UNIT II

AROMATICITY
ANTIAROMATICITY
NON AROMATICITY

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3 Difference between aromatic, antiaromatic,nonaromatic

4 Aromatic hetrocyclic compound

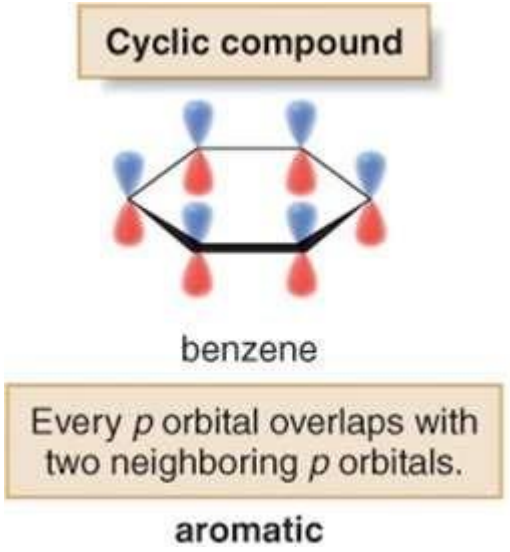
5-Annulene

Introduction about aromatic compound

The Criteria for Aromaticity

Four structural criteria must be satisfied for a compound to be aromatic.

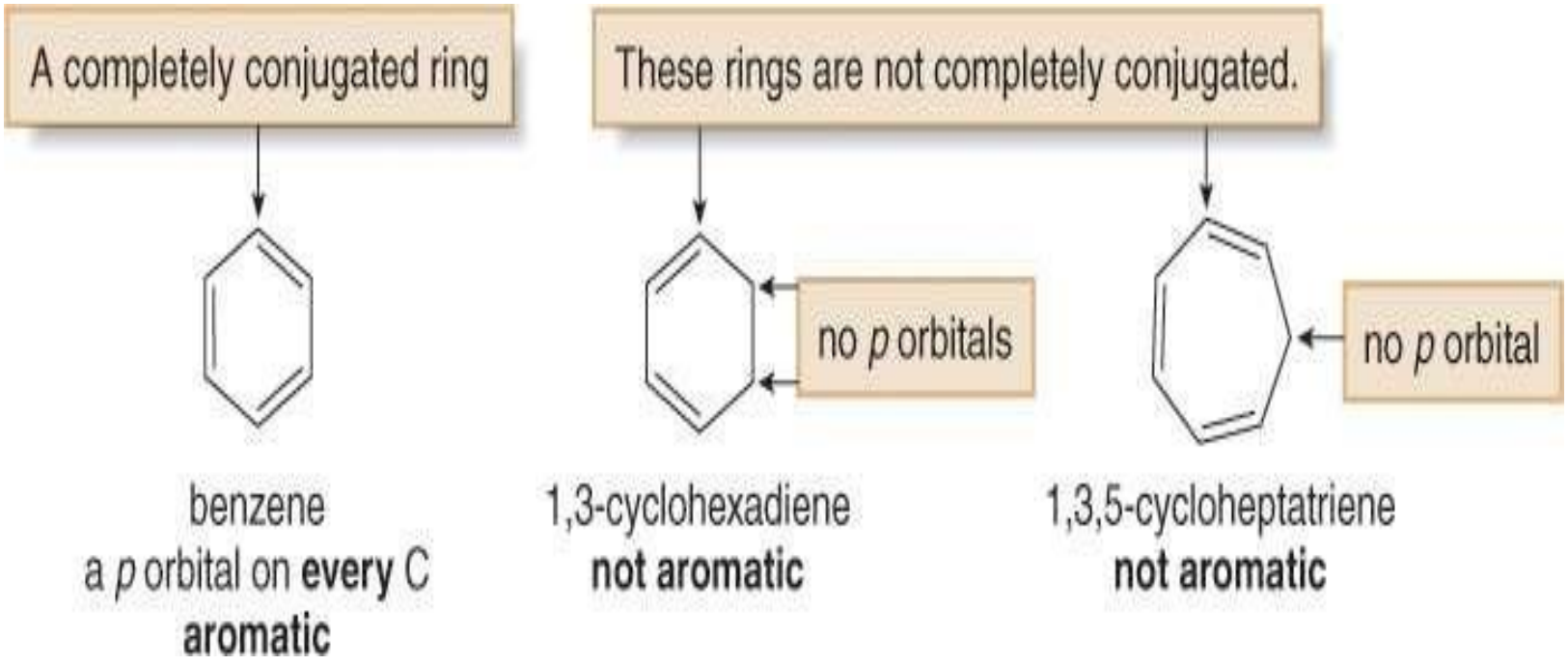
[1] A molecule must be cyclic.



To be aromatic, each *p* orbital must overlap with *p* orbitals on adjacent atoms.

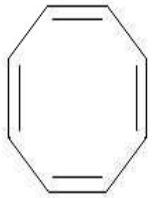
[3] A molecule must be completely conjugated.

Aromatic compounds must have a *p* orbital on every atom.

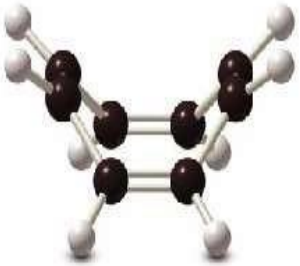


[2] A molecule must be planar.

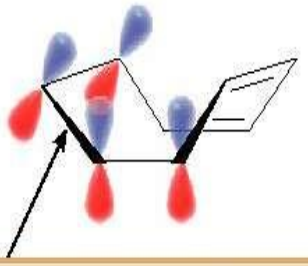
All adjacent *p* orbitals must be aligned so that the π electron density can be delocalized.



cyclooctatetraene
not aromatic

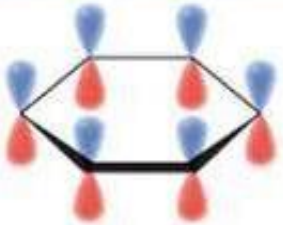


a tub-shaped,
eight-membered ring



Adjacent *p* orbitals cannot overlap.
Electrons cannot delocalize.

Cyclic compound



benzene

[4] A molecule must satisfy Hückel's rule, and contain a particular number of π electrons.

Hückel's rule:

- An aromatic compound must contain $4n + 2$ π electrons ($n = 0, 1, 2$, and so forth).
- Cyclic, planar, and completely conjugated compounds that contain $4n$ π electrons are especially unstable, and are said to be *antiaromatic*.

Benzene is aromatic and especially stable because it contains 6 π electrons. Cyclobutadiene is antiaromatic and especially unstable because it contains 4 π electrons.

Benzene An aromatic compound	Cyclobutadiene An antiaromatic compound
	
$4n + 2 = 4(1) + 2 =$ 6 π electrons aromatic	$4n = 4(1) =$ 4 π electrons antiaromatic

Considering aromaticity, a compound can be classified in one of three ways:

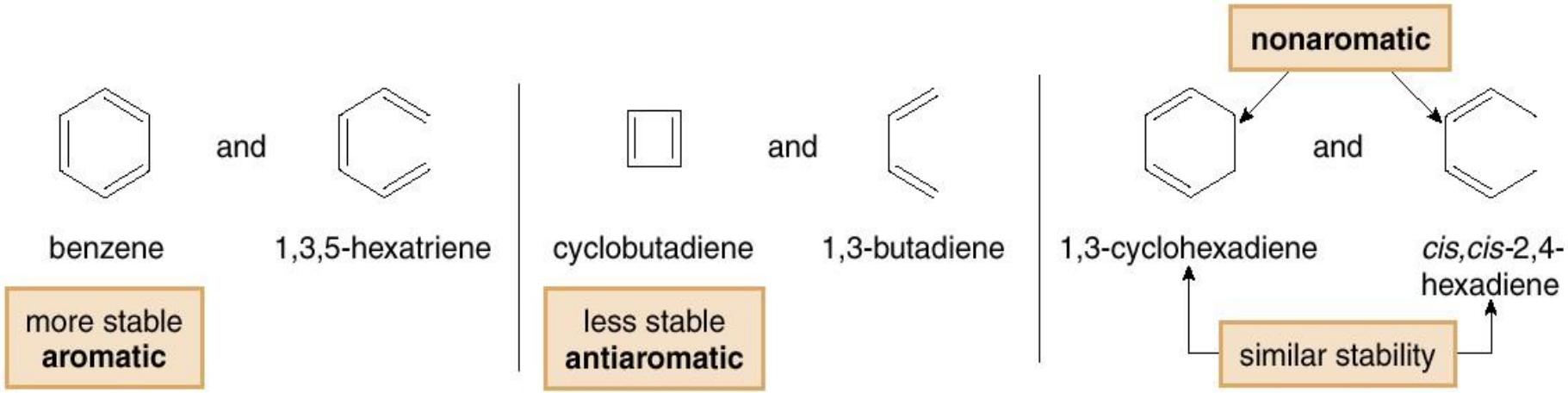
1. Aromatic—A cyclic, planar, completely conjugated compound with $4n + 2\ \pi$ electrons.

2. Antiaromatic—A cyclic, planar, completely conjugated compound with $4n\ \pi$ electrons.

3. Not aromatic (nonaromatic)—A compound that lacks one (or more) of the following requirements for aromaticity: being cyclic, planar, and completely conjugated.

Note the relationship between each compound type and a similar open-chained molecule having the same number of π

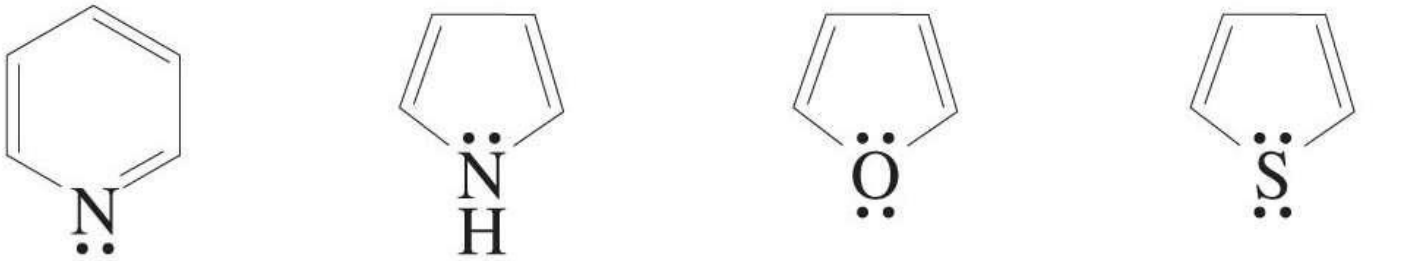
- An aromatic compound is *more* stable than a similar acyclic compound having the same number of π electrons. Benzene is more stable than 1,3,5-hexatriene.
- An antiaromatic compound is *less* stable than an acyclic compound having the same number of π electrons. Cyclobutadiene is less stable than 1,3-butadiene.
- A compound that is not aromatic is *similar* in stability to an acyclic compound having the same number of π electrons. 1,3-Cyclohexadiene is similar in stability to *cis,cis*-2,4-hexadiene, so it is not aromatic.



Aromatic Heterocyclic Compounds

Heteroatom donates one electron

Heteroatom donates two electrons



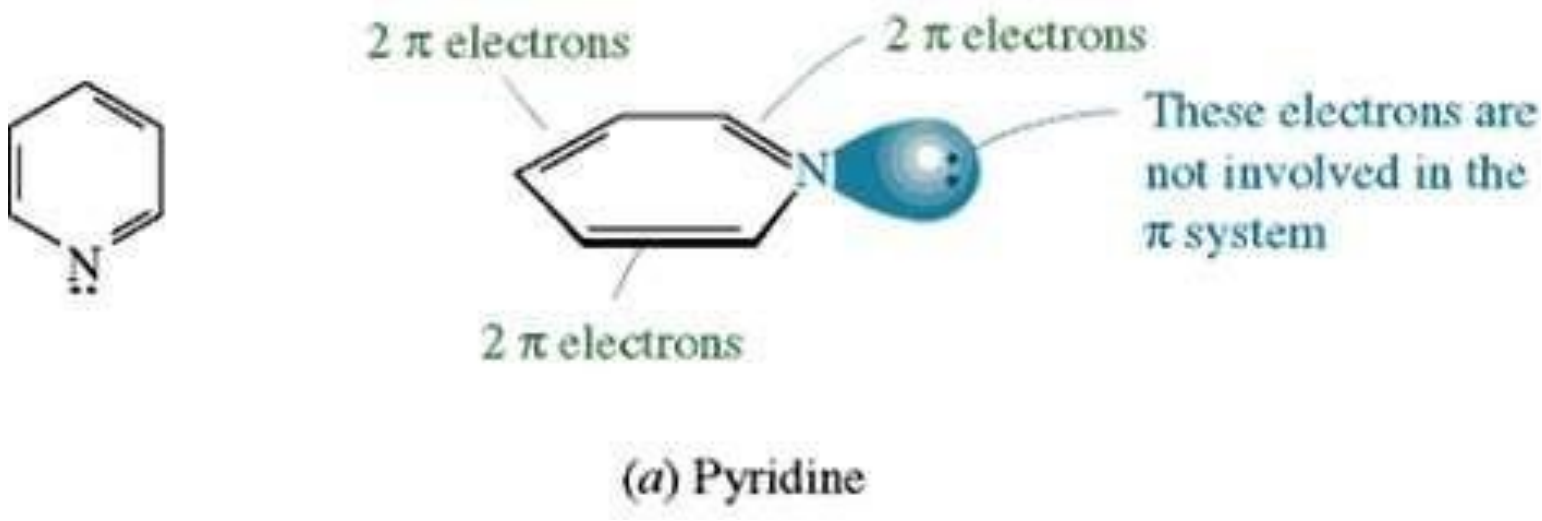
pyridine pyrrole furan thiophene

A heterocyclic compound has ring atoms other than carbon

The heteroatom donates either one or two electrons to the π system

Pyridine

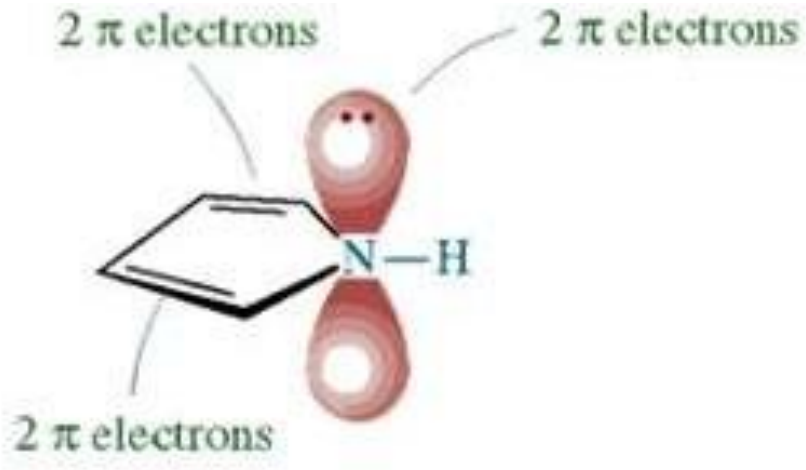
- A six-membered heterocycle with a nitrogen atom in its ring
- π electron structure resembles benzene (6 electrons)
- The nitrogen lone pair electrons are not part of the aromatic system (perpendicular orbital)



(*a*) Pyridine

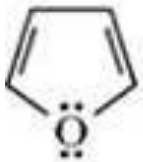
Pyrrole

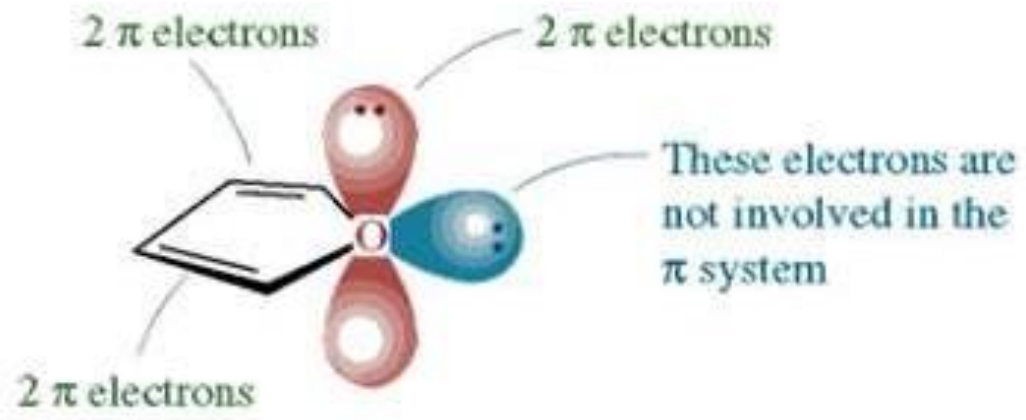
- A five-membered heterocycle with one nitrogen
- π electron system similar to that of cyclopentadienyl anion
- Nitrogen atom is sp^2-hybridized, and lone pair of electrons occupies a *p* orbital (6 π electrons)



(*b*) Pyrrole

Furan structure





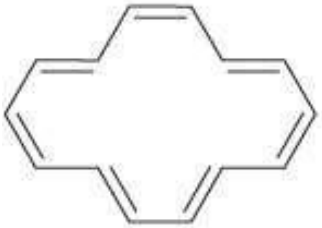
(c) Furan

Furan and Thiphene structure are simil

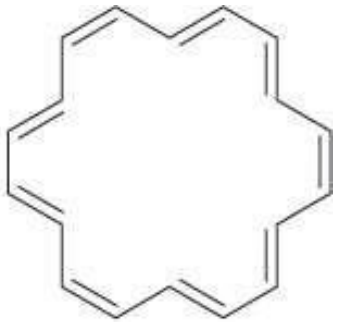
thiophene

Annulene

- Hydrocarbons containing a single ring with alternating double and single bonds are called annulenes.
- Completely conjugated rings larger than benzene are also aromatic if they are planar and have $4n + 2$ π electrons.
- To name an annulene, indicate the number of atoms in the ring in brackets and add the word annulene.



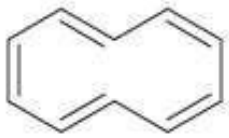
[14]-annulene
$4n + 2 = 4(3) + 2 =$
14 π electrons
aromatic



[18]-annulene
$4n + 2 = 4(4) + 2 =$
18 π electrons
aromatic

- [10]-Annulene has 10 π electrons, which satisfies Hückel's rule, but a planar molecule would place the two H atoms inside the ring too close to each other. Thus, the ring puckers to relieve this strain.
- Since [10]-annulene is not planar, the 10 π electrons can't delocalize over the entire ring and it is not aromatic.

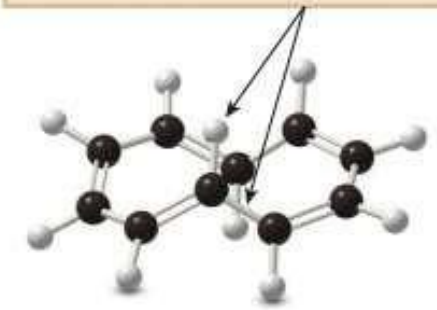
[10]-Annulene fits Hückel's rule, but it's **not planar**.



[10]-annulene
10 π electrons
not aromatic

=

The molecule puckers to keep these H's further away from each other.



3-D representation

CYCLODEXTRIN AND IT'S APPLICATION

Content

- Introduction
- Types Of Cyclodextrin
- Properties Of Cyclodextrin
- Characteristics
- Synthesis
- Inclusion Complex
- Methods For Making Inclusion Complexes
- Modifications
- Applications
- Side Effect
- Conclusion
- References

Introduction

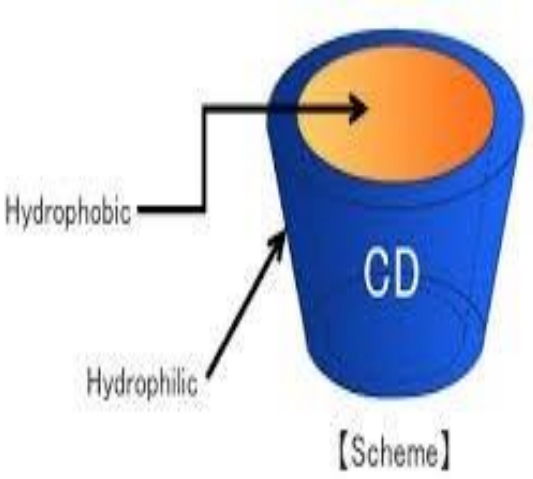
- Cyclodextrins are formed by the action of cyclodextrin glucosyltransferase enzyme (CGTase) on the medium containing starch. Cyclodextrins are macrocyclic oligosaccharides containing at least six D-(+)- glucopyranose units attached by α (1-4) bonds.

- One of the important feature of cyclodextrins is their ability to form inclusion complexes with a variety of compounds, by entrapping their molecules inside the cyclodextrin cavity, which act as a host.

Continue…

The complex formed results-

¬Increased solubility
¬Increased dissolution rate
¬Increased stability
¬Decreased volatility



【Scheme】

¬Cyclodextrin are relatively hydrophobic central cavity and hydrophilic outer surface.

Synonyms- cellulosine

Types of Cyclodextrin-

α -cyclodextrin:

¬6 membered sugar ring molecule

¬relatively irritating after i.m. injection

¬binds lipids.

β -cyclodextrin:

¬7 membered sugar ring molecule

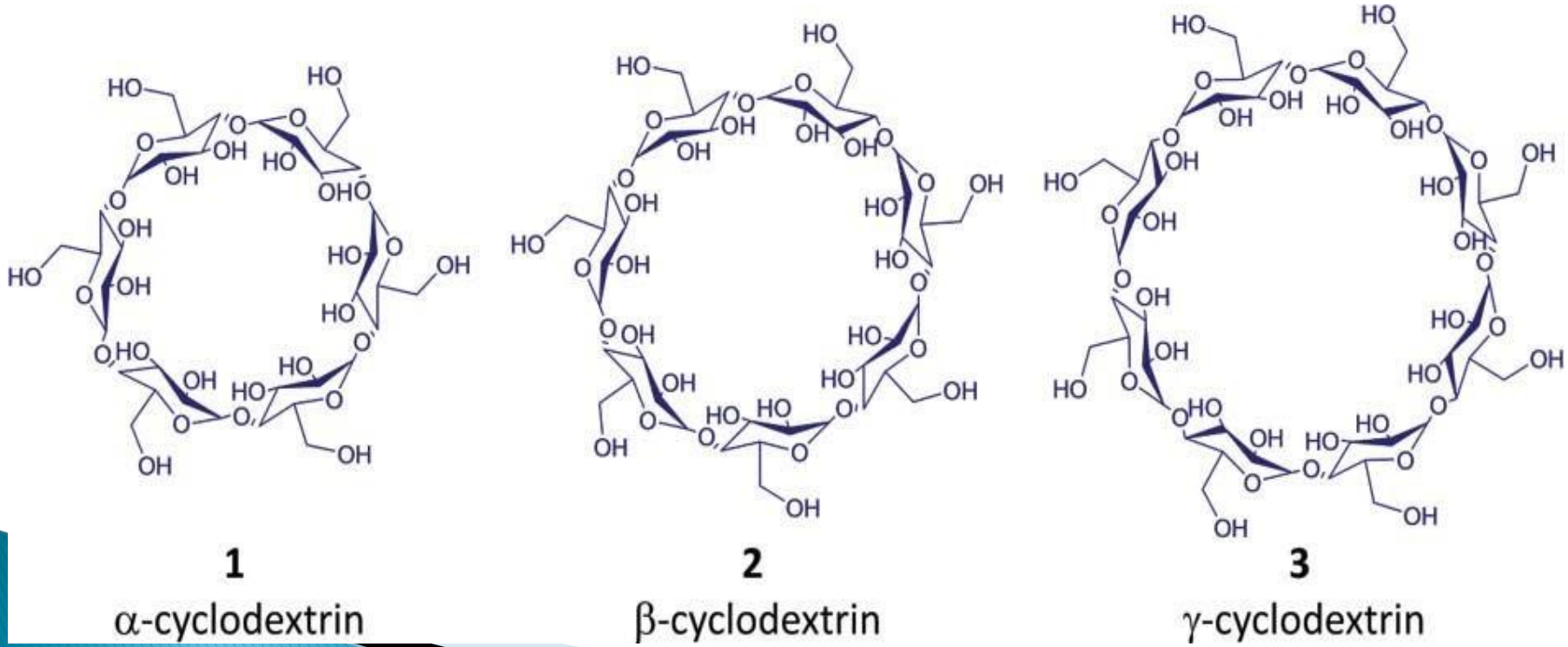
¬ less irritating than-cyclodextrin after i.m. injection

¬binds cholesterol.

γ-Cyclodextrin :

¬8 membered sugar ring molecule

¬ 0.1% absorption after oral administration



1
α-cyclodextrin

2
β-cyclodextrin

3
γ-cyclodextrin

Properties of cyclodextrin

Property	Cyclodextrin		
	α	β	γ
Molecular weight (D)	972	1135	1297
Water solubility (gm/100mL at 25°C)	14.2	1.85	23.2
Melting range (°C)	255-260	255-265	240-245
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
Outer diameter (Å)	14.6	15.4	17.5
Height (nm)	6	11	17

Characteristics-

¬It is a white in colour

¬practically odorless

¬ fine crystalline powders

¬ slightly sweet taste

¬It is chemically inert

Synthesis-

¬The production of cyclodextrin is relatively simple and involves treatment of ordinary starch with a set of enzymes.

¬Commonly cyclodextrin glucosyltransferase (CGTase) is employed along with α-amylase.

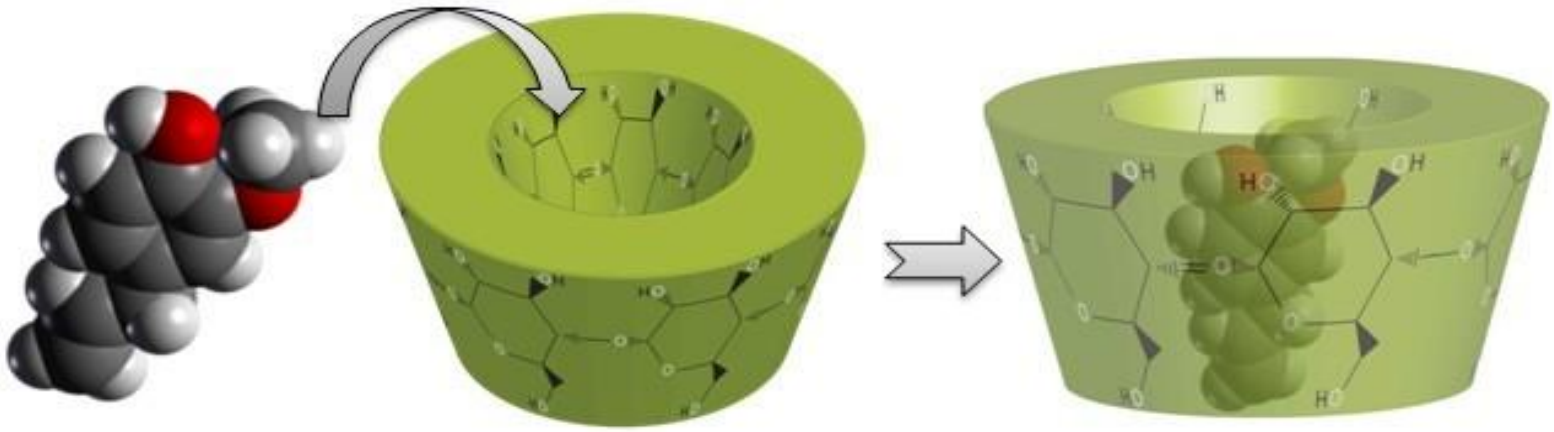
¬First starch is liquefied either by heat treatment or using α-amylase, then CGTase is added for the enzymatic conversion.

¬CGTases can synthesize all forms of cyclodextrins.

Inclusion Complex -

¬Internal hydrophobic cavity is the key feature for complex formation.

¬Inclusion complex formation can be regarded as encapsulation of drug molecule or at least part of molecule.



Methods for making Inclusion Complexes-

1.Physical Blending method

2.Solvent Evaporation method

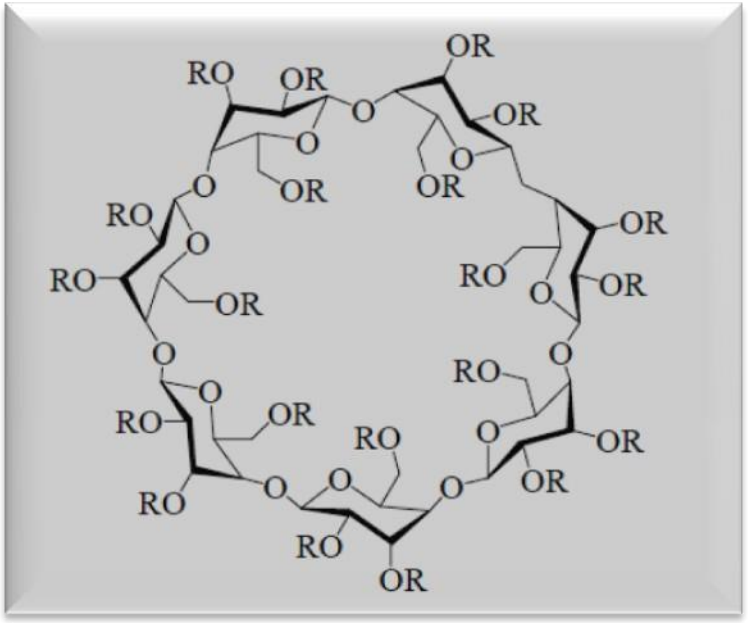
3.Microwave Irradiation Technique

4.Melting Method

5.Freeze Drying Technique

6.Kneading Method

Modifications-



Cyclodextrin	R	Molecular Wt. (D)	Solubility (mg/ml)
2-HP-**β**-CD	$-CH_2CHOHCH_3$	1400	600
SBE-**β**-CD	$-(CH_2)_4SO_3$	2163	500
RM-**β**-CD	-CH3	1312	500

APPLICATIONS-

¬Oral Drug Delivery

¬Parenteral Drug Delivery

¬Ophthalmic Drug Delivery

¬Nasal Drug Delivery

¬Peptide and Protein Delivery

Continue…

¬Topical Drug Delivery

¬Novel Delivery Systems

¬Bioavailability Enhancement

¬Odor and Taste masking

Side Effect -

¬Nephrotoxicity

¬Causes irritation at the site of administration

¬Diarrhoea

Conclusion-

The ability of CDs to form inclusion complexes with many guest molecule by taking up whole or part of it, into cavity. Helps to alter the Solubility, to increase stability, to decrease volatility of compound.

These properties have resulted in the growing importance in pharmaceutical field.

References :-

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¬Chordiya Mayur A. and Senthilkumaran K. (2012) *Cyclodextrin in Drug Delivery: A Review*, Department of Pharmaceutics, CL Baid Metha College of Pharmacy, Thorapakkam, Chennai, India. Department of Pharmaceutics, KK College of Pharmacy, Mangadu, Chennai, India.

¬Del Valle, E.M., 2004. Cyclodextrins and their uses: a review. *Process biochemistry*, *39*(9), pp.1033-1046.

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University of Iceland, Faculty of Pharmacy, Hagi, Hofsvallagata 53, IS-107, Reykjavik, Iceland.

¬*Cyclodextrins: An Excipent Tool In drug Delivery* By Ali Nasir, Harikumar S.L. And Kaur Amanpreet, Department of Pharmaceutics, Rayat and Bahra Institute of pharmacy ,Sahauran, Dist. Mohali, Punjab, India.