بسم أللہ الرحمن الرحیم

ISOMERISM

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4th lecture in Medical Chemistry

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ISOMERS

INTRODUCTION

Isomerism

Occurs when certain compounds, having the same molecular formula, exist in different forms each form called **isomer**.

Isomers

Compounds having the same molecular formula but different **linkages** or **spatial arrangements** of atoms

Classification Isomerism

Two main types of isomerism

1.Structural isomerism

Same molecular formula.
Different structural formula.
Different linkages of atoms.

2.Stereoisomerism

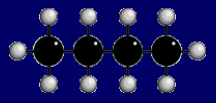
Same molecular formula & structural formula
Different spatial arrangements of atoms

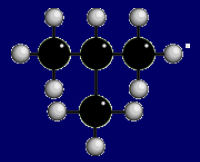
Isomerism

STRUCTURAL ISOMERISM

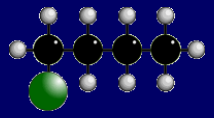
Same molecular formula but different structural formulae

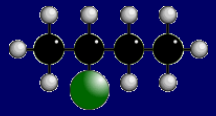
- **CHAIN ISOMERISM**



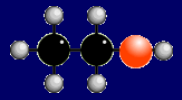


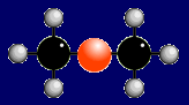
- **POSITION ISOMERISM**





- **FUNCTIONAL GROUP ISOMERISM**



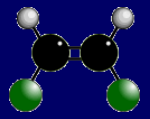


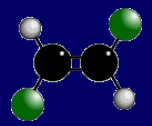
STEREOISOMERISM

Same molecular formula but atoms occupy different positions in space.

- **GEOMETRICAL ISOMERISM**

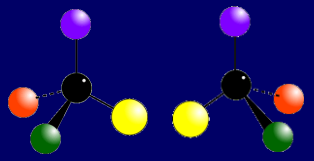
Occurs due to the restricted rotation of C=C double bonds... two forms - CIS and TRANS





- **OPTICAL ISOMERISM**

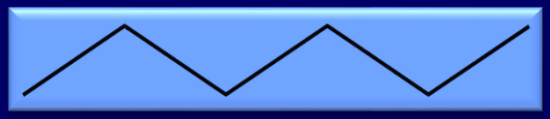
Occurs when molecules have a chiral centre. Get two non-superimposable mirror images.

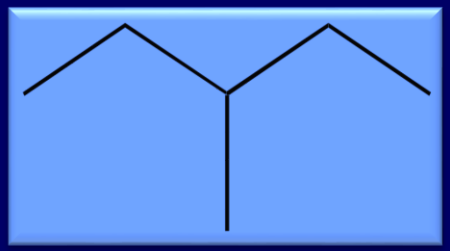


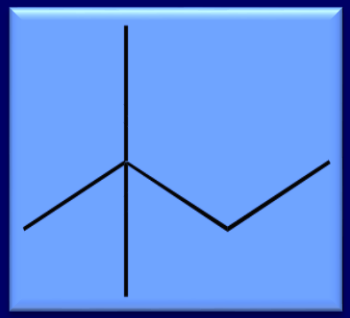
Structural Isomerism

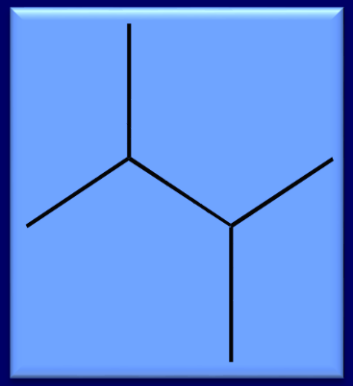
Due to the presence of different carbon skeletons.

1. Chain isomerism C_6H_{14}









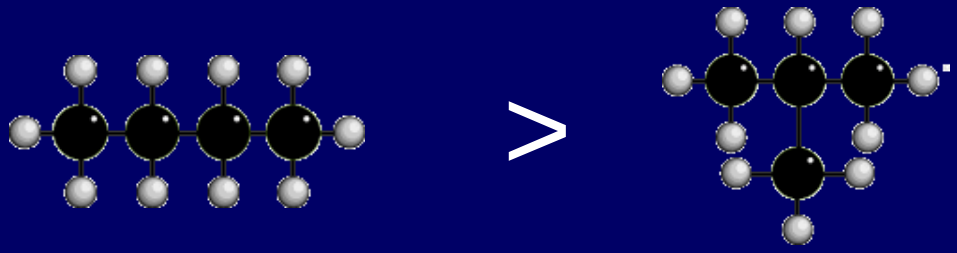
Properties

Different physical properties

e.g : Boiling point

Straight-chain > branched-chain

Because the larger surface area and thus stronger van der Waals force



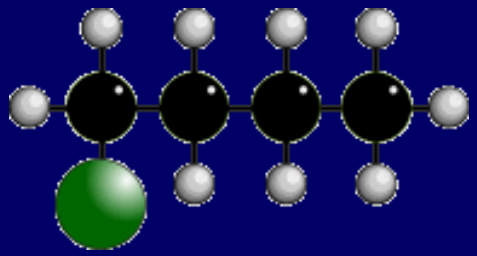
Butane (b.p= -0.5 ˚C) *Methylpropane (b.p= -11 ˚C)*

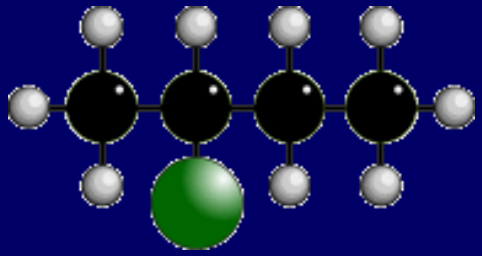
Same Chemical properties

Chain isomers have similar chemical properties because they have the same functional groups.

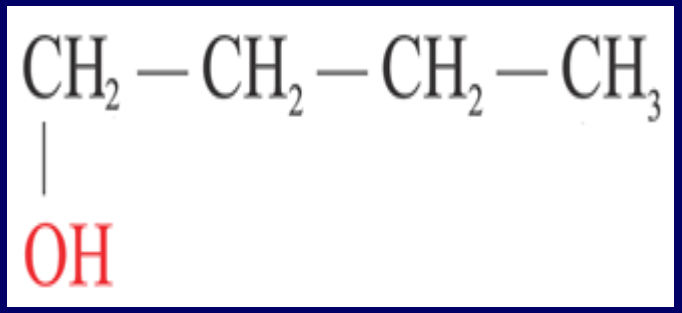
Position isomerism

e.g. Butan-1-ol and butan-2-ol
(molecular formula: $C_4H_{10}O$)

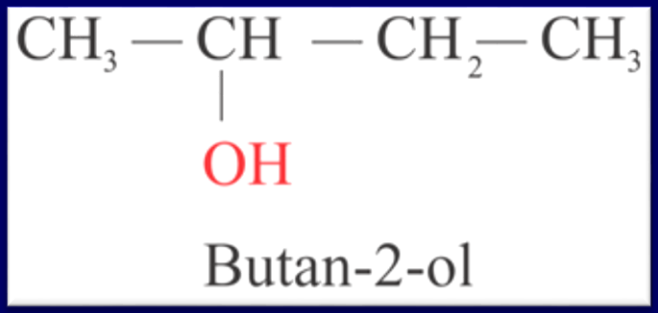




Butan-1-ol



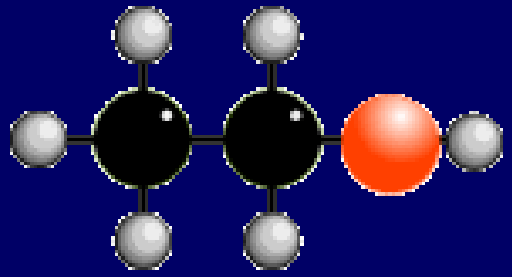
butan-2-ol

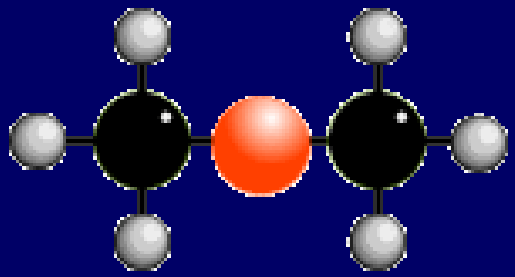


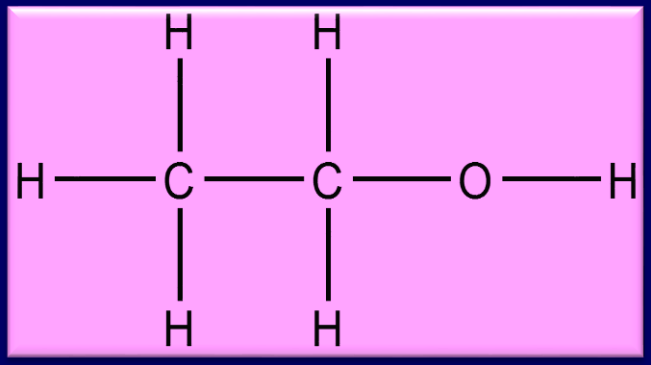
Functional Group Isomerism

Due to the presence of different functional groups

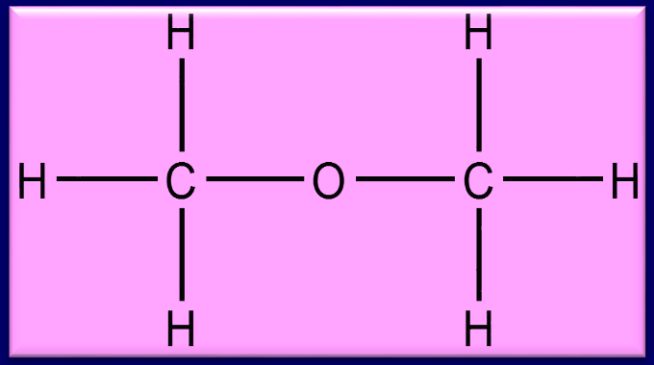
e.g. C_2H_6O





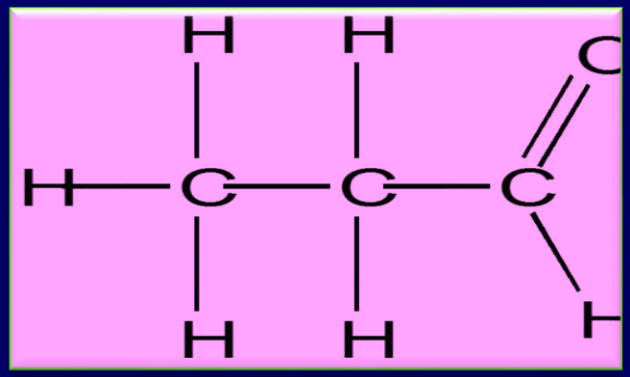


Alcohol

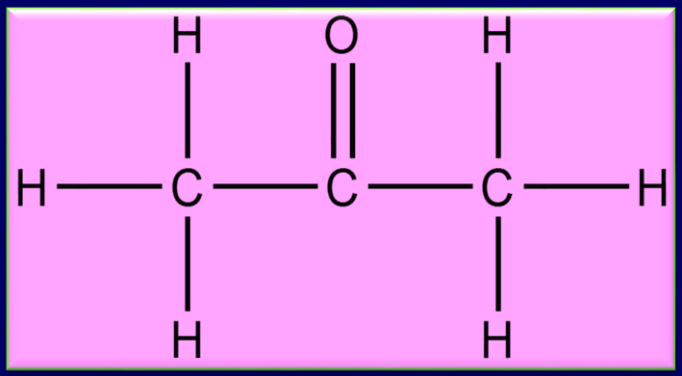


Ether

e.g. C_3H_6O

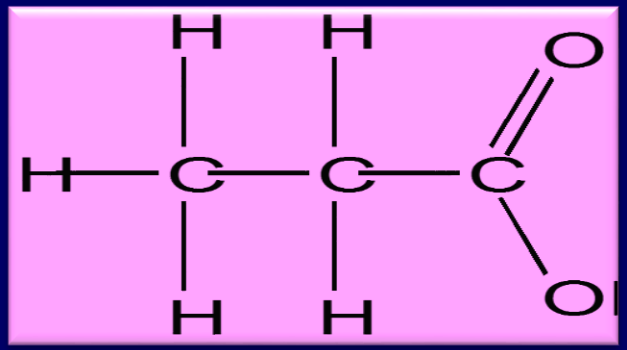


Aldehyde

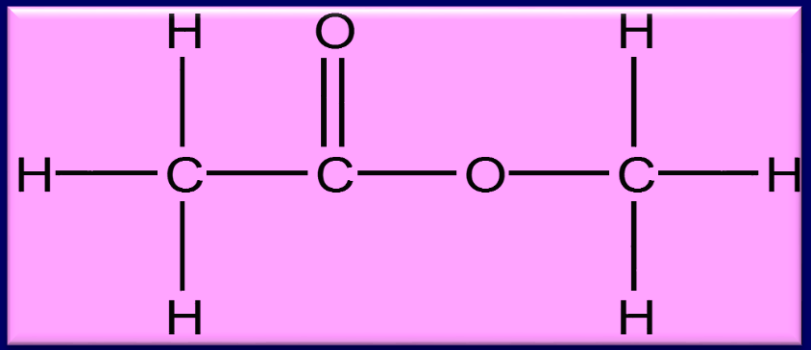


Ketone

e.g. $C_3H_6O_2$



Carboxylic acid



Ester

Metamerism

Occurs when the functional group (-oxy or –carbonyl) **interrupts** the main carbon skeleton at different positions.

e.g. Methoxypropane and ethoxyethane
(molecular formula: $C_4H_{10}O$)

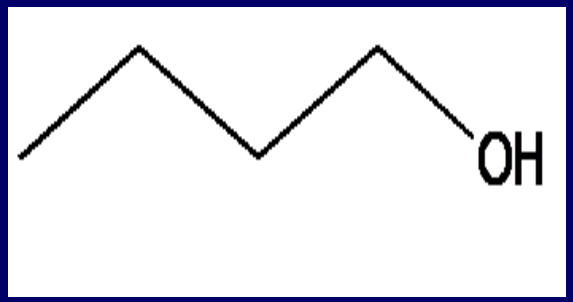
CH_3-O-CH_2-CH_2-CH_3 Methoxypropane

CH_3-CH_2-O-CH_2-CH_3 Ethoxyethane

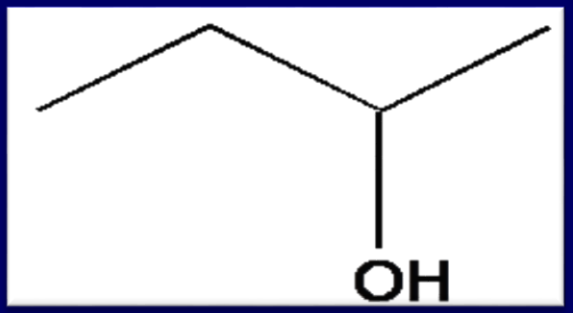
Position Isomers

e.g. Pentan-2-one and pentan-3-one
(molecular formula: $C_5H_{10}O$)

Write the chemical structure?

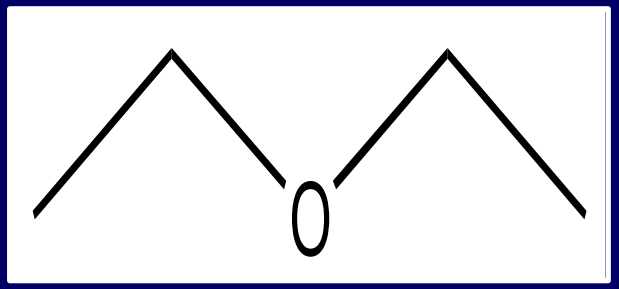


Position isomers

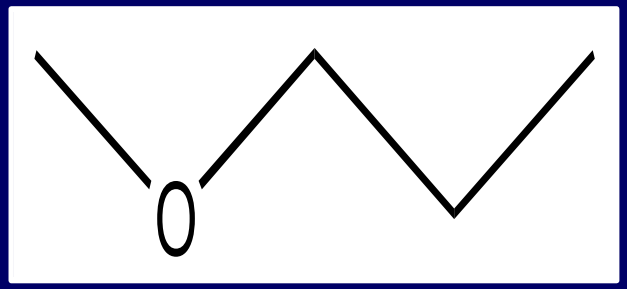


functional group isomers

$C_4H_{10}O$

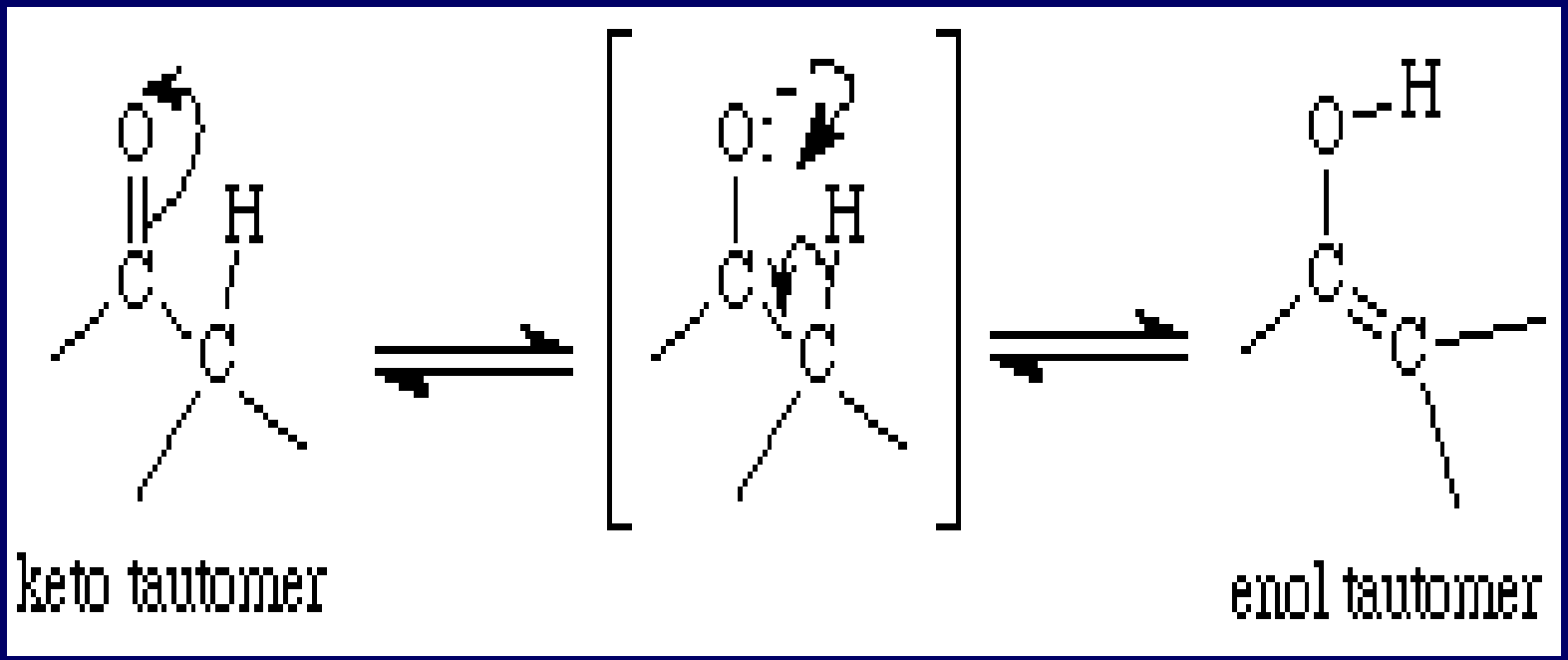


Metamers



Tautomerism

Occurs when **functional group isomers** are **in dynamic equilibrium** with each other.



ethanal ethanol

Stereoisomerism

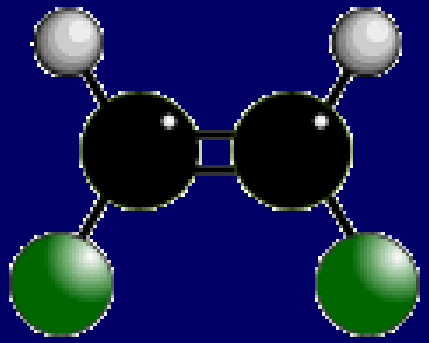
Stereoisomerism occurs when compounds having the same structural formula show different spatial arrangements of atoms in the space .

Two categories of stereoisomerism:

1. Geometrical isomerism
2. Optical isomerism

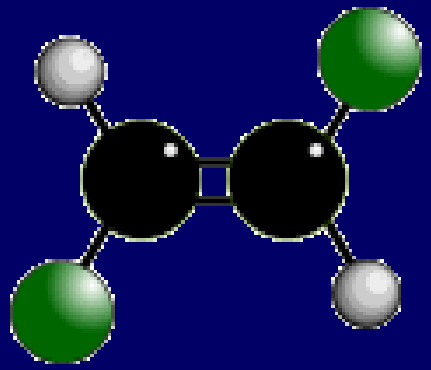
GEOMETRICAL ISOMERISM

- An example of geometrical isomerism found in some, but not all, alkenes.
- Occurs due to the restricted rotation of C=C bonds
- Get two forms....



CIS

Groups/atoms are on the SAME SIDE of the double bond



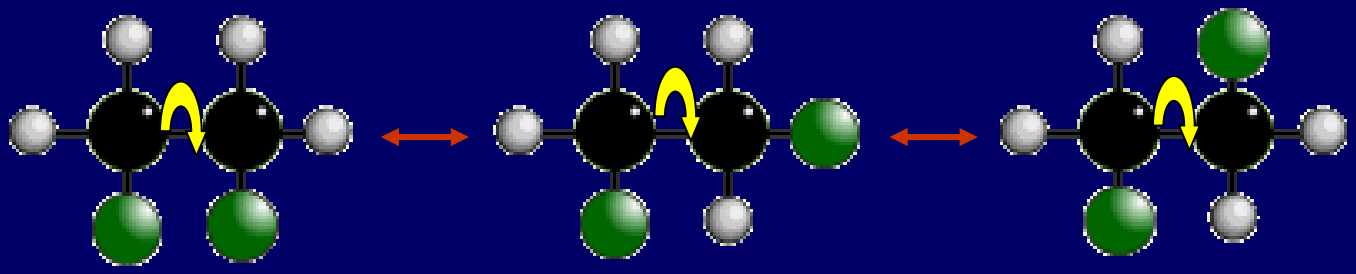
TRANS

Groups/atoms are on OPPOSITE SIDES across the double bond

GEOMETRICAL ISOMERISM

FREE ROTATION OF C-C BONDS

Single covalent bonds can easily rotate.

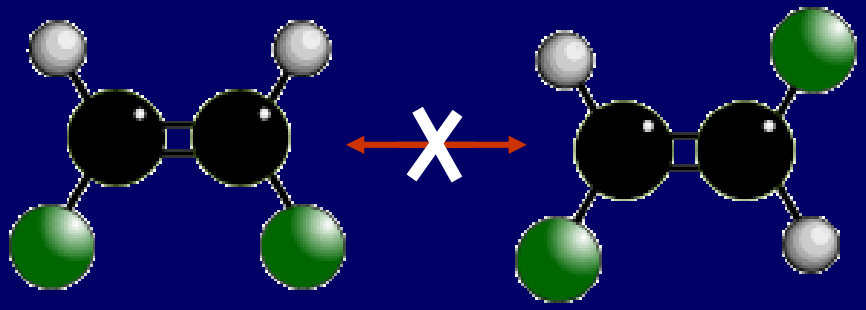


All these structures are the same because C-C bonds have free rotation

GEOMETRICAL ISOMERISM

RESTRICTED ROTATION OF C=C BONDS

C=C bonds have restricted rotation so the groups on either end of the bond are 'frozen' in one position; it isn't easy to flip between the two.

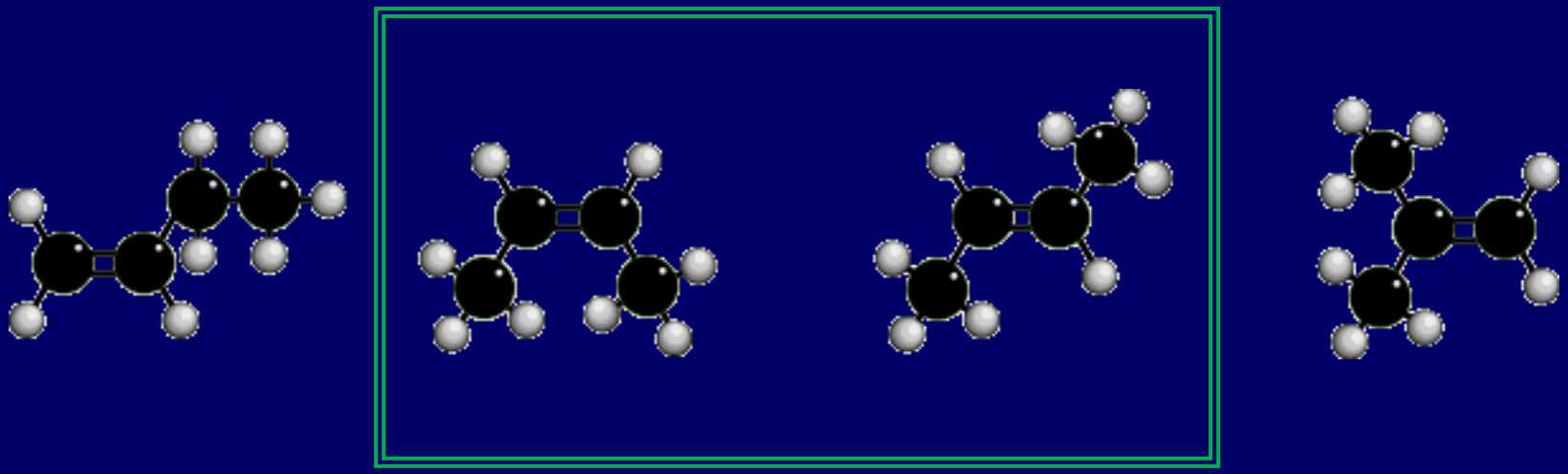


This produces two possibilities.. The two structures cannot interchange easily so the atoms in the two molecules occupy different positions in space.

GEOMETRICAL ISOMERISM

Isomerism in butene

There are 3 structural isomers of C_4H_8 that are alkenes*. Of these ONLY ONE exhibits geometrical isomerism



BUT-1-ENE ***cis*** **BUT-2-ENE** ***trans*** **BUT-2-ENE** **2-METHYLPROPENE**

Stereoisomers

Isomers with same connectivity but differ in the arrangement of atoms in space

stereoisomers subdivided into:

1. *Enantiomers* non superposable mirror images
2. *Diasteromers* non mirror images

Geometric isomers cis/trans-isomers are diastereomers

Enantiomers (Optical Isomers)

- Enantiomers occur when compounds have non-superimposable mirror images

- The two different forms are known as optical isomers or , Chiral molecules enantiomer

- They occur when molecules have a chiral centre

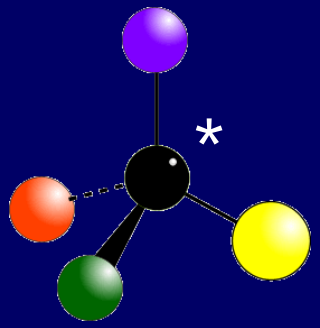
A chiral centre contains an asymmetric carbon atom

An asymmetric carbon has four different atoms (or groups) arranged tetrahedrally around it.

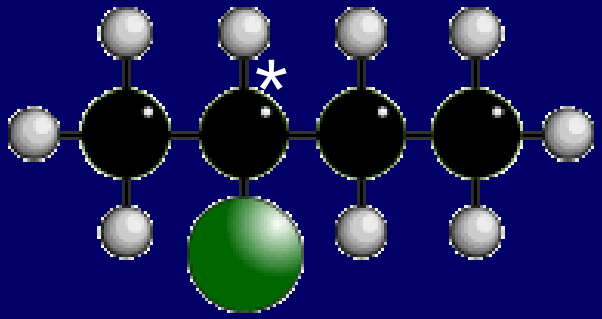
A chiral ≠ Achiral
Asymmetric ≠ symmetric

Achiral (not chiral) if object and its mirror image are identical (symmetry element)

Optical activity arises from asymmetry or chirality
Any molecule with an sp^3 carbon atom bonded to FOUR different groups arranged tetrahedrally show optical activity



There are four different colours arranged tetrahedrally about the carbon atom

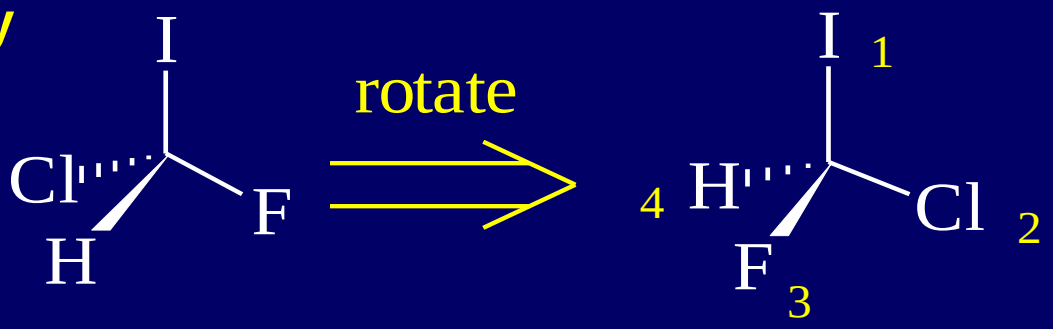


2-chlorobutane exhibits optical isomerism because the second carbon atom has four different atoms/groups attached

In compounds with *n* chiral centers, the maximum number of stereoisomers is 2^n.

(R) And (S) Nomenclature

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

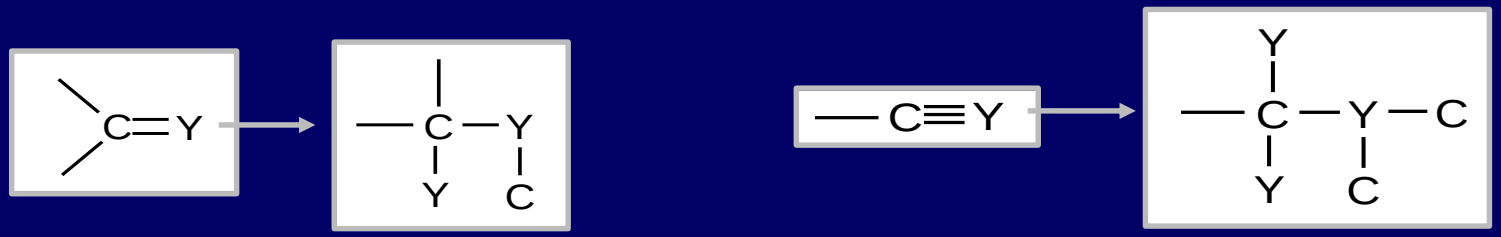


focus down C-4 bond

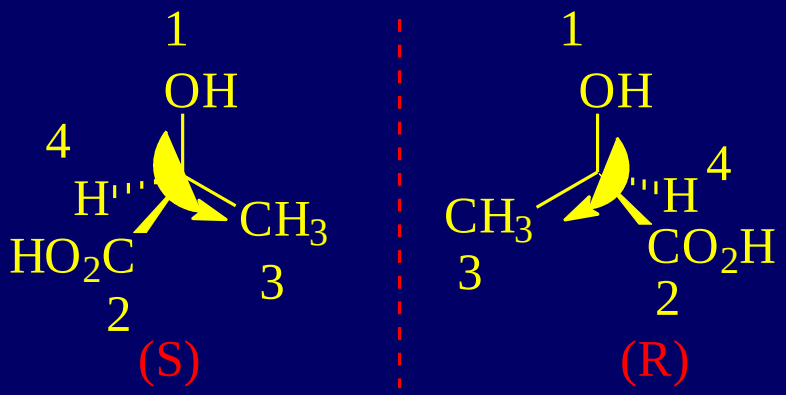
Atoms with higher atomic numbers have higher priority

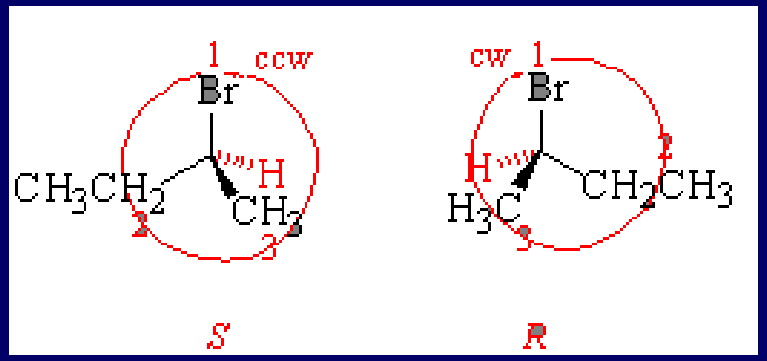
I > Br > Cl > S > F > O > N > ^{13}C > ^{12}C > ^{3}H > ^{2}H > ^{1}H

$CH(CH_3)_2$ > CH_2CH_2Br > CH_3CH_2



Draw an arrow from the 1st priority group to the 2nd group to the 3rd group.
Clockwise arrow (R) configuration
Counterclockwise arrow (S) configuration
Once the relative priorities of the four substituents have been determined, the chiral center must be viewed from the side opposite the lowest priority group



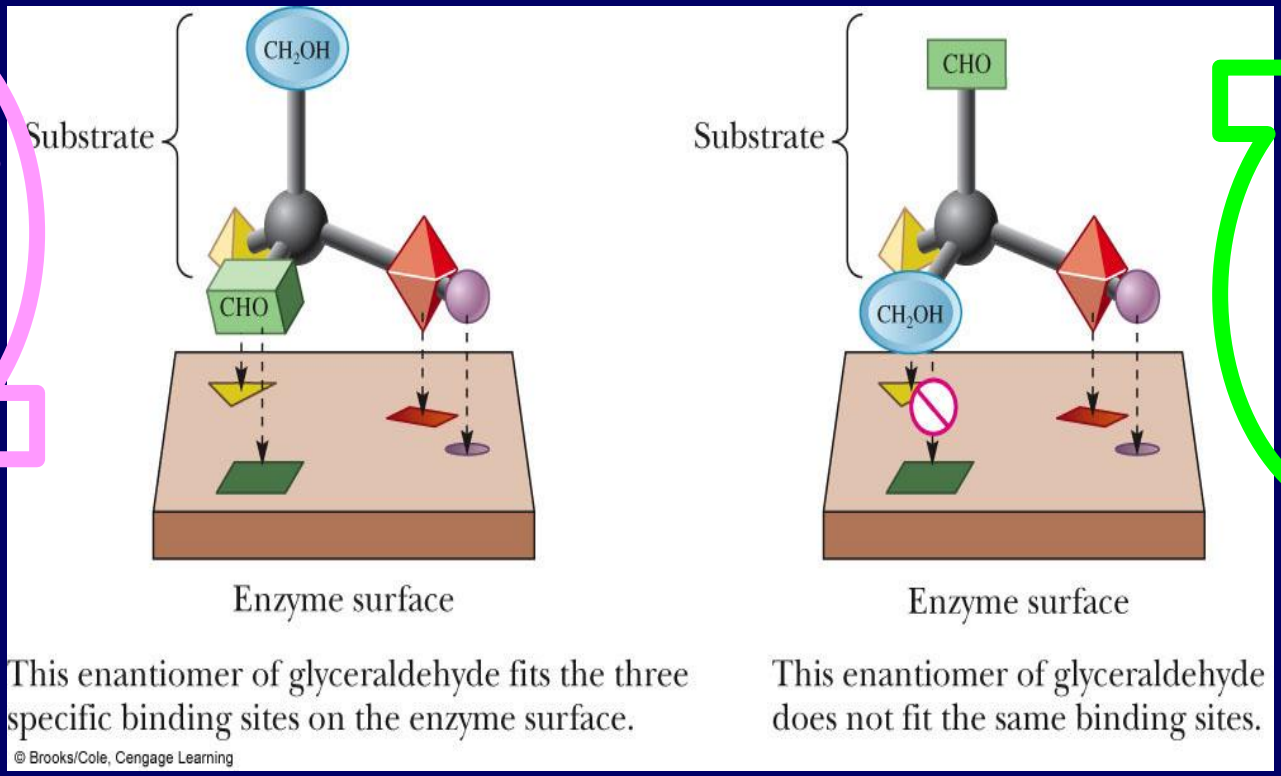


Chirality in the Biological World

1. An enzyme distinguishes between a molecule and its enantiomer

A schematic diagram of an enzyme surface capable of binding with (*R*)-glyceraldehyde but not with (*S*)-glyceraldehyde.

All three substituents match up with sites on the enzyme.

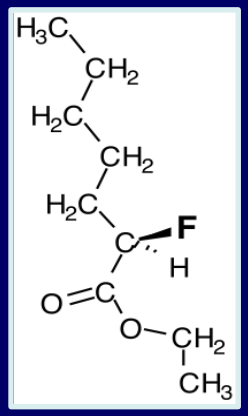


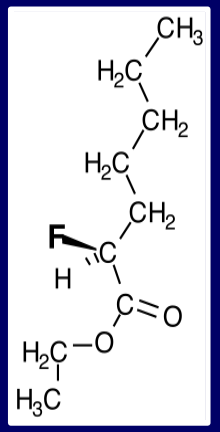
This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface.

This enantiomer of glyceraldehyde does not fit the same binding sites.

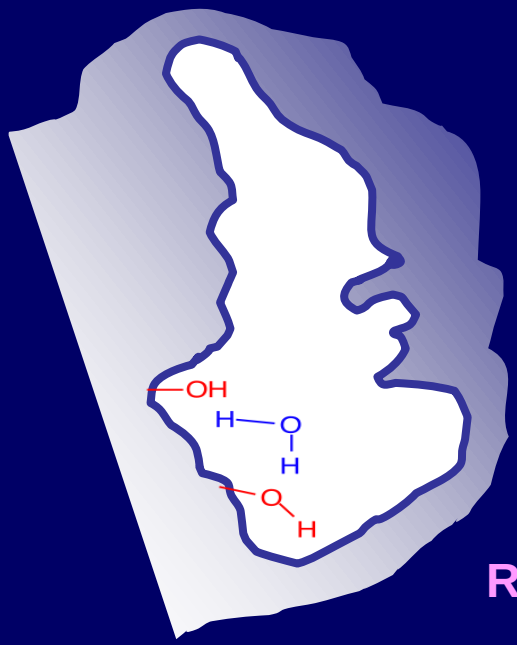
If two are matched up then the third will fail

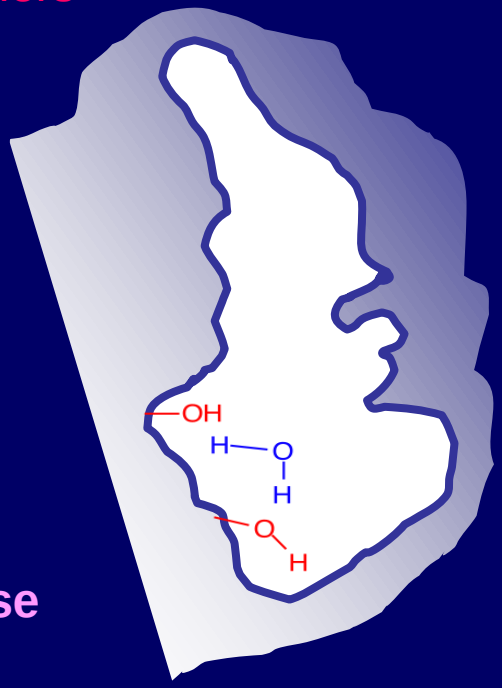
mirror





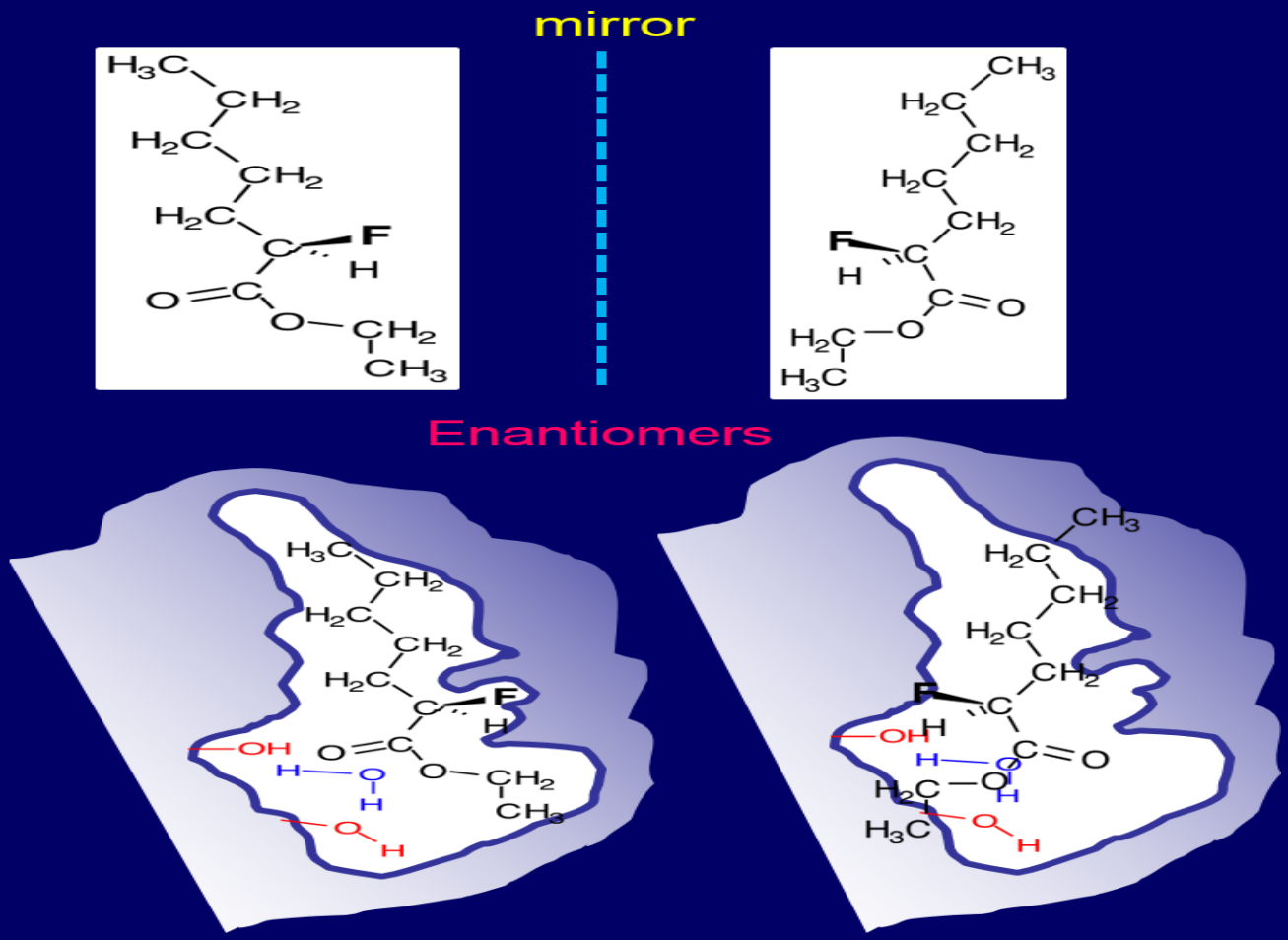
Enantiomers

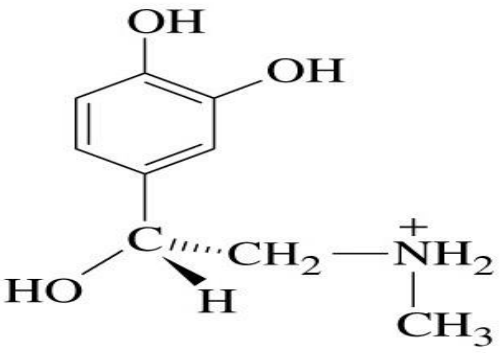




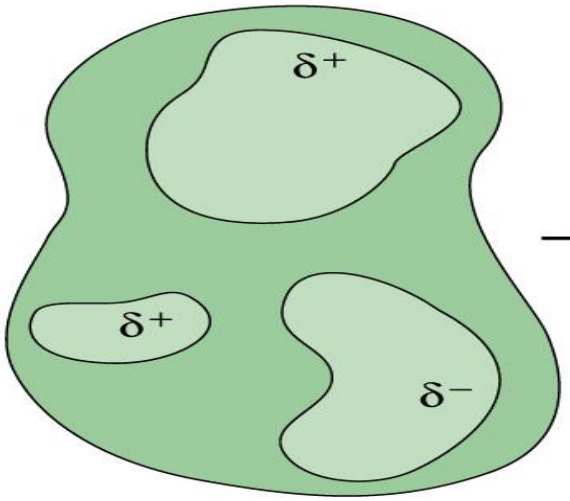
R-lipase

Enzymes are like hands in a handshake the substrate fits into a binding site on the enzyme surface

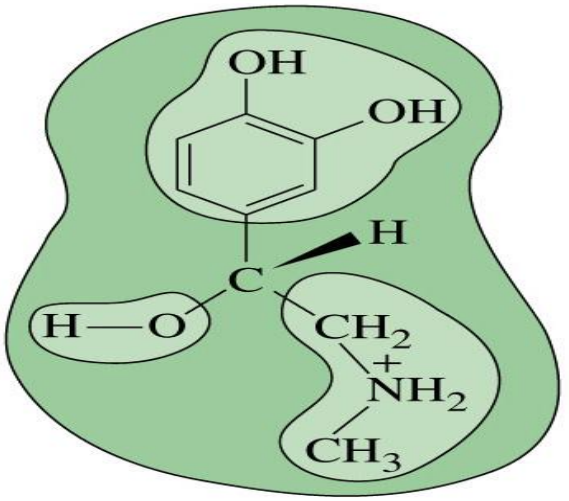




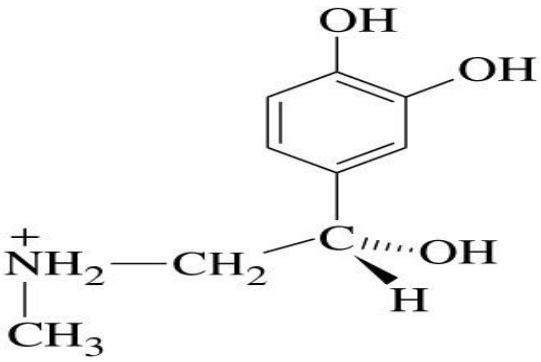
(*R*)-(−)-epinephrine
natural epinephrine



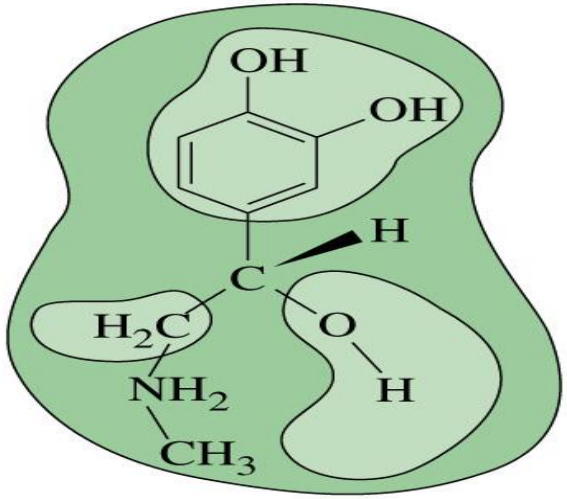
enzyme active site



enzyme–substrate complex



(*S*)-(+)-epinephrine
unnatural epinephrine

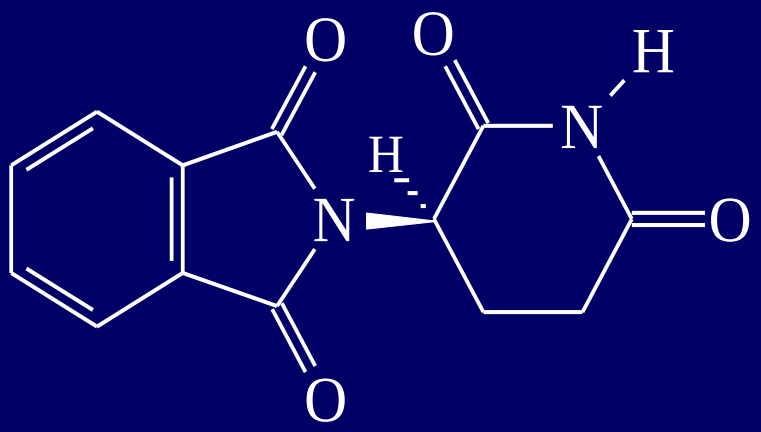


does not fit the enzyme's active site

2. The properties of many drugs depends on their stereochemistry

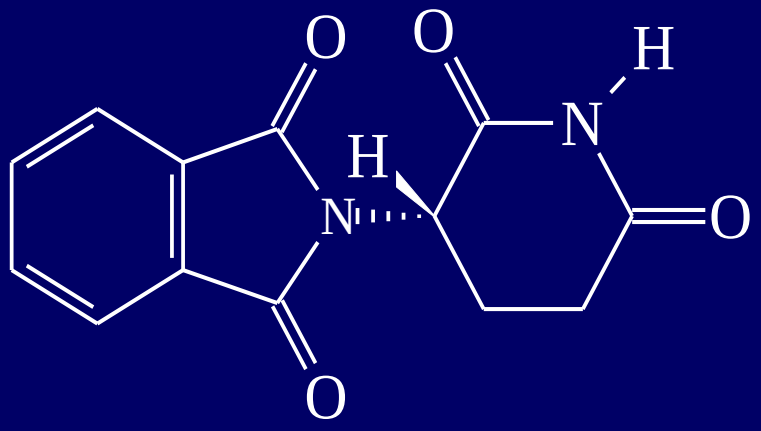
e.g.Thalidomide one mirror image causes birth defects the other cures morning sickness

(R)(+) Thalidomide



a sedative and hypnotic

(S)(-) Thalidomide

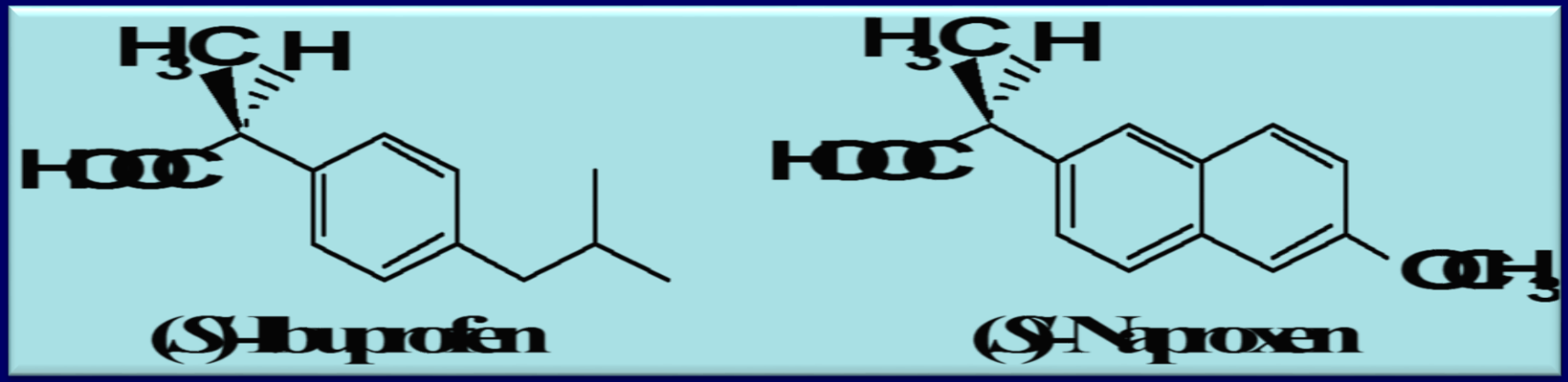


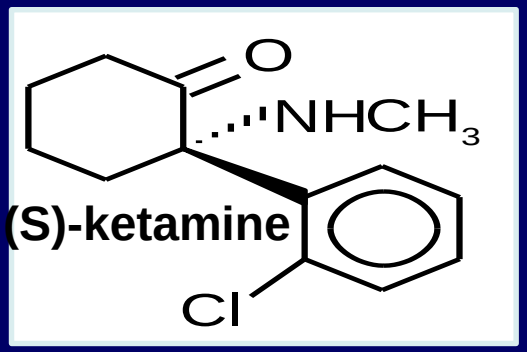
a teratogen

Enantiomers elicit different physiological responses

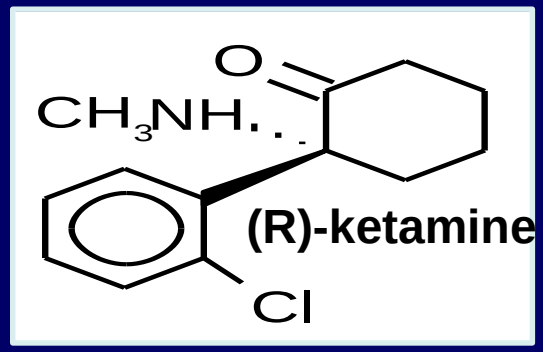
(*S*)-ibuprofen is active as a pain and fever reliever, while its R enantiomer is inactive

S enantiomer of naproxen active as pain reliever, but R enantiomer is a liver toxin!

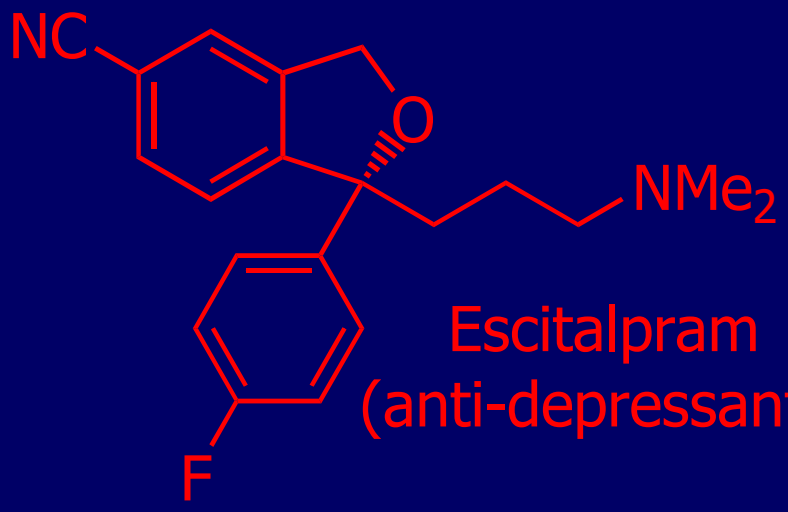




anesthetic



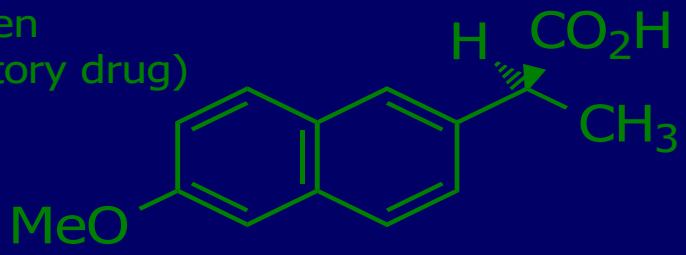
hallucinogen

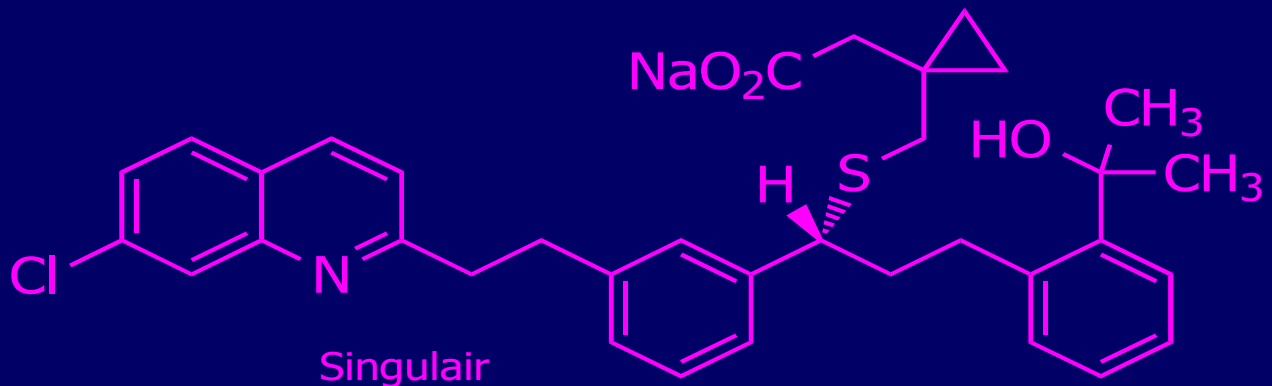


Escitalpram
(anti-depressant)

L-DOPA
(treatment for Parkinson's)

Naproxen
(anti-inflammatory drug)





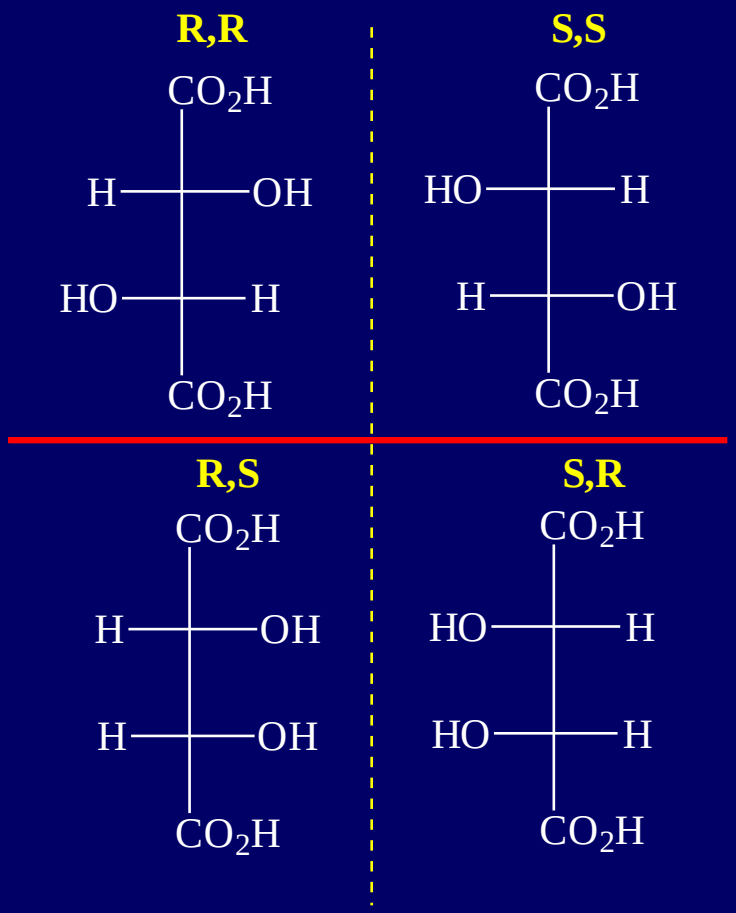
Singulair
(asthma and allergy treatment)

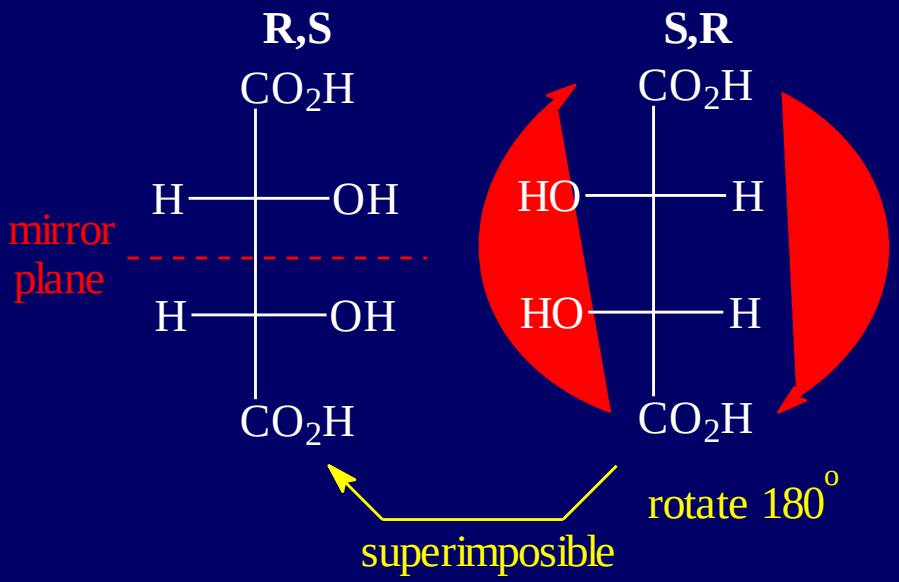
Miso Compounds

Compounds with 2 stereocenters do not always have 4 stereoisomers ($2^2 = 4$)

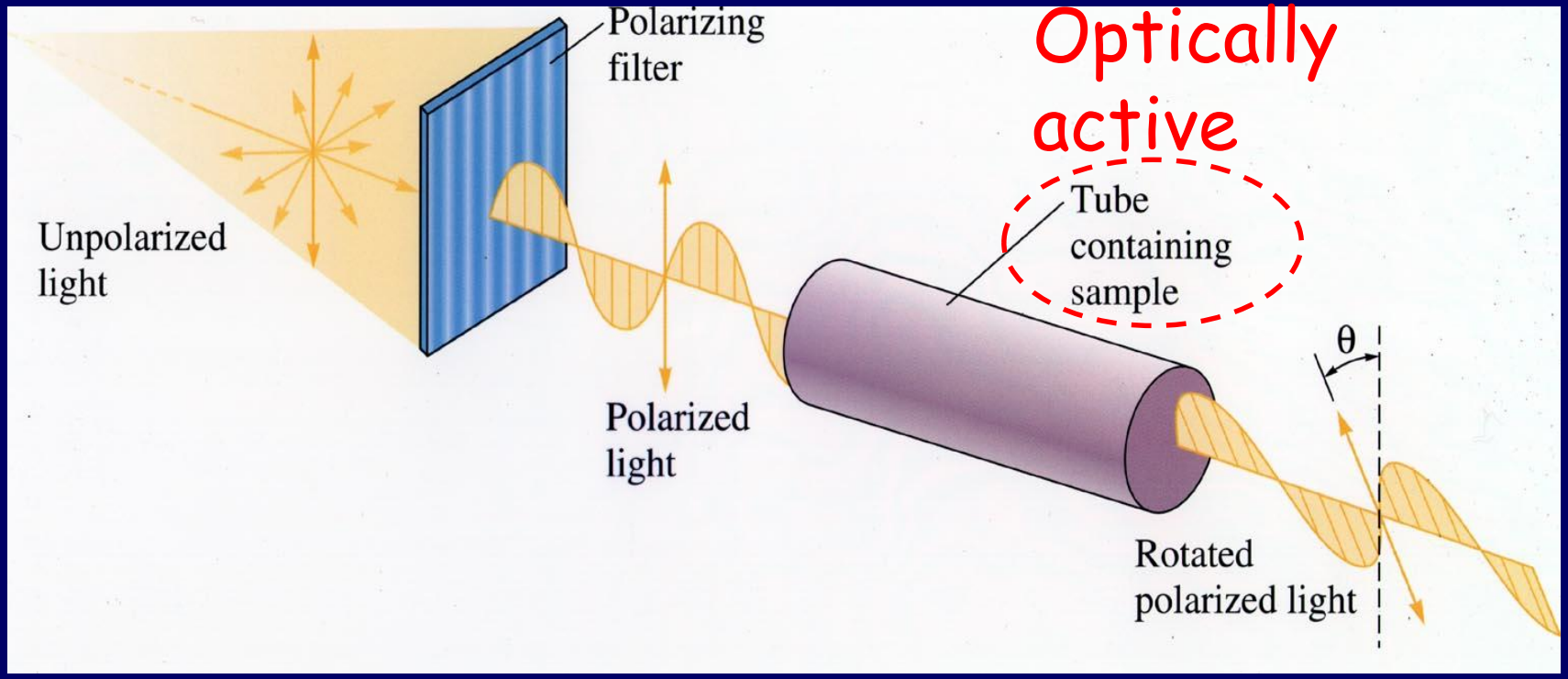
Some stereoisomers are achiral, even though they contain stereocenters

Example: tartaric acid has two stereocenters, but only has 3 stereoisomers





Optically active substance can rotate the plane of polarization of plane-polarized light
Measured by a **polarimeter**.
Dextrorotatory(+) : clockwise (to the right)
Laevorotatory(-): anti-clockwise (to the left



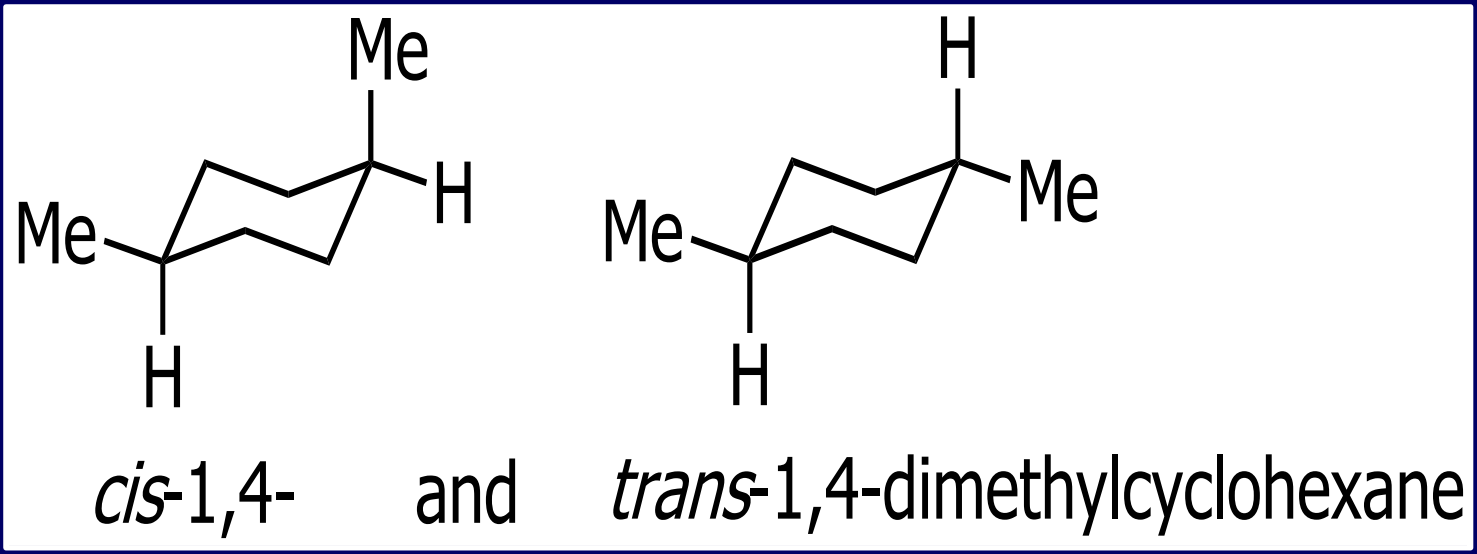
Properties of enantiomers

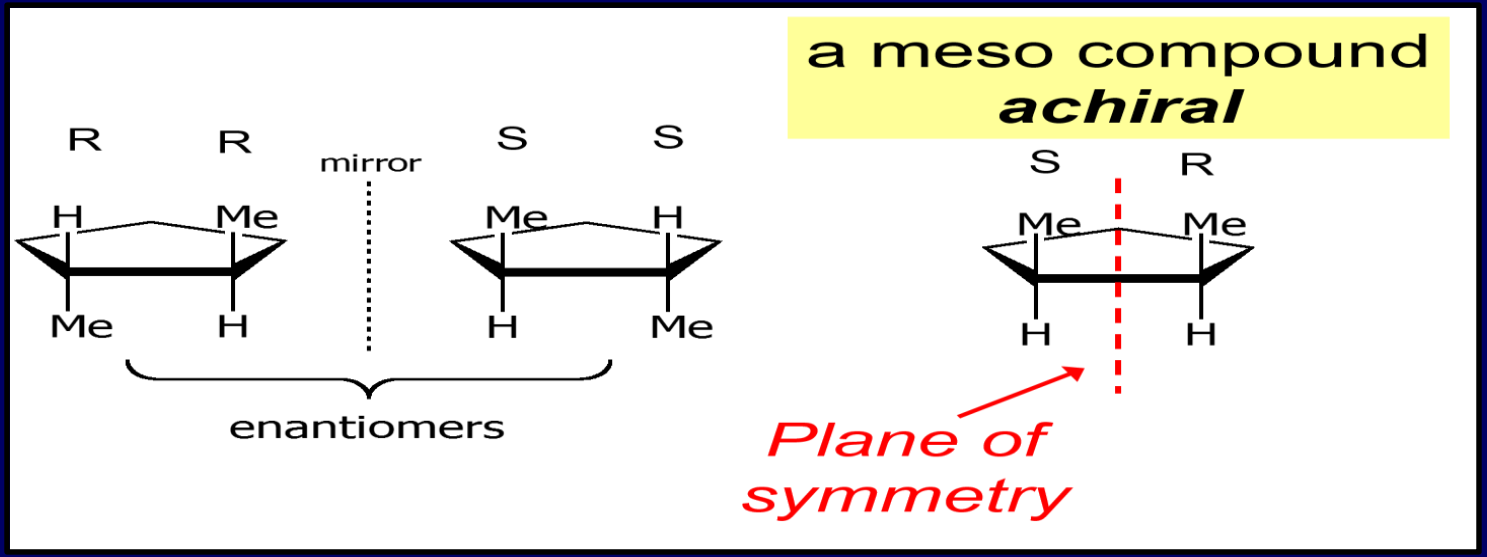
- Identical physical properties except their optical activities.
- Identical chemical properties except their reactions with optically active substances.

Racemic mixture (racemate)

- The racemic mixture (racemate) is a 50:50 mixture of the two enantiomers.
- The specific rotation is zero.
- The racemic mixture may have different physical properties (m.p., b.p., etc.) than the enantiomers.

Stereoisomerism of Cyclic system

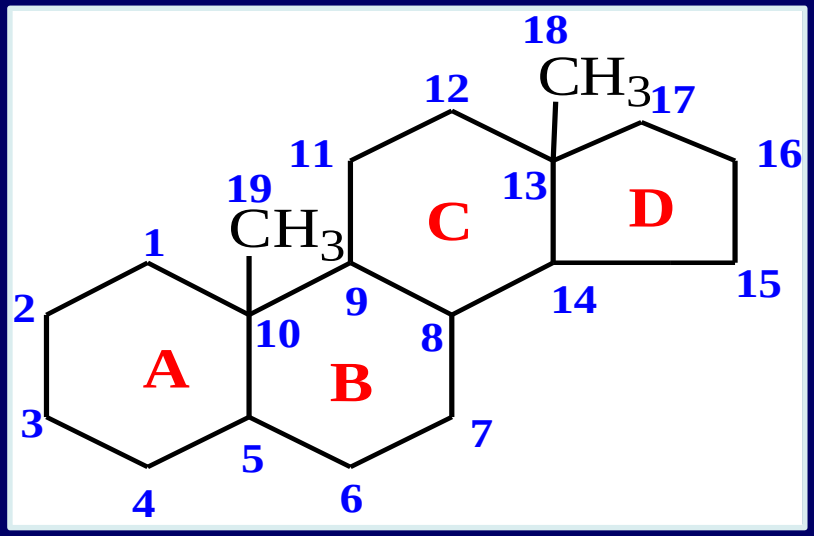




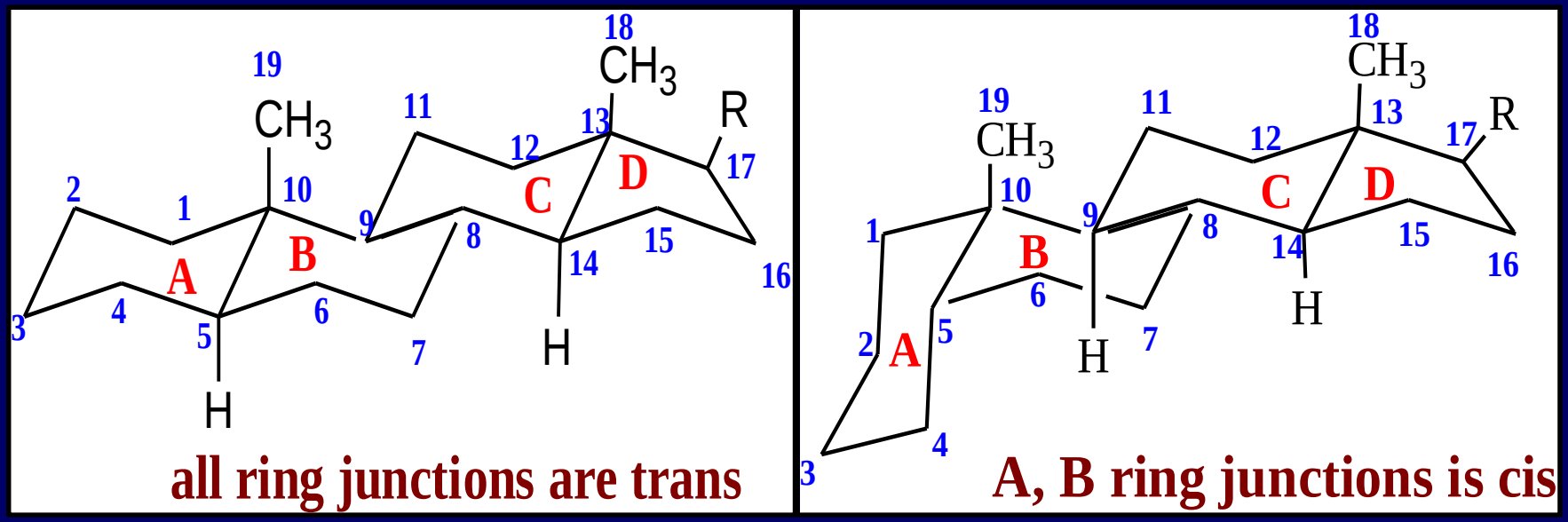
STEROIDS

Steroids are important “biological regulators” that nearly always show dramatic physiological effects when they are administered to living organisms.

Steroids are derivatives of the following ring system

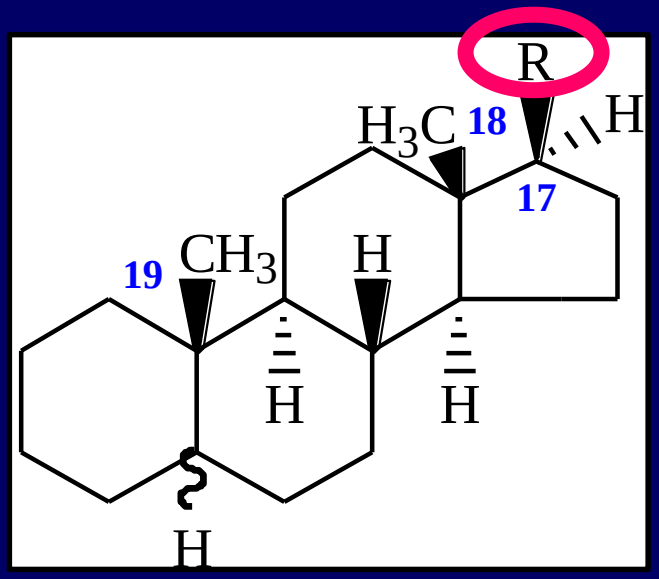


In most steroids the B, C and C, D ring junctions are trans. The A, B ring junction may be either cis or trans.



When α and β designation are applied to the hydrogen atom at position 5,the ring system in which the A, B ring junction is trans become the 5 α series; and the ring system in which the A, B ring junction is cis becomes the 5 β series.

In systematic nomenclature of the R group at position 17 determines the base name of an individual steroid.

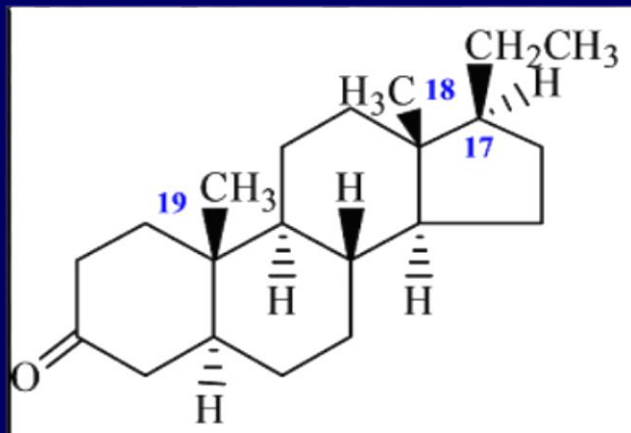


For example:

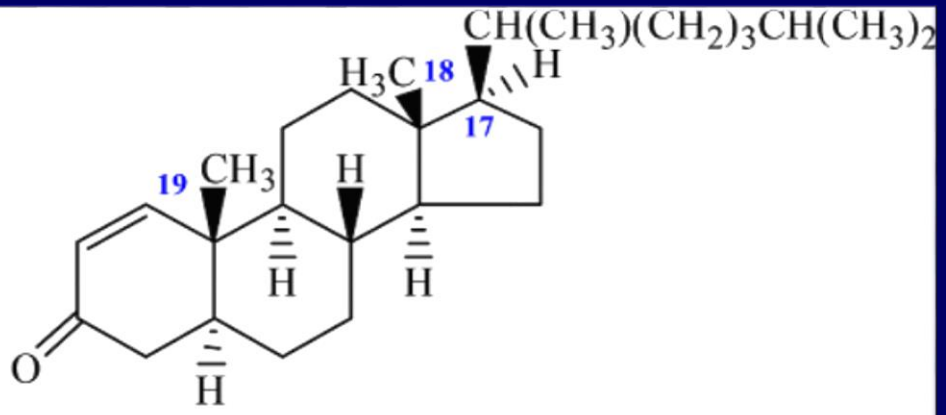
-H → **Androstane**

-CH_2CH_3 (20, 21) → **Pregnane**

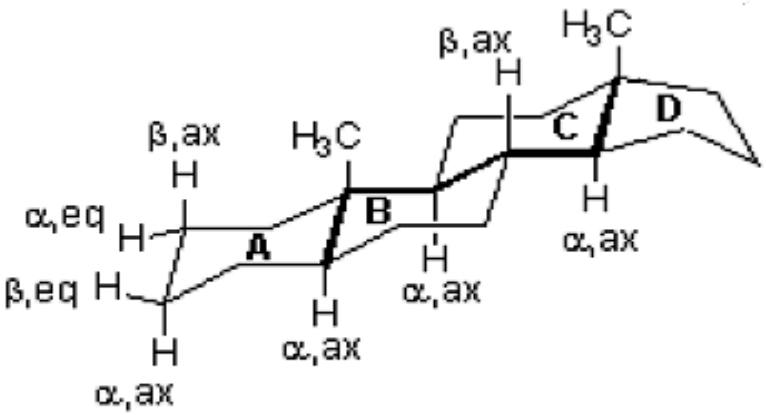
-$CH(CH_3)CH_2CH_2CH_3$ (20, 21, 22, 23, 24) → **Cholane**



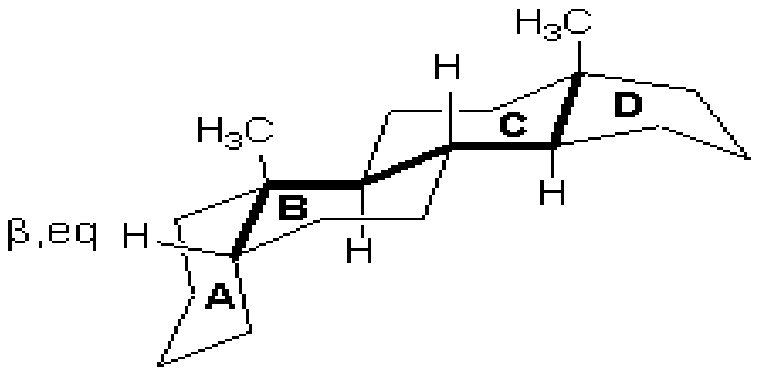
5α-Pregnan-3-one



5α-Cholest-1-en-3-one



5α-Androstane



5β-Androstane


Thank you for your attention