Heterocyclic compounds

Dr. Dawood S. Abid

Syllabus

Introduction and

- Heterocyclic compound: Definition.
- Uses and Relevance of heterocyclic compounds.
- Classes of heterocycles.
  - ✓ π-Deficient aromatic heterocycles
  - ✓ π-Excedent aromatic heterocycles
  - ✓ Other aromatic heterocycles
  - ✓ Non-aromatic heterocycles
- Nomenclature of heterocyclic compounds

Synthesis of heterocyclic compounds

Reaction of heterocyclic compounds

REFERENCES

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Chapter 1

INTRODUCTION

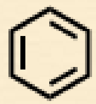
General concepts about heterocyclic chemistry

- Heterocyclic compound: Definition.
- Uses and Relevance of heterocyclic compounds.
- Classes of heterocycles.
  - ✓ π-Deficient aromatic heterocycles
  - ✓ π-Excedent aromatic heterocycles
  - ✓ Other aromatic heterocycles
  - ✓ Non-aromatic heterocycles
- Nomenclature of heterocyclic compounds

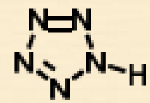
HETEROCYCLIC COMPOUNDS: DEFINITION

CYCLIC COMPOUNDS

ISOCYCLIC COMPOUNDS: Cyclic compounds in which the cycle is formed by atoms of the same element

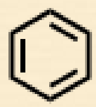


Benzene



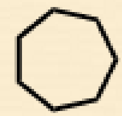
Pentazole

Carbocycles: Isocyclic compounds formed exclusively by carbon atoms



Benzene

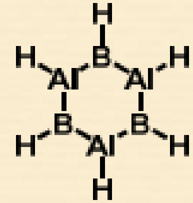
Cyclopentadiene



Cycloheptane

HETEROCYCLIC COMPOUNDS: Cyclic compounds which are formed by atoms of at least two different elements

Inorganic heterocycles: Heterocycles which *do not contain* any carbon atom on the cyclic scaffold



Organic heterocycles: Heterocycles which *contain at least* one carbon atom on the cyclic scaffold

Piperidine

ORGANIC HETEROCYCLES

Most common heteroatoms: Nitrogen (the most abundant and important), Oxygen and Sulfur (rather abundant)

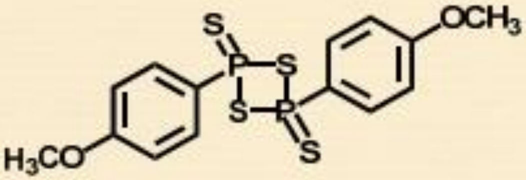
Structure Ball and stick Space filling

Pyridine

Structure Ball and stick Space filling

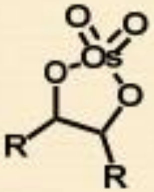
Furane

Other heteroatoms: Se, Te, P, As, Sb, Bi, Si, Ge, Sn, Pb, B (less common not easily found among natural products but useful as synthetic intermediates and/or chemical reagents)



Lawesson Reagent
(Used for sulfur transfer reactions)

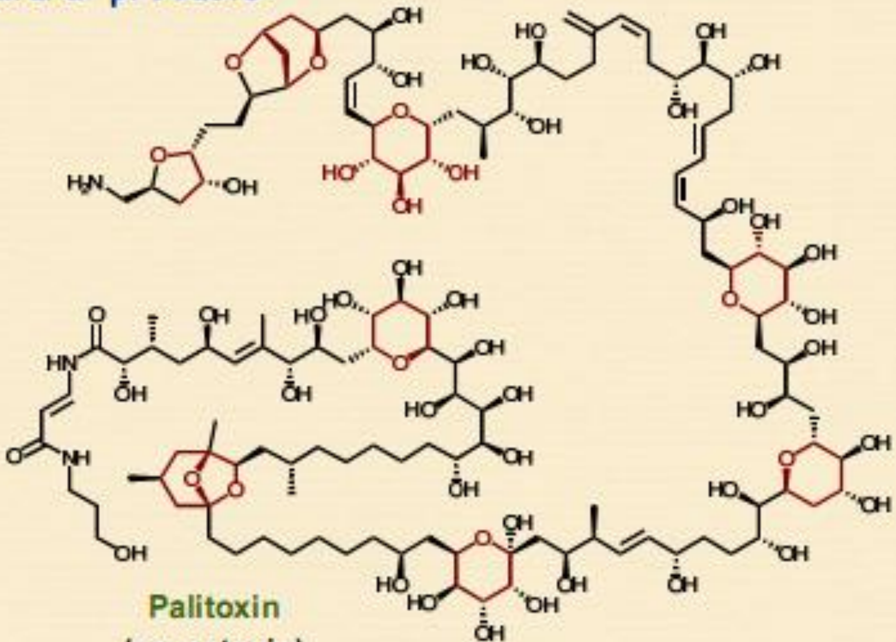
Metal atoms: Pd, Ru, Co… etc. (Metalacycles)



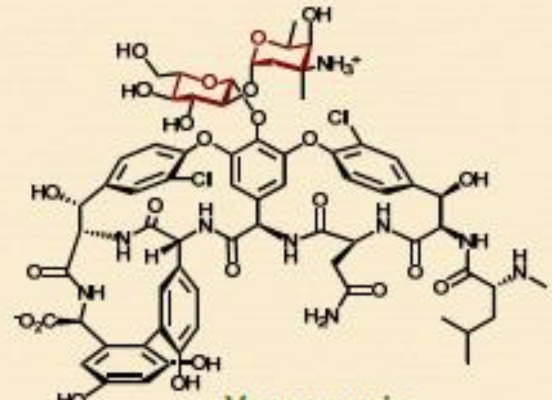
An intermediate in the OsO_4-mediated dihydroxylation of alkenes

USES AND RELEVANCE OF HETEROCYCLIC COMPOUNDS :

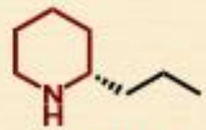
Natural products:



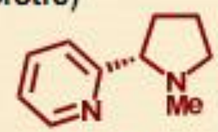
Palitoxin
(neurotoxin)



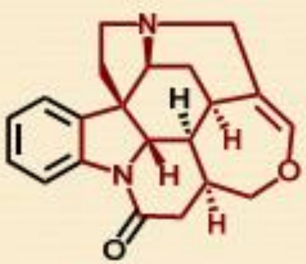
Vancomycin
(antibiotic)



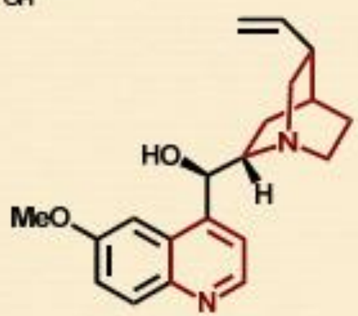
Coniine
(cicuta leaves)



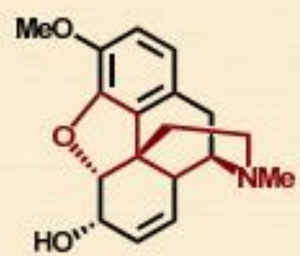
Nicotin
(tobacco leaves)



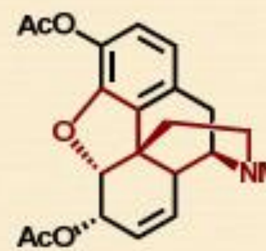
Strichnine
(poison)



Quinine
(antimalaria)



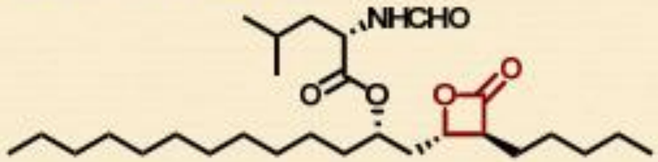
Codeine
(analgesic)



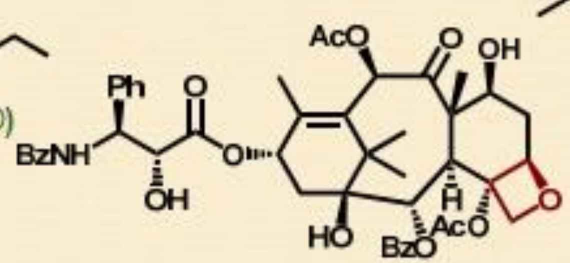
Heroine
(allucinogen)

USES AND RELEVANCE OF HETEROCYCLIC COMPOUNDS

Synthetic Drugs:



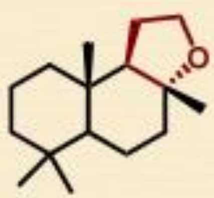
Tetrahydrolipstatin (xenical®)
(obesity treatment)



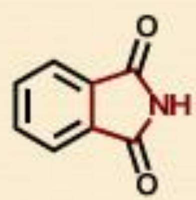
Taxol®
(intitumoral)

Crixivan®
(anti- HIV)

Food additives and health-care consumables:



Abrox®
(Chanel N.5)



Saccharin
(sweetener)

Structural Biomolecules:

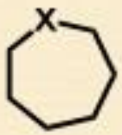
Carbohydrates
Nucleic acids
Vitamins
Several aminoacids and proteins
Co-enzimes (porphirin, chlorophile....
And so on..

CLASSES OF HETEROCYCLES

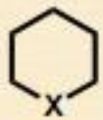
Heterocycles can be classified into three general groups

- ➤ Saturated
- ➤ Partially saturated
- ➤ Aromatic

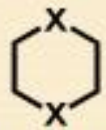
SATURATED HETEROCYCLES



X=O: Oxepane
X=NH: Azepane

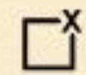


X=O: Oxane
X=S: Thiane
X=NH: Piperidine



X=O: 1,4-Dioxane
X=S: 1,4-Dithiane
X=NH: Piperazine

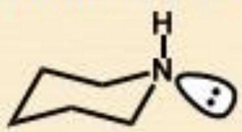
X=O: tetrahydrofurane
X=S: tetrahydrothiophene
X=NH: Pyrrolidine



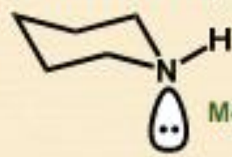
X=O: Oxetane
X=NH: Azetidine

➔ Non-planar structure (sp^3 hybridization of C atoms and heteroatoms)

Different conformations



vs



More stable

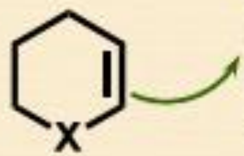
➔ Reactivity: Similar behaviour than that of the corresponding open-chain analogues

- ➤ Oxane like dialkylethers
- ➤ Thiane like dialkylsulfides
- ➤ Piperidine like a secondary amine

Consider bond-angle strain and lack of conformational freedom for reactivity
(e.g. pyrrolidine is more basic than Et_2NH)

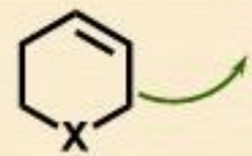
PARTIALLY SATURATED HETEROCYCLES

➔ **C-C double bond:** React essentially as alkenes



Electron-rich alkene
(X=N: enamine)
(X=O: Enol)
Nucleophilic character

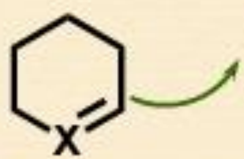
X=O: 3,4-Dihydro-2H-pyrane
X=NH: 1,2,3,4-Tetrahydropyridine



"Standard" alkene
Typical alkene reactivity
(halogenation, hydroalogenation, hydration, hydroboration, oxymercuriation, cycloadditions...

X=O: 3,6-Dihydro-2H-pyrane
X=NH: 1,2,3,6-Tetrahydropyridine

➔ **C-Heteroatom double bond:** React essentially as carbonyls, azomethine or related derivatives



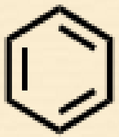
C=X polar bond
- Electrophilic character,
- Confer high acidity to α-H

X=O+: 2,3,4-Tetrahydropyrilium cation
X=N: 2,3,4,5-Tetrahydropyridine

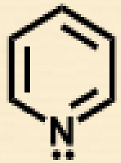
AROMATIC HETEROCYCLES

- **Aromaticity confers high stability (lower reactivity)**
  - Difficult to oxidize or reduce
  - REACTIVITY: Aromatic electrophilic substitution (S_EAr)/Aromatic nucleophilic substitution (S_NAr)/ or aromatic radical substitutions (S_RAr) (addition/elimination mechanism retaining aromaticity)

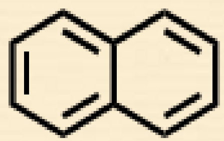
- **Aromaticity: Hückel rule**
  - For a molecule to be aromatic it must:
    - ✓ Be cyclic
    - ✓ Have a *p*-orbital on every atom in ring
    - ✓ Be planar
    - ✓ Posses 4n+2 π electrons (n = any integer)



Benzene
6π e⁻ (4x1 + 2)



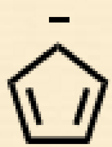
Pyridine
6π e⁻ (4x1 + 2)



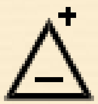
Naphtalene
10π e⁻ (4x2 + 2)

Erich Hückel
(1896-1980)

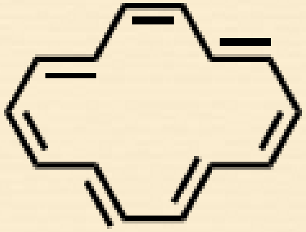
Furane
6π e⁻ (4x1 + 2)



Cyclopentadienyl anion
6π e⁻ (4x1 + 2)



Cyclopropenyl cation
2π e⁻ (4x0 + 2)



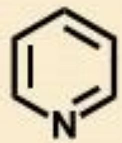
[14]-Annulene
14π e⁻ (4x3 + 2)

CLASSES OF HETEROCYCLES

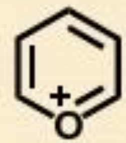
AROMATIC HETEROCYCLES

➔ π-Deficient aromatic heterocycles:

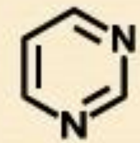
These result from replacing one or more CH units from an aromatic hydrocarbon with (one) heteroatom(s).



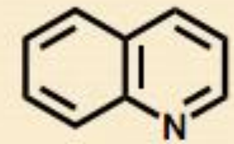
Pyridine



Pyrilium cation



Pyrimidine



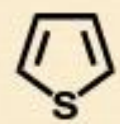
Quinoline

➔ π-Excedent aromatic heterocycles:

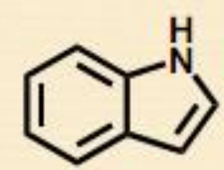
These result from replacing one or more CH=CH units from an aromatic hydrocarbon with (one) heteroatom(s).

Furane

Pyrrol



Pyrimidine



Indole

π-DEFICIENT AROMATIC HETEROCYCLES

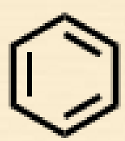
PYRIDINE *vs* BENZENE

SIMILARITIES

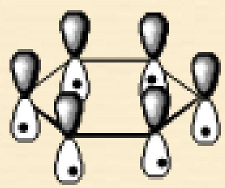
- Both fullfil Hückel rule
- All atoms in the ring are sp^2-hybridized
- σ-bond skeleton formeb by sp^2-sp^2 orbital interactions
- π-Framework formed by a single electron of each atom at p_z orbital

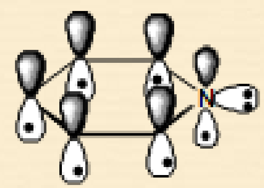
DIFFERENCES

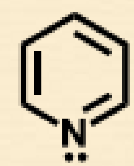
- Nitrogen lone pair on sp2 orbital
- Lone pair lies perpendicular to the molecule axis (coplanar with the ring)
- Different electronegativities of C and N distort electronic distribution



Benzene

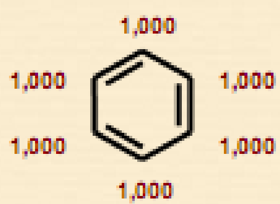


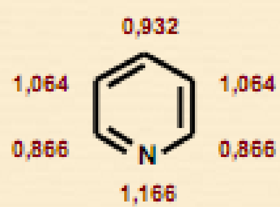




Pyridine

Distortion of electronic distribution:





Nitrogen is more electronegative than carbon and attracts electrons, therefore increasing the electron density on N and C3 and C5 (>1), while electron density is decreased on C2, C4 and C6 (<1).

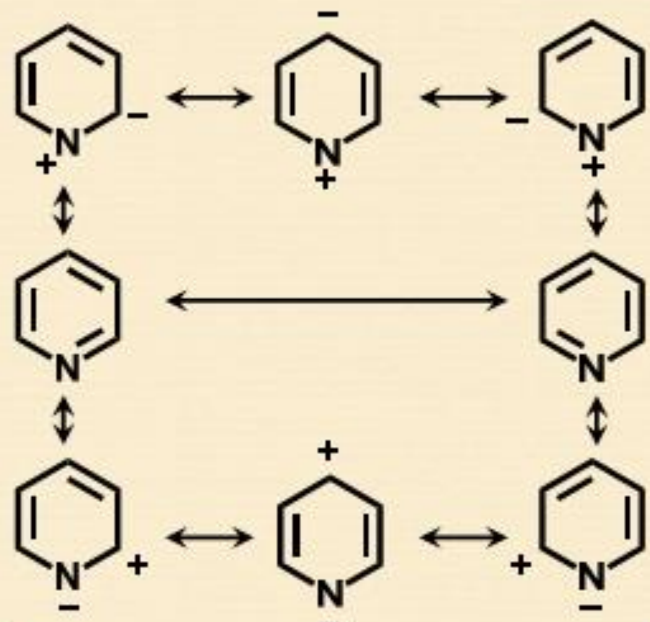
π-DEFICIENT AROMATIC HETEROCYCLES

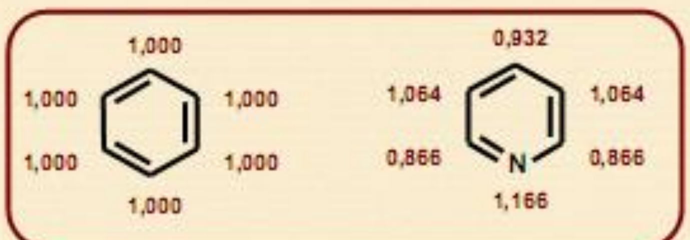
PYRIDINE *vs* BENZENE

This can be explained in terms of resonance structures

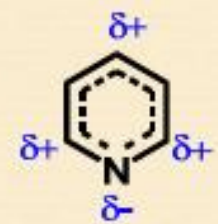
These forms have the less contribution (positive charge on N)

Resonance hybrid





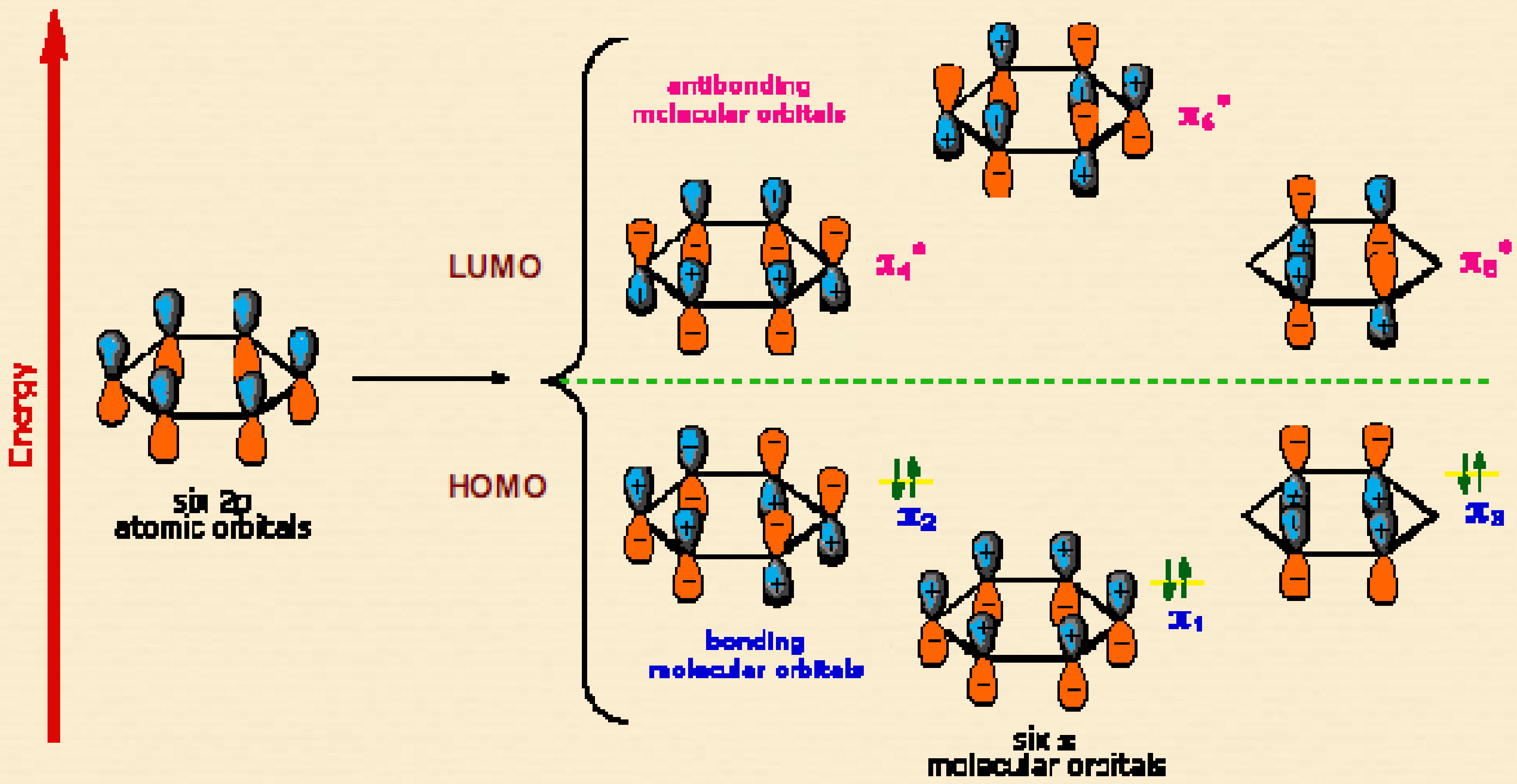
Resonance hybrid



π-DEFICIENT AROMATIC HETEROCYCLES

PYRIDINE *vs* BENZENE

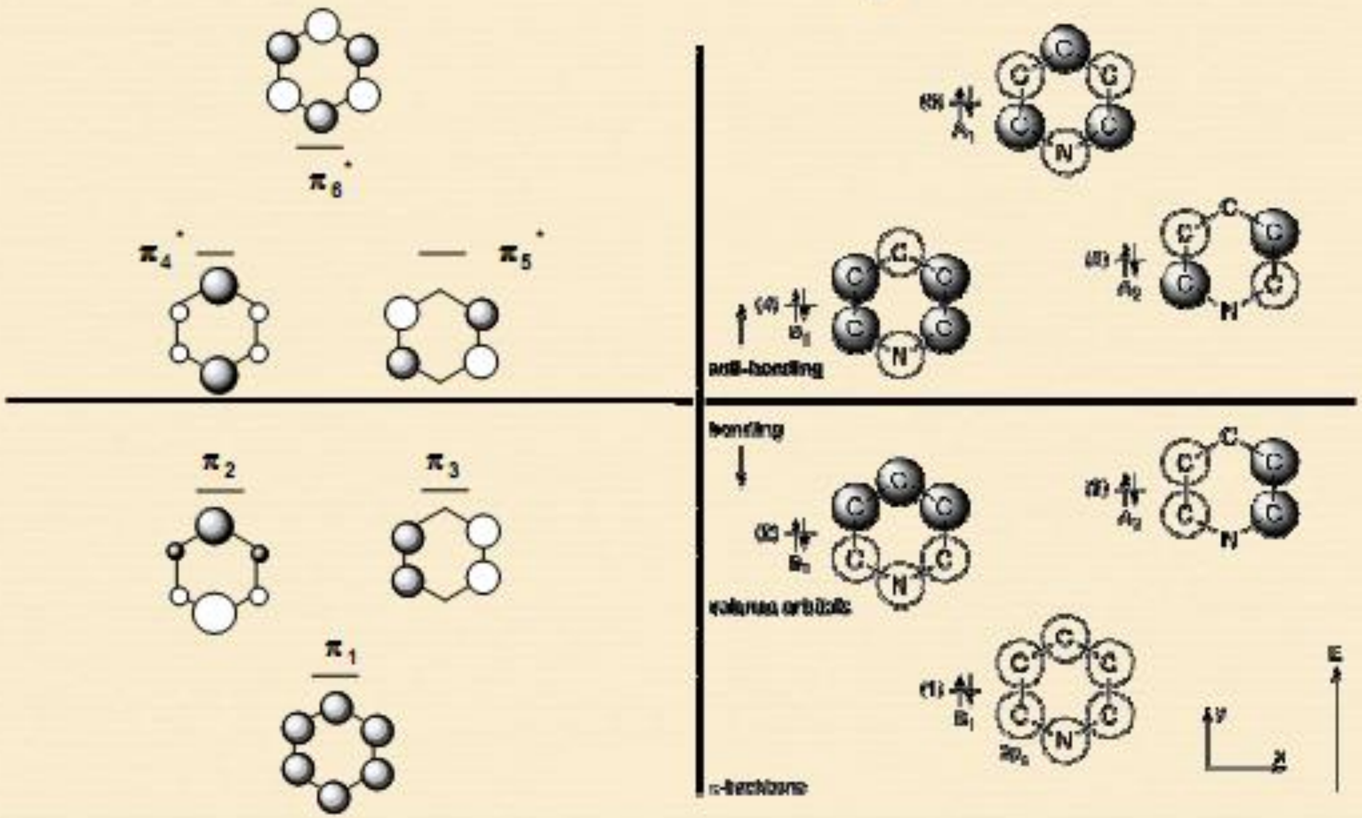
Molecular orbitals of Benzene



π-DEFICIENT AROMATIC HETEROCYCLES

PYRIDINE *vs* BENZENE

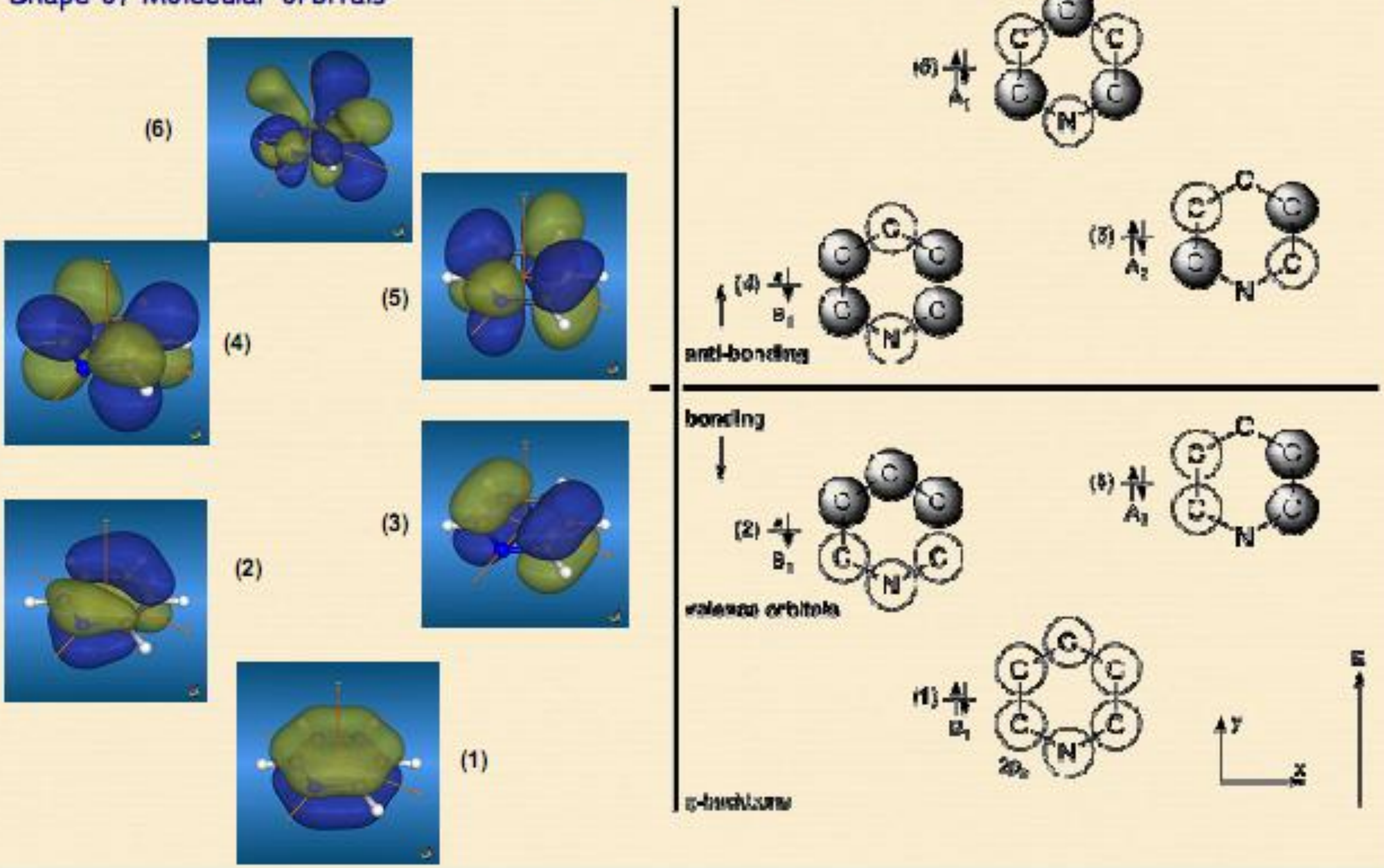
Molecular orbitals of Benzene vs Pyridine



HOMO: π-MO's are lower in energy in pyridine compated with benzene (π-defficient)
LUMO: π*-MO's are lower in energy in pyridine compated with benzene (more tendency to accept electrons, more reactive towards aromatic electrophilic substitution)

PYRIDINE *vs* BENZENE

Shape of Molecular orbitals



OTHER π-DEFICIENT HETEROCYCLES

➔ **One heteroatom (pyridine-like):**

Behave essentially like pyridine. Differences arise from the different electronegativity of the heteroatom

O^+ is more electronegative than N
(Carbon atoms at ring more electron-deficient)

P and Si are less electronegative than N
(Carbon atoms at ring less electron-deficient)

➔ **Two or more heteroatoms:**

The higher the number of heteroatoms on the structure, the more electron-deficient the heterocycle will become

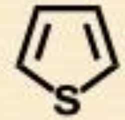
π-EXCEDENT AROMATIC HETEROCYCLES

These result from replacing one or more CH=CH units from an aromatic hydrocarbon with (one) heteroatoms).
Isoelectronic with cyclopentadienyl anion

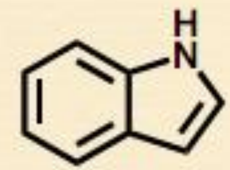
Cyclopentadienyl anion

Furane

Pyrrol



Thiophene

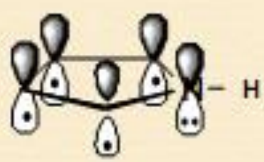


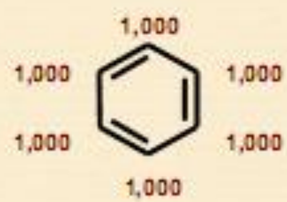
Indole

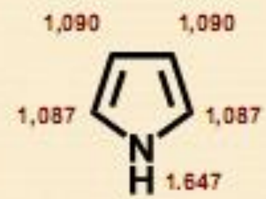
FEATURES

- All atoms in the ring are sp^2-hybridized
- σ-bond skeleton formed by sp^2-sp^2 orbital interactions
- π-Framework formed by a single electron of each atom at p_z orbital
- The heteroatom lone pair that participates on the aromatic π-system lies perpendicular to the molecule axis (coplanar with the ring)
- Heteroatom bonds to adjacent atoms by single bonds
- ELECTRON DENSITY: Six π-electrons shared by five atoms ⇨ Electron rich ring system
- ELECTRON DENSITY: The carbon atoms of the ring have more electron density compared with benzene but less than the heteroatom

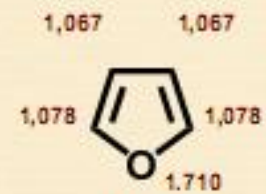
Pyrrol







Pyrrol



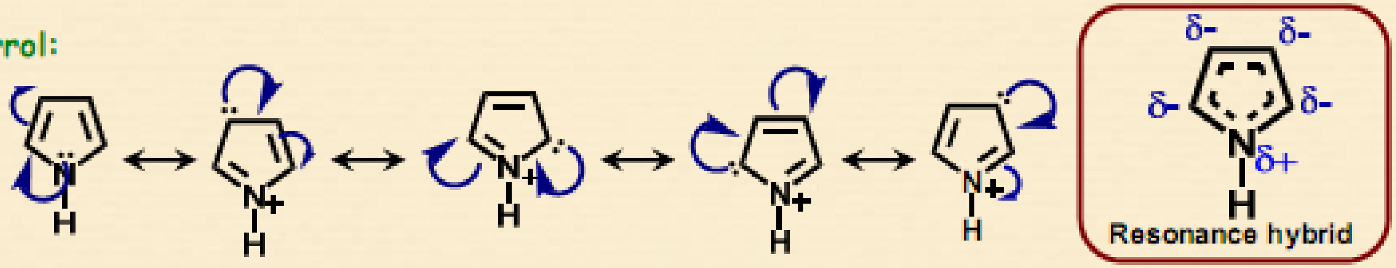
Furane

π-EXCEDENT AROMATIC HETEROCYCLES

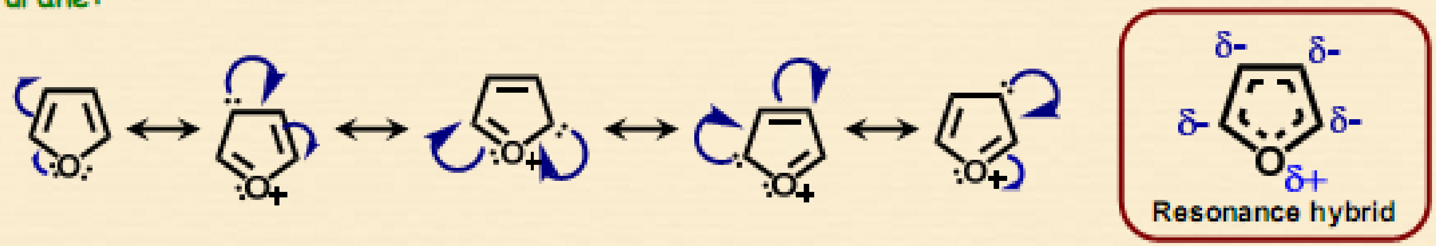
ELECTRON DENSITY MAP

Can be understood in terms of resonance structures

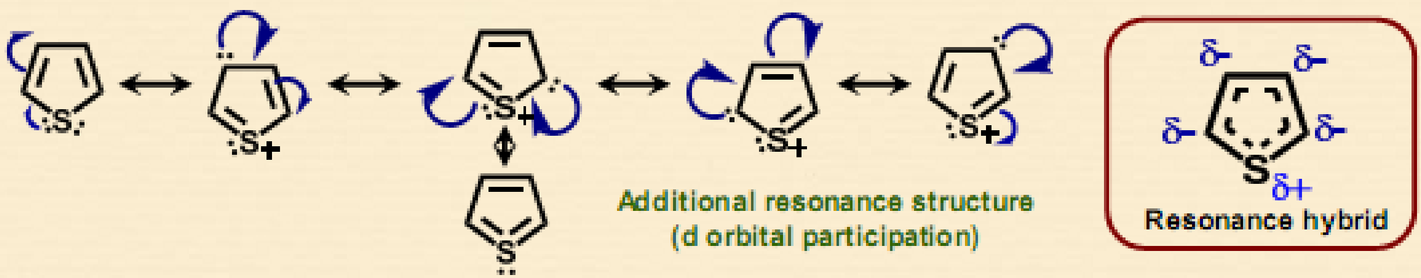
➔ Pyrrol:



➔ Furane:



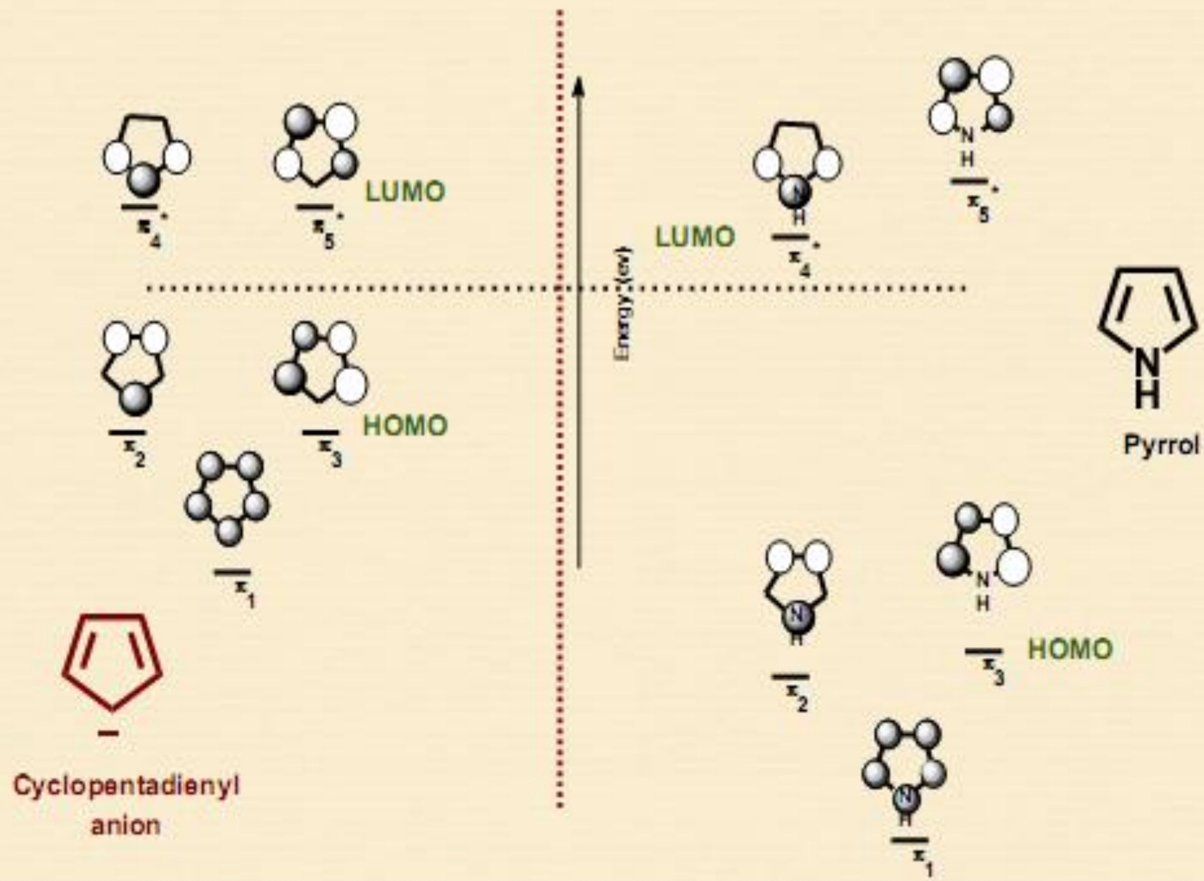
➔ Thiophene:



- Thiophene has a more aromatic character (contribution of additional resonance structure without charge separation)
- Furane has the less aromatic character (unstability of resonance structures with a possitively charged oxygen atom.

π-EXCEDENT AROMATIC HETEROCYCLES

PYRROL vs CYCLOPENTADIENYL ANION



- HOMO in pyrrole is less energetic (more accessible and therefore with more tendency to donate electrons: π-excedent)
- GEOMETRY OF HOMO: Largest coeficients at C2 and C5: More reactive possitions