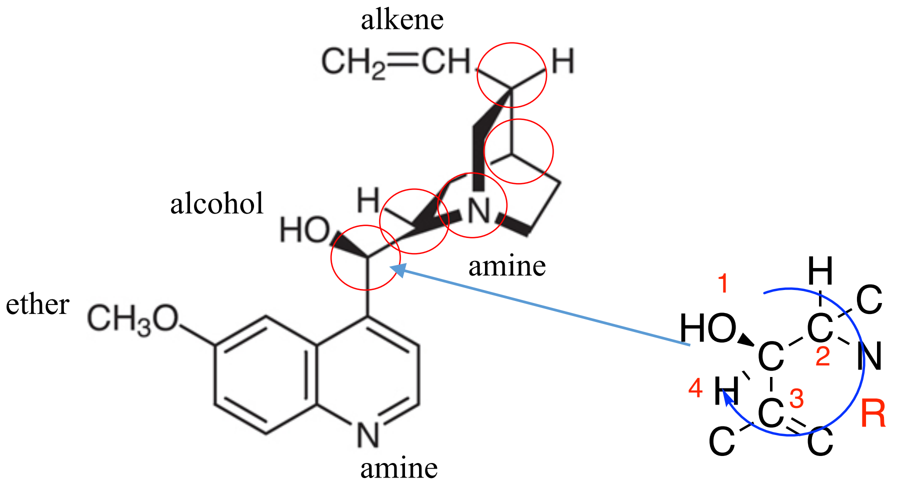
Quinine:

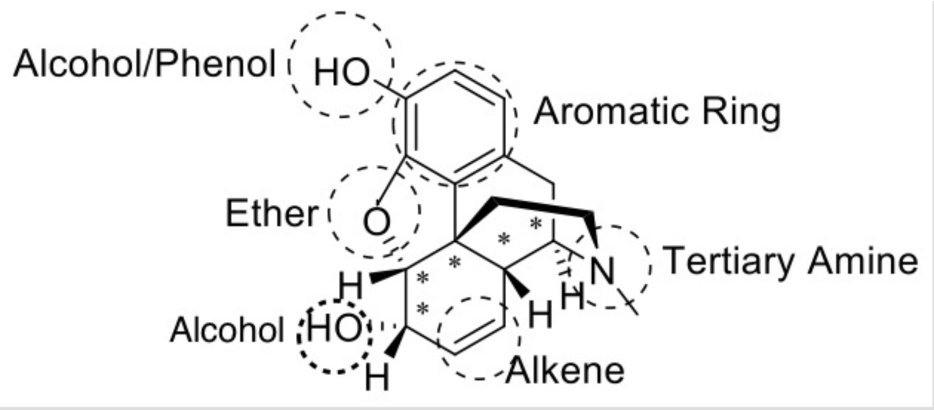
- An anti-malarial agent found in cinchona trees in South America
- Was brought to Spain by Jesuit missionaries in 1632 but was used by native populations long before
- Has 5 chiral centers (labeled in red)
- Here nitrogen is all tied back and **is** a stereogenic center, but typically it is not
- $2^5 = 32$ stereoisomers
    - 1 is quinine (itself)
    - 1 is the enantiomer
    - 30 are diastereomers



C attached to N will gain the 2nd priority because N has higher atomic number

Morphine:

- Is an alkaloid, meaning it contains nitrogen, can be isolated from a plant (or bacteria) and is considered a natural product.
- From Morpheus, Greek god of sleep
- Opium: Sap from the seed pod of opium poppy (*Papaver somniferum*)
    - (poppy sleep-carrying)
- ~10% of opium is morphine
- Morphine is used as an analgesic
- Heroin (diacetylmorphine) is even more potent (and more addictive)



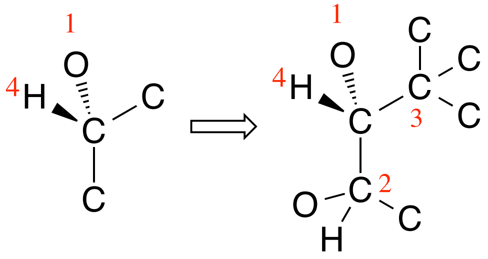
- 5 stereogenic centers in morphine (represented by *) – Nitrogen NOT a stereogenic centre because the methyl group can move up or down
    - 2^5 = 32 stereoisomers possible, where:
    - 1 morphine (itself)
    - 1 enantiomer
    - 30 diastereoisomers

Mithridates VI (135-63 BC)

- Poisoned slaves and attempted to cure them using mixtures of different plants
- Favorite mixture was Theriac, which contained morphine

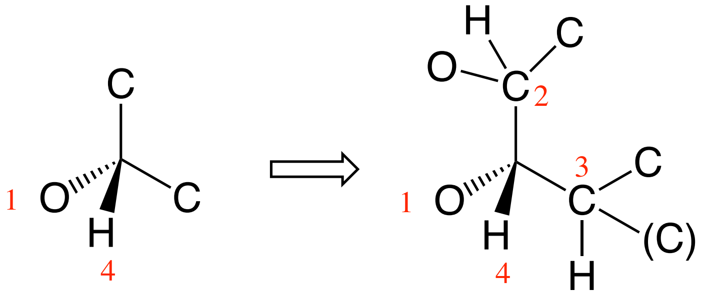
Examples of Configuration in Stereocenters of Morphine

Configuration at the **ether** stereocenter:



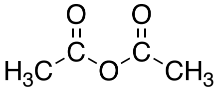
- Cannot assign 2, 3 at first try
- At the second atoms in the chain, there is a difference. The alcohol carbon is attached to one oxygen, one carbon, and one hydrogen. It has a higher priority than the other carbon which is attached to three carbons.
- Count 1, 2, 3: Counterclockwise
- This center is *R* and not *S* because the lowest priority group (the hydrogen) is pointing toward the front, not to the back.

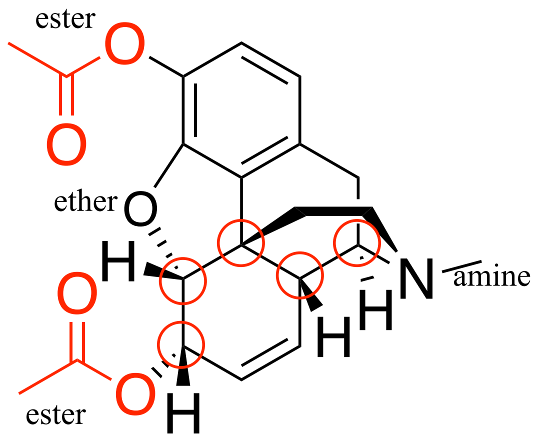
Configuration at the **alcohol** stereocenter:



- Cannot assign 2, 3 at first try
- At the second atoms in the chain, the eth carbon is attached to one oxygen, one carb and one hydrogen. It has a higher priority the alkene carbon which is attached to two carbons and one hydrogen
- Count 1, 2, 3: Clockwise
- This center is *S* and not *R* because the lo priority group (the hydrogen) is pointing toward the front, not the back

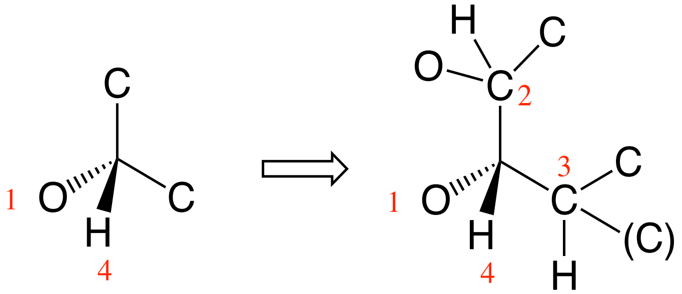
If you substitute CH_3COO for the two alcohol residues in morphine by reacting with

acetic anhydride ( $H_3C-C(=O)-O-C(=O)-CH_3$), you then create **HEROIN.**



1000x stronger as analgesic and more addictive than morphine

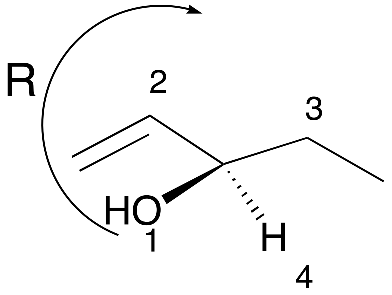
Configuration at the **C** attached to ester stereocenter:



- Cannot assign 2, 3 at first try
- At the second atoms in the chain, the eth
carbon is attached to one oxygen, one carl
and one hydrogen. It has a higher priority
the alkene carbon which is attached to tw
carbons and one hydrogen
- Count 1, 2, 3: Clockwise
- This center is *S* and not *R* because the lo
priority group (the hydrogen) is pointing
toward the front, not the back

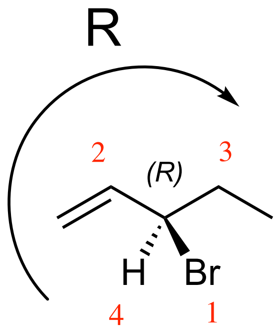
<u>Stereocentres Centres (Stereogenic Centres):</u>

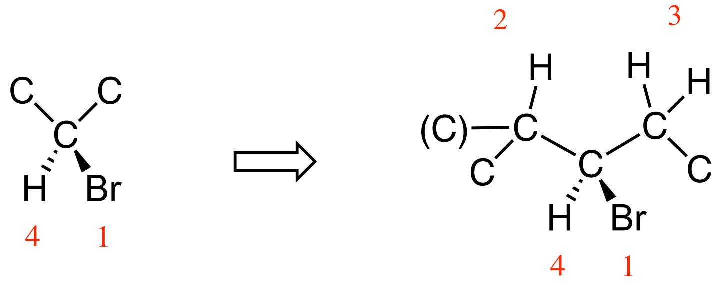
Example: 3-hydroxy-pent-1-ene



Carbon double bounded to another carbon is equivalent to a carbon bound to two carbons when considering priority

Example:





Example:

Achiral

meso compound - has stereogenic centers, but has a mirror plane of symmetry, so is achiral

Cis

1R,2S-dimethylcyclobutane

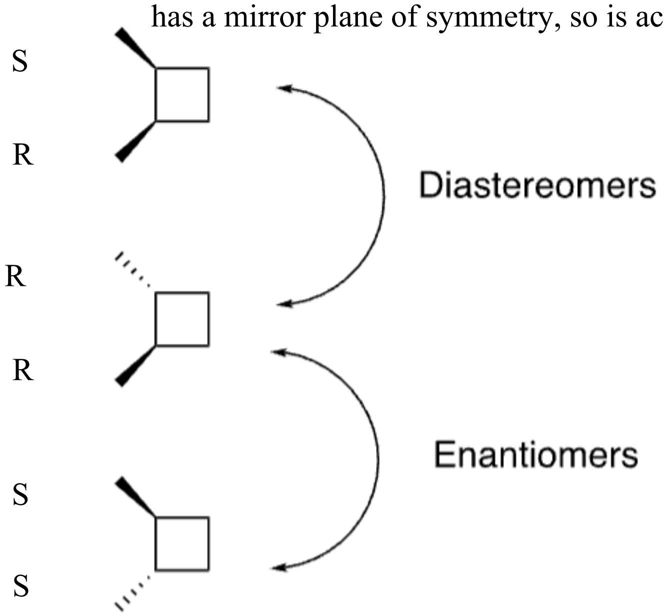
1S,2R-dimethylcyclobutane

Trans

RR-1,2-dimethylcyclobutane

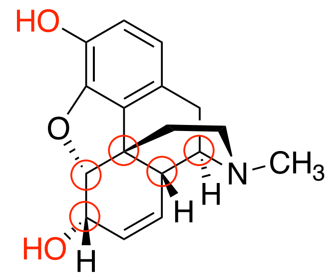
Trans

SS-1,2-dimethylcyclobutane



Recall:

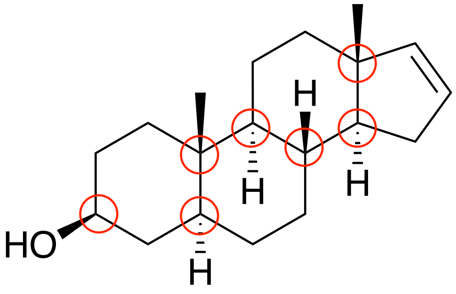
Morphine



-contains 5 stereogenic centres (marked with red circles)

Pheromones: from Greek “pherein horman” meaning to carry excitement. Discovered by Adolf Butenandt.

Male Pheromone:



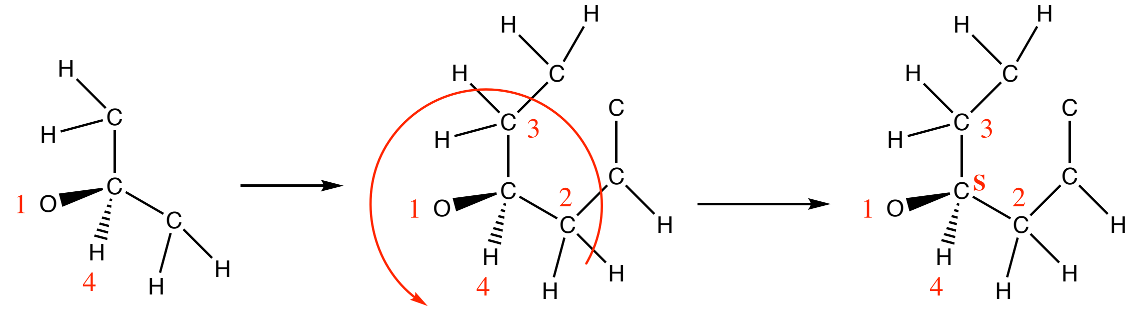
Androstenol

Only about 50 % of the population can smell this compound, which is genetically determined. About half find the smell disgusting while the other half find it tolerable or pleasant.

Some pheromones can be detected by insects at concentrations of 10^{-17} molar.

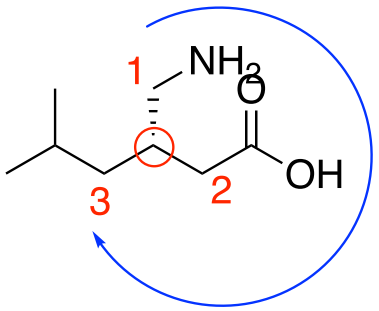
Contain 7 stereogenic centers, circled in red above.

What is the R/S configuration of the carbon attached to OH?

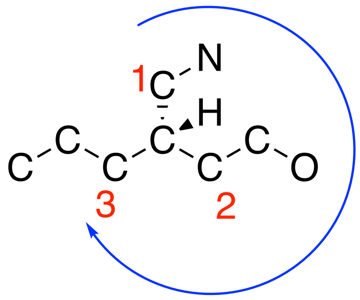


S configuration of stereogenic center

Lyrica Pregabalin- An analgesic developed by Richard Silverman

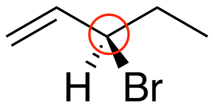


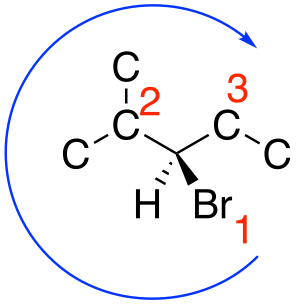
S-pregabalin



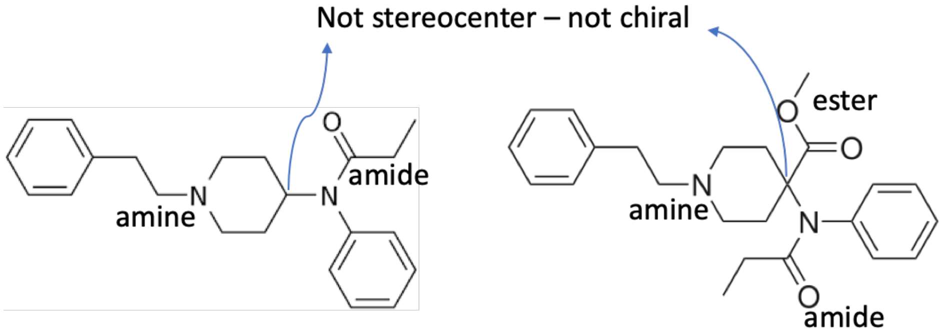
Note: The priority numbers are rotating clockwise however the lowest priority (H) is pointing towards you, hence it is S.

More example





Priorities are rotating clockwise, hence this is **R**



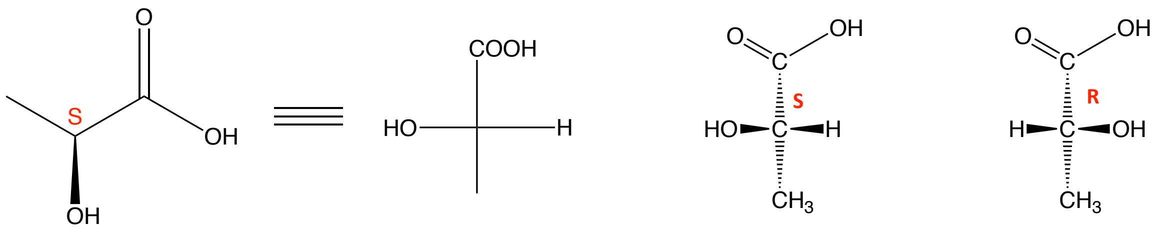
Fentanyl

Carfentanil

Fischer Projections

A method of drawing chemical structures, where the horizontal components are coming towards you and the vertical ones are going back.

Example #1: Lactic Acid



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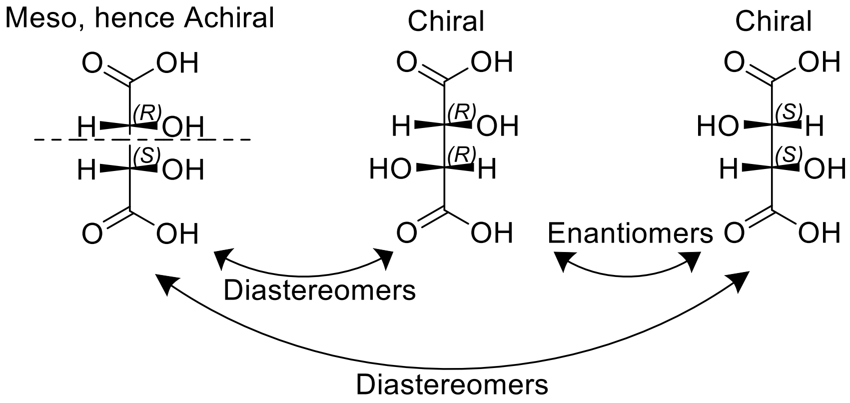
Example #2: Tartaric acid



Meso compounds have stereogenic centers but contain a plane of symmetry and are achiral

Racemic mixtures (or racemate) contain a 1:1 ratio of each enantiomer

Physical Properties of Enantiomers

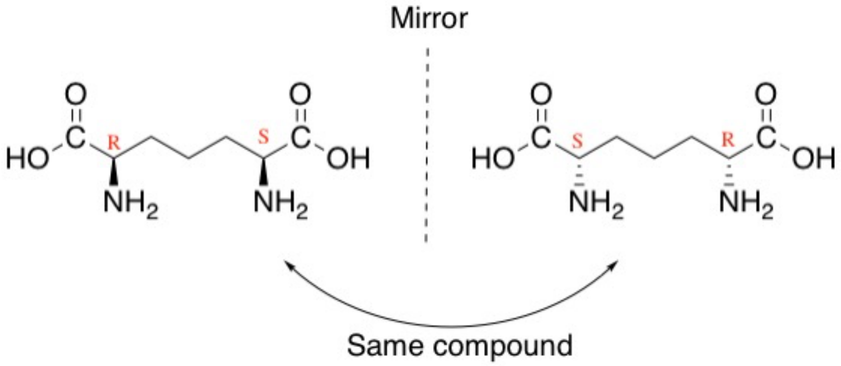
- Same physical properties with achiral agents or procedures
    - Melting point, boiling point, solubility in achiral solvents
- Separation of enantiomers (resolution) require a chiral agent

- **Diastereomers** have different physical properties (m.p, b.p, density, solubility)

Resolution: defined as the separation of enantiomers

Identification of Chiral and Achiral (not chiral) compounds

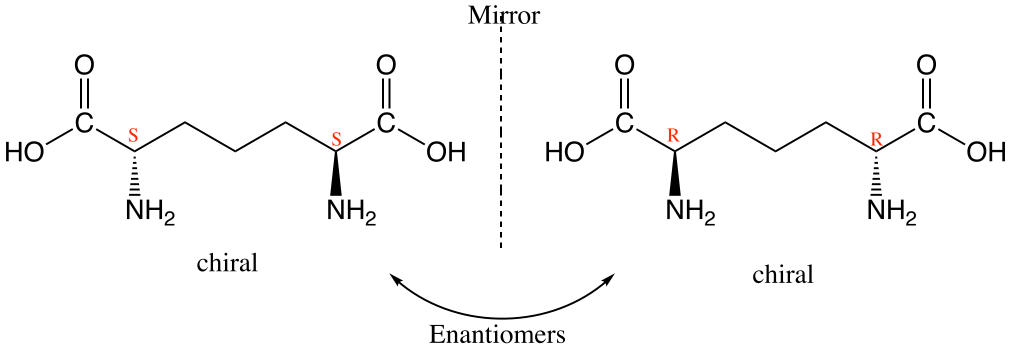
Example: Diaminopimelic acid



- The above molecule is achiral even though there are stereogenic center (s), because there is symmetry within the molecule
- These kinds of molecules are called **meso compounds,** which are compounds that contain stereocenters yet because of their symmetry, have mirror images that can be superimposed.

- All achiral molecules, including meso compounds do not rotate polarized light (i.e. $[\alpha]_D = 0$)

- Diaminopimelic acid - a component of bacterial cell wall and biosynthetic precursor to the amino acid known as lysine
- this R,S diaminopimelic acid (above) is a diastereomer of the enantiomers (S,S or R,R diaminopimelic acid) below:



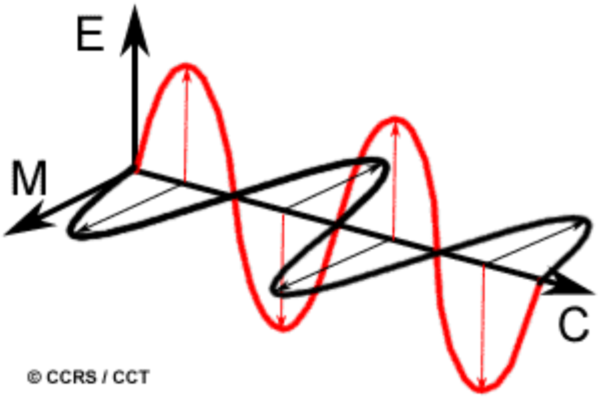
A racemic mixture (racemate) of two enantiomers in a 1:1 ratio also has an $[\alpha]_D = 0$

Optical Activity/Rotation

- Rotation of plane of polarized light
- α = measured rotation (°)

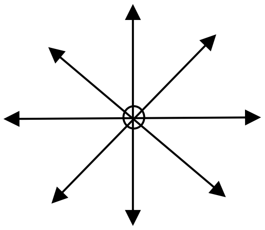
- $[\alpha]_D$ = Absolute rotation
    - (+) (clockwise = dextrorotatory)
    - (-) (counter-clockwise = levorotatory)
- Absolute rotation is 0 ° for achiral molecules

Pure enantiomers show equal but opposite rotation

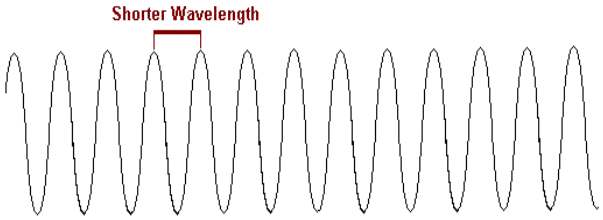


© CCRS / CCT

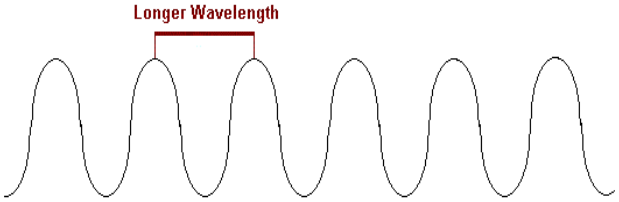
Light has an oscillating electric field (red) intersecting with a magnetic field (black)



End on view of vector components of normal light. It is possible to polarize light and remove some of those vectors.



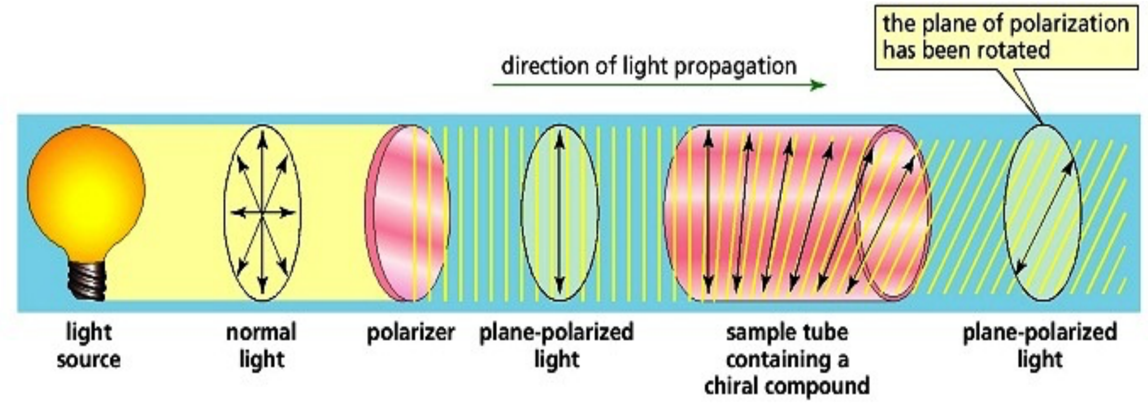
- ➢ Shorter Wavelength
- ➢ Higher Energy
- ➢ Higher Frequency



- ➢ Longer Wavelength
- ➢ Low Energy
- ➢ Low Frequency

$$\mathbf{E = h\nu = \frac{hc}{\lambda}}$$

E = energy
H = Planck's Constant (6.6 x 10^{-34} Joules•sec
ν = frequency
λ = wavelength



Optical Rotation

Factors affecting optical rotation:

- Concentration of compound, g/cm^3 (c)
- Path length that light travels through the solution, cm (l)

$[\alpha]_D$ = Absolute rotation at the D line of sodium (589 nm or 5890 Å)

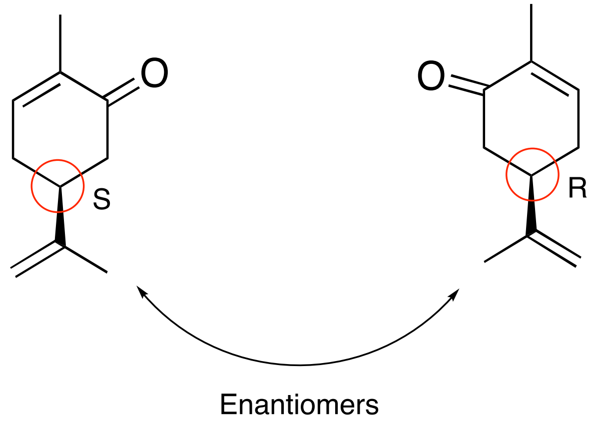
$$[\alpha]_D = \frac{\alpha}{c \bullet l}$$

α = measured rotation (°) c = concentration (g/cm^3) l = path length (cm)
D = D-line of sodium light $[\alpha]$ = absolute rotation

Degrees (°) = + : Clockwise (dextrorotatory/D)
– : Anticlockwise (levorotatory/L)
Note: not correlated with R/S configuration

Example: Carvone

$[\alpha]_D = -60\,^{\circ}$ $[\alpha]_D = +60\,^{\circ}$ (made up values, not real rotation)



S-carvone (caraway) R-carvone (spearmint)

Note: enantiomers will always have equal but opposite rotation, as such, they would cancel the rotation of the other when present as mixtures in solution.

Calculating Optical Purity

For this example, for S-carvone, assume the pure S enantiomer has –60° rotation

R	**S**	**Rotation (°)**	**Optical Purity (%)**
100 %	0 %	+ 60 °	100 %
75 %	25 %	+ 30 °	50 %
50 %	50 %	0 °	0 %
25 %	75 %	–30 °	50 %
0 %	100 %	–60 °	100 %

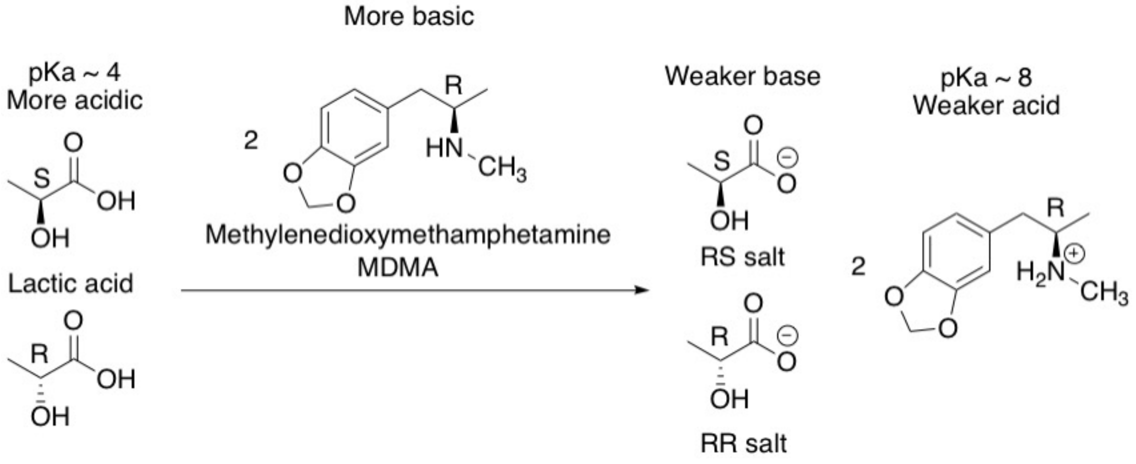
If a solution is an equivalent mix of 1:1 R + S enantiomers, α measured = 0 °
A 50:50 mixture of enantiomers is called a *racemic mixture* (or racemate)

Optical Purity (measured experimentally) = Enantiomeric Excess (ee) (Theoretical value)

Resolution of Enantiomers

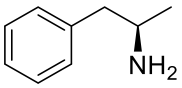
Definition: separation of two enantiomers
- Requires a chiral reagent to convert enantiomers to diastereomeric salts

Racemic mixture: 1:1 ratio of enantiomers in a mixture
Example: Lactic Acid

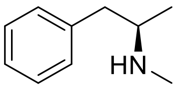


The starting material lactic acids are enantiomers of each other.
By reacting enantiomers to make a salt with an enantiomer of MDMA (another chiral molecule that is optically pure), also known as ecstasy, one can obtain salts which are now diastereomers of each other (RS and RR). The resulting diastereomers have different melting points, boiling points, solubilities, and can be separated by crystallization.

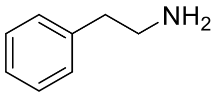
More examples of amines:



Amphetamine



Methamphetamine
Methedrine= speed



Cannot be used for resolution of enantiomers.
Need a stereogenic centre

Review of concepts: