

# Lecture No. 04

## Resolution of racemic mixtures

# Session Objectives

By the end of this session, students will be able to:

- Define racemic modification
- Discuss factors which lead to formation of racemic modification
- Explain various methods for resolving racemic mixtures

# Resolution of racemic modifications

- It is a process where by a racemic modification is separated into its two enantiomers
- It is quantitative and sometimes only one isomer will be isolated
- Several methods have been developed and type of separation will be selected depending upon the nature of compound

## 1) Mechanical separation

- Introduced by Pasteur and also known as spontaneous resolution by crystallisation
- Applicable only for the racemic mixtures where the crystal forms of enantiomers are enantiomorphous – which are separated by hand

# Resolution of racemic modifications

- Pasteur separated sodium ammonium **tartrate** racemate in this way
- He crystallized sodium ammonium **tartrate** racemate from a concentrated solution at room temperature below 28 °C and separated mechanically

## 2) Preferential crystallization through inoculation

- Supersaturated solution of the racemic modification is treated with a crystal of one enantiomer, this form is precipitated
- Resolution of glutamic acid by inoculation has been perfectly suitable for industrial use
- But this method was found impractical with amino acids

# Resolution of racemic modifications

## 3) Biochemical separation

- Certain bacteria and moulds when they grow in dilute solution of racemic modification, destroy one enantiomer
- For example, *Pencillium glaucum* when grown in solution of racemic ammonium tartrate, attacks the (+)-form and leaves (-)-form

## Drawbacks

- Dilute solutions must be used, so amounts obtained will be small
- One form is always destroyed and other form is not always obtained in 50%, some may also be destroyed
- To find a microorganism which will attack only one enantiomer

# Resolution of racemic modifications

## 4) Conversion into diastereoisomers

- Best of all methods of resolution
- Racemic modification is treated with optically active substance
- Diastereoisomers produced are separated by fractional crystallization
- For example, racemic acids can be separated by optically active bases



- Now the two diastereoisomers can be separated by fractional crystallization

# Resolution of racemic modifications

- Enantiomers of acids can be regenerated by hydrolysis with inorganic acids or with alkalis
- Further purification can be done by chromatography
- For resolution, compounds used are-
- **Acids**: optically active bases are alkaloids- brucine, quinine, strychnine, morphine, cinchonine
- **Bases**: optically active acids used are tartaric acid, camphor- $\beta$ -sulphonic acid
- **Alcohols**: converted to acid ester using succinic or phthalic anhydride
- **Aldehydes and ketones**: by means of optically active hydrazines
- **Amino compounds**: by means of optically active aldehydes

# Resolution of racemic modifications

## 5) Chromatography

- Optically active substances may be selectively adsorbed by some optically active adsorbent
- For example, Henderson and Rule (1939) partially resolved p-Phenylene bisimino camphor on lactose as adsorbent
- Bradley and Easty (1951) have found that wool and casein selectively adsorb (+)-mandelic acid from an aqueous solution of ( $\pm$ )-mandelic acid
- Separation of quinine and quinidine, cinchonine and cinchonidine by passing through silica gel



# Resolution of racemic modifications

## 6) Resolution through formation of Molecular Complexes

- Common method of resolution because of weak interactions between substrate and resolving agent
- Other methods involves formation of stable salts or covalent compounds
- Complexes should be easy to form and easy to decompose
- For example, complexation with platinum reagents has been used to resolve trans-cyclooctane

# Resolution of racemic modifications

## 7) Biochemical methods of resolution using enzymes

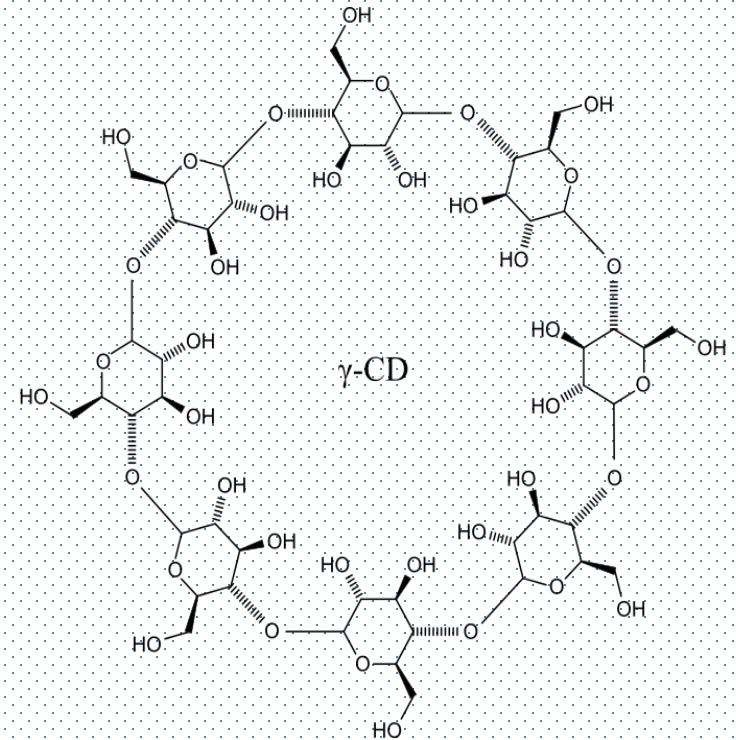
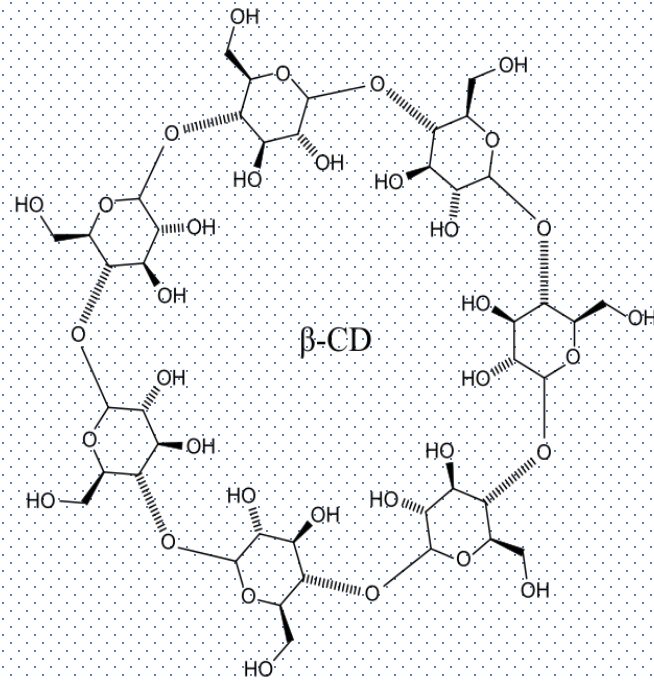
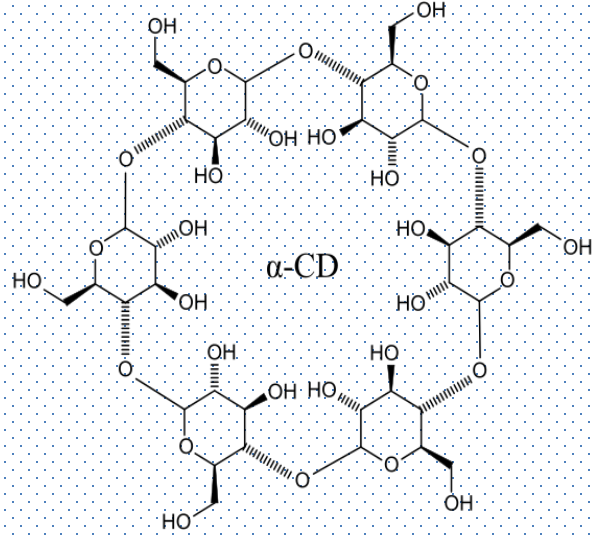
- Laboratory reduction of 2-butanone gives racemic product of 2-butanol
- But reduction in the presence of chiral enzyme gives optically pure (R)-2-butanol
- Easy to acetylate racemic alcohol and treat racemic esters with lipase
- One enantiomer is hydrolyzed to alcohol while other remains as ester
- Further separated by chromatography
- Enzyme acylase 1 (hog kidney acylase) is capable of hydrolyzing amide links (-NHAc) of L-amino acids only (stereospecificity)

# Resolution of racemic modifications

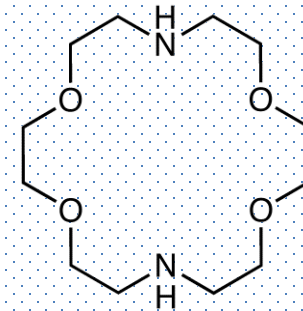
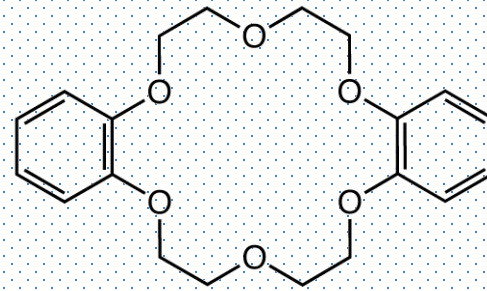
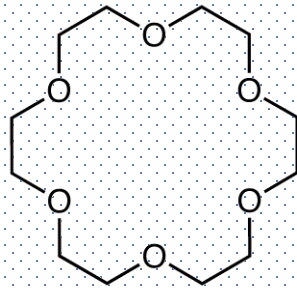
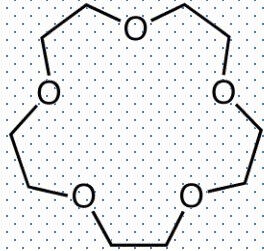
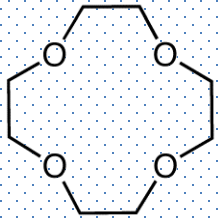
## 8) Resolution via chiral recognition and Inclusion compounds

- Chiral recognition- only one enantiomer fits into chiral host **activity**, while the other does not
- Generally both diastereoisomers may be formed, one is formed more readily than other
- For example, aqueous solution of rac-amine salt is mixed with chloroform solution of optically active crown ether, could separate complex of chiral crown ether and (R) amine salt
- Cyclodextrins (CDs) are made up of six, seven or eight glucose units connected in a large ring termed as  $\alpha$ ,  $\beta$  and  $\gamma$  CDs
- CDs are of tub shape with primary OH groups projecting from narrow side and secondary OH groups from wide side
- Can be used for resolution of variety of compounds via inclusion complexes

# Structure of cyclodextrins



## Structures of common crown ethers



# Summary

- Racemic modification is separation of its isomers
- Supersaturated solution of the racemic modification is treated with a crystal of one enantiomer, this form is precipitated
- Racemic modification is treated with optically active substance is the best method
- Optically active substances may be selectively adsorbed by some optically active adsorbent

# Thank You

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