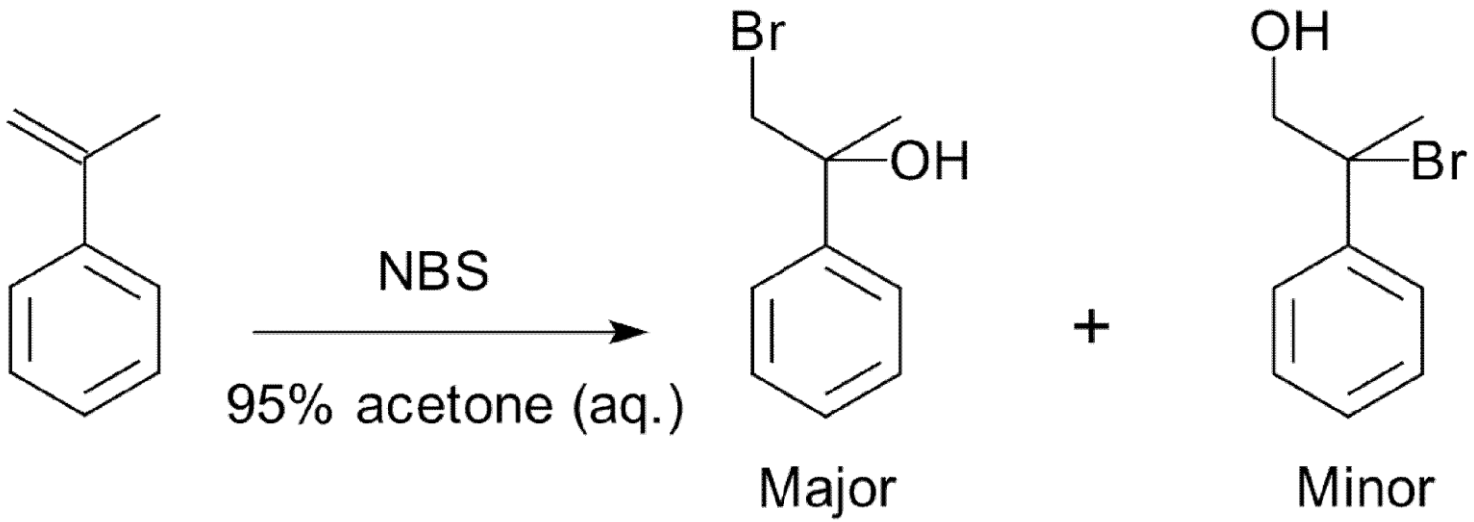


Stereospecific and stereoselective reaction

A regioselective reaction: preferential formation of one constitutional isomer

more B is formed than C where B and C are constitutional isomers

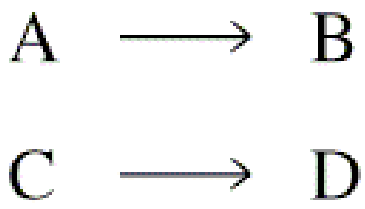
A specific example is a halohydrin formation reaction with 2-propenylbenzene



A stereoselective reaction: preferential formation of a stereoisomer

more B is formed than C where B and C are stereoisomers

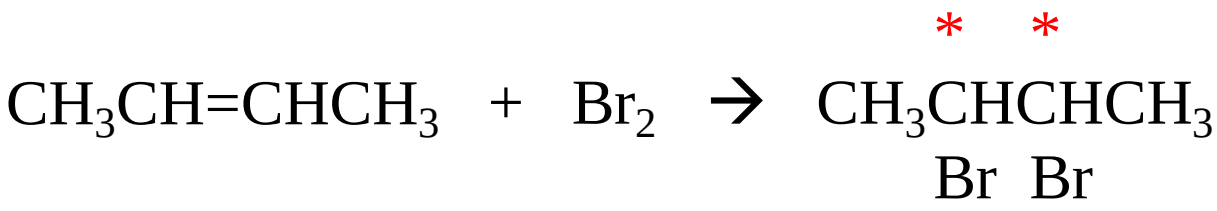
A stereospecific reaction: each stereoisomeric reactant produces a different stereoisomeric product or a different set of products



A and C are stereoisomers
B and D are stereoisomers

All stereospecific reactions are stereoselective

Not all stereoselective reactions are stereospecific



2-butene

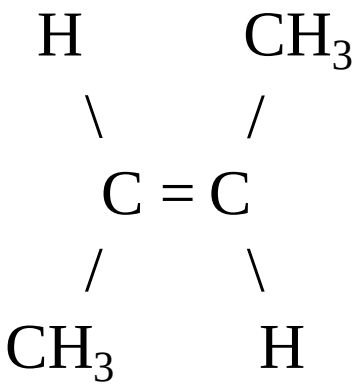
2,3-dibromobutane

2 geometric isomers

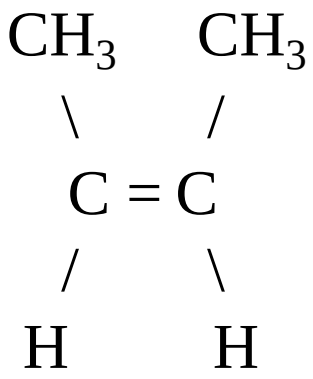
cis- and *trans*-

3 stereoisomers

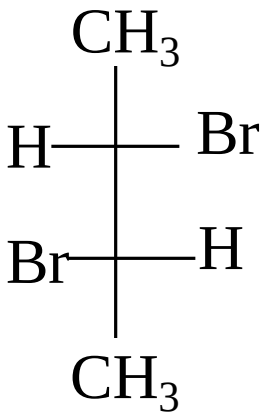
(*S*,*S*)-, (*R*,*R*)-, and (*R*,*S*)-*meso*-



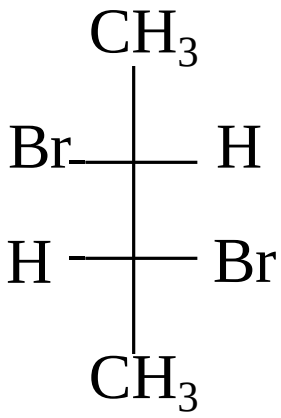
trans-2-butene



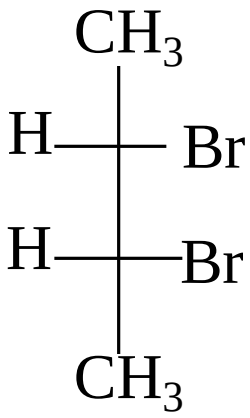
cis-2-butene



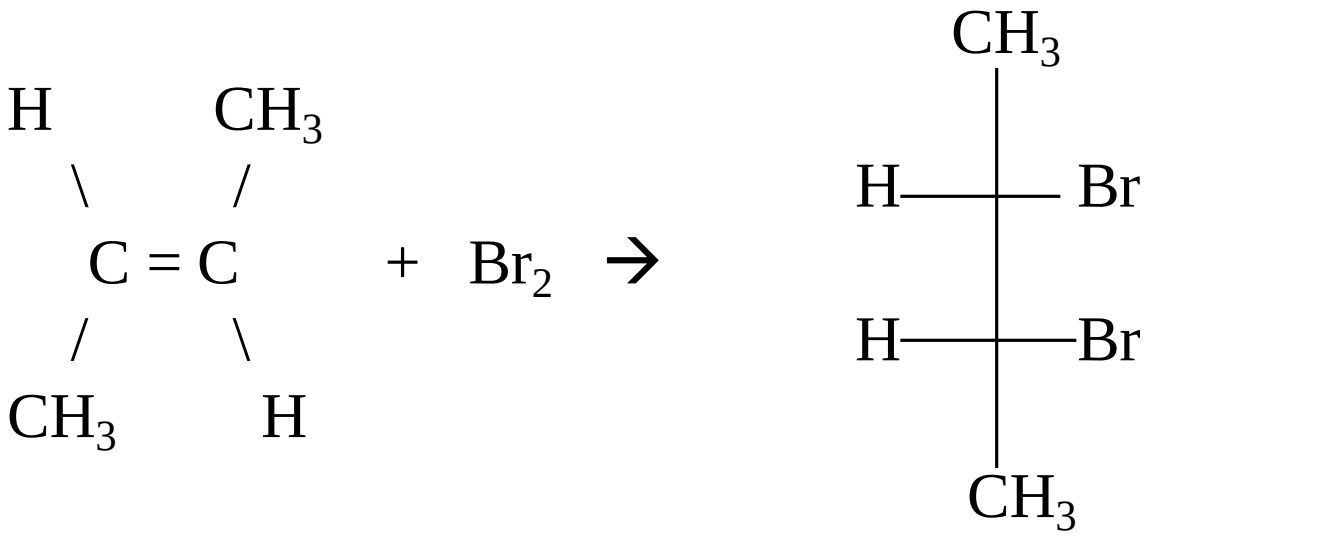
(S,S)



(R,R)



meso

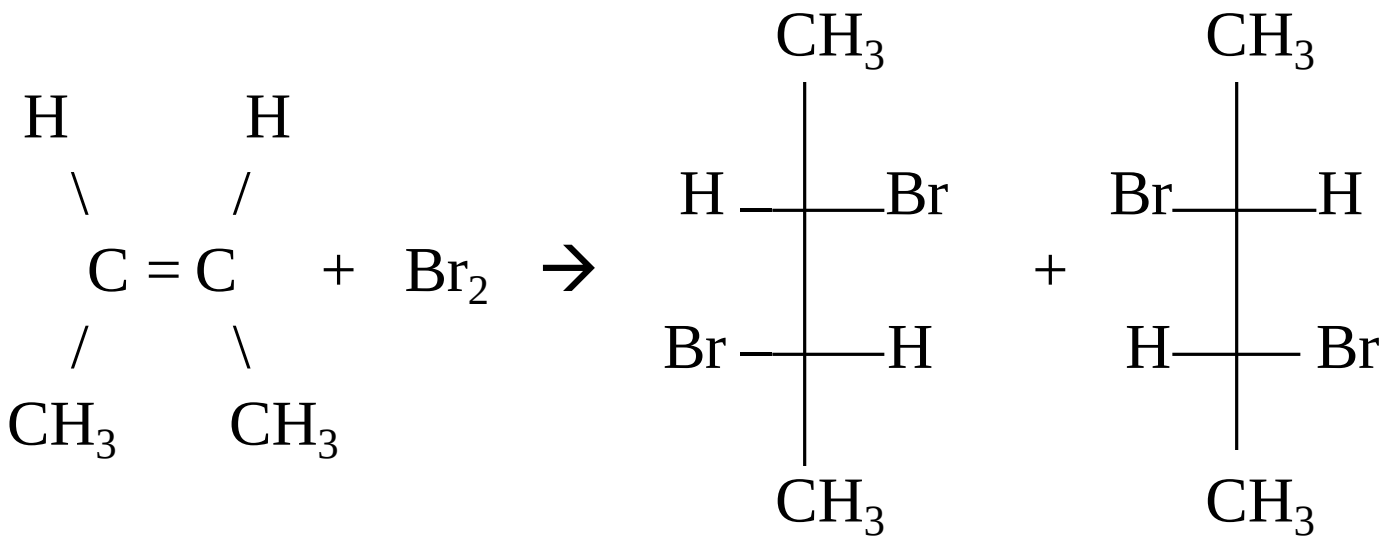


trans-2-butene

meso-2,3-dibromobutane

only product

A reaction that yields predominately one stereoisomer (or one pair of enantiomers) of several diastereomers is called a stereoselective reaction. In this case the *meso*- product is produced and not the other two diastereomers.

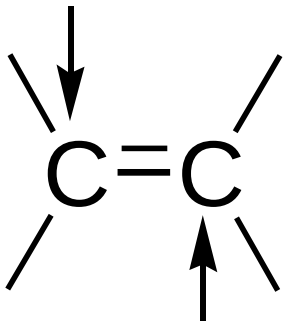


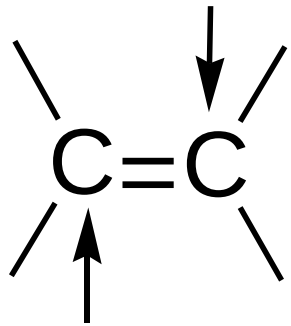
cis-2-butene (*S*,*S*)- & (*R*,*R*)-2,3-dibromobutane

racemic modification *only products*

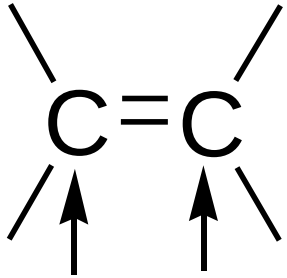
A reaction in which stereochemically different molecules react differently is called a stereospecific reaction. In this case the *cis*- and *trans*- stereoisomers give different products.

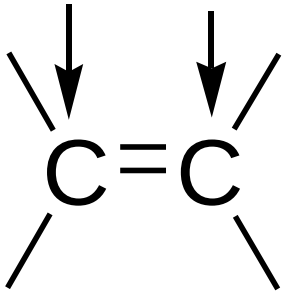
The fact that the addition of halogens to alkenes is both stereoselective and stereospecific gives us additional information about the stereochemistry of the addition and the mechanism for the reaction.



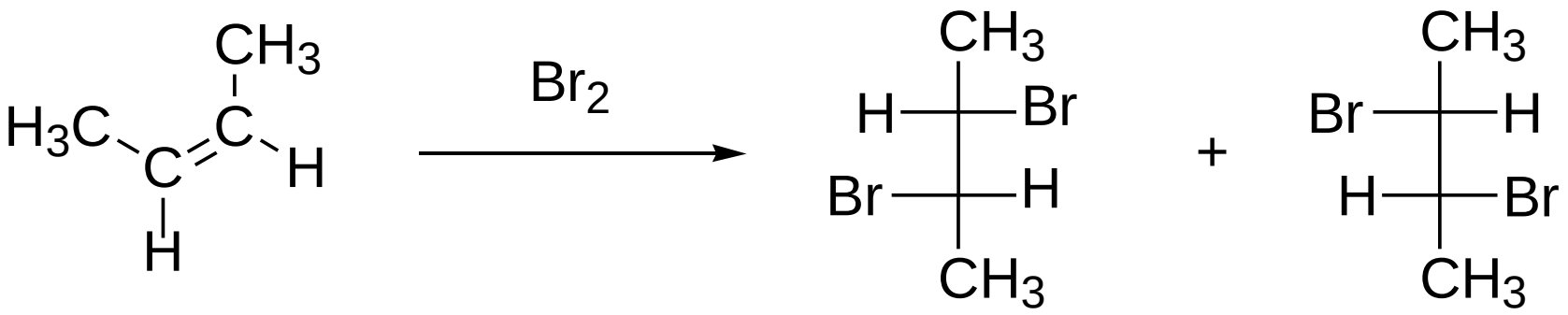


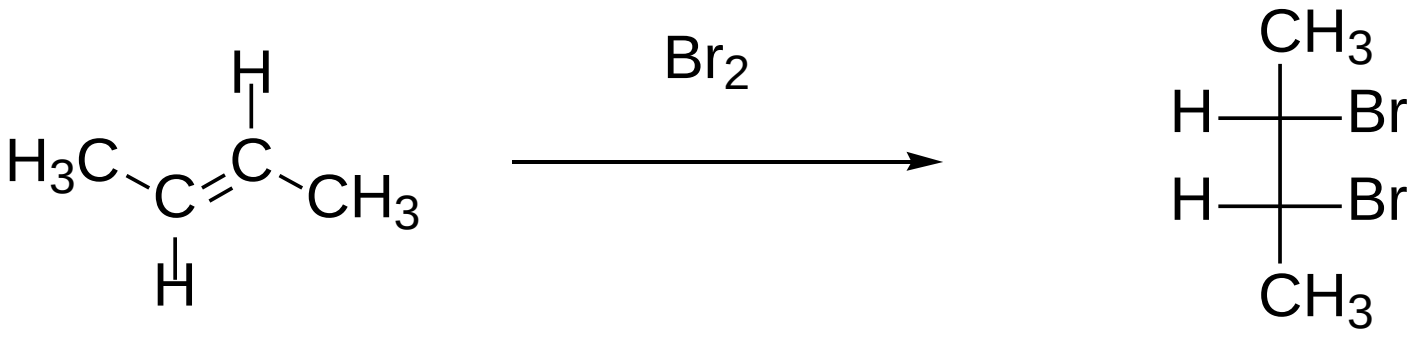
anti-addition



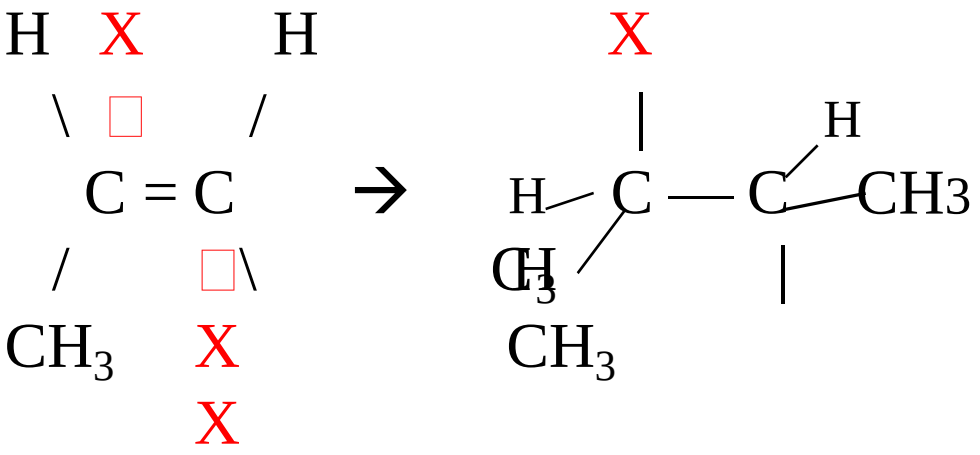


syn-addition



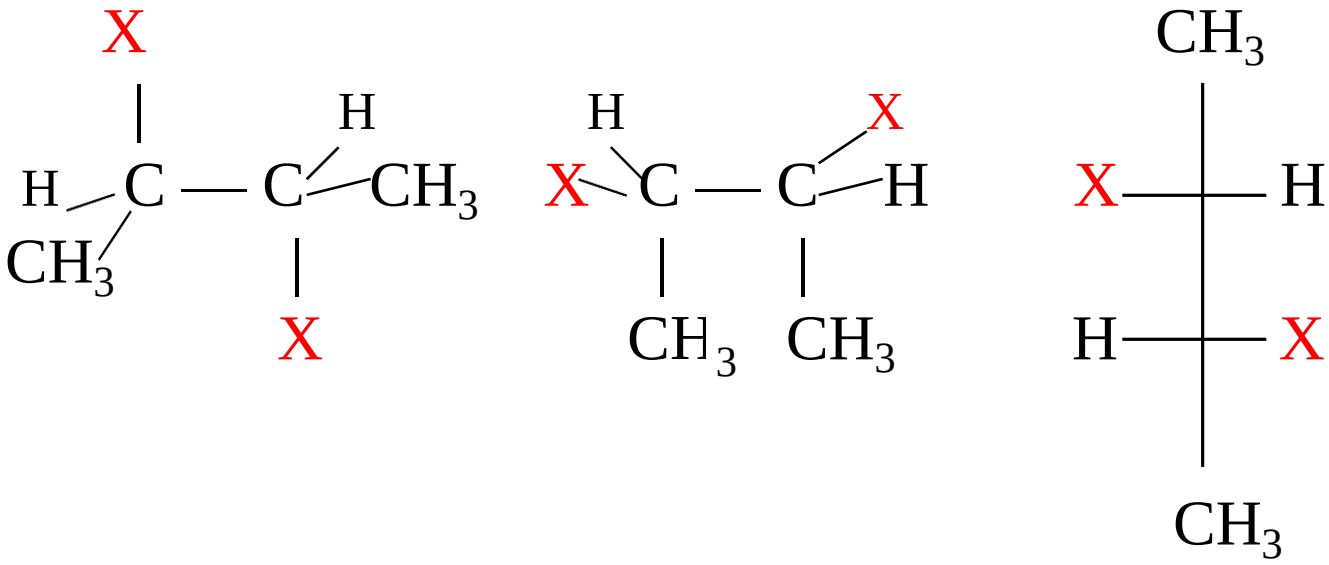


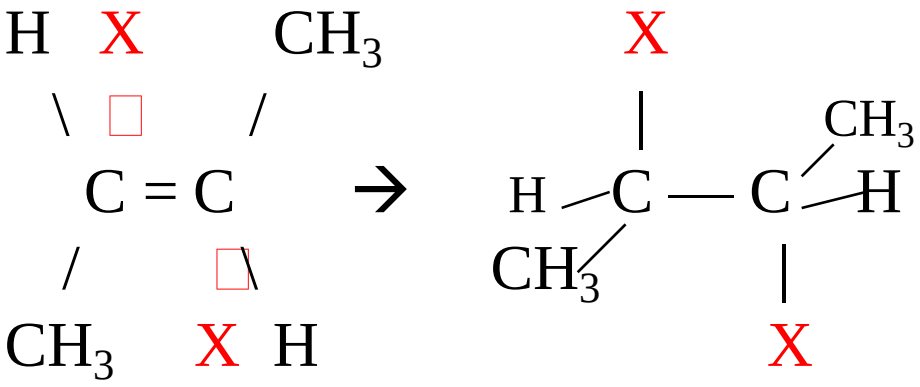
Is the addition of Br_2 *syn* *or* *anti*?



anti-addition of X_2 to the *cis*-isomer

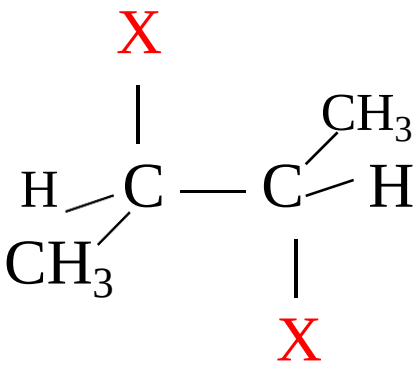
Note: must rotate about C-C to get to the Fischer projection!

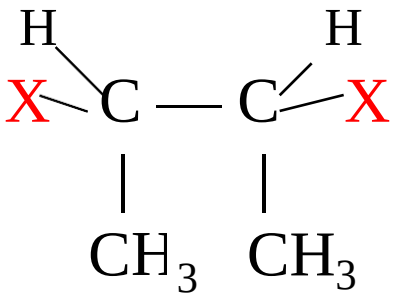


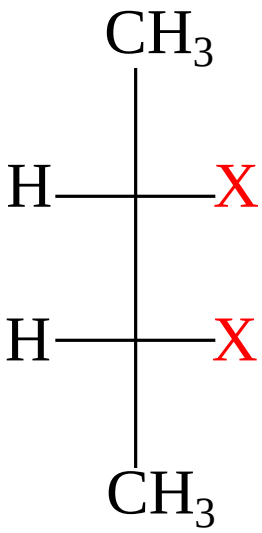


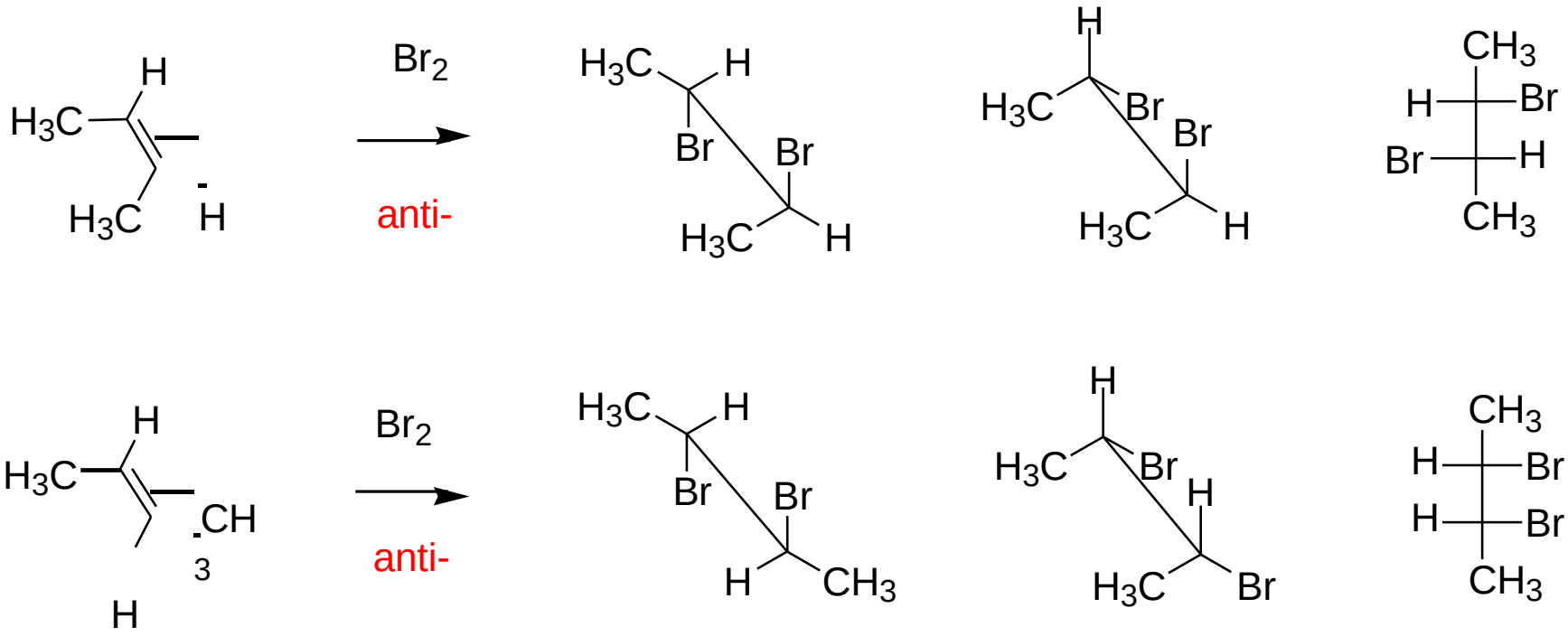
anti-addition of X_2 to the *trans*-isomer

Note: must rotate about C-C to get to the Fischer projection!





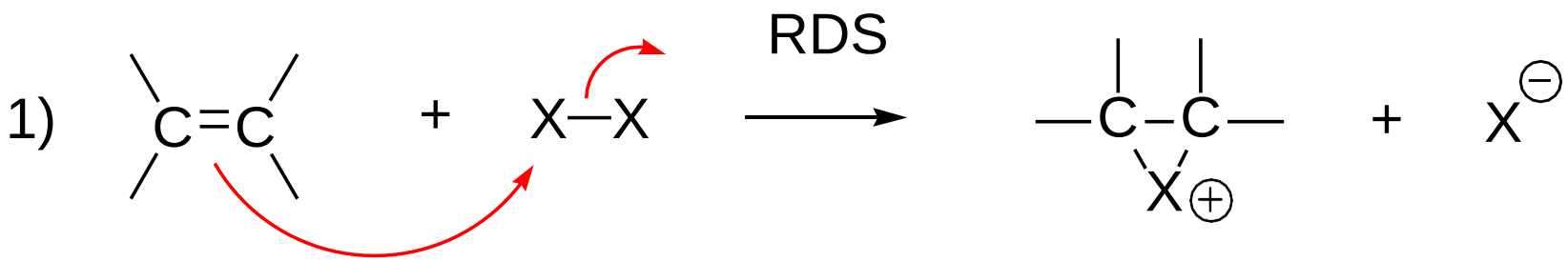




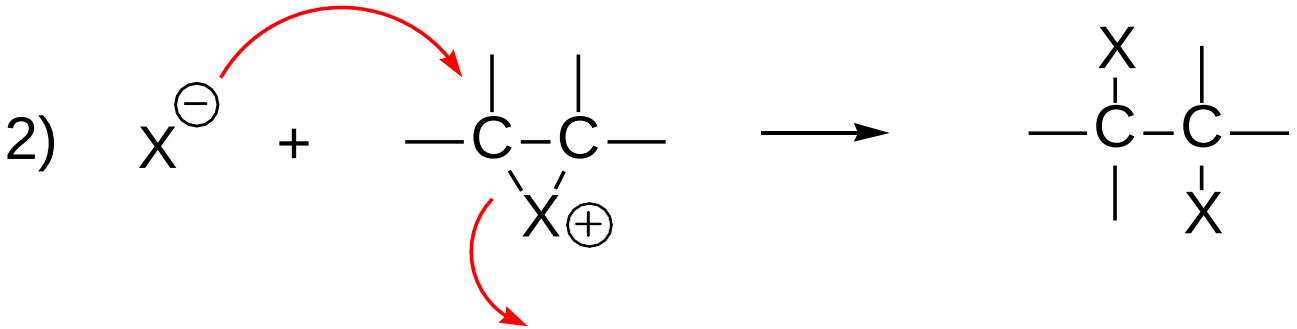
rotate about C2-C3 to get to Fischer projection!

In determining whether a stereoselective addition is *syn*- or *anti*- you cannot simply look at the Fischer projection. Remember it is often necessary to rotate about a carbon-carbon bond to get a molecule into the conformation that corresponds to the Fischer projection! Use your model kit to verify!

What does the stereochemistr tell us about the mechanism of addition of halogens to alker es?

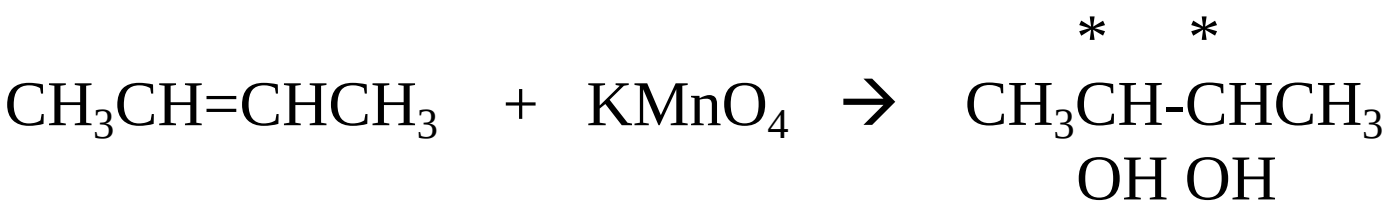


"halonium ion"



anti-addition

Hydroxylation of alkenes:



2-butene

2,3-butanediol

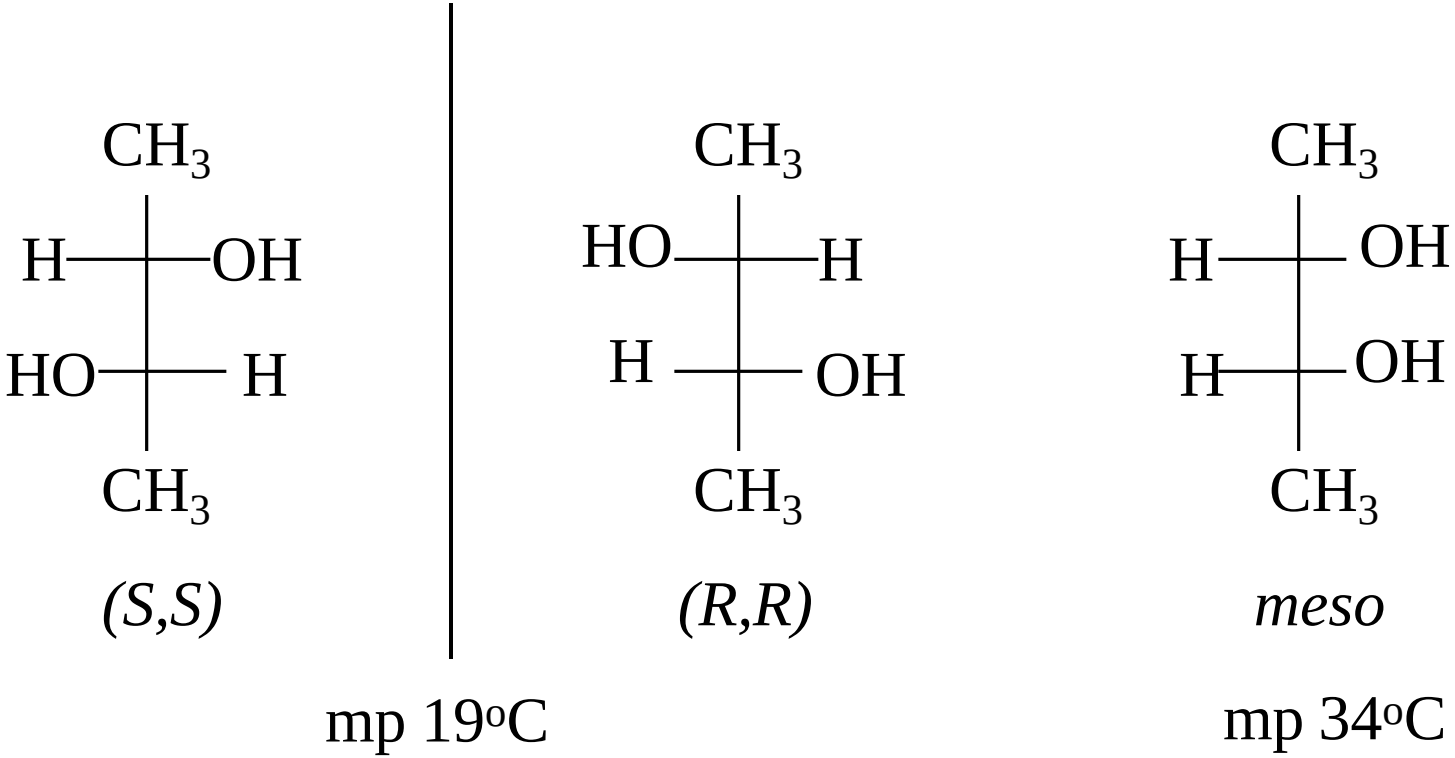
2 geometric isomers

3 stereoisomers

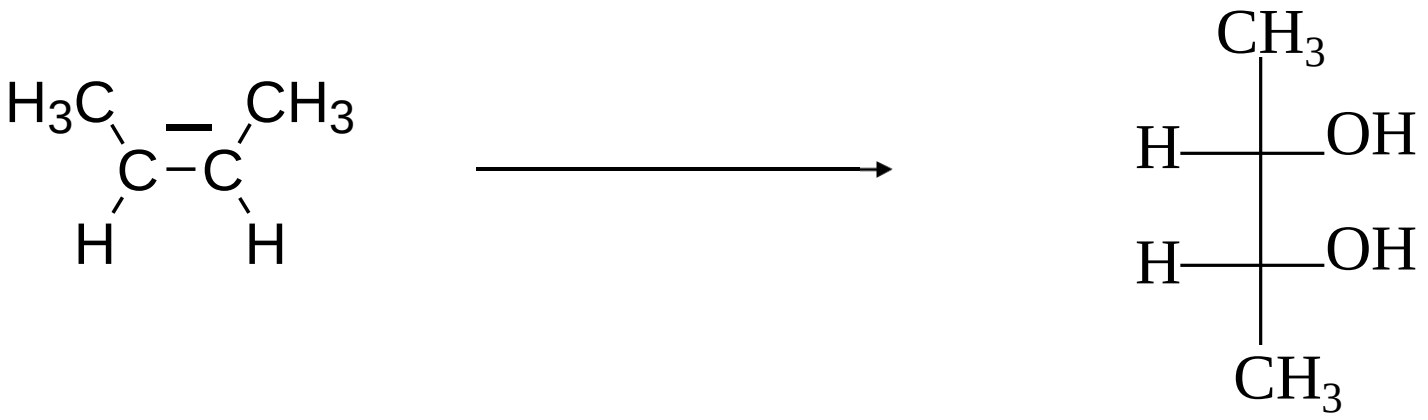
cis-2-butene + $KMnO_4$ → 2,3-butanediol mp 34°C

trans-2-butene + $KMnO_4$ → 2,3-butanediol mp 19°C

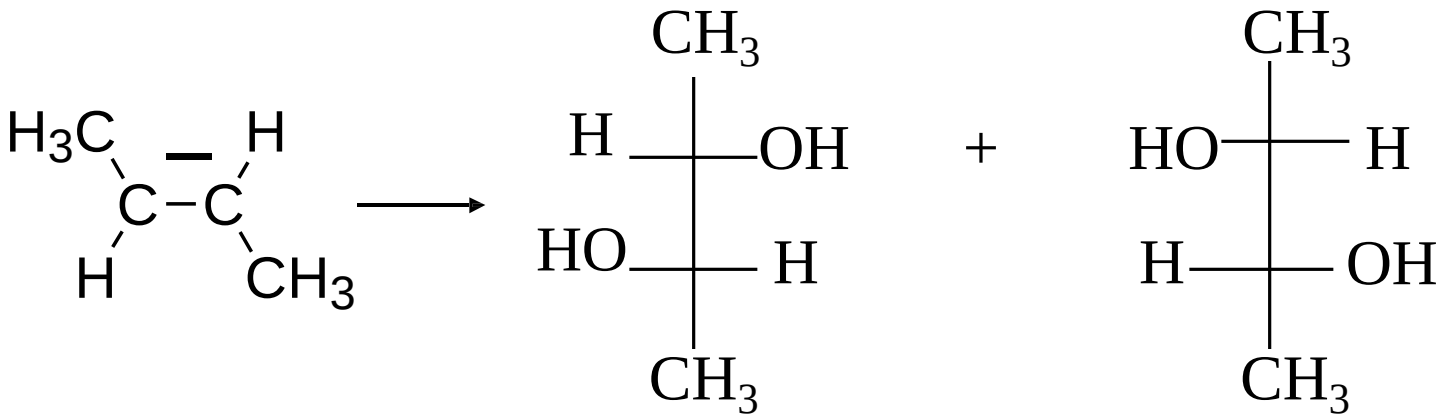
2,3-butanediol (mp 19°C) is separable into enantiomers.



cis-2-butene + $KMnO_4$ → *meso*-2,3-dihydroxybutane mp 34°

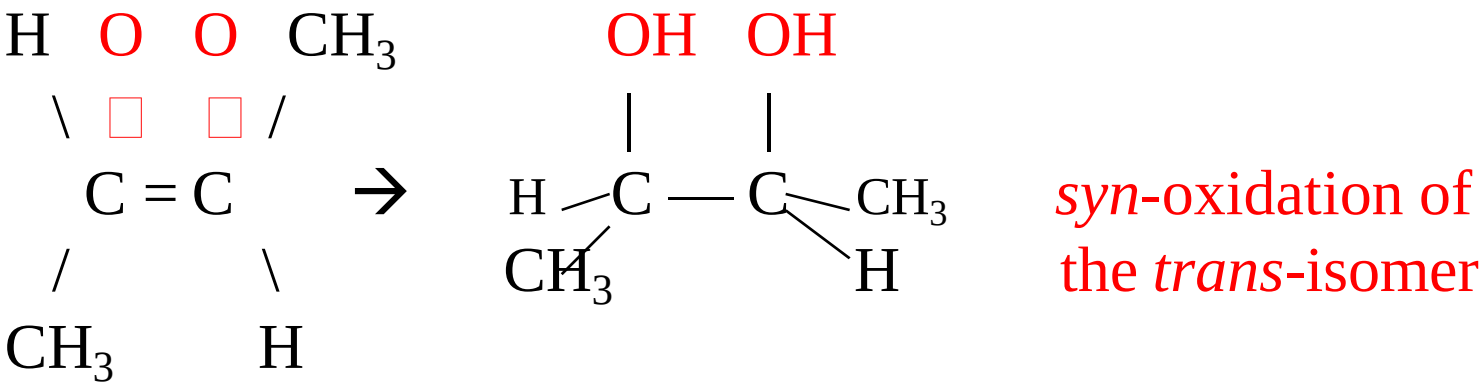


trans-2-butene + $KMnO_4$ → (*S*,*S*) & (*R*,*R*)-2,3-dihydroxybutane mp 19°



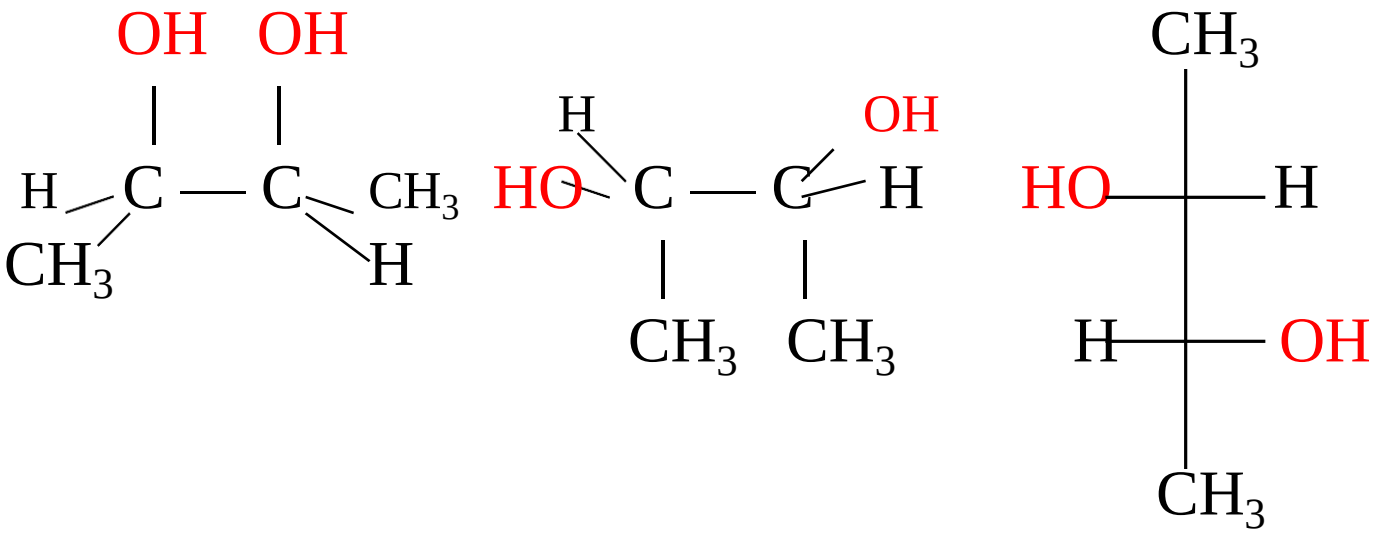
stereoselective and stereospecific

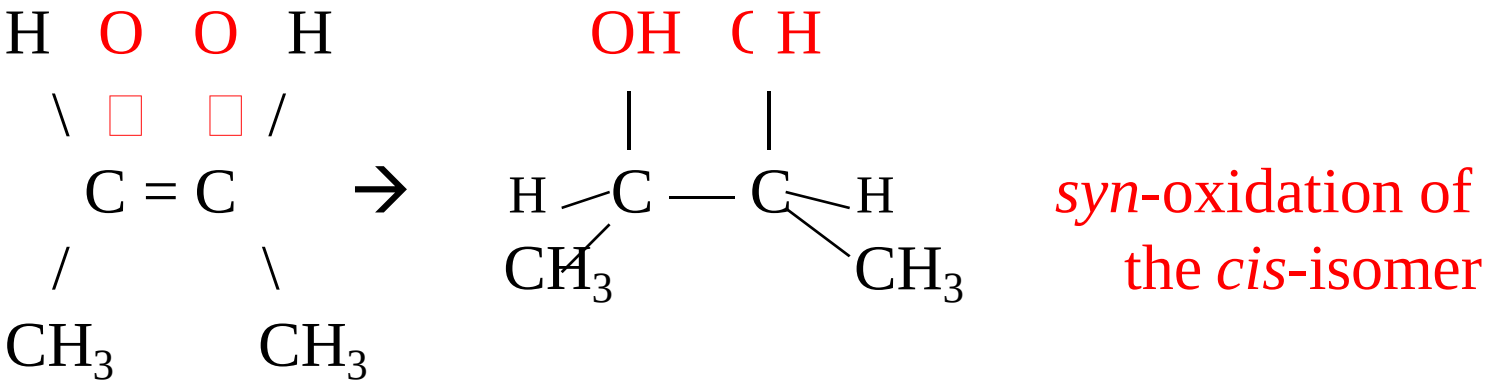
Is hydroxylation with $KMnO_4$ *syn-* or *anti-*?



syn-oxidation of the *trans*-isomer

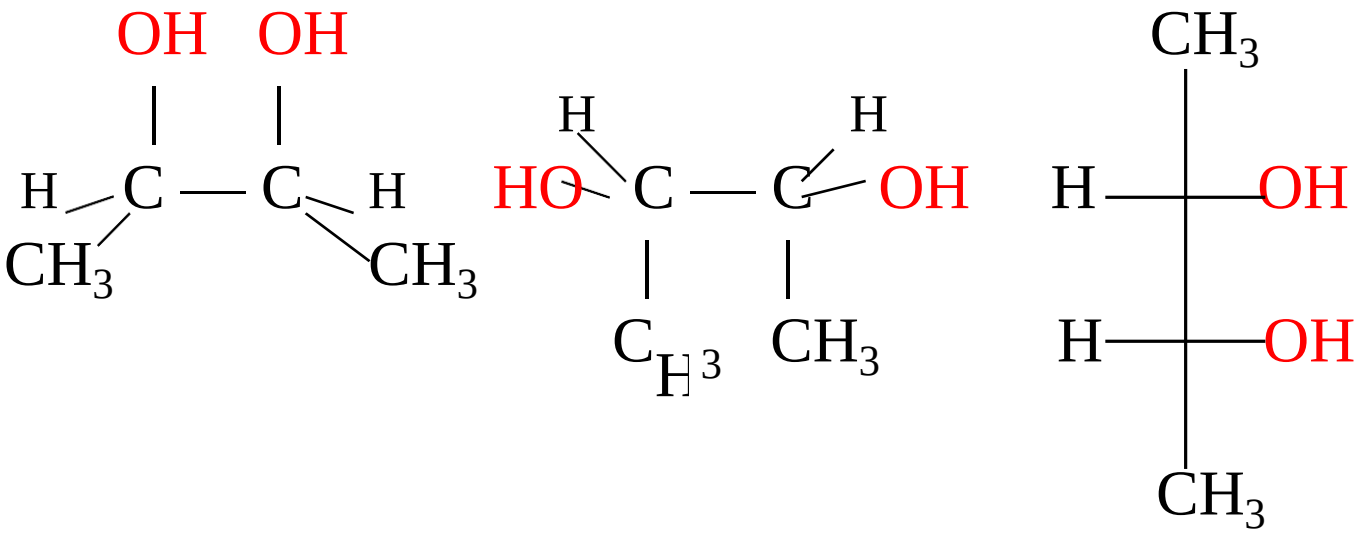
Note: must rotate about C-C to get to the Fischer projection!





syn-oxidation of the *cis*-isomer

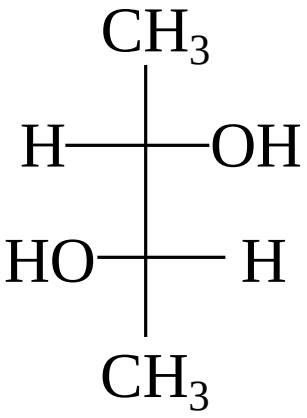
Note: no rotation necessary to get to Fischer projection!



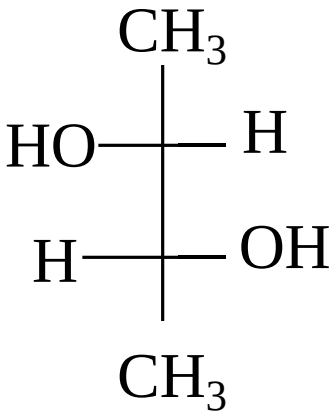
cis-2-butene + HCO_3H → 2,3-butanediol mp 19°C

trans-2-butene + HCO_3H → 2,3-butanediol mp 34°C

2,3-butanediol mp 19°C is separable into enantiomers.

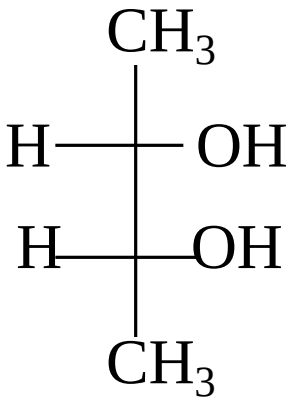


(S,S)



(R,R)

mp 19°C



meso

mp 34°C

Oxidation with $KMnO_4$ *syn*-oxidation

cis-2-butene → *meso*-2,3-diɬ ydroxybutane

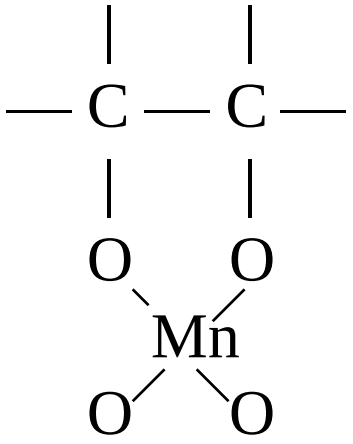
trans-butene → (*S*,*S*)- & (*R*,*R*)-2,3-dihydroxybutane

Oxidation with HCO_2OH gives the opposite

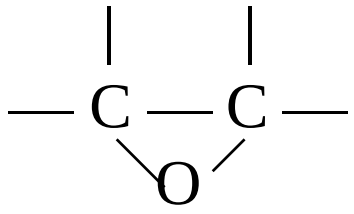
cis-2-butene → (*S*,*S*)- & (*R*,*I*)-2,3-dihydroxybutane

trans-2-butene → *meso*-2,3-dihydroxybutane

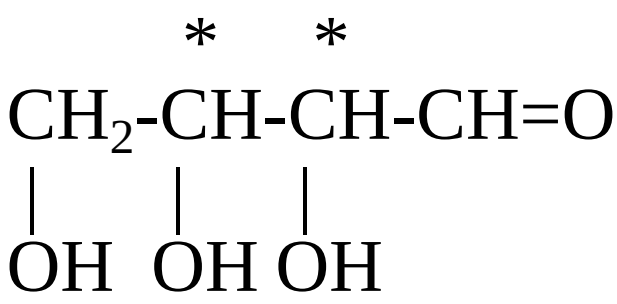
Oxidation with HCO_2OH is *anti*-oxidation.



hydroxylation with $KMnO_4$ is *syn-* because of an intermediate permanganate addition product.

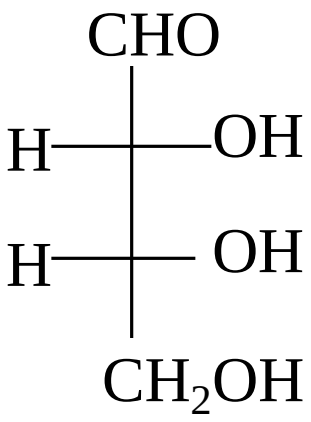


hydroxylation with HCO_2OH is *anti-* because of an intermediate epoxide.

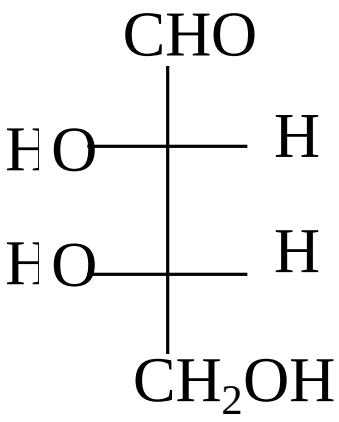


Four carbon sugar, an aldotetrose.

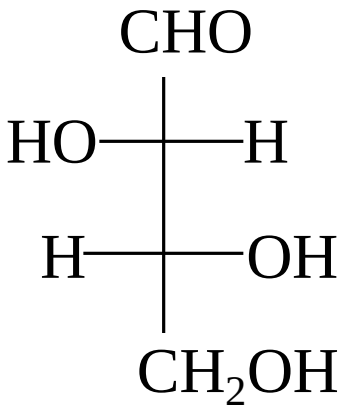
Two chiral centers, four stereoisomers



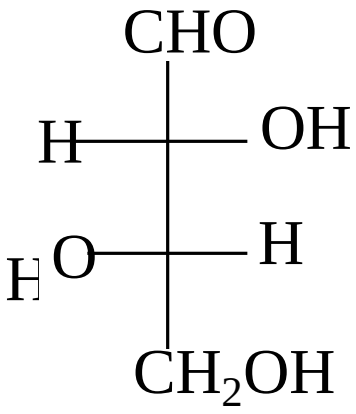
D-erythrose



L-erythrose

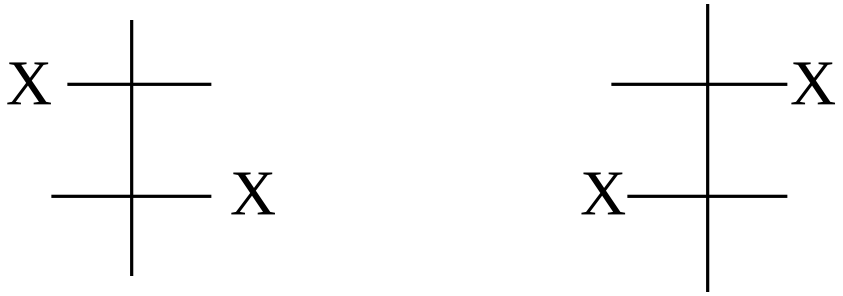


D-threose

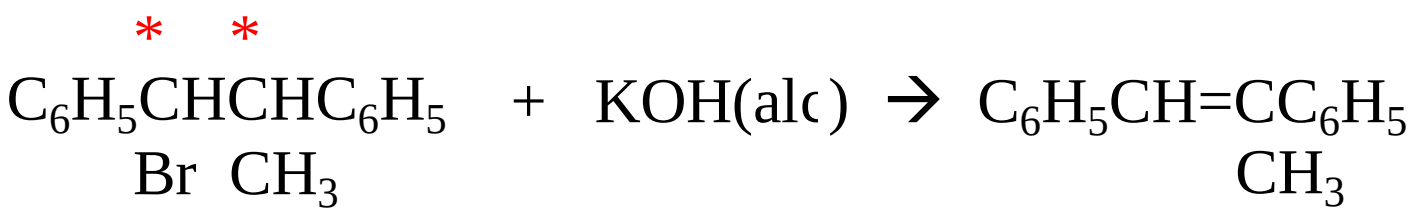


L-threose

“*erythro-*”



“*threo-*”



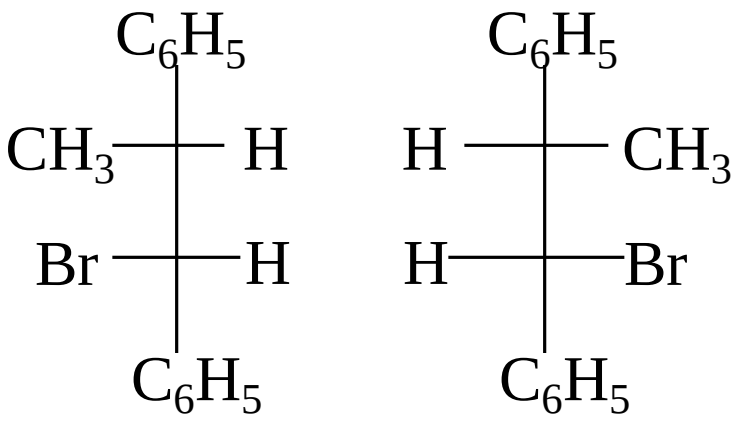
1-bromo-1,2-diphenylpropane

1,2-diphenylpropene

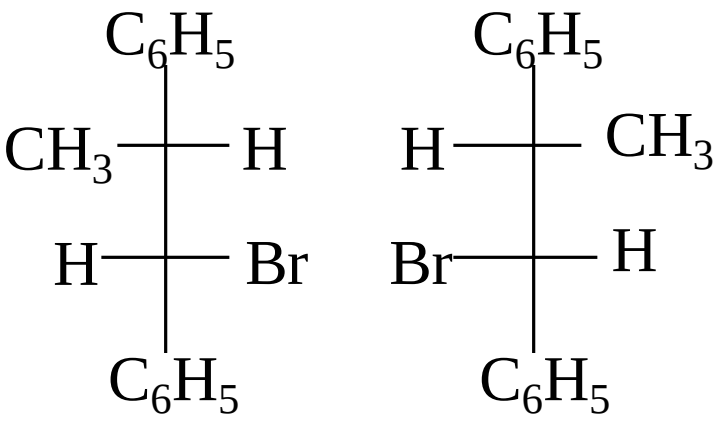
4 stereoisomers

2 stereoisomers
(*E*)- & (*Z*)-

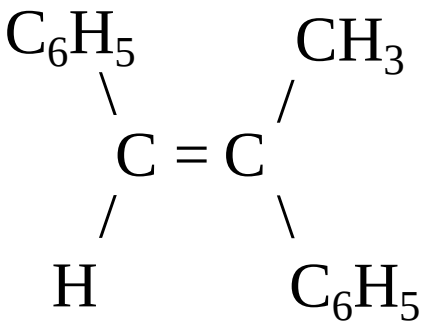
dehydrohalogenation of an alkyl halide via E2 *mechanism*



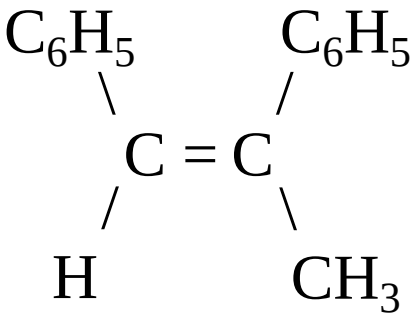
erythro-



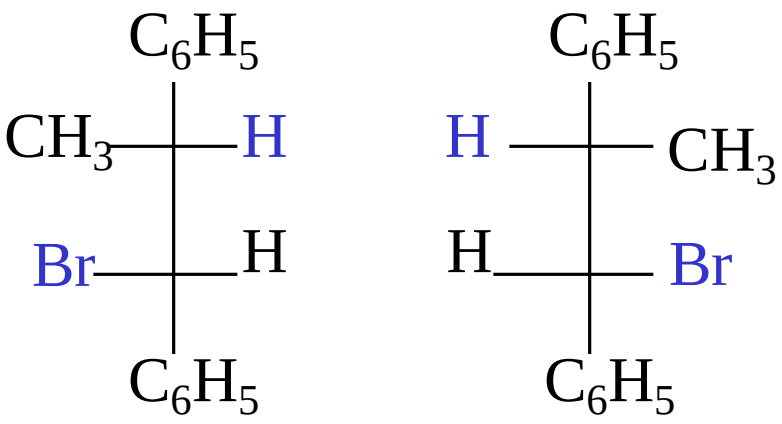
threo-



(*E*)-



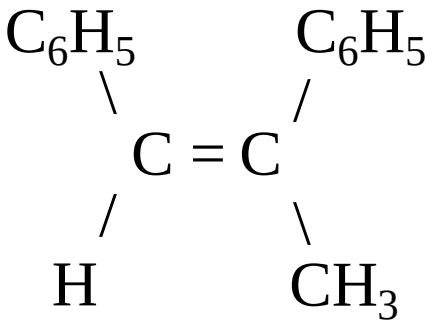
(*Z*)-



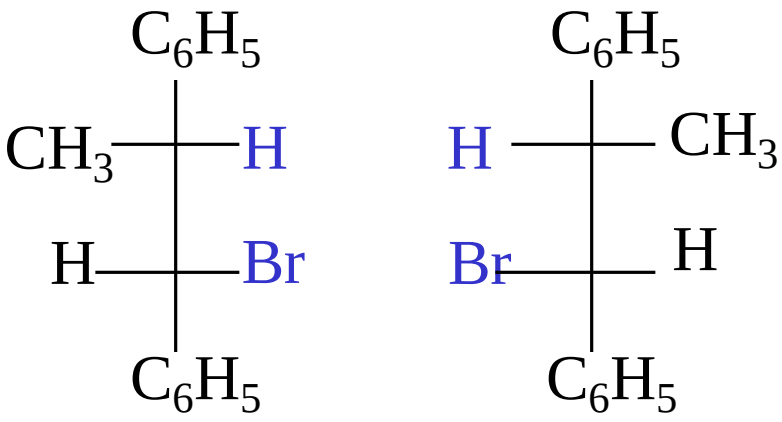
erythro-

KOH(alc)

→



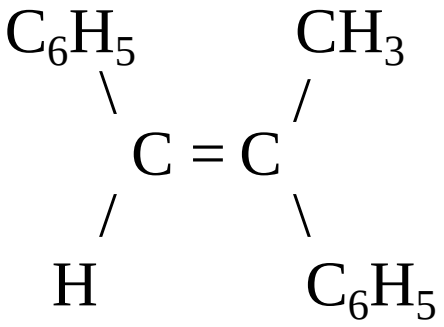
(*Z*)-



threo-

KOH(alc)

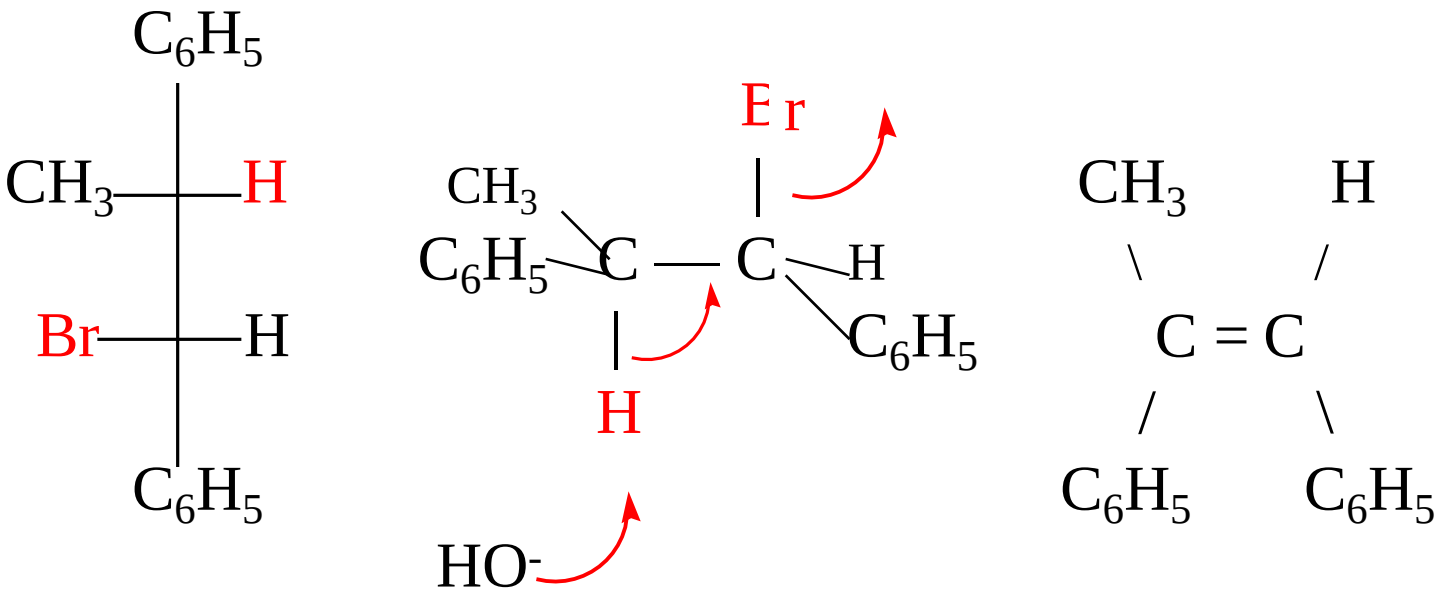
→



(*E*)-

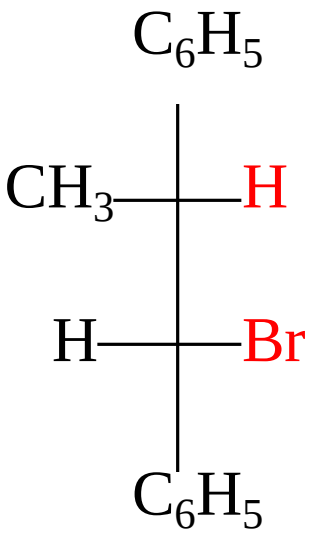
E2 is both stereoselective and stereospecific.

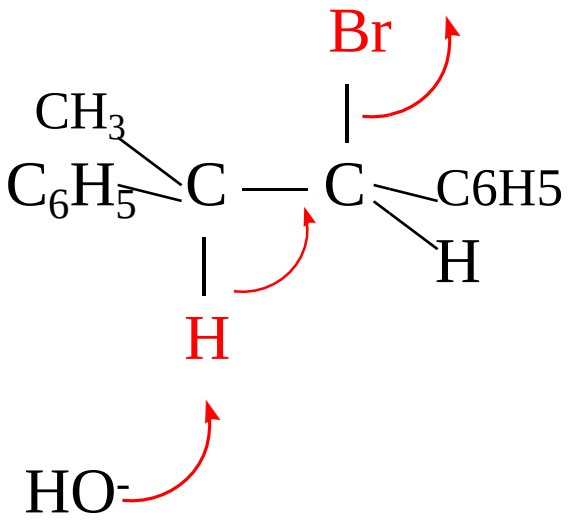
- 100% anti-elimination of the H & Br:

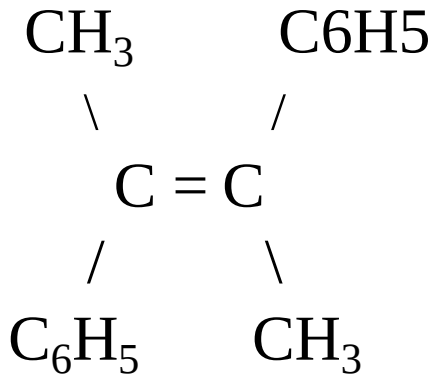


erythro-

(*Z*)-







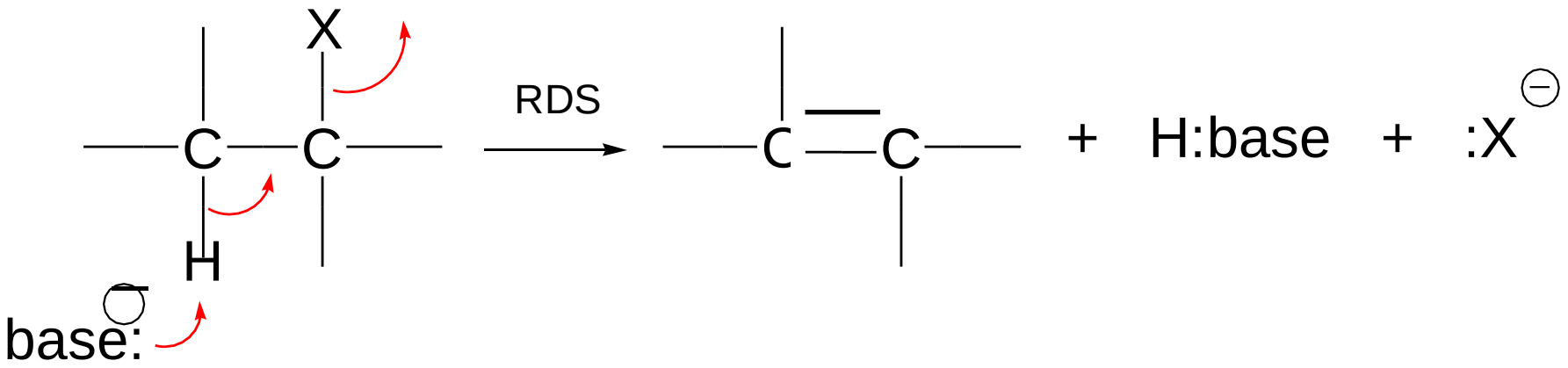
threo-

(*E*)-

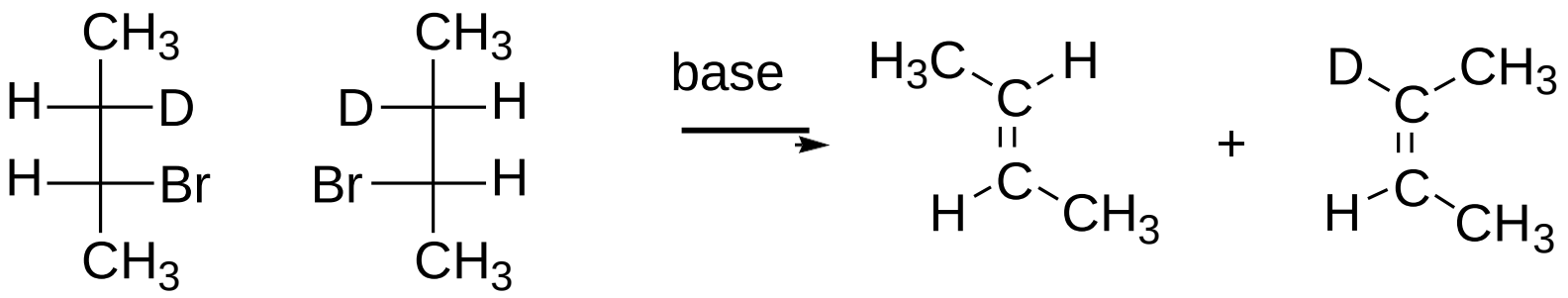
Once again, you must rotate about the C—C bond in the Fischer projection to get the H & Br *anti* to one another.

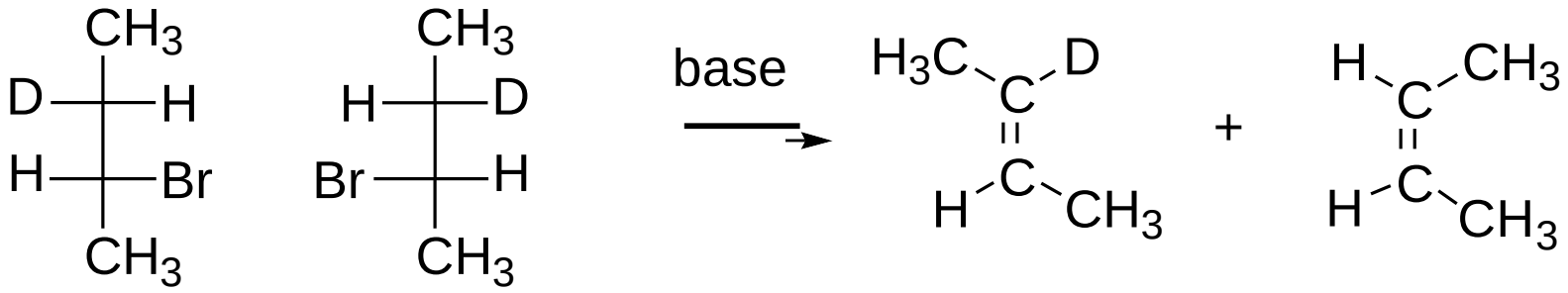
E2 is an *anti*-elimination. The hydrogen and the halogen must be on opposite sides of the molecule before the E2 elimination can take place. This makes sense as both the base and the leaving group are negatively charged. Therefore they would try to be as far apart as possible. In addition, the leaving group is large and there is more room for the removal of the adjacent proton if it is on the opposite side from the leaving group.

Mechanism = elimination, bimolecular **E2**



100% *anti*-elimination!

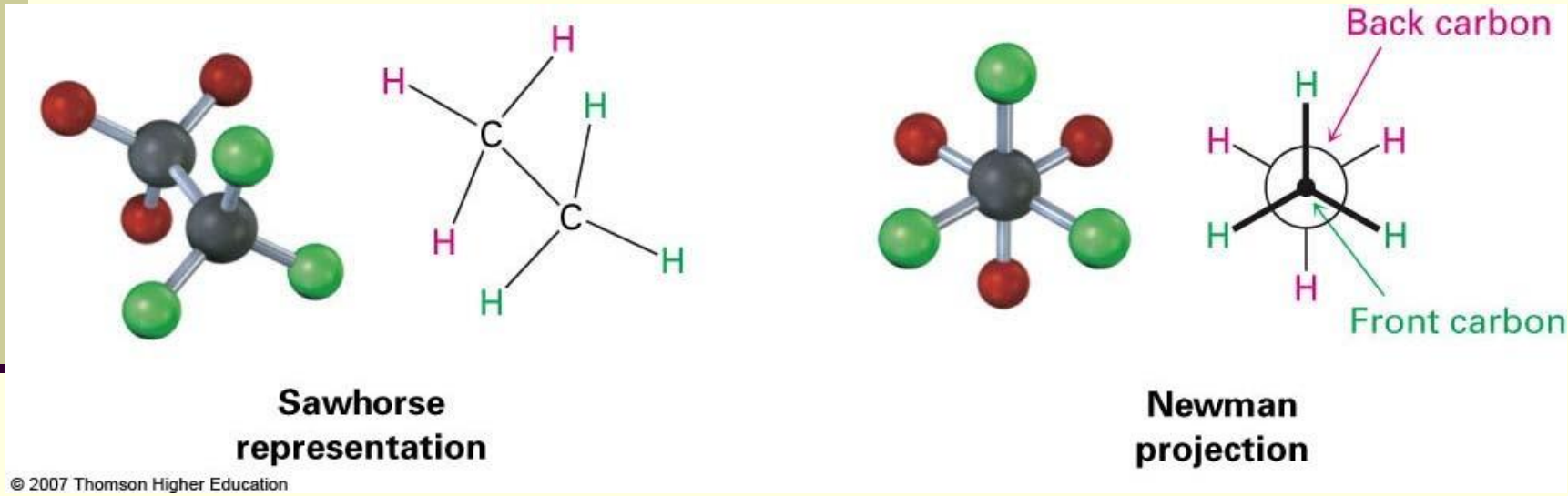

CH3
H
D
H
Br
CH3
CH3
D
H
Br
H
CH3
base
H3C
C
H
C
H
CH3
+
D
C
CH3
C
H
CH3


CH3
D
H
H
Br
CH3
CH3
H
D
Br
H
CH3
base
H3C
C
D
C
H
CH3
+
H
C
CH3
C
H
CH3

Addition of halogens to alkenes	*anti*-addition
Hydoxylation with $KMnO_4$	*syn*-oxidation
Hydroxylation with HCO_2OH	*anti*-oxidation
Dehydrohalogenation of alkyl halides E2	*anti*-elimination

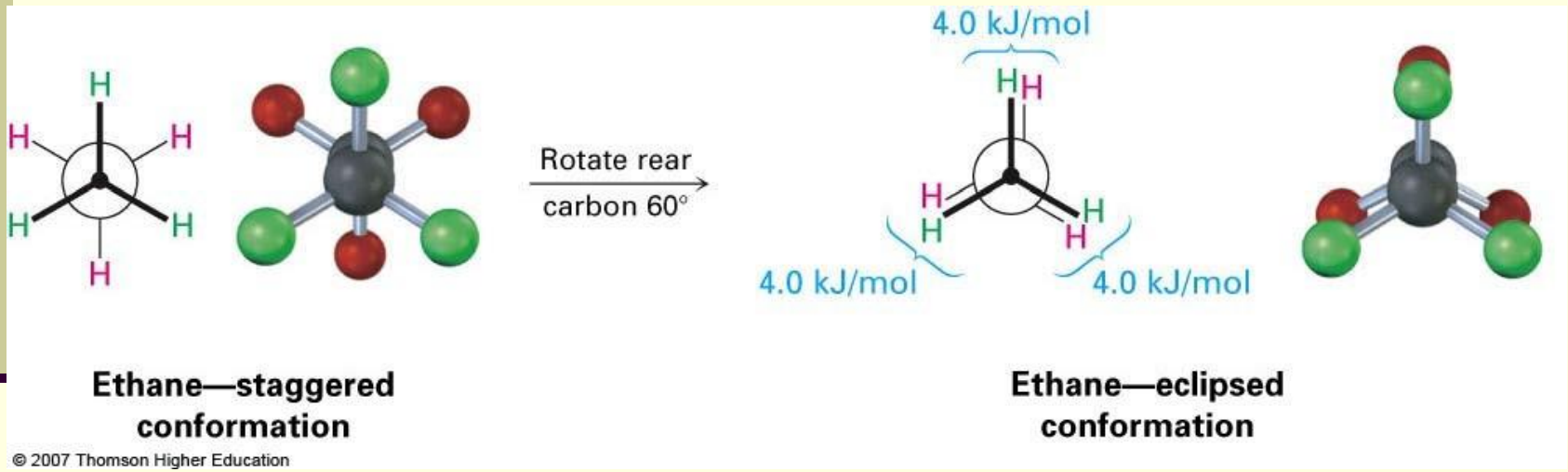
Conformational Isomers

- Isomers that differ as a result of sigma bond rotation of C-C bond in alkanes



Bond Rotation and Newman Projections

- As carbon-carbon bond rotates, interconvert between staggered and eclipsed conformers

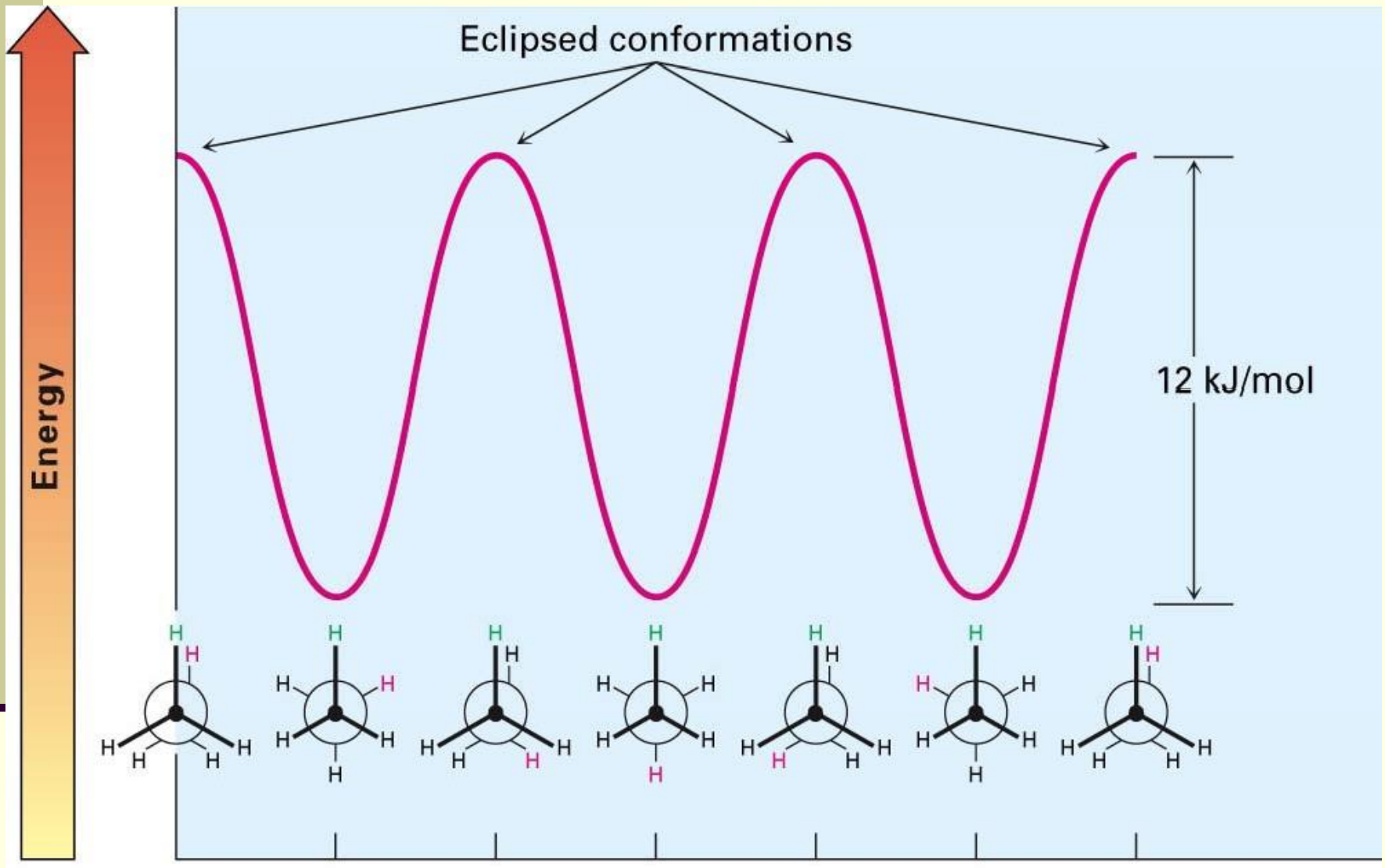


Eclipsed conformer is 12.0 kJ/mol higher in energy ('free' rotation at room temperature)

Torsional Strain Energy

Force that opposes rotation due to the repulsion of bonding electrons

- We do not observe perfectly free rotation
- There is a barrier to rotation, and some conformers are more stable than others
- Small energy barrier easily overcome at RT
- **Each eclipsed H-H costs 4 kJ/mol of Torsional Energy**


Eclipsed conformations
Energy
12 kJ/mol

Strain Energy in Alkanes

- **Torsional Strain**
- **Steric strain-** repulsive interaction occurring between atoms that are forced closer together than their atomic radii allow

In Class: Conformations of Higher and Branched Alkanes

- Propane
- Butane
- 2-methylbutane
- 2-chlorobutane

- draw conformers (id most/least stable)
- define anti and gauche staggered conformers
- predict relative energies and draw diagrams
- determine relative percentages of conformers

What does ΔE tell us?

- $\Delta G = -RT\ln K$
  $= -2.303RT\log K$

(1 kcal = 4.14 kJ)

- which can rearrange to
  $\log K = -\Delta G/1.36$ where R = 0.001987 **kcal**/K*mol
  or T = 298 K

$$K = 10^{-(\Delta G/1.36)}$$

less stable ⟷ more stable
0.9 kcal 0.0 kcal

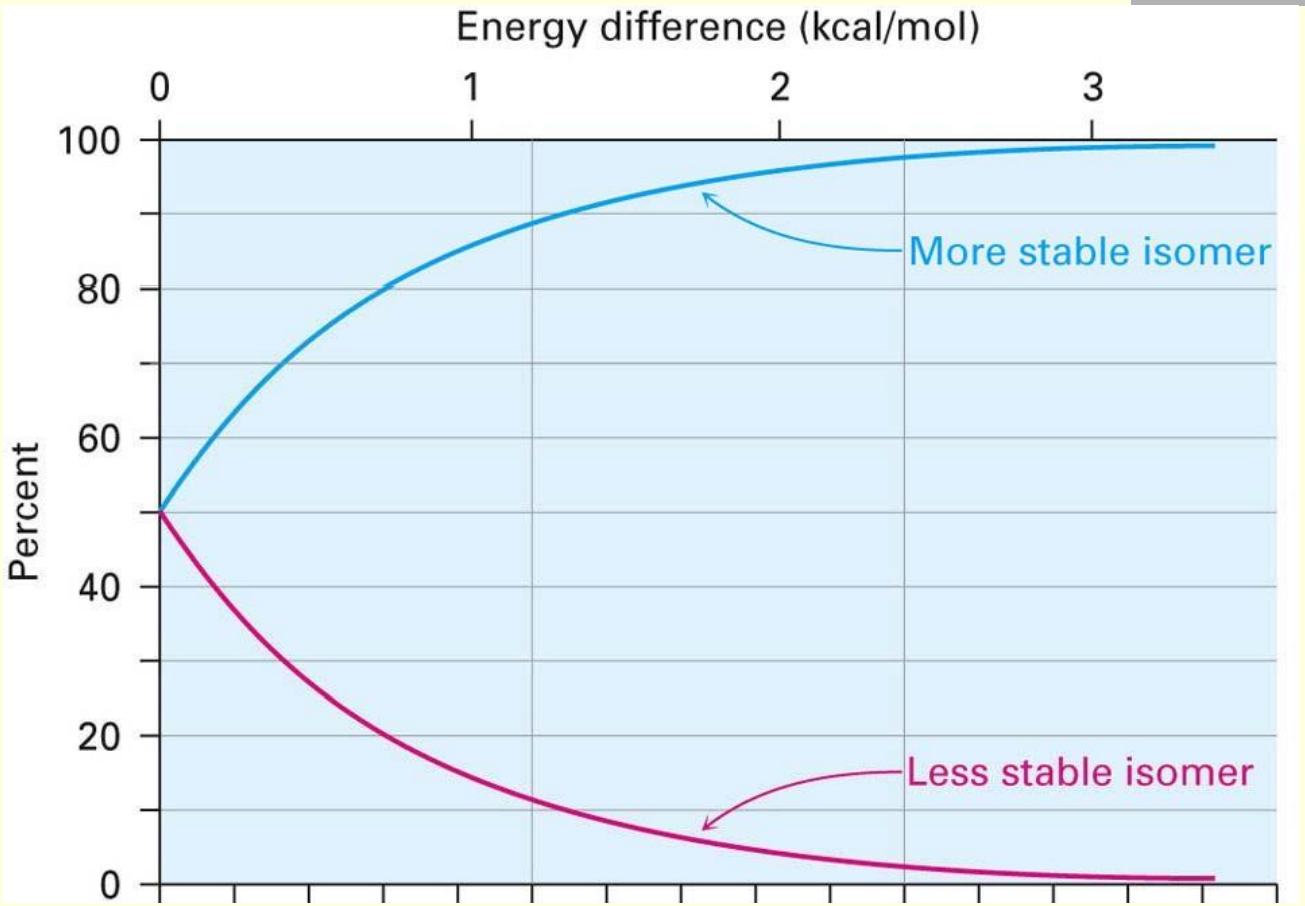
$K = 10^{-(-0.9/1.36)} = 4.5$

ΔG = -0.9 kcal/mol
(product - reactant)

so product : reactant is 4.5:1

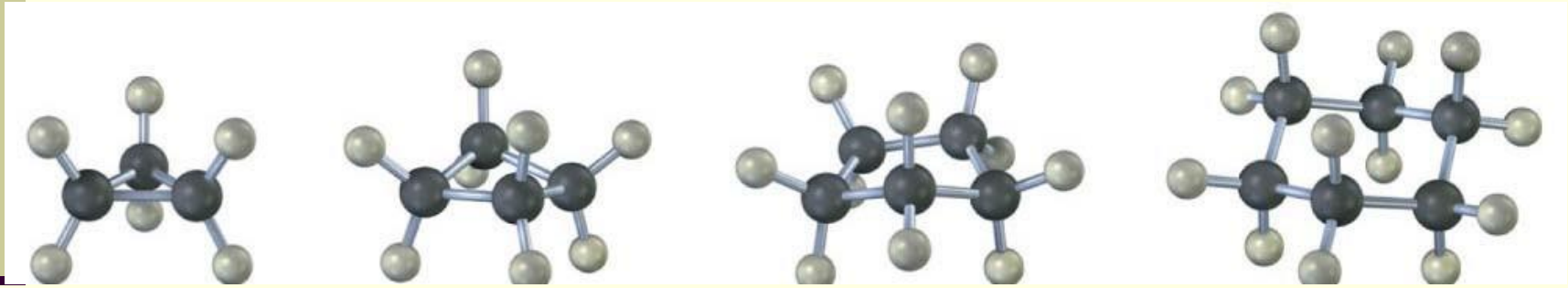
or **82% pdt** and **18% reactant**

What does ΔE tell us?



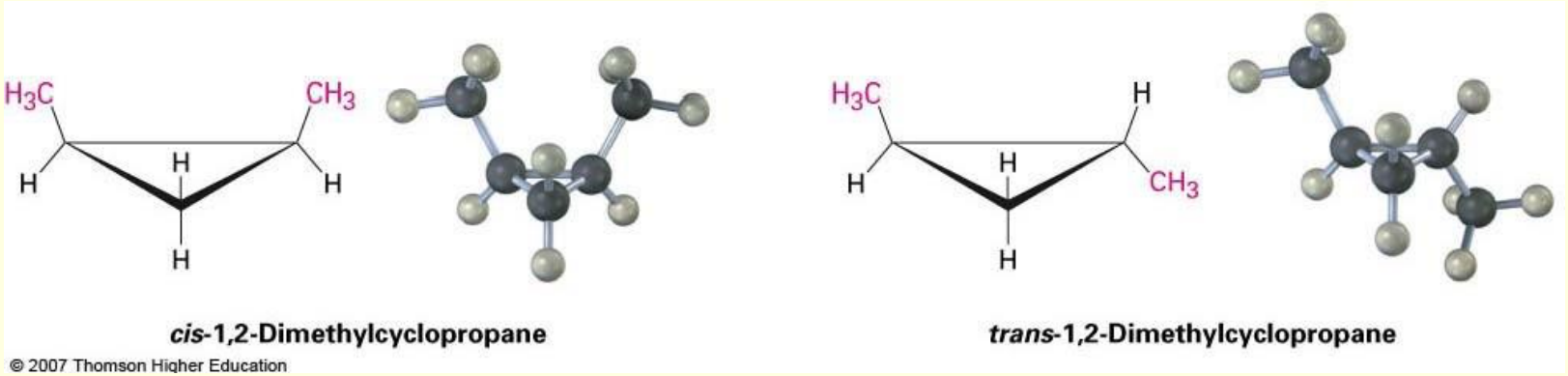
Cycloalkanes

- **Cycloalkanes** are alkanes that have carbon atoms that form a ring (called alicyclic compounds)
- Simple cycloalkanes rings of —CH2— units, (CH2)*n*, or C*n*H2*n*



Cis-Trans Isomerism in Cycloalkanes

- Rotation about C-C bonds in cycloalkanes is limited by the ring structure
- Rings have two “faces” and substituents are labeled as to their relative facial positions
- There are two different 1,2-dimethyl-cyclopropane isomers, one with the two methyls on the same side (cis) of the ring and one with the methyls on opposite sides (trans)



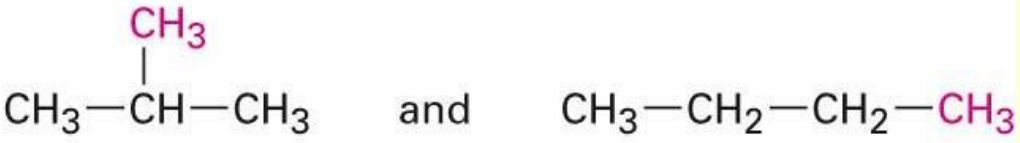
cis-1,2-Dimethylcyclopropane

trans-1,2-Dimethylcyclopropane

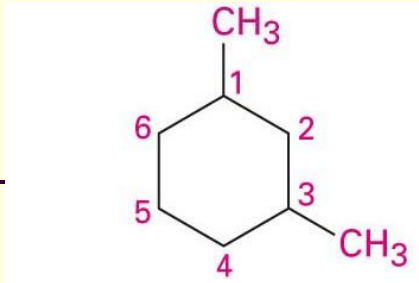
Stereoisomers

- Compounds with atoms connected in the same order but which differ in three-dimensional orientation, are **stereoisomers**
- The terms “cis” and “trans” should be used to specify stereoisomeric ring structures

Constitutional isomers
(different connections between atoms)

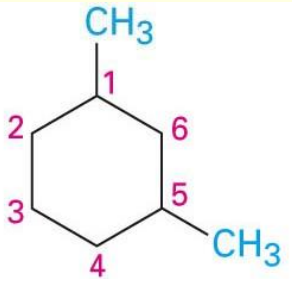


Stereoisomers
(same connections but different three-dimensional geometry)

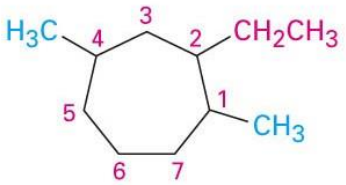


1,3-Dimethylcyclohexane

NOT



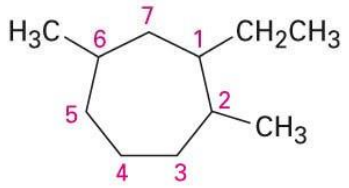
1,5-Dimethylcyclohexane



2-Ethyl-1,4-dimethylcycloheptane

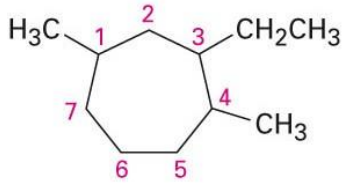
Lower Lower

NOT



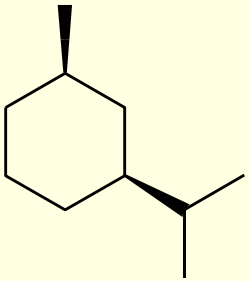
1-Ethyl-2,6-dimethylcycloheptane

Higher

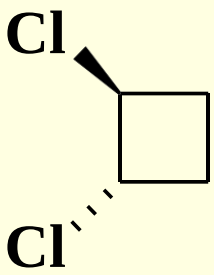


3-Ethyl-1,4-dimethylcycloheptane

Higher



cis-1-isopropyl-3-methylcyclohexane



trans-1,2-dichlorocyclobutane

Summary: Types of Strain

- **Angle strain** - expansion or compression of bond angles away from most stable
- **Torsional strain** - eclipsing of bonds on neighboring atoms
- **Steric strain** - repulsive interactions between nonbonded atoms in close proximity

- **RING STRAIN** = combination of Angle Strain + Torsional Strain

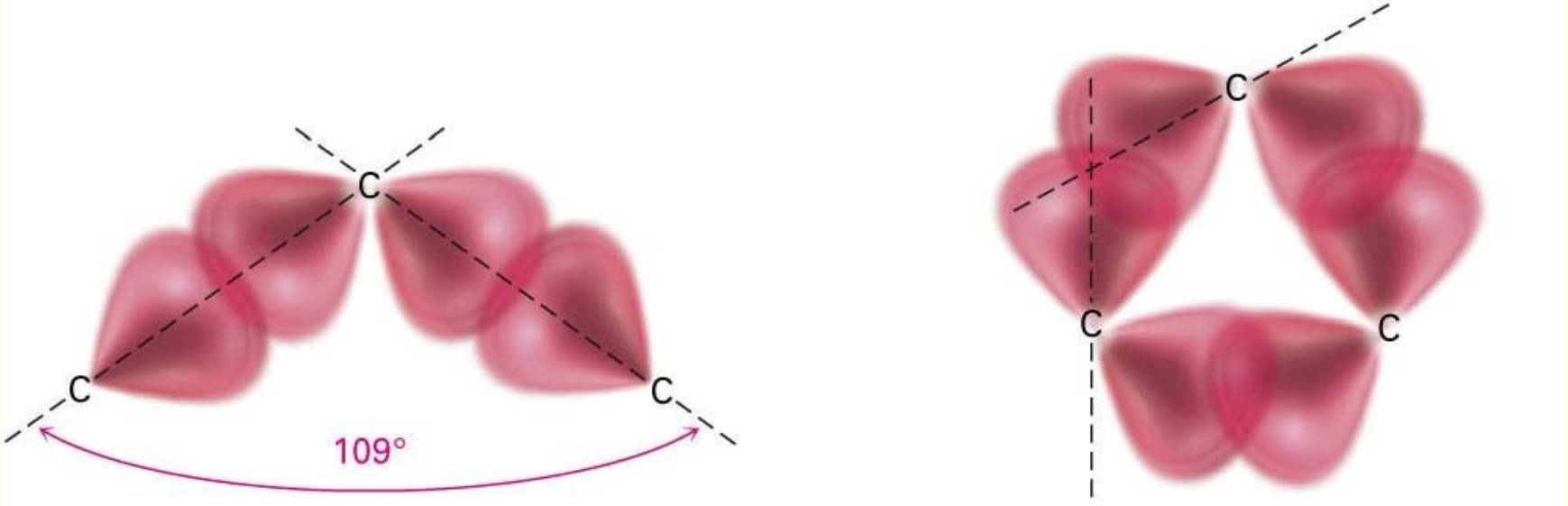
Conformations of Cycloalkanes

Cyclopropane

- 3-membered ring must have planar structure
- Symmetrical with C–C–C bond angles of 60°
- Requires that sp^3 based bonds are bent (and weakened)
- All C-H bonds are eclipsed

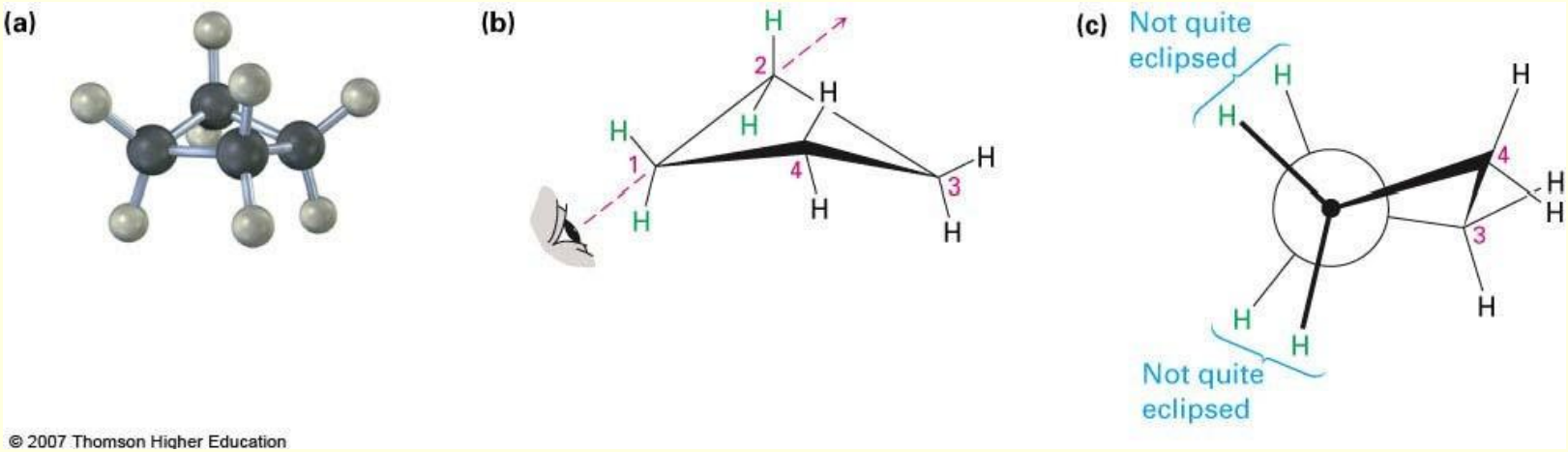
Bent Bonds of Cyclopropane

- In cyclopropane, the C-C bond is displaced outward from internuclear axis



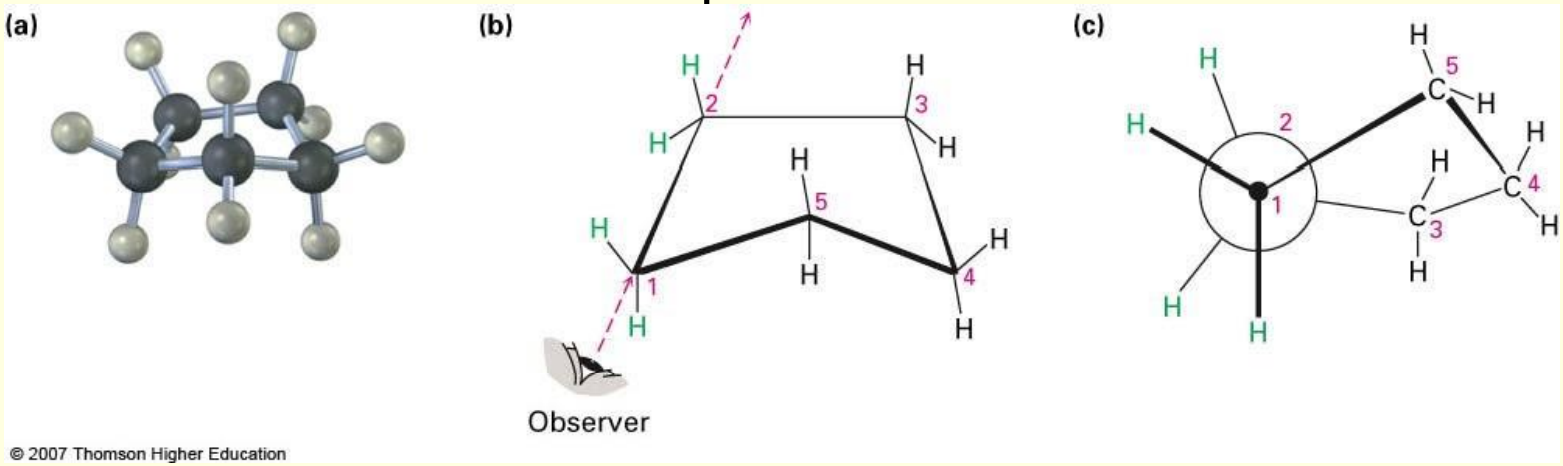
Cyclobutane

- Cyclobutane has less angle strain than cyclopropane but more torsional strain because of its larger number of ring hydrogens
- Cyclobutane is slightly bent out of plane - one carbon atom is about 25° above
  - The bend *increases* angle strain but *decreases* torsional strain



Cyclopentane

- Planar cyclopentane would have no angle strain but very high torsional strain
- Actual conformations of cyclopentane are nonplanar, reducing torsional strain
- Four carbon atoms are in a plane
  - The fifth carbon atom is above or below the plane – looks like an envelope



Conformations of Cyclohexane

- Substituted cyclohexanes occur widely in nature
- The cyclohexane ring is free of angle strain and torsional strain
- The conformation is has alternating atoms in a common plane and tetrahedral angles between all carbons
- This is called a **chair conformation**

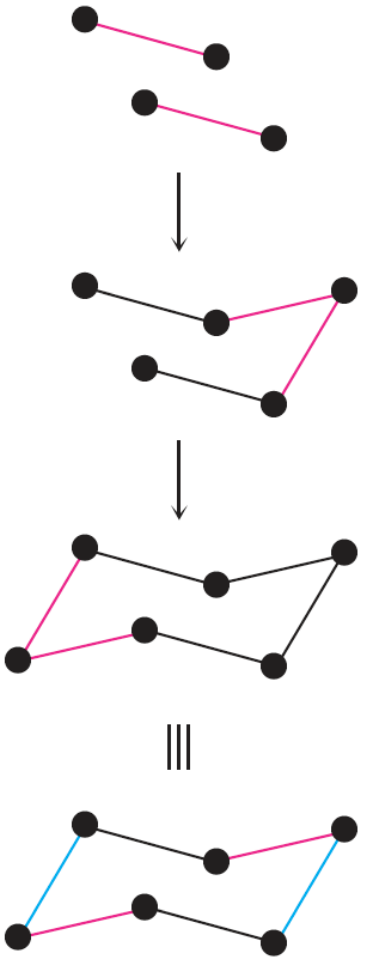
All bond angles 109.5^{o}, and all hydrogens staggered

How to Draw Chair Cyclohexane

Step 1 Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.

Step 2 Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.

Step 3 Place the bottommost carbon atom below and to the left of the plane of the middle four, and connect the bonds. Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.



The Hofmann Elimination

The Hofmann Elimination

a quaternary ammonium hydroxide is the reactant and an alkene is the product

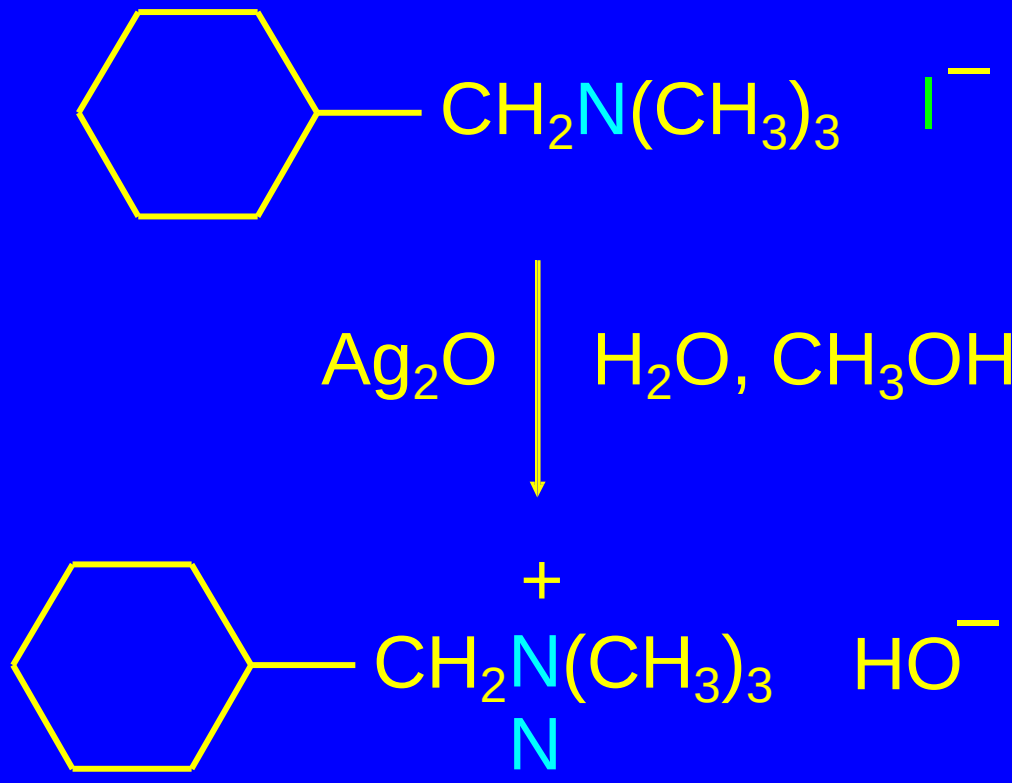
is an anti elimination

the leaving group is a trialkylamine

the regioselectivity is opposite to the Zaitsev rule.

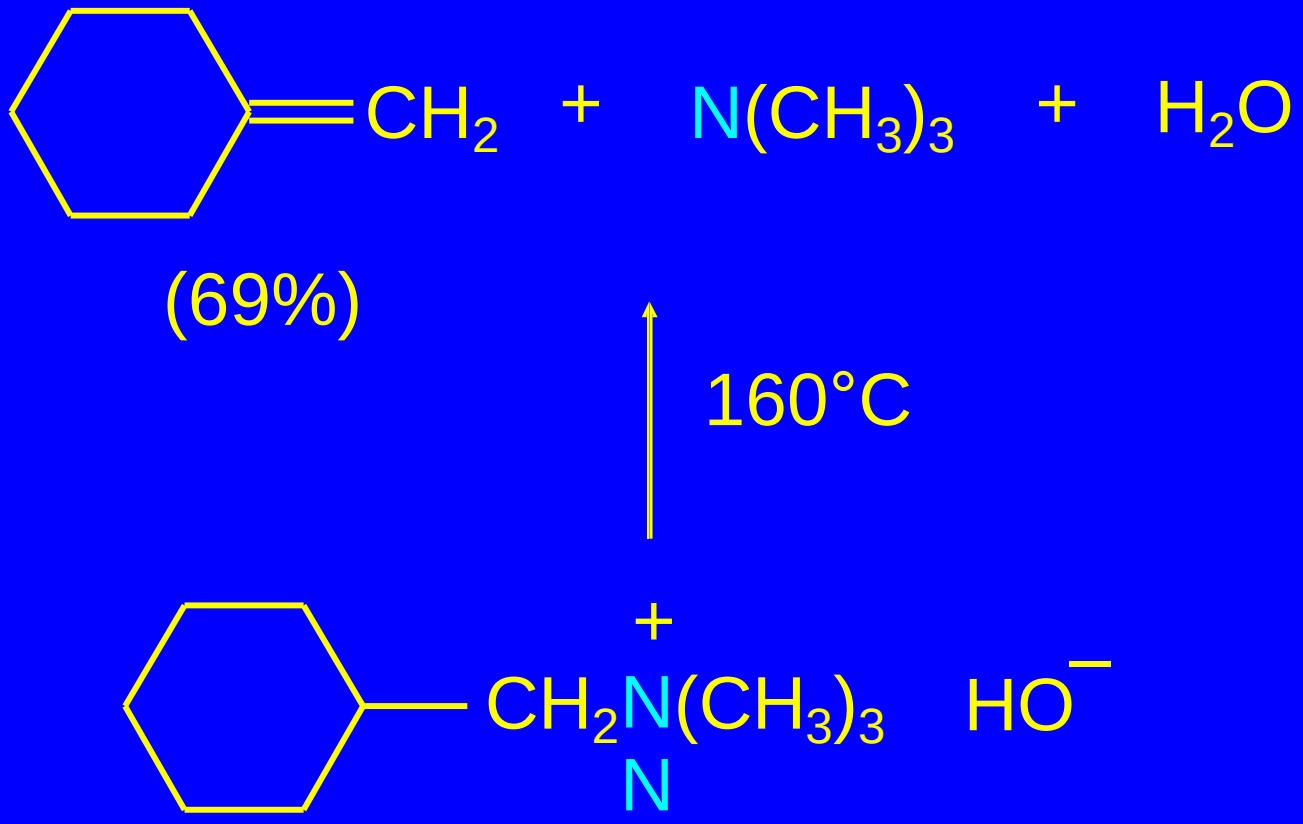
Quaternary Ammonium Hydroxides

are prepared by treating quaternary ammmonium halides with moist silver oxide

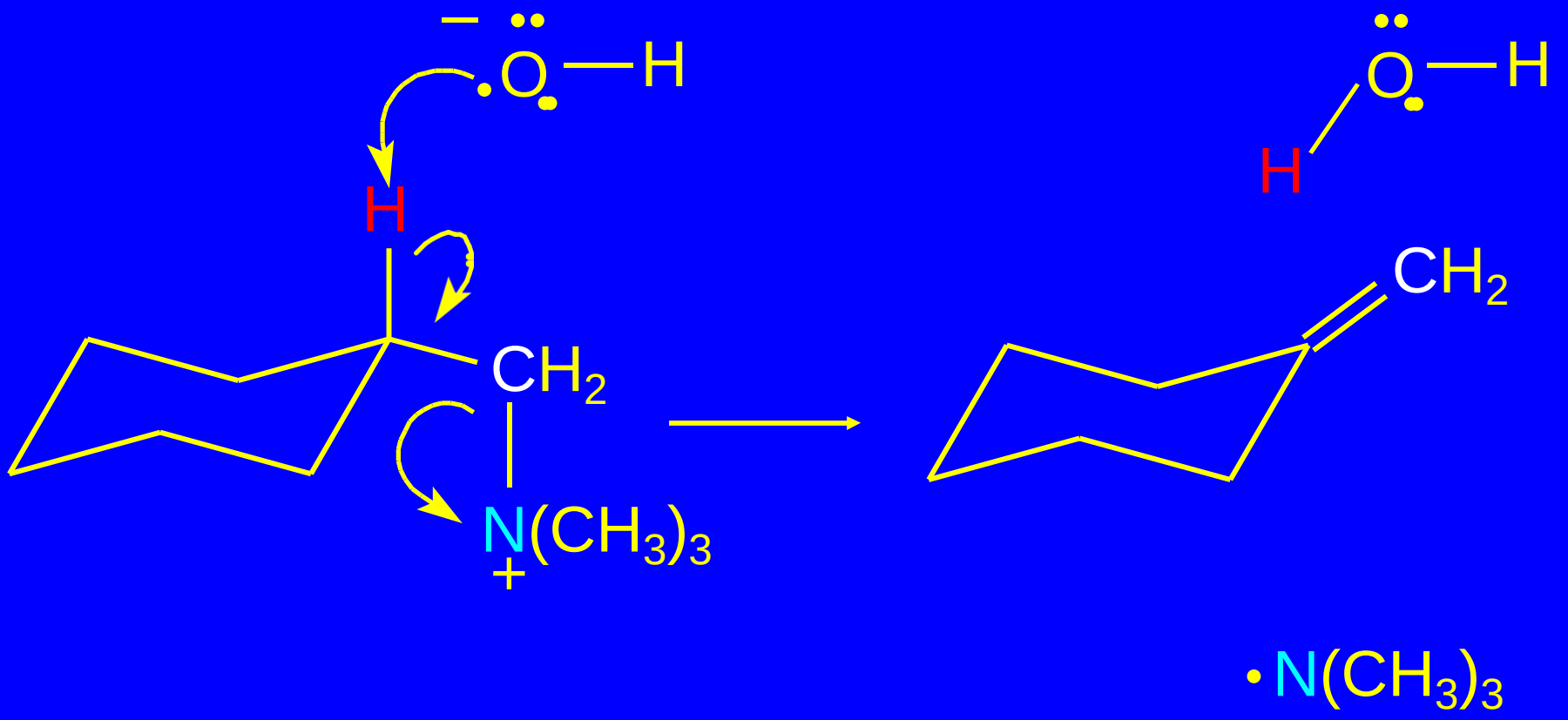


The Hofmann Elimination

on being heated, quaternary ammonium hydroxides undergo elimination

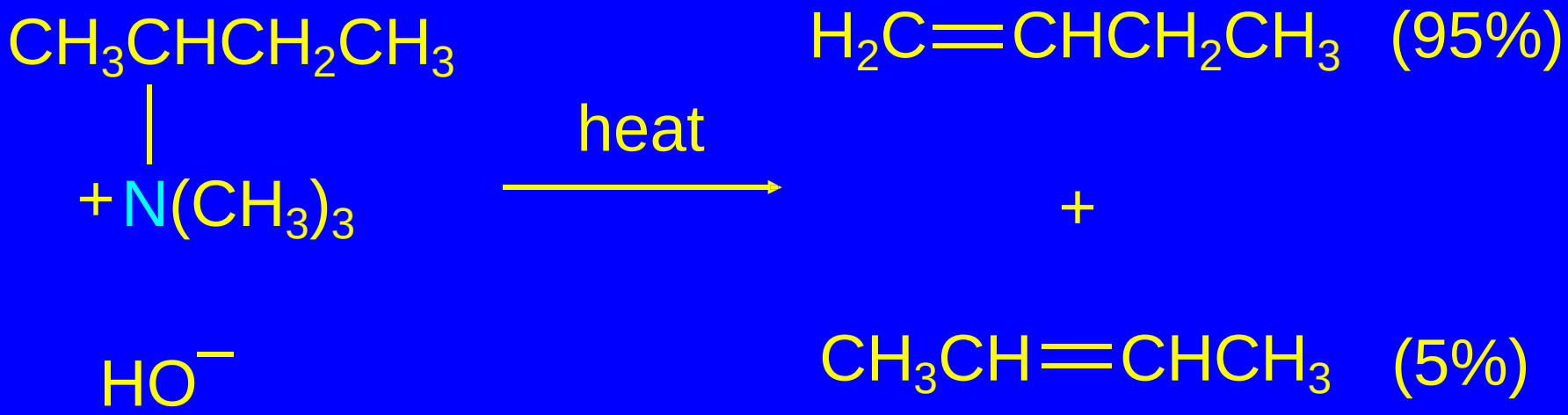


Mechanism



Regioselectivity

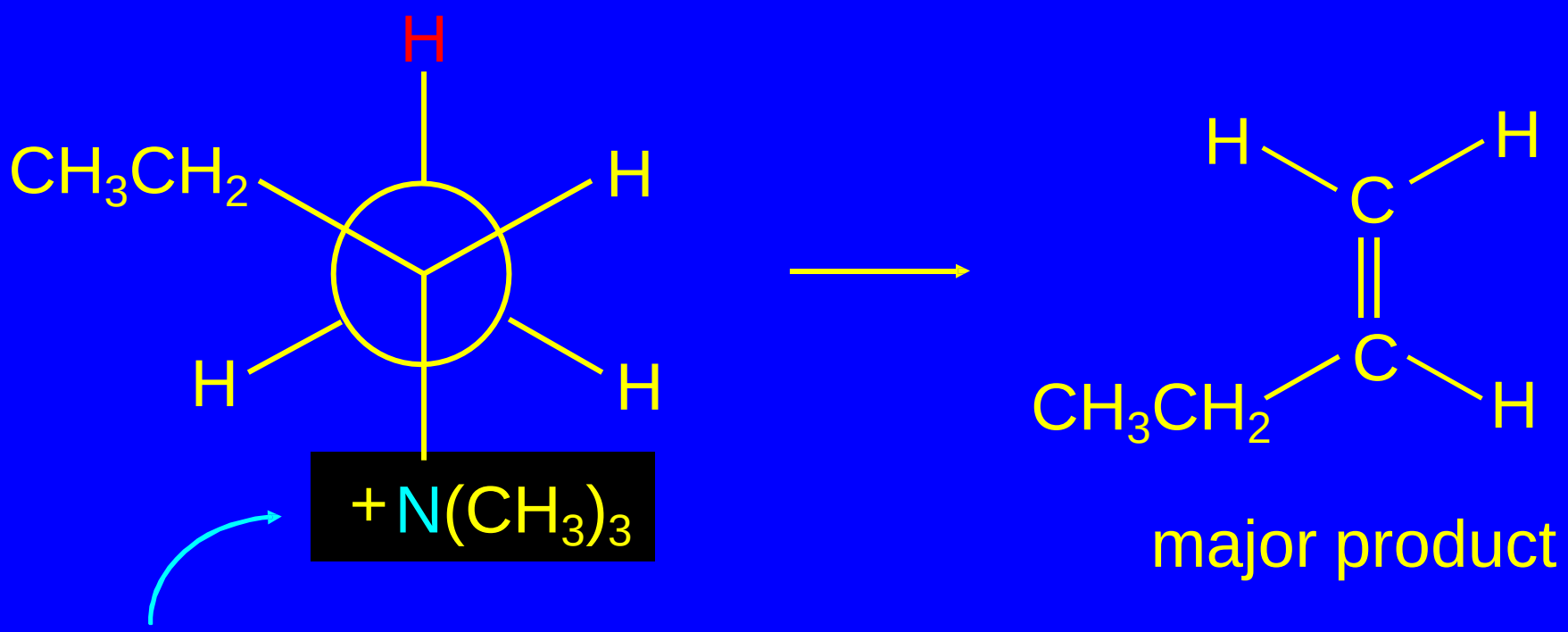
Elimination occurs in the direction that gives the less-substituted double bond. This is called the Hofmann rule.



Regioselectivity

Steric factors seem to control the regioselectivity. The transition state that leads to 1-butene is less crowded than the one leading to cis or trans-2-butene.

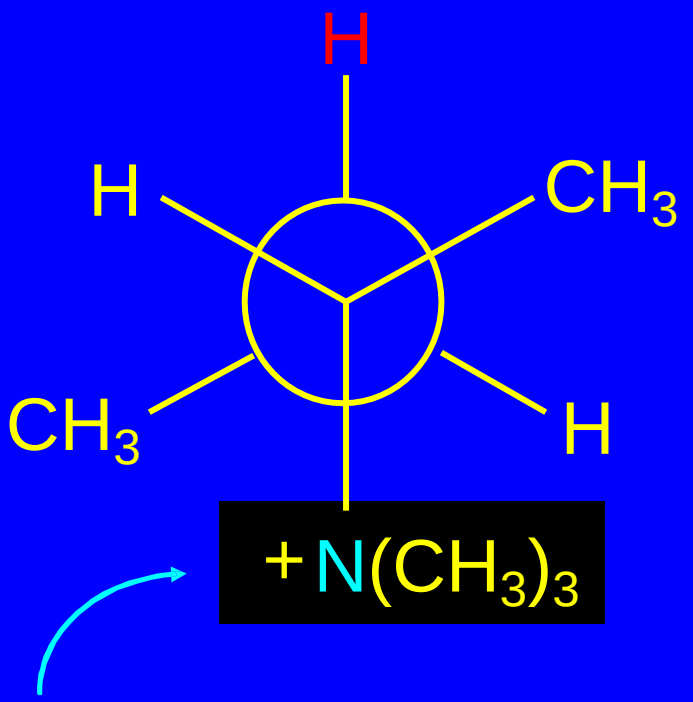
Regioselectivity



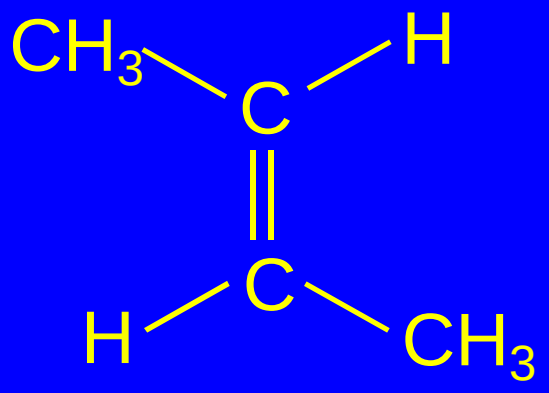
major product

largest group is between two H atoms

Regioselectivity



largest group is between an H atom and a methyl group



minor product

Electrophilic Aromatic Substitution in Arylamines

2-D representations of stereoisomer's

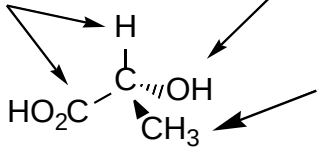
(line drawings, Fischer projections, Haworth projections)

You must be able to draw tetrahedral carbons properly!!

In the plane of the paper and in the same plane as the tetrahedral carbon (adjacent position off the tetrahedral carbon)

Dash: projecting behind the plane of the paper away from you

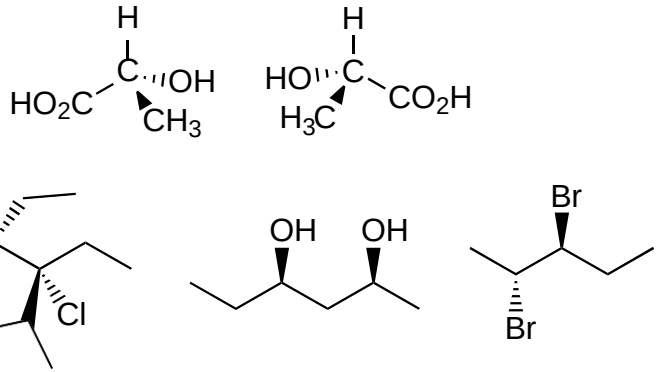
Dash and Wedge are on adjacent position off the tetrahedral carbon



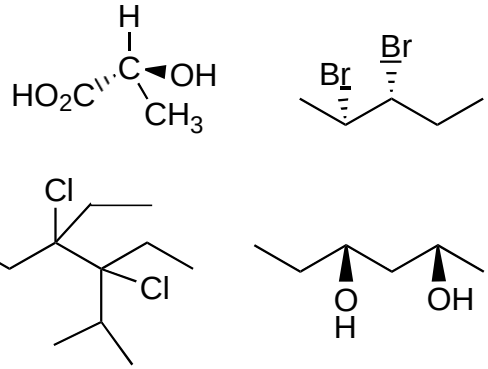
Wedge: projecting out of the plane of the paper toward you

LINEAR ALKANES: You should draw the carbon backbone in the plane of the paper, and draw substituents either coming towards you (with wedges) or going away from you (with dashes). Note that each carbon should look like a tetrahedron.

Correct ☺



Incorrect ☹



Fischer projection formulas represent 3 - D tetrahedral carbon atoms and their substituent's in two dimensions.

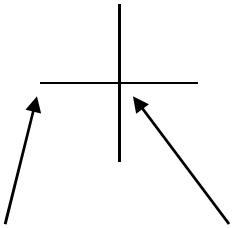
• The molecule is drawn in the form of a cross.

•The tetrahedral carbon is in the plane of the paper at the center of the cross
•Atoms connected to the tetrahedral carbon by horizontal bonds are behind the plane of the paper.

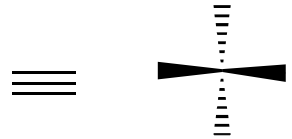
Atoms connected to the tetrahedral carbon by vertical bonds are in front of the plane of the paper

Fischer Projections - representation of a three-dimensional molecule as a flat structure. A tetrahedral carbon is represented by two crossed lines:

horizontal line is coming out of the plane of the page (toward you)

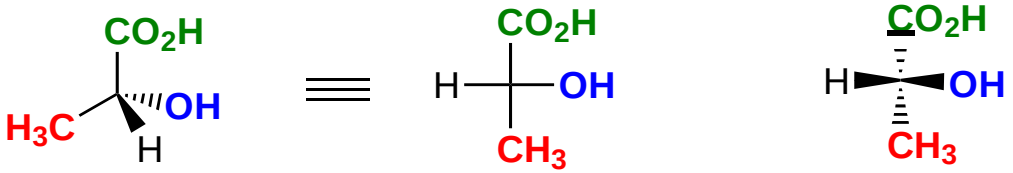


vertical line is going back behind the plane of the paper (away from you)

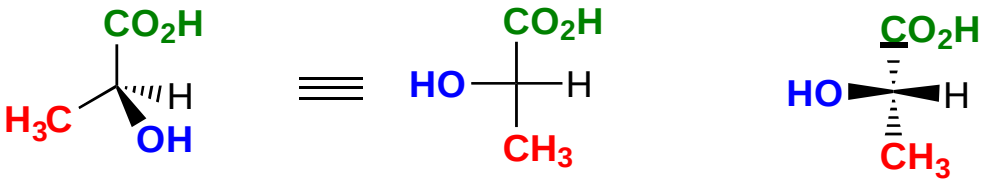


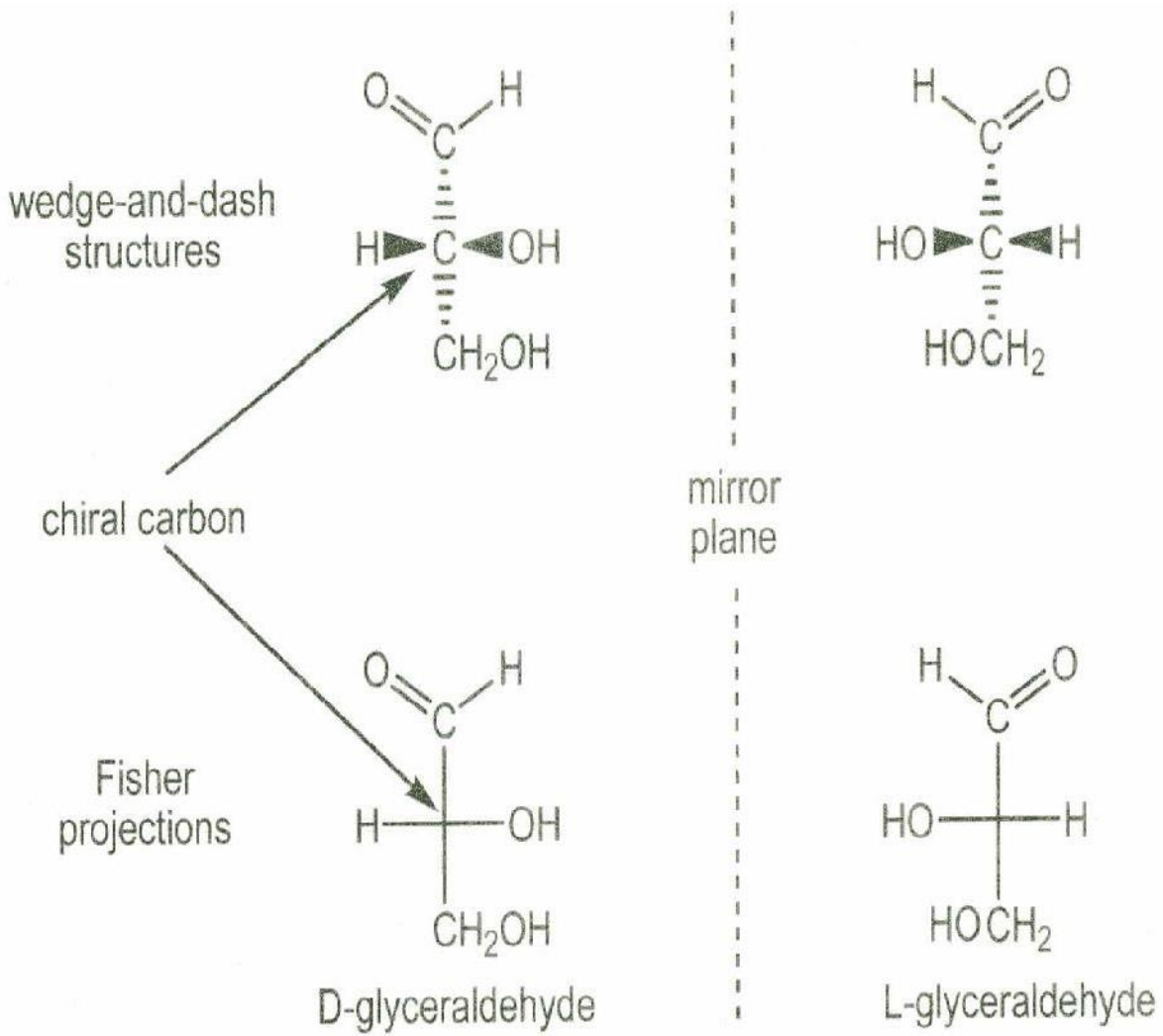
substituent carbon

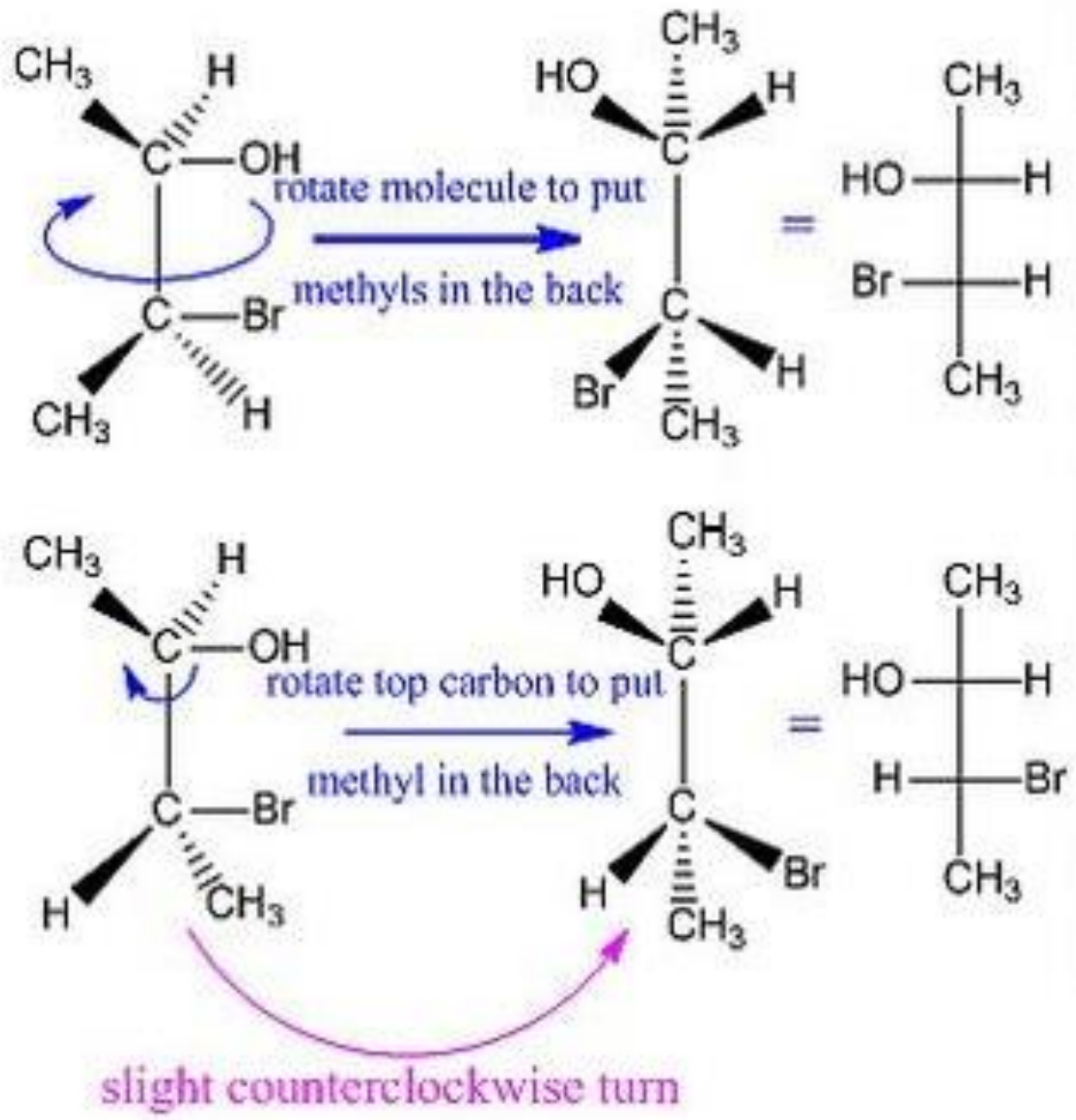
(*R*)-lactic acid



(*S*)-lactic acid




wedge-and-dash structures
chiral carbon
Fisher projections
mirror plane
D-glyceraldehyde
L-glyceraldehyde


CH3
H
C
OH
C
Br
CH3
H
rotate molecule to put
methyls in the back
HO
CH3
H
C
C
Br
H
CH3
=
CH3
HO
H
Br
H
CH3
rotate top carbon to put
methyl in the back
slight counterclockwise turn

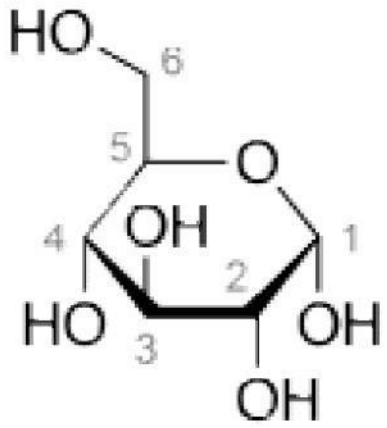
Haworth projection

A **Haworth projection** is a common way of writing a structural formula to represent the cyclic structure of monosaccharides with a simple three-dimensional perspective. Organic chemistry and especially biochemistry are the areas of chemistry that use the Haworth projection the most.

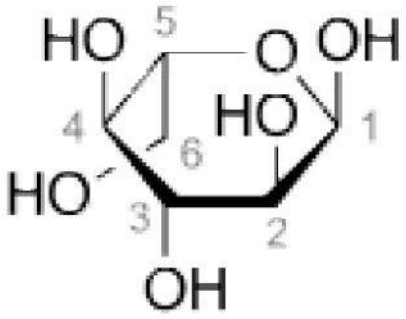
The Haworth projection was named after the English chemist Sir Norman Haworth.

A Haworth projection has the following characteristics:

- Carbon is the implicit type of atom. In the example on the right, the atoms numbered from 1 to 6 are all carbon atoms. Carbon 1 is known as the anomeric carbon.



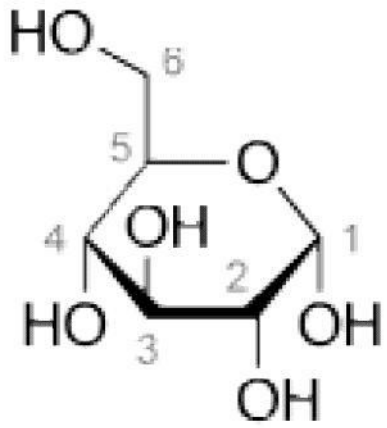
α-D-glucopyranose



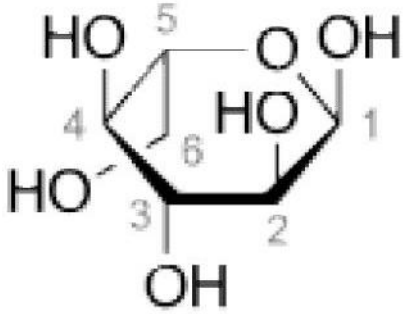
α-L-glucopyranose

- Hydrogen atoms on carbon are implicit. In the example, atoms 1 to 6 have extra hydrogen atoms not depicted.

➢A thicker line indicates atoms that are closer to the observer. In the example on the right, atoms 2 and 3 (and their corresponding OH groups) are the closest to the observer. Atoms 1 and 4 are farther from the observer. Atom 5 and the other atoms are the farthest.



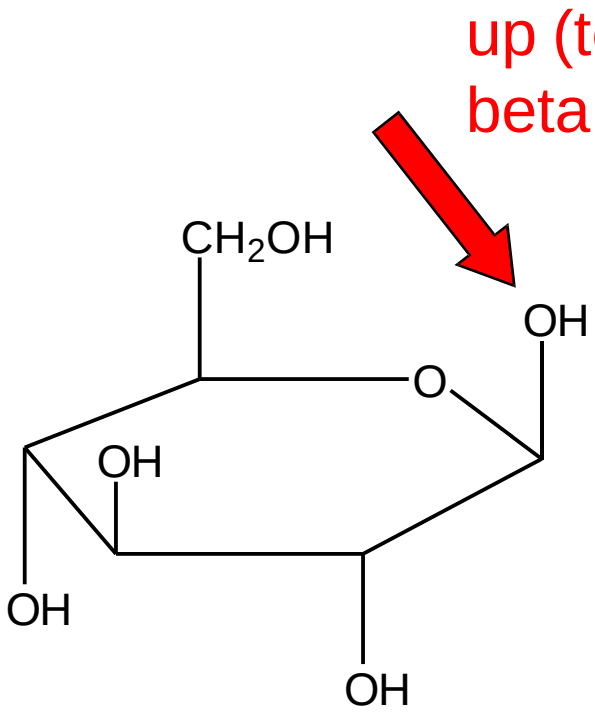
α-D-glucopyranose

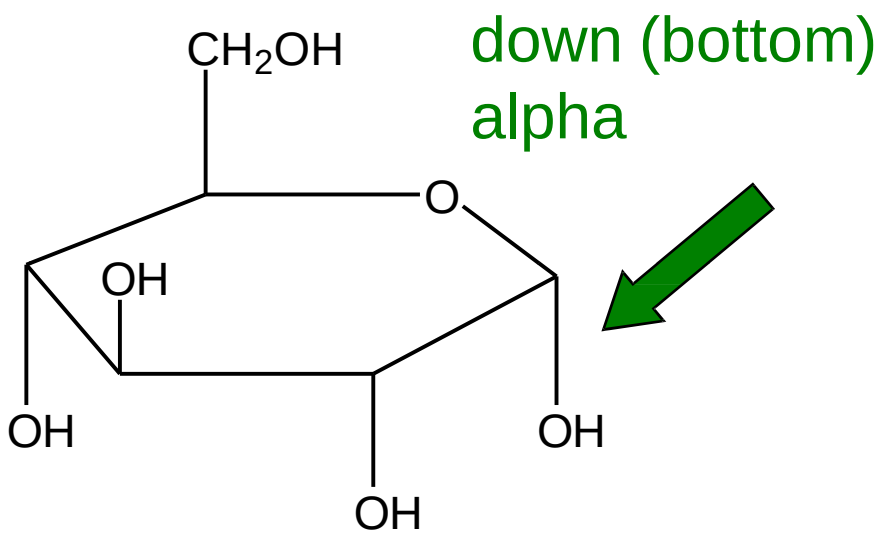


α-L-glucopyranose

➢The groups below the plane of the ring in Haworth projections correspond to those on the right-hand side of a Fischer projection. This rule does not apply to the groups on the two ring carbons bonded to the endocyclic oxygen atom.

Haworth Projections of Glucopyranose Anomers





β-D-(+)-Glucopyranose

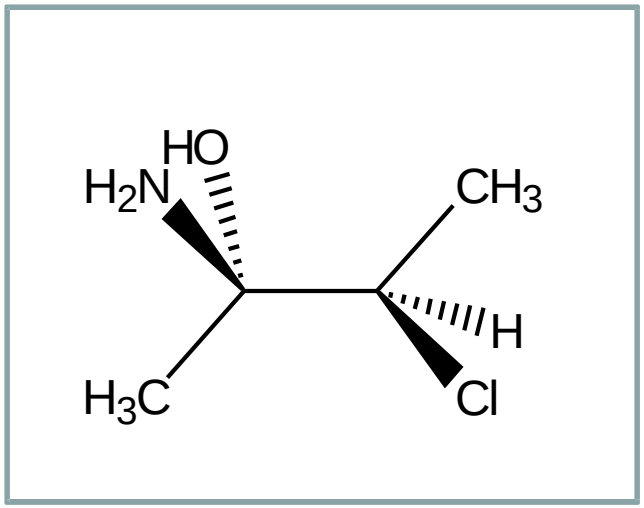
α-D-(+)-Glucopyranose

There are certain rules that are to be followed while making the Fischer projection

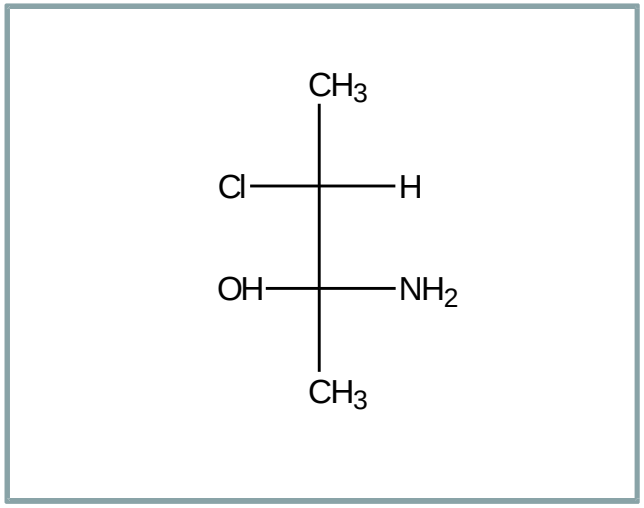
Rule no 1) User should view the molecule from the same place while making the projection i.e. top right, top left, bottom right, bottom left.

Rule no 2) In Fischer projection the atoms/bonds which are in the horizontal line should come out of the plane while those are in vertical line should be going inside the plane.

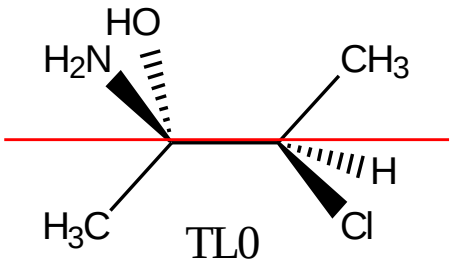
Rule no 3) While rotating the bonds about any atom (chiral) the stereochemistry of the molecule does not changes.



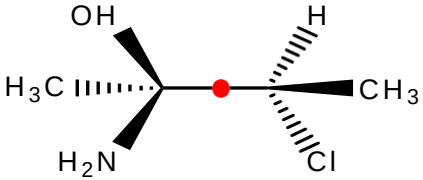
Initial display of the page



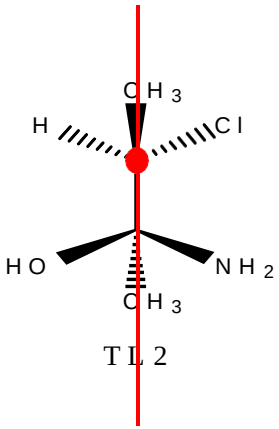
final display of the page



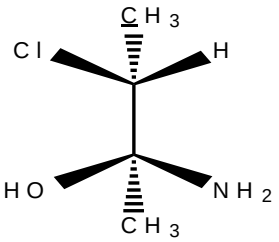
TL0



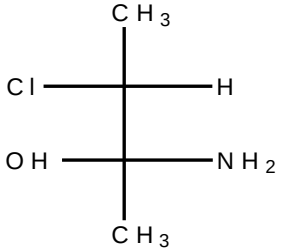
TL1



TL2



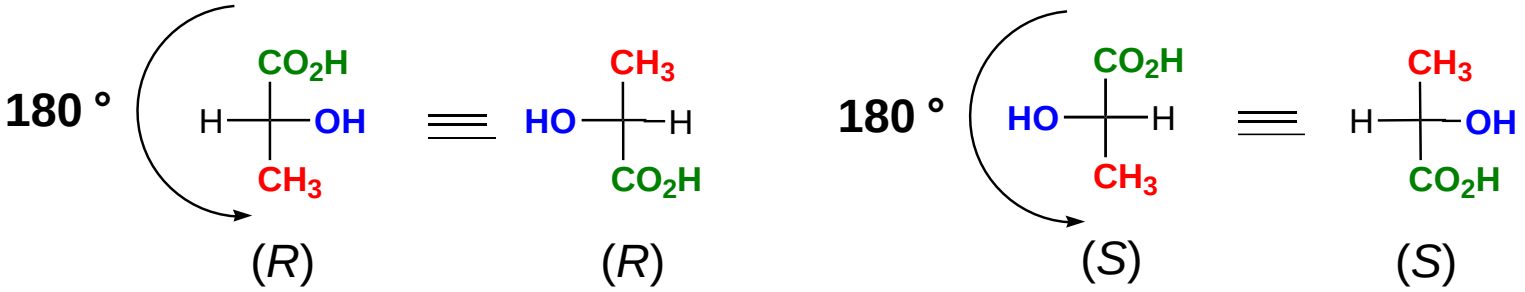
TL3



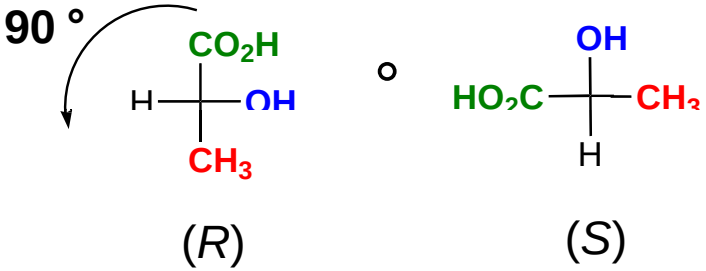
TL4

Manipulation of Fischer Projections

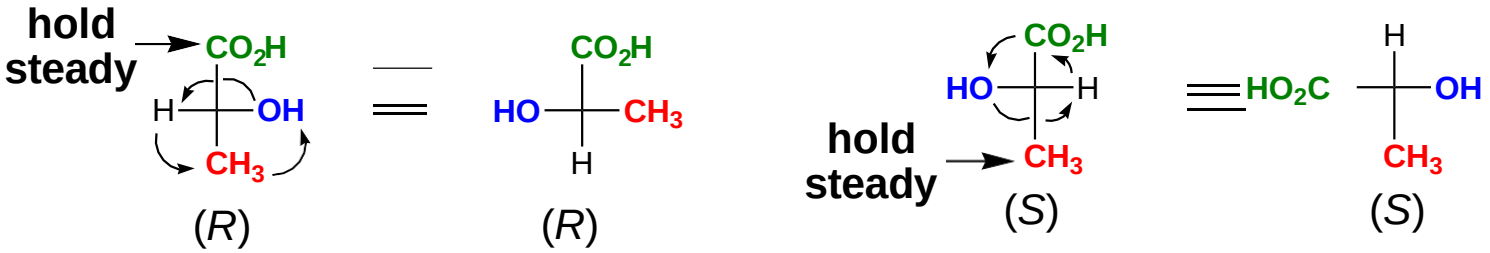
1. Fischer projections can be rotated by 180°only!



a 90°rotation inverts the stereochemistry and is illegal!

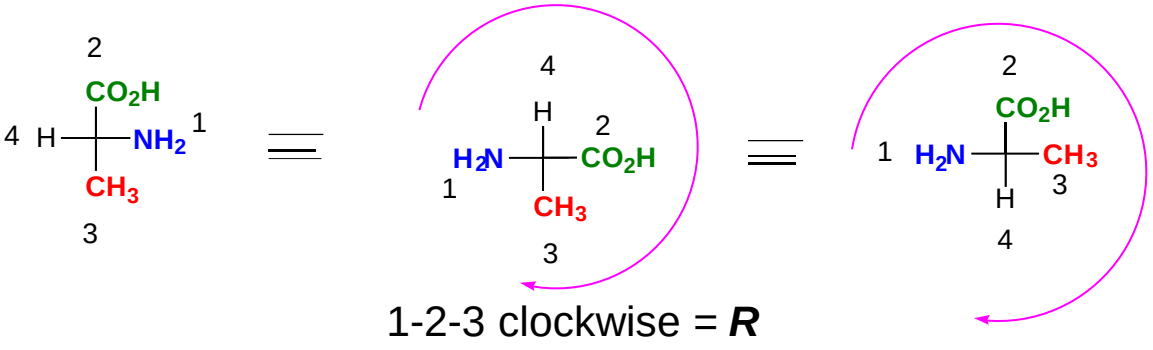


2. If one group of a Fischer projection is held steady, the other three groups can be rotated clockwise or counterclockwise.



Assigning R and S Configuration to Fischer Projections

1. Assign priorities to the four substitutents according to the Cahn-Ingold-Prelog rules
2. Perform the two allowed manipulations of the Fischer projection to place the lowest priority group at the <u>top</u> (or bottom).
3. If the priority of the groups 1→2→3 are clockwise then assign the center as *R*, if 1→2→3 are counterclockwise then assign the center as *S*.



Enantiomers must have the opposite configuration at **all** chiral centers.

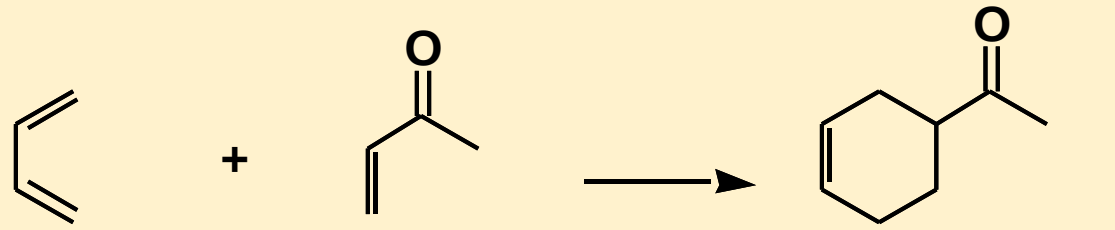
In general, enantiomers have identical physical properties except optical rotation (which is equal in magnitude but opposite in sign). Diastereomers may have completely different physical properties.

For a molecule with n chiral centers, there are 2^n number of stereoisomers possible, not including geometric stereoisomers of double bonds.

Erythro: substituents on same side of a Fischer projection
i.e., (2*R*, 3*R*)- and (2*S*, 3*S*)-threonine
Threo: substituents on opposite sides of a Fischer projection
i.e., (2*S*, 3*R*)- and (2*R*, 3*S*)-threonine

Diels-Alder Reaction

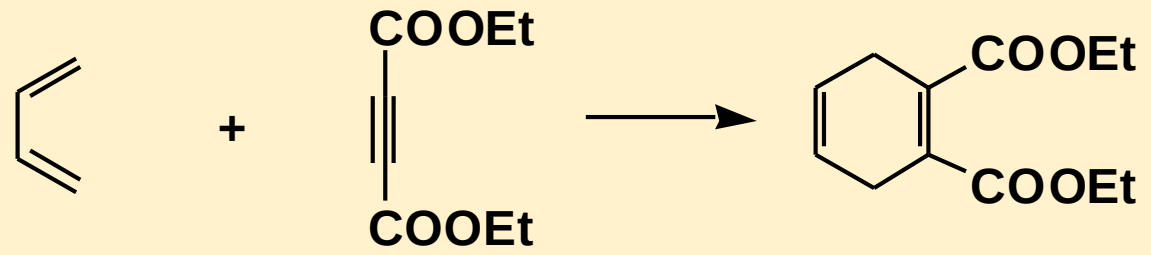
- **Diels-Alder reaction: A cycloaddition reaction of a conjugated diene and certain types of double and triple bonds.**
  - **dienophile: Diene-loving.**
  - **Diels-Alder adduct: The product of a Diels-Alder reaction**



1,3-Butadiene (a diene) **3-Buten-2-one (a dienophile)** **Diels-Alder adduct**

Diels-Alder Reaction

- **Alkynes also function as dienophiles.**

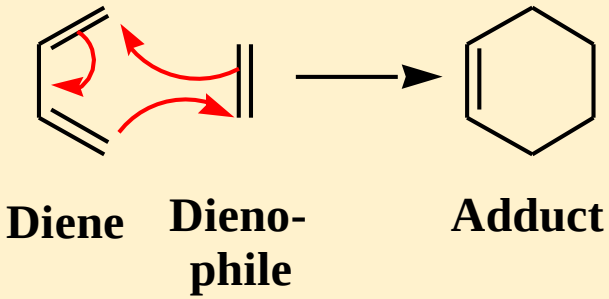


1,3-butadiene (a diene) + **Diethyl 2-butynedioate (a dienophile)** → **Diels-Alder adduct**

- **Cycloaddition reaction: A reaction in which two reactants add together in a single step to form a cyclic product.**

Diels-Alder Reaction

- **We write a Diels-Alder reaction in the following way:**



- **The special value of D-A reactions are that they:**

  1. form six-membered rings.

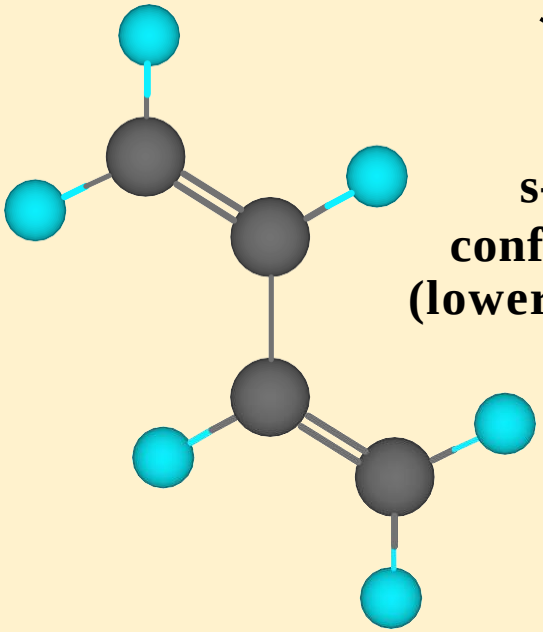
  2. form two new C-C bonds at the same time.

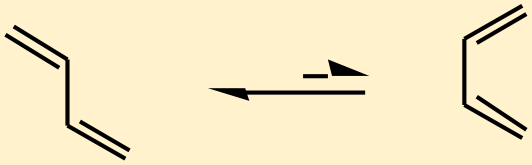
  3. are stereospecific and regioselective.

  Note the reaction of butadiene and ethylene gives only traces of cyclohexene.

Diels-Alder Reaction

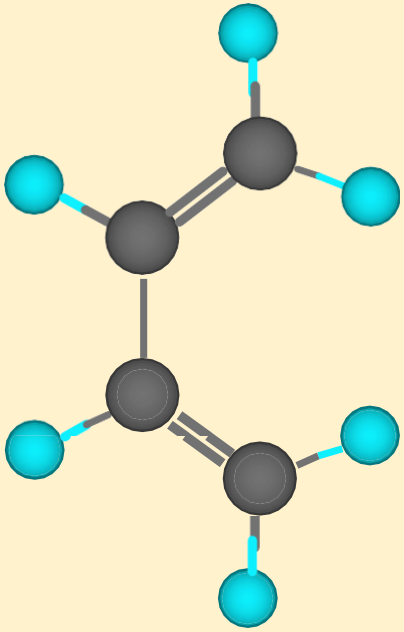
- **The conformation of the diene must be s-*cis*.**





s-*trans* conformation (lower in energy)

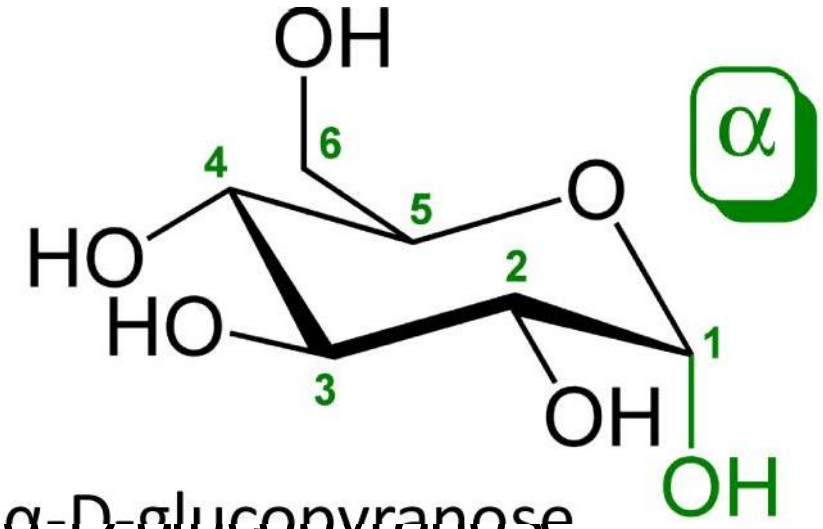
s-*cis* conformation (higher in energy)



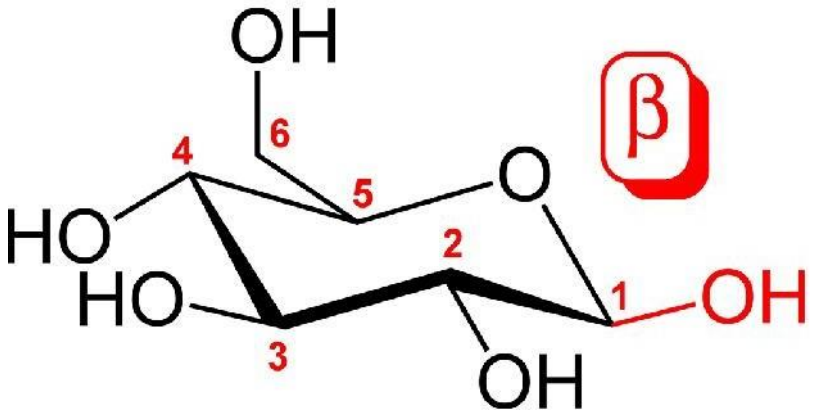
Monosaccharides: Stereoisomer Nomenclature

Epimers:-

- **Epimers** are a specific type of stereoisomer that have multiple stereocenters, but only differ from one another by the configuration at one of the stereogenic centers.



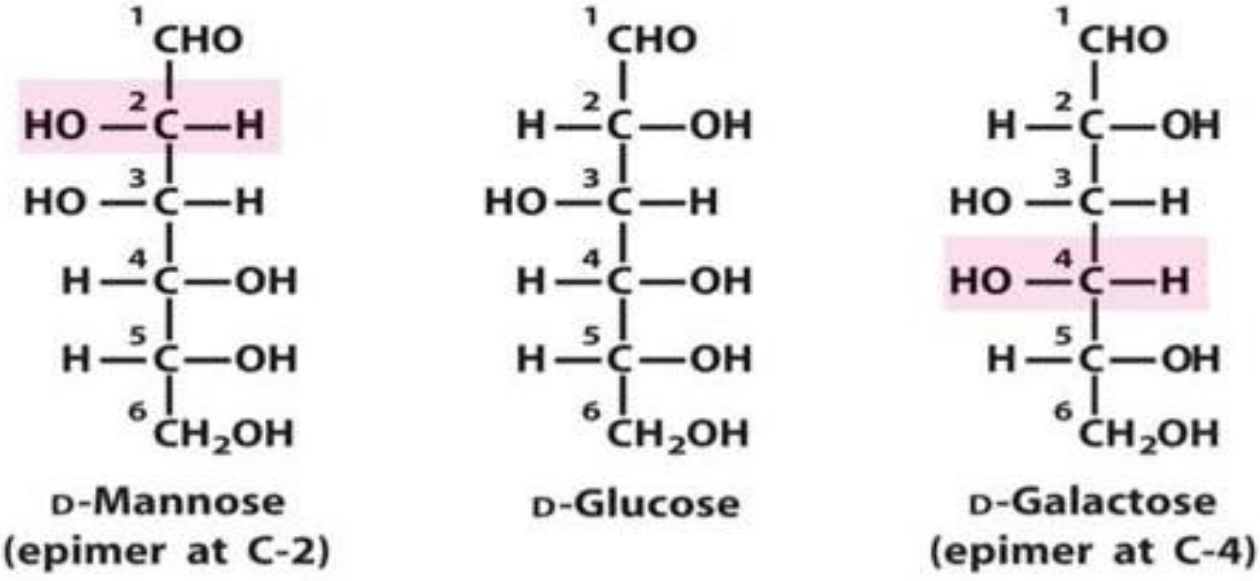
- α-D-glucopyranose



β-D-glucopyranose

Epimers are optical isomers that differ in the configuration of a single carbon atom

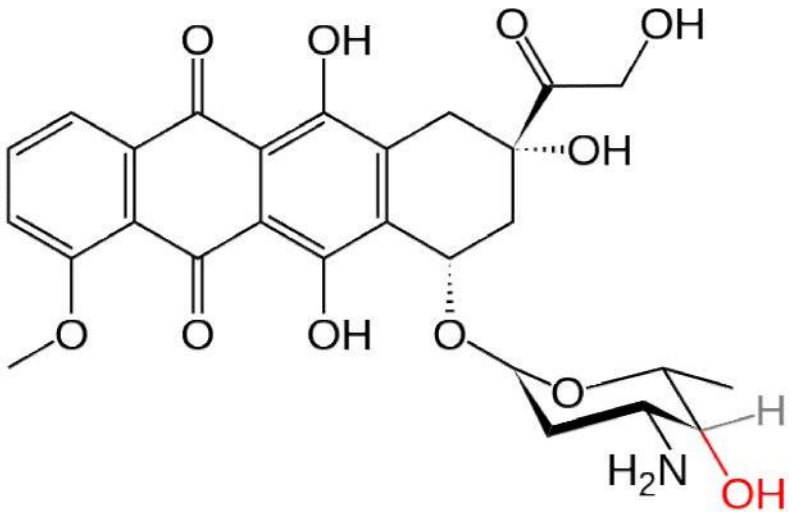
For example, D-galactose and D-mannose are epimers of D-glucose.

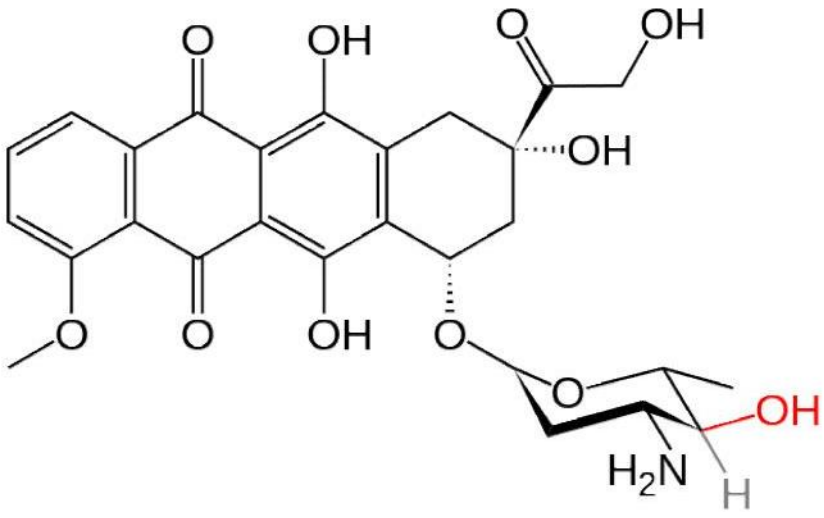


D-Galactose is an epimer of D-glucose because the two sugars differ only in the configuration at C-4.

D-Mannose is an epimer of D-glucose because the two sugars differ only in the configuration at C-2.

Doxorubicin and epirubicin are two epimers that are used as drugs

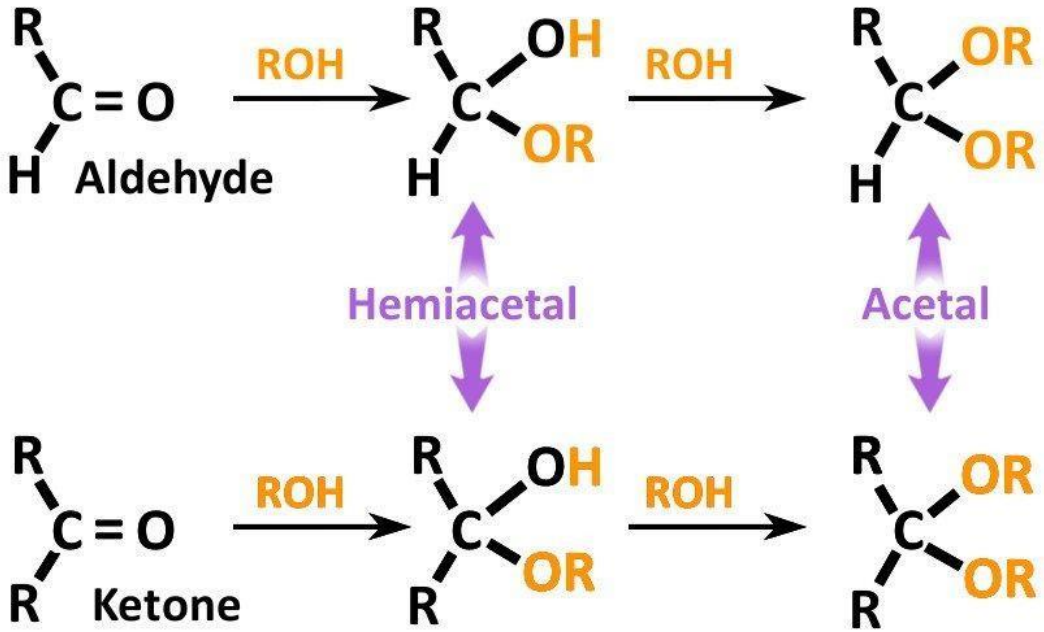




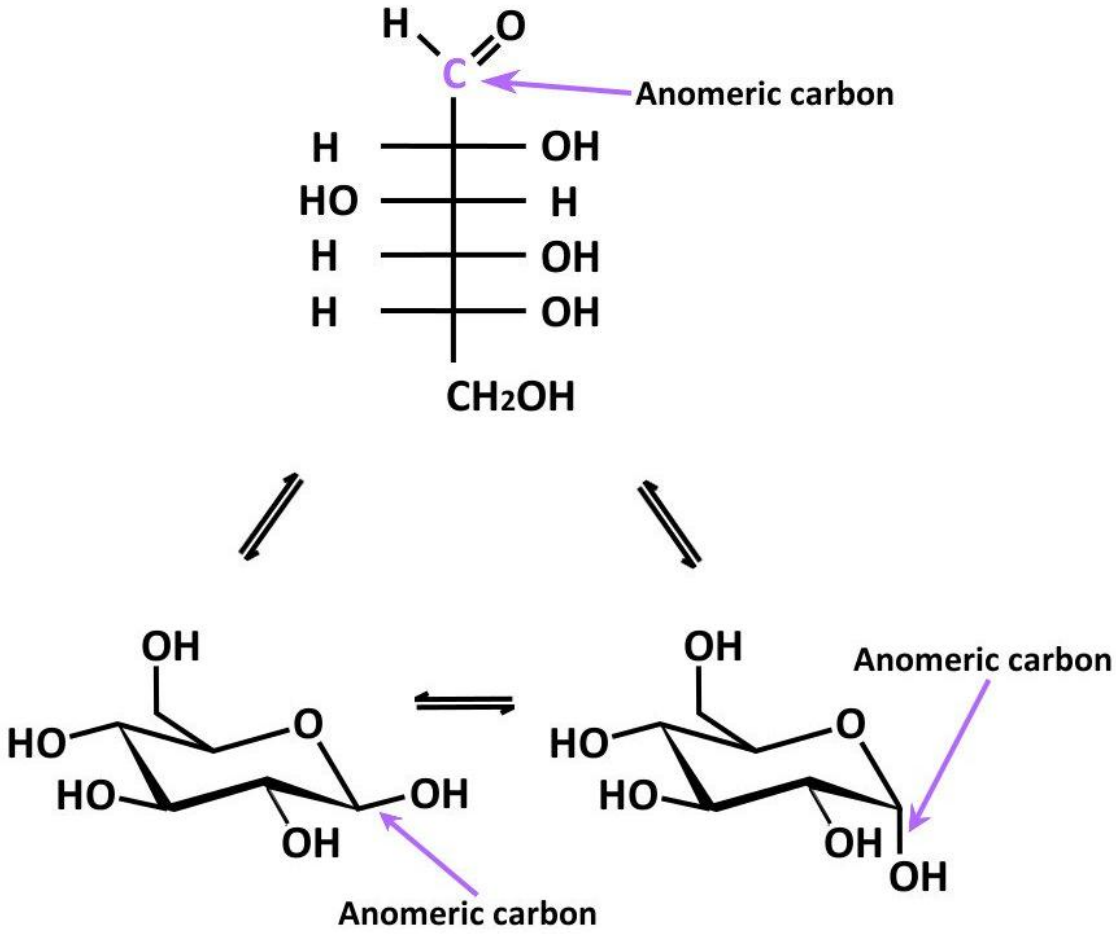
Anomers:-

While an epimer is one of a pair of stereoisomers that differ in configuration at only one chiral (stereogenic)center.

an anomer is actually an epimer (also a cyclic saccharide) that differs in configuration, especially at the acetal or hemiacetal carbon (refer to the image below to differentiate between acetal and hemiacetal carbons).



An anomer is a kind of stereoisomer; anomers are saccharides or glycosides that are epimers, which are distinct from each other in the configuration at C-2, if they are ketoses, or in the configuration of C-1, if they are aldoses.



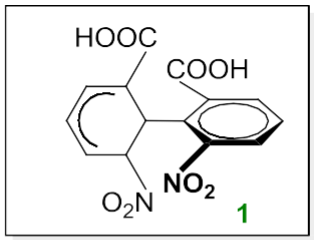
Atropisomerism: The Axis of Chirality

Outline of the presentation

1. **Introduction**
2. **Conditions for Atropisomerism**
3. **Nomenclature of Atropisomers**
4. **Classification of Atropisomers**
5. **Methods to study Atropisomerism**
6. **Methods for Atroposelective Conversion**
7. **Uses of Atropisomers**
8. **Conclusion**

Introduction

- Though “optical activity due to axial chirality” was first reported by **Christie and Kenner** in **1922**,[1] but the term “Atropisomerism” was coined by **Richard Kuhn** later in **1933**.[2]



1

single isomer was isolated
from the racemic mixture
via diastereoselective chrystallisation
with a chiral resolving agent

Richard Kuhn (1900-1967)
Nobel Laureate in chemistry (1938)

- From Greek: ***a*** – **not**
  tropos – **to turn**

- Atropisomerism is that kind of isomerism, where the conformers (called atropisomers) can be isolated as separate chemical species and which arise from restricted rotation about a single bond.

- **Axis of Chirality**: An axis about which a set of atoms/functional groups/ligands is held so that it results in a spatial arrangement that is not superimposable on its mirror image.

Conditions for Atropisomerism

1. Two necessary preconditions for axial chirality are:
   i. a rotationally stable axis
   ii. Presence of different substituents on both sides of the axis
2. Atropisomers are recognised as physically separable species when, at a given temperature, they have a half life of atleast 1000 s (16.7 min) [**$\tau \geq 1000$ s**].
3. The minimum required free energy barriers at different temperatures are as below.
   ΔG_{200K} = 61.6 kJmol^{-1}
   ΔG_{300K} = 93.5 kJmol^{-1}
   ΔG_{350K} = 109 kJmol^{-1}
4. The configurational stability of axially chiral biaryl compounds is mainly determined by three following factors:
   i. The **combined steric demand of the substituents** in the proximity of the axis
   ii. The **existence, length, and rigidity of bridges**
   iii. Atropsiomerization **mechanism different from a merely physical rotation** about the axis, e.g. photochemically or chemically induced processes.

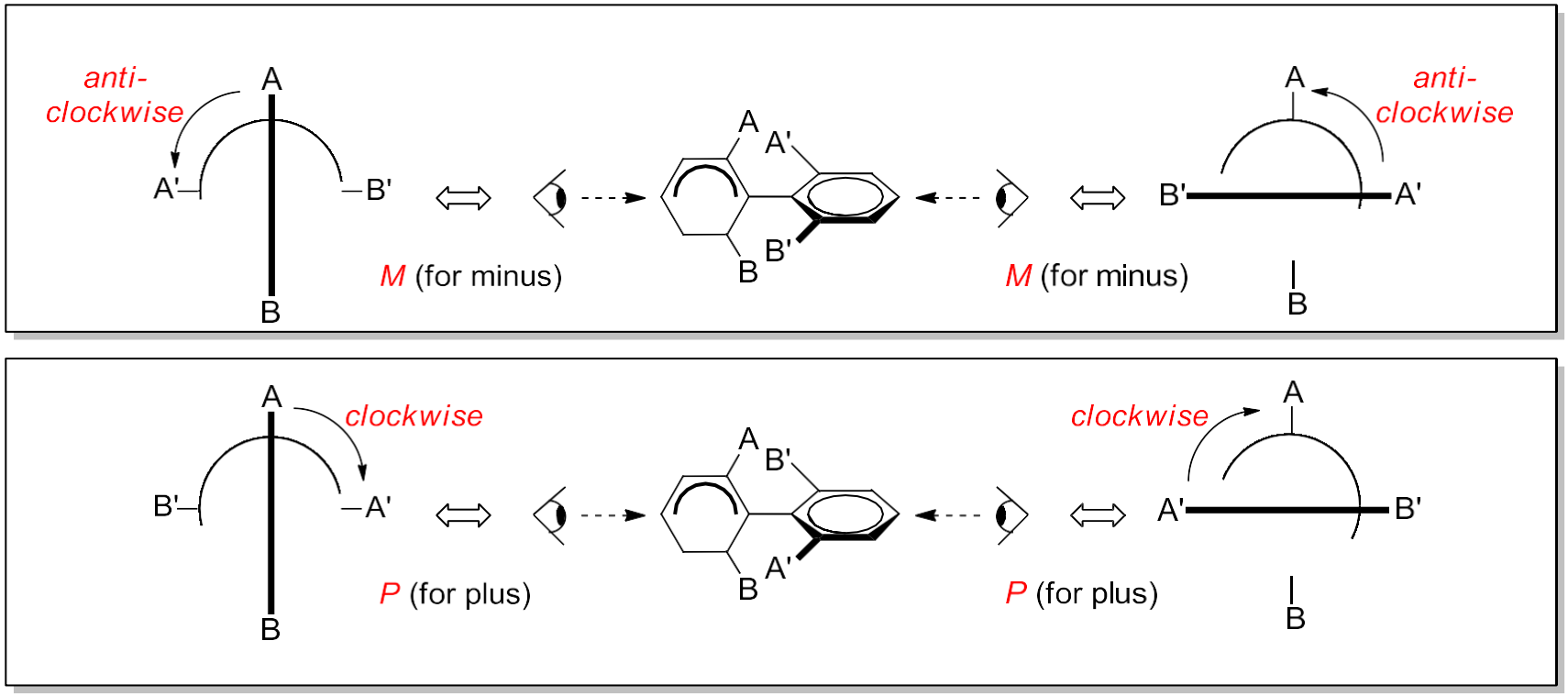
Nomenclature of Atropisomers

1. **Notations used for Atropisomers:**

   a*R* (axially Rectus) or *P* (plus)

   a*S* (axially Sinister) or *M* (minus)

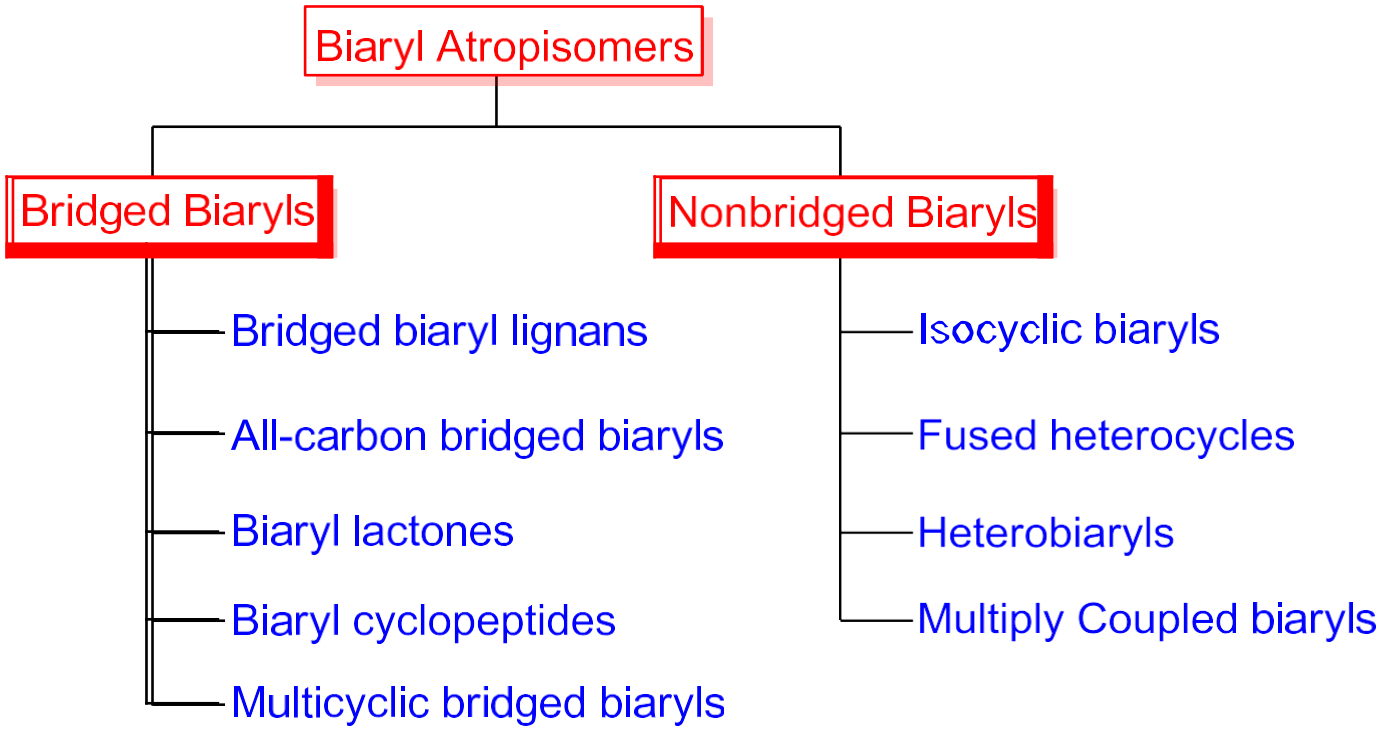
2. **Priority of the substituents are determined by the CIP rule.**
3. **Here it is assumed that priority of A>B and A'>B'.**



*same descriptor results, regardless of the position of the observer

Classification of Atropisomers

The following classification is based upon the basic structure of the "Biaryl Atropisomers".



Conclusion

1. Based on the famous atropisomer antiboiotic ”VANCOMYCIN”, it is explained in a limerick.

It's a chemical stroke of good luck
When a hindered rotation gets
stuck.
If conformers are cool,
Atropisomers rule
When Gram-positive germs run amuck.

2. Atropisomers are abundant in nature and their structural variety is broad ranging from simple biphenyls to highly complex glycopeptides.
3. Quite a number of powerful and reliable methods have been developed for the construction of the chiral biaryl axis.
4. However, atropoenantioselective methods are still rare.
5. With the steadily growing number of natural products with chiral biaryl axis, both further refinement of the existing methods and development of novel strategies are necessary to address their syntheses.

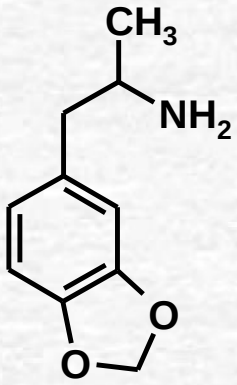
Stereochemistry and Drug Action

- ✓ **Isomers and types of isomers**
  - ➢ **Constitutional Isomers**
    - **Functional Group Isomers**
    - **Positional Isomers**
    - **Geometric Isomers**
  - ➢ **Stereoisomers**
    - **Enantiomers**
    - **Diastereomers**
    - **Meso Compounds**
  - ➢ **Conformational Isomers**
    - **Eclipsed, gauche, staggered, syn-clinal, anti-clinal forms**
    - **Chair, boat, pseudo-chair, skew-boat**

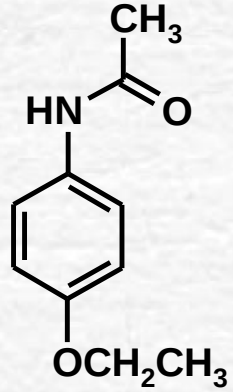
Stereochemistry and Drug Action

- ✓ **Functional Group Isomers**

  Same molecular formula, but different functional groups, e.g., n-propanol and methyl ethyl ether



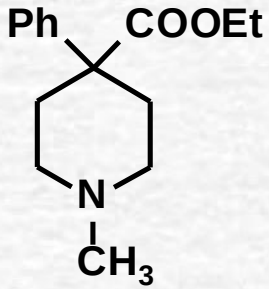
3,4-MDA
(Ecstasy)



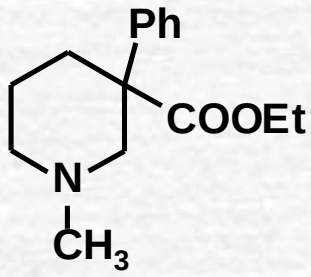
phenacetin
(analgesic)

- ✓ **Positional Isomers**

  Same molecular formula, same functional groups, but different positions of functional groups, e.g., n-propanol and i-propanol



Mepiridine
(Analgesic)

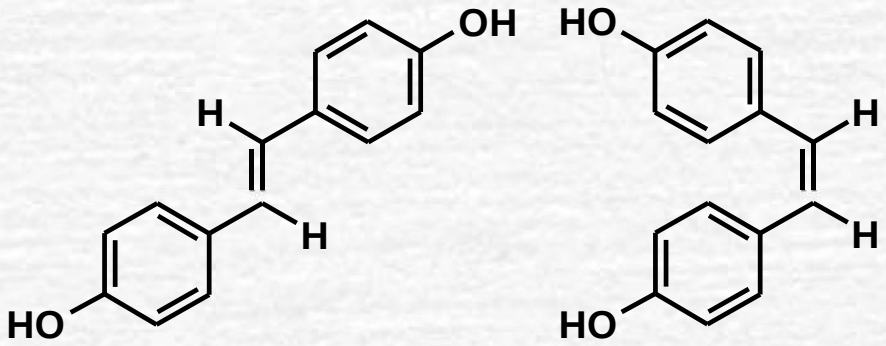


(not analgesic)

- ✓ **Geometric Isomers (cis/trans)**

Same molecular formula, same functional groups, same positions, but different orientation around a double bond or on a ring.

An important criteria to exhibit geometric isomerism is that the isomers cannot be interconverted through mere rotation around a single bond.

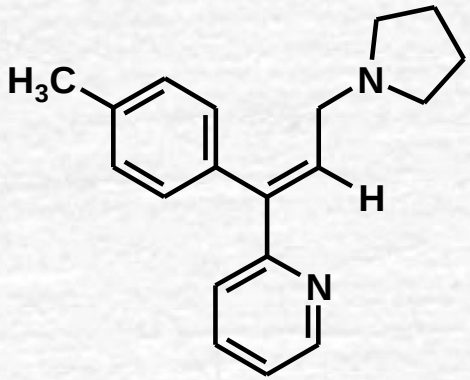


***trans*-DEC**
(Estrogenic)

***cis*-DES**
(non estrogenic)

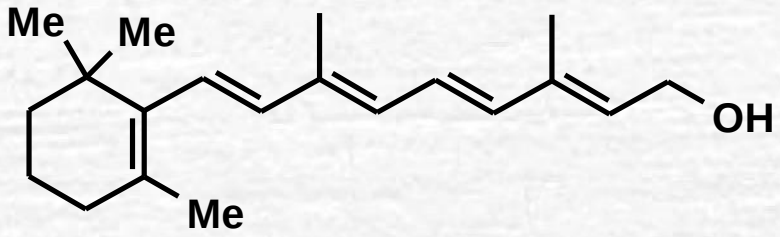
Stereochemistry and Drug Action

- ✓ **Geometric Isomers (cis/trans) … other examples**



Triprolidine (E)

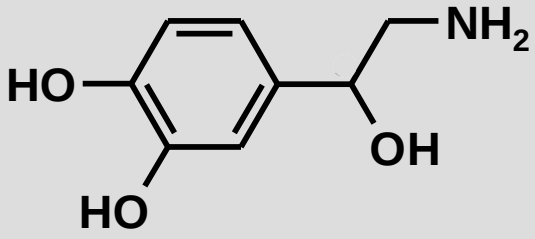
Trans isomer, i.e., E, is 1000-times more histaminic than cis, Z



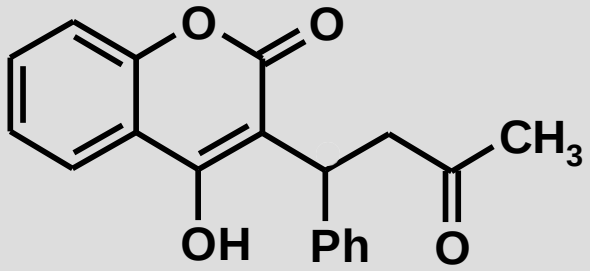
Vitamin A has all E double bonds, any Z would make it inactive!

Stereochemistry and Drug Action

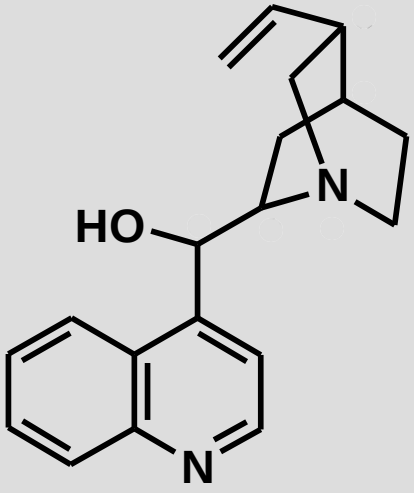
- ✓ **Identify chiral centers (carbon, nitrogen, phosphorus)**



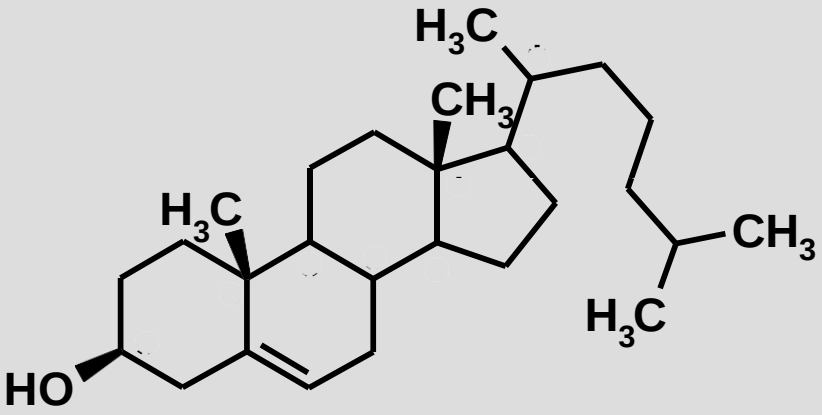
Nor-epinephrine



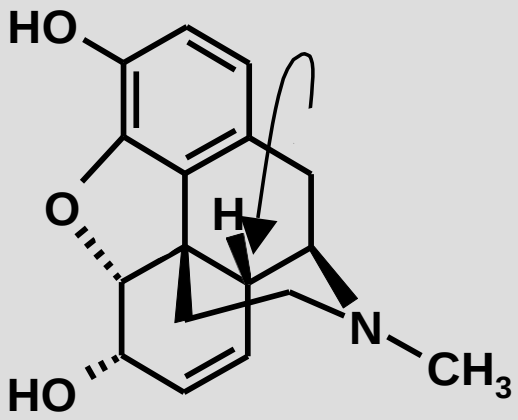
warfarin



quinine



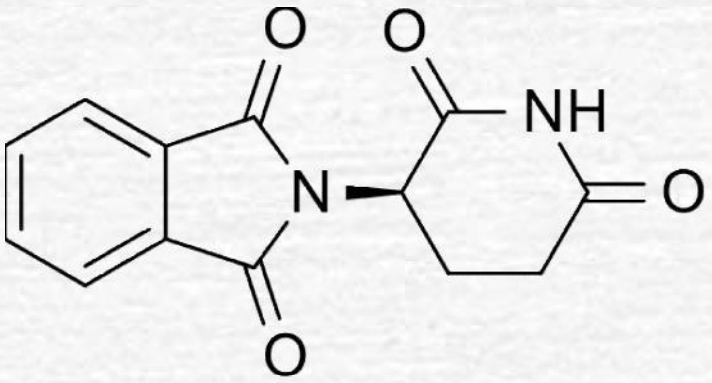
cholesterol



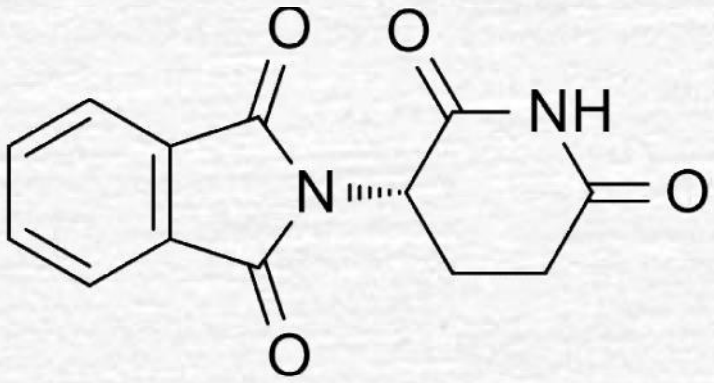
morphine

Stereochemistry and Drug Action

Thalidomide is racemic. One enantiomer is effective against morning sickness, whereas the other is teratogenic.



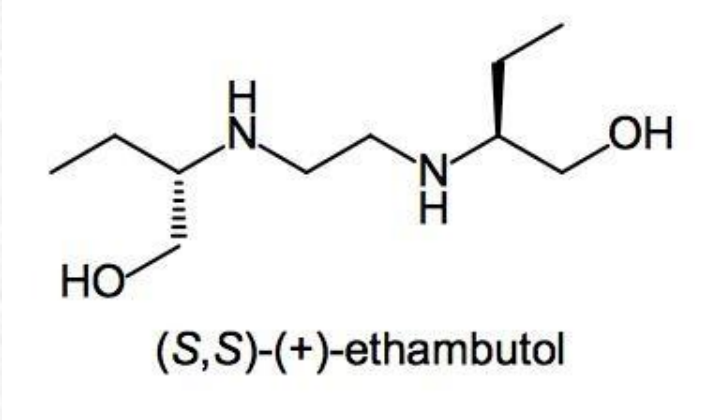
(R)-thalidomide



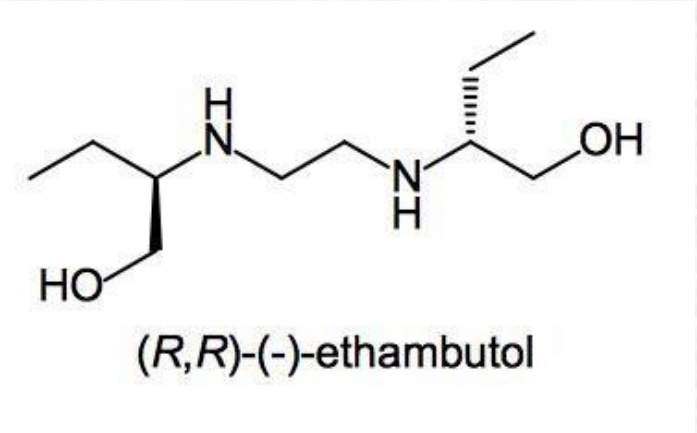
(S)-thalidomide

The *S* enantiomer causes birth defects, while the *R* enantiomer is effective against morning sickness.

Ethambutol: Whereas the (*S*,*S*)-(+)-enantiomer is used to treat tuberculosis, the (*R*,*R*)-(–)-ethambutol causes blindness.



(*S*,*S*)-(+)-ethambutol



(*R*,*R*)-(-)-ethambutol

Naproxen: (*S*)-(+)-naproxen is used to treat arthritis pain, but (*R*)-(–)-naproxen causes liver poisoning with no analgesic effect.

Methorphan: The L-isomer of methorphan, levomethorphan, is a potent opioid analgesic, while the D-isomer, dextromethorphan, is a dissociative cough suppressant.

- ✓ **Why do chiral molecules react differently with biological molecules?**

A majority of biomolecules (amino acids, proteins, sugars, nucleic acids) are chiral. And in nature, they exist in only one of two possible enantiomeric forms. For example, (-) amino acids are predominant in living systems; (+) forms, on the other hand, occur only rarely (e.g., in antibiotic peptides).

In contrast, most monosaccharides exist only in dextrorotatory forms. Also, an amino acid such as threonine has two optical centers and four enantiomers, but of the latter, only one form is commonly found in nature. All these indicate a preference for one form among all forms of a given molecule.

The laevorotatory amino acids always give rise to right-handed helical proteins. Dextrorotatory amino acids, on the other hand, always give the right to left-handed proteins. A mixture of both forms cannot form helices at all.

Similarly, the genetic material deoxyribonucleic acid is always coiled as a right-handed helix.