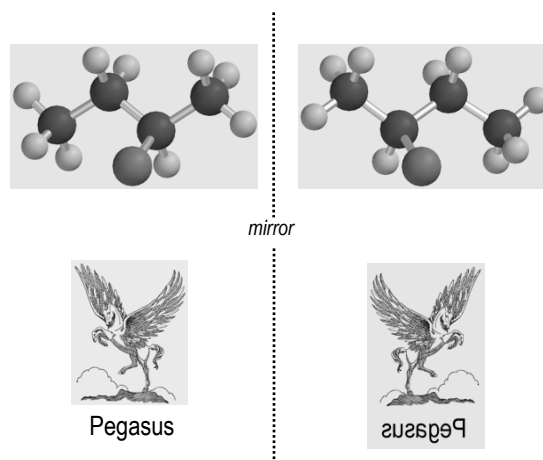


Stereochemistry Part 1



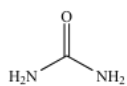
Stereochemistry: What is It?

Isomers: Molecules with same chemical formula but different spatial arrangement of atoms

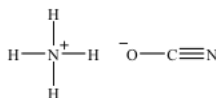
• Jöns Jakob Berzelius, 1830



Constitutional isomers: Isomers that differ in sequence of atom connectivity



Urea
 $\text{CH}_4\text{N}_2\text{O}$



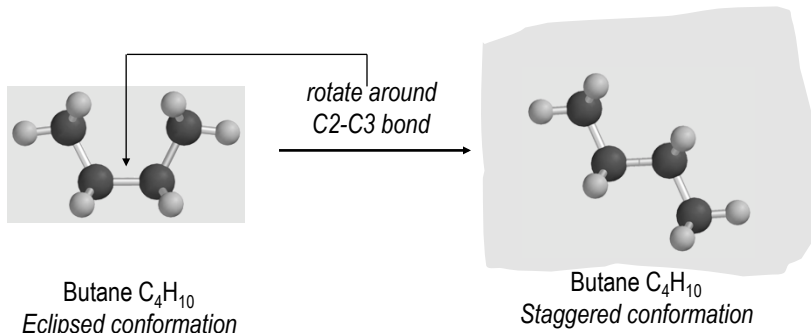
Ammonium cyanate
 $\text{CH}_4\text{N}_2\text{O}$

Stereochemistry: What is It?

Isomers

Conformational isomers

- Same sequence of connectivity; can be interconverted by rotation around a single bond

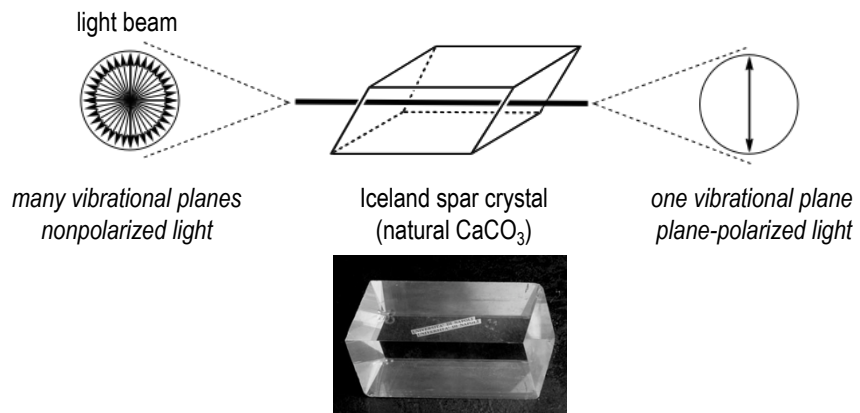


- Are other isomer types possible?

Historical Background

Timeline A: Light

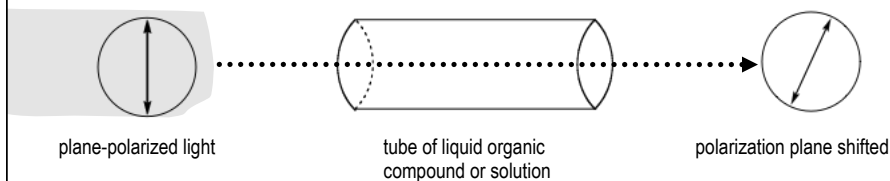
1678: Christiaan Huygens discovers **plane-polarized light**



Historical Background

Timeline A: Light

1815: Jean Baptiste Biot notes some natural substances rotate plane-polarized light



Optically active: rotates plane-polarized light

Optically inactive: does not rotate plane-polarized light

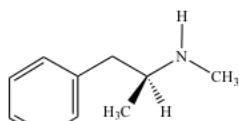
Historical Background

Timeline A: Light

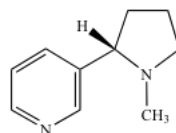
Optical activity

Dextrorotatory: rotates plane-polarized light in a clockwise direction (+)

Levorotatory: rotates plane-polarized light in a counterclockwise direction (-)



(+)-Methamphetamine



(-)-Nicotine

Historical Background

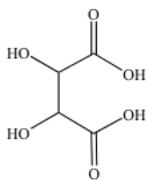
Timeline B: Tartaric Acid

1769: Carl Wilhelm Scheele examines tartar (deposited in casks during wine fermentation); isolates tartaric acid



1819: Paul Kester isolates racemic acid from tartar
From Latin *racemus*: bunch of grapes

1828: Joseph Louis Gay-Lussac shows tartaric acid and racemic acid are isomers



Tartaric acid

Racemic acid

Historical Background

Timeline B: Tartaric Acid

1832: Jean Baptiste-Biot notes tartaric acid is optically active



1838: Biot notes racemic acid is optically inactive

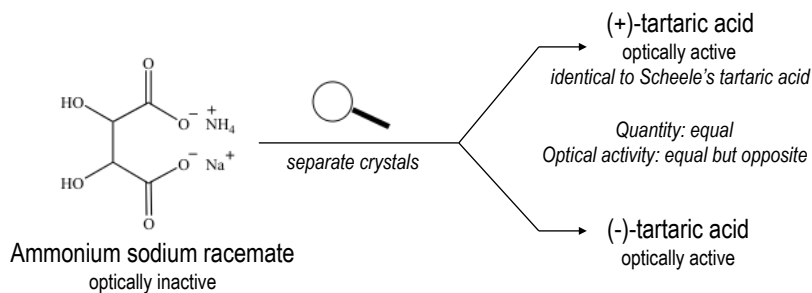
1847: Louis Pasteur separates ammonium sodium salt of racemic acid into (+) and (-) crystals



Historical Background

Timeline B: Tartaric Acid

Pasteur's separation of racemic acid



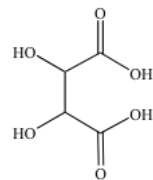
Conclusion: Racemic acid is a 1:1 mixture of two optically-active substances

Historical Background

Timeline B: Tartaric Acid

1853: Pasteur investigates mesotartaric acid

- Optically inactive isomer of tartaric acid
- Pasteur cannot separate into (+) and (-) forms



1854: Pasteur notes a certain plant mold metabolizes (+) but not (-)-tartaric acid

- Tartaric acid isomers have different biological properties

Historical Background

Timeline C: Tetrahedral Carbon

1874: Joseph Achille Le Bel (age 27) and Jacobus Henricus van't Hoff (age 22) propose:

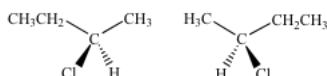


A molecule having a tetrahedral carbon atom with four unequal attachments exists as a pair of isomers.

Historical Background

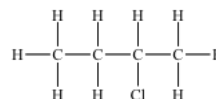
Timeline C: Tetrahedral Carbon

Example: 2-chlorobutane



Constitutional isomers?

Same atom connectivity sequence



Conformational isomers?

Cannot be made superposable by bond rotation
Verify with models

Identical?

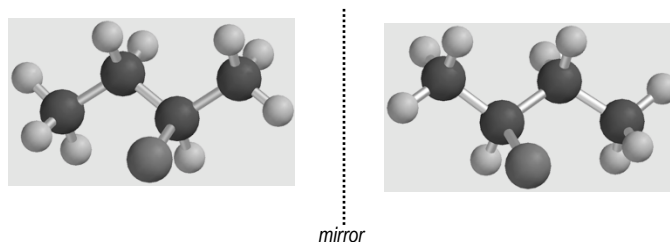
Not superposable *Verify with models*

Stereoisomers: isomers that differ only in the position of atoms in space, and cannot be interconverted by bond rotation

Historical Background

Timeline C: Tetrahedral Carbon

The 2-chlorobutane stereoisomers have another relationship:



Observations: mirror images
nonsuperposable } *Verify with models*

Enantiomers: stereoisomers that are nonsuperposable mirror images

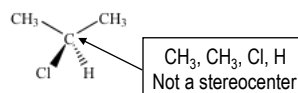
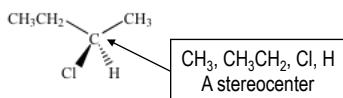
Historical Background

Timeline C: Tetrahedral Carbon

Other useful stereochemistry vocabulary

Stereocenter: a carbon atom bearing four different attachments.

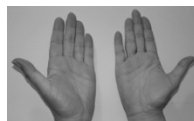
Better definition: an atom bearing three or more different attachments whose juxtaposition leads to stereoisomers.



Chiral: any object that is not superposable on its mirror image

Example: your hands

Not same meaning as enantiomers



Achiral: any object that is not chiral

Historical Background

Timeline C: Tetrahedral Carbon

At first the “stereoisomer theory” was not well accepted...

1877: Hermann Kolbe comments on “The Arrangement of Atoms in Space” (van’t Hoff’s Ph. D. thesis) in which tetrahedral carbon isomers were proposed.



“Not long ago, I expressed the view that the lack of general education and of thorough training in chemistry was one of ... the causes of the deterioration of chemical research in Germany..”

Historical Background

Timeline C: Tetrahedral Carbon

“Will anyone to whom my worries seem exaggerated please read, if he can, a recent memoir by a Herr van’t Hoff on ‘The Arrangement of Atoms in Space,’ a document crammed to the hilt with the outpouring of childish fantasy... This Dr. J. H. van’t Hoff, employed by the Veterinary College at Utrecht [Germany], has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus (evidently taken from the stables at the Veterinary College) and announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in space.



Pegasus

Mount Parnassus: home of the Muses in Greek legend

Nobel Prize in Chemistry 1901: J. H. van’t Hoff for his studies of chemical dynamics and osmotic pressure

Historical Background

Timeline C: Tetrahedral Carbon

Why tetrahedral carbon stereoisomer theory not accepted at first?

- All physical properties of enantiomers identical

Exception: direction of plane-polarized light rotation

- Physical properties used to separate substances (bp, solubility, etc.)
- Enantiomers could not be separated, so their existence was questioned

Stereocenter Nomenclature

Absolute configuration: spatial arrangement of groups at stereocenter

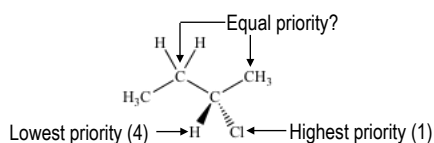
- Stereocenter can have only two absolute configurations *Verify with models*
- Therefore need only two stereocenter designators

Cahn-Ingold-Prelog System Example: 2-chlorobutane

Step 1: Assign priorities based on atomic number of atoms attached to stereocenter:

↑ atomic number = ↑ priority

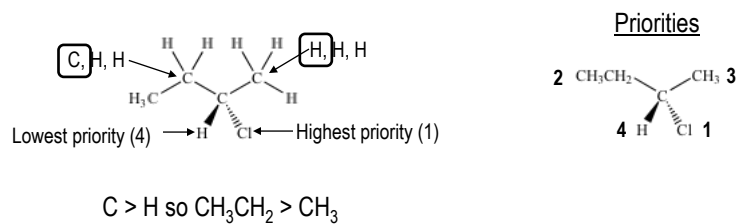
H = 1 C = 6 Cl = 17



Stereocenter Nomenclature

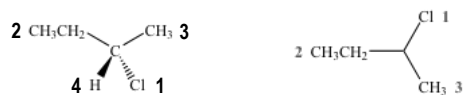
When atoms are of equal priority, move out to next set of atoms

- Select highest priority atom in each set



Stereocenter Nomenclature

Step 2: View with lowest priority group in the back



Stereocenter Nomenclature

Step 3: Assign absolute configuration

- Priorities decrease clockwise:

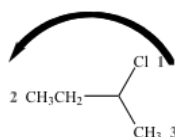


Configuration = *R* (Latin *rectus*, to the right)

- Priorities decrease counterclockwise:



Configuration = *S* (Latin *sinister*, to the left)

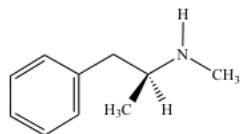


(*S*)-2-chlorobutane *More details in text, website tutorials, etc.*

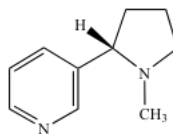
Stereocenter Nomenclature

Avoid this common misconception:

“*R/S* (absolute configuration) and +/- (optical rotation) are related”



(*S*)-(+)-Methamphetamine



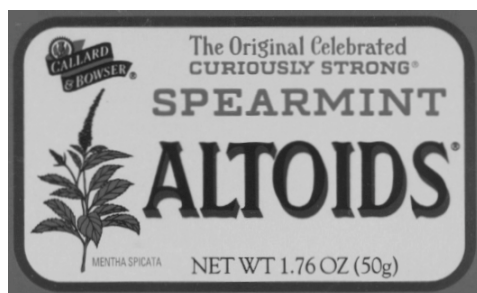
(*S*)-(-)-Nicotine

The Truth

- There is no easily predictable relationship between *R/S* and +/-
- Enantiomer of (*S*)-(-) is (*R*)-(+)

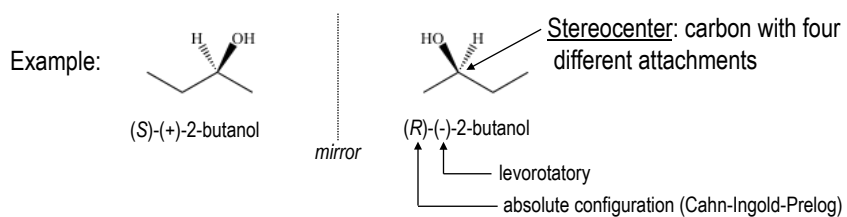
Practice: verify absolute configurations. *Use models.*

Stereochemistry Part 2



Summary of Part 1

Stereoisomers: isomers (i.e., same chemical formula) that differ by the position of atoms in space, and cannot be interconverted by rotation around a single bond



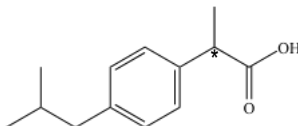
Enantiomers: nonsuperposable mirror image molecules **Verify with models**

- Most physical properties identical, except direction of rotation of plane-polarized light

Molecules with Multiple Stereocenters

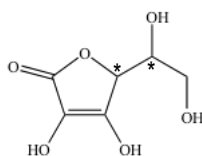
More stereocenters = more stereoisomers possible

Ibuprofen
analgesic



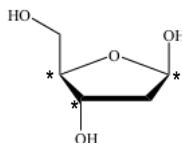
One stereocenter
R or S

Ascorbic acid
vitamin C



Two stereocenters
R,R R,S S,R S,S
Four stereoisomers

Deoxyribofuranose
in DNA

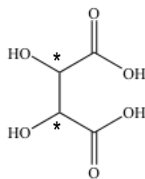


Three stereocenters
Eight stereoisomers

Molecules with Multiple Stereocenters

General rule: molecule with n stereocenters has **up to** 2^n stereoisomers

Tartaric acid



Number of stereocenters =

$2^2 =$ up to 4 stereoisomers

Consistent with Pasteur's observations?

(+)-tartaric acid

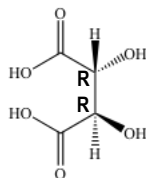
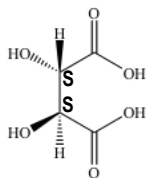
(-)-tartaric acid

mesotartaric acid

} three stereoisomers

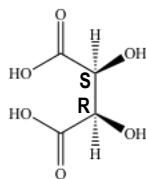
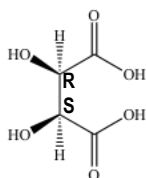
Molecules with Multiple Stereocenters

Stereoisomers of tartaric acid



Create enantiomer by
inverting all stereocenters

Invert stereocenter by switching
position of any two groups
(example: OH and COOH)

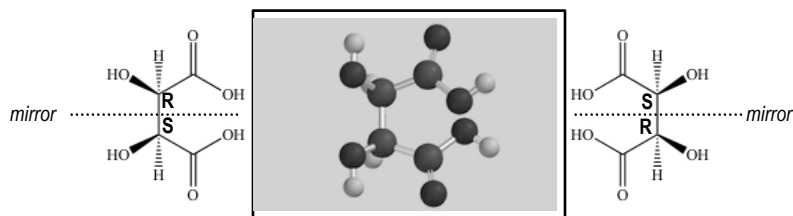


Diastereomers: stereoisomers
that are not enantiomers

Create diastereomer by
inverting at least one, but not
all, stereocenters

Molecules with Multiple Stereocenters

(2S,3R) and (2R,3S)-tartaric acid



Enantiomers are nonsuperposable mirror images

no

yes

These molecules are *identical*

Meso compound: a molecule with stereocenters that is identical with (i.e., superposable on) its mirror image

•Internal mirror plane

•Achiral and therefore optically inactive

Molecules with Multiple Stereocenters

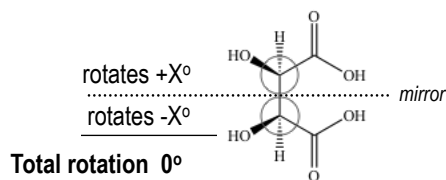
Common questions about meso compounds

Why is a meso compound achiral?

- Superposable on its mirror image

A meso compound has stereocenters but is optically inactive!?

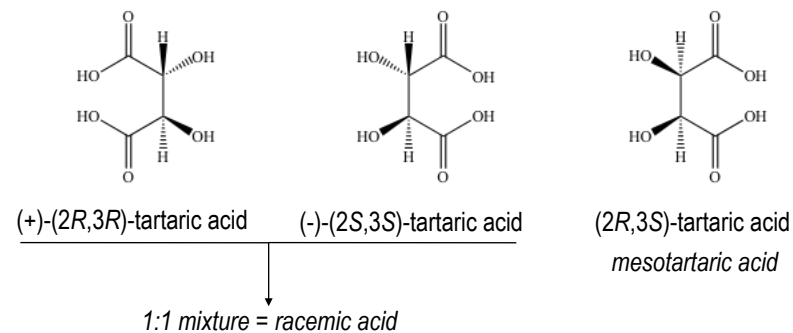
- All achiral compounds are optically inactive
- Rotation of plane-polarized light cancelled by internal symmetry



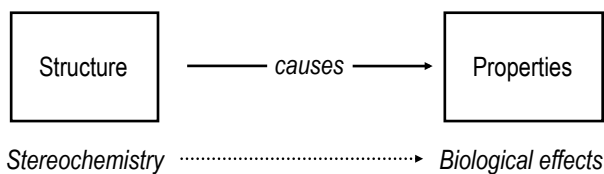
Molecules with Multiple Stereocenters

Pasteur got it right

Tartaric acid has only three stereoisomers:



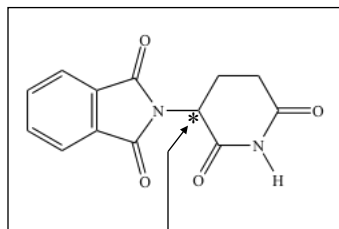
Biological Significance of Stereoisomers



Example: Pasteur's plant mold metabolized (+)-tartaric acid but not (-)-tartaric acid

Biological Significance of Stereoisomers

Thalidomide



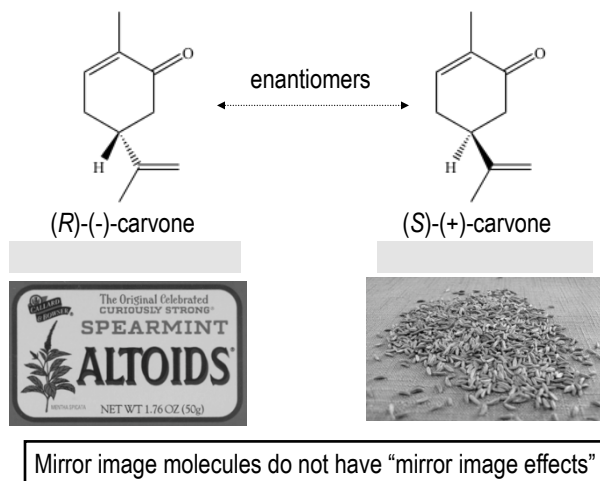
One stereocenter

- Marketed in 50 countries 1956-1962
- Sedative for "hysterical" pregnant women
- Antiemetic to combat morning sickness
- Caused thousands of birth defects
- Teratogen:** causes fetal abnormalities

- Sold as **racemic mixture:** 1:1 mixture of enantiomers
 - R enantiomer = antiemetic (not teratogenic)
 - S enantiomer = teratogenic (not antiemetic)
- Single-enantiomer drug not useful: quickly racemizes in body

Biological Significance of Stereoisomers

Another biological effect: odor



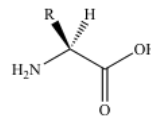
Biological Significance of Stereoisomers

Of hands, gloves, and biology

Why do stereoisomers have different biological properties?

- Many biological effects involve interaction with a pocket in enzyme or receptor
- Good fit to pocket (i.e., strong binding) triggers enzyme or receptor

- Enzymes and receptors are proteins; built from amino acids:



- Most amino acids are chiral ($R \neq H$), so pocket is also chiral
- Metaphor: Stereoisomer = left hand or right hand
 - Protein pocket = left glove or right glove
 - Left hand fits left glove but not right glove
 - Left hand triggers "left hand protein" but not "right hand protein"
- (*R*)-carvone triggers spearmint smell receptor but not caraway smell receptor

Separation of Stereoisomers

Why is separation necessary?

- Extra stereoisomer(s) may have undesirable effects
- Mixtures from natural sources or synthesis
 - Achiral reactants produce optically inactive product or product mixture
 - Example: thalidomide manufactured as racemic mixture

How is separation achieved?

- Physical properties
 - Different boiling point → use distillation
 - Different solubility → use crystallization
- Chemical properties
 - One stereoisomer reacts faster or slower than others

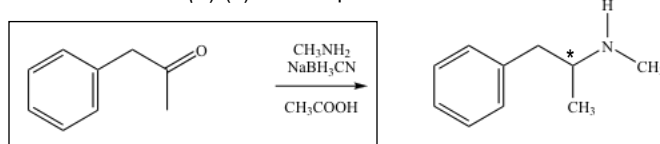
Separation of diastereomers

- Diastereomers have different physical properties
- Separation methods on solubility, boiling point, etc.

Separation of Stereoisomers

Separation of enantiomers

- No difference in physical properties except direction of rotation of plane-polarized light
- Thermodynamic restrictions: achiral reactants → optically inactive product or product mix
- Example: manufacture of (S)-(+)-methamphetamine



All reactants achiral

Product has 1 stereocenter → 2 enantiomers

Therefore product mixture must be racemic

- Optically inactive
- 1:1 mixture of enantiomers
 - (R)-(-)-methamphetamine: weaker CNS stimulant
 - (S)-(+)-methamphetamine: stronger CNS stimulant

Separation of Stereoisomers

Resolution: separation of enantiomers

Resolution strategy

Key issue: enantiomers not easily separated but diastereomers are

Step 1: Convert enantiomers into diastereomers

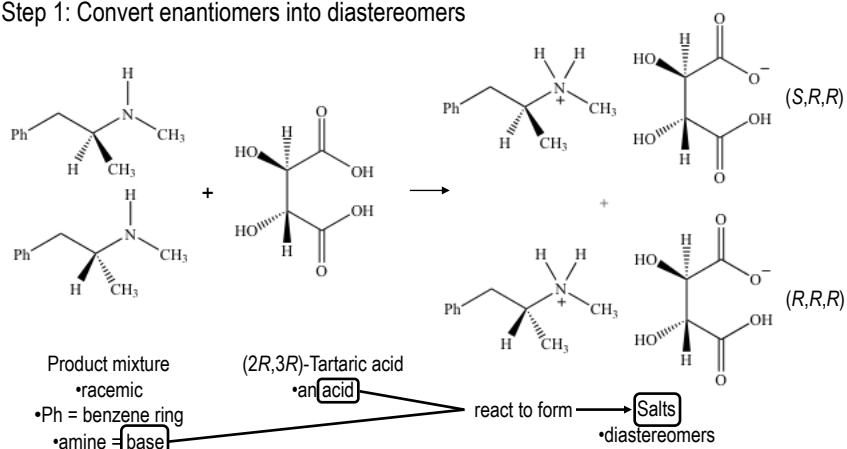
Step 2: Separate diastereomers

Step 3: Reverse diastereomer formation to give separated enantiomers

Separation of Stereoisomers

Methamphetamine Resolution

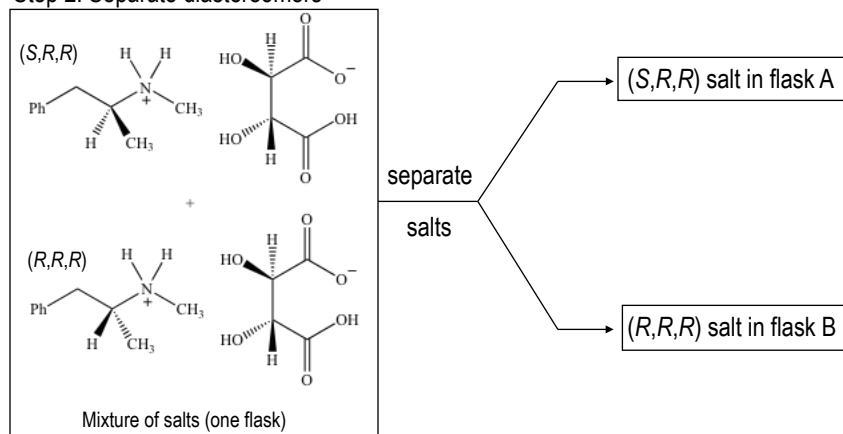
Step 1: Convert enantiomers into diastereomers



Separation of Stereoisomers

Methamphetamine Resolution

Step 2: Separate diastereomers



Separation of Stereoisomers

Methamphetamine Resolution

Step 3: Recover enantiomers from diastereomers

