2302687 – Heterocyclic Compounds – Part I

Lecture 1-5

Heteroaromaticity

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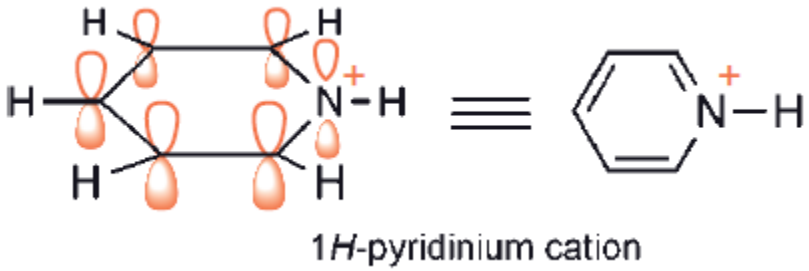
Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

Heteroaromaticity – Six-Membered

Pyridinium cation

Electrophilic addition to the pyridine nitrogen generates pyridinium ions, the simplest being 1*H*-pyridinium formed by addition of a proton

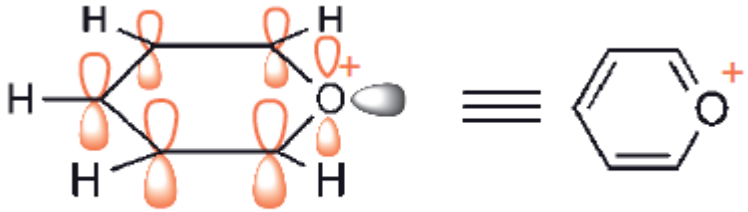


1*H*-pyridinium cation

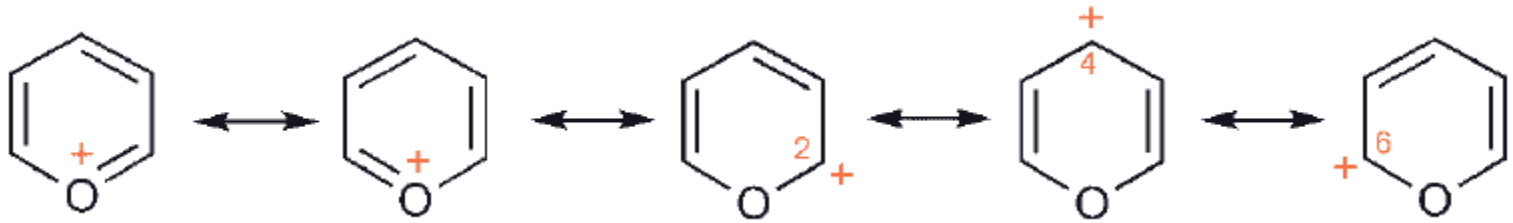
(isoelectronic with benzene)

Pyrylium cation

the positively charged oxygen also has an unshared electron pair, in an sp^2 orbital in the plane of the ring, exactly as in pyridine



pyrylium cation

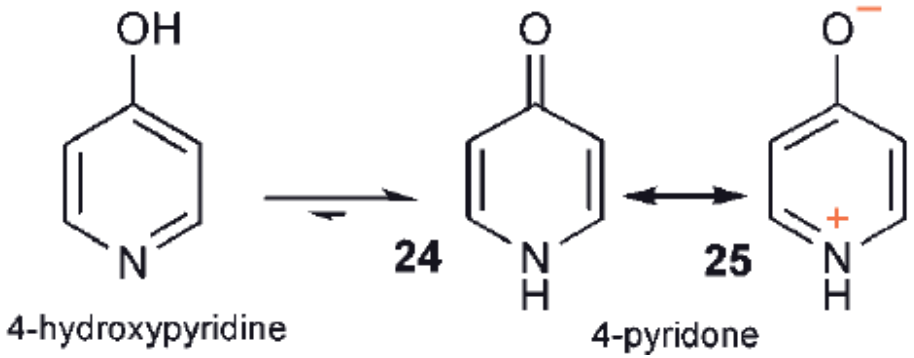


- A set of resonance contributors indicates that pyrylium is strongly positively charged at the 2-, 4- and 6-positions

Heteroaromaticity – Six-Membered

Pyridone

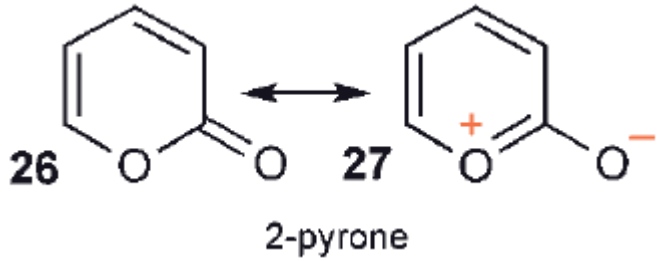
Pyridines with an oxygen at either the 2- or 4- position exist predominantly as **carbonyl tautomers**



The **degree of aromaticity** depends on the contribution that dipolar structures, **25**, with a 'complete' pyridinium ring make to the overall structure

Pyrones

(oxygen analogue of pyridone); no alternative tautomer is possible

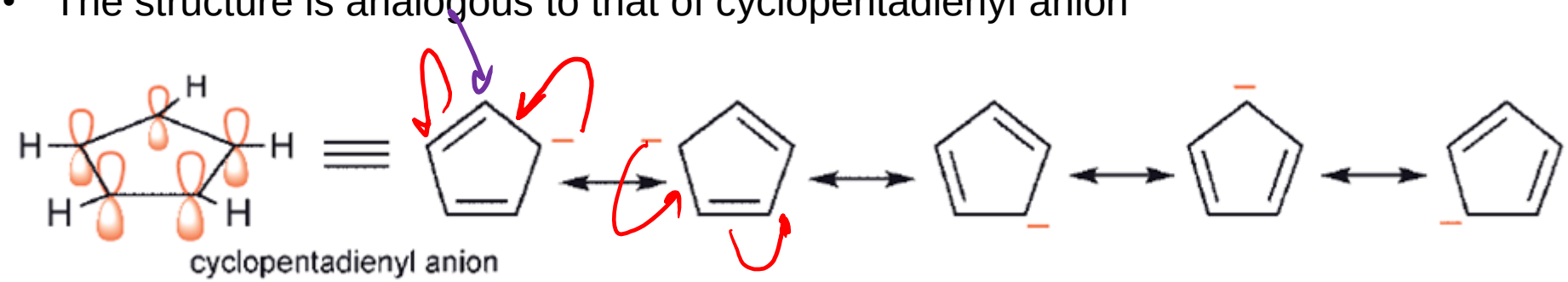


Pyrones are **less aromatic** than pyridones as would be expected by comparing the 'aromatic' contributors, **25** and **27**; positive charge at oxygen is less favourable than at nitrogen

As a result, pyrones are more likely to react with other reagents

Heteroaromaticity – Five-Membered

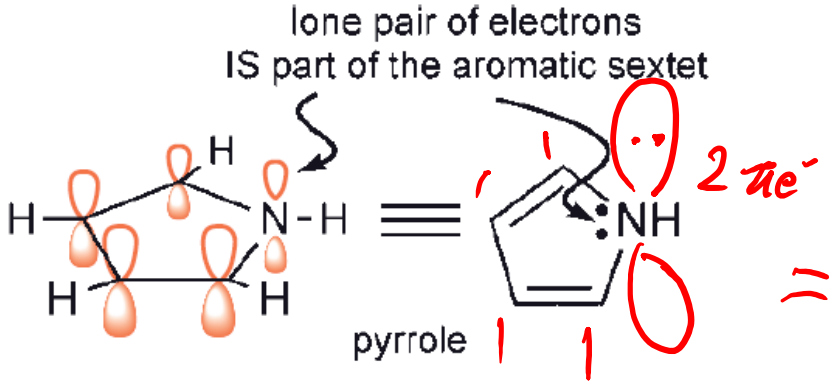
- The structure is analogous to that of cyclopentadienyl anion

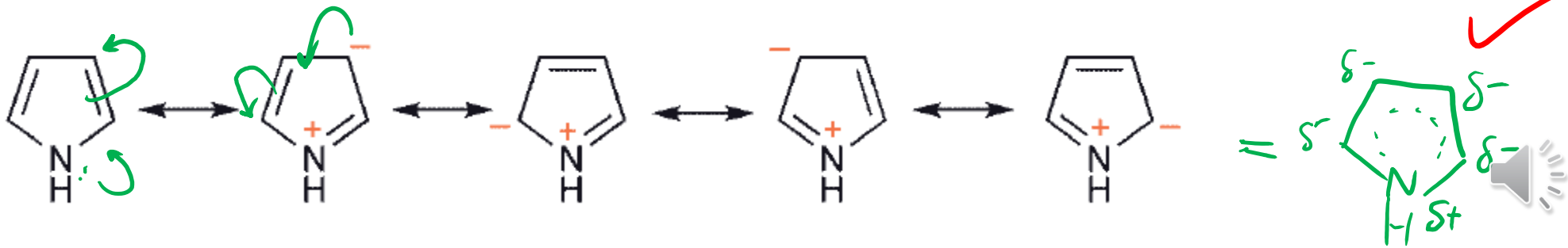


- Each carbon atom is equivalent and carry one fifth of the negative charge

Pyrrole

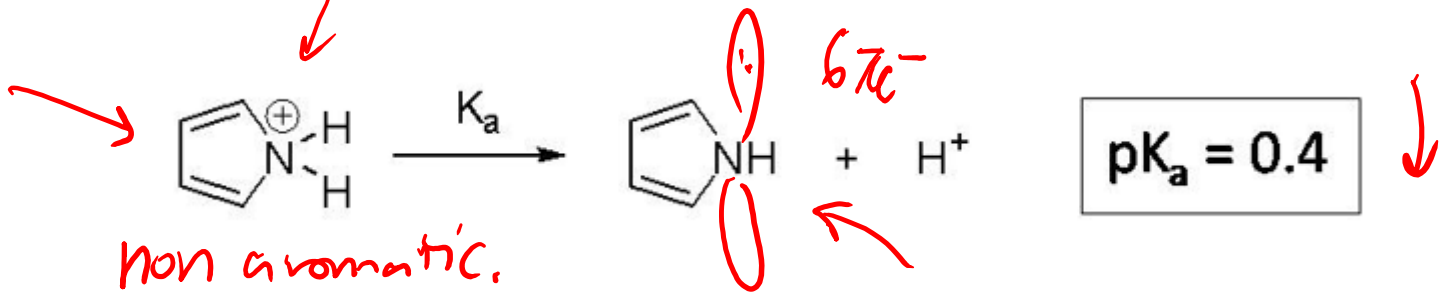
- Isoelectronic with the cyclopentadienyl anion, but is electrically neutral
- Nitrogen lone pair in pyrrole forms part of the aromatic six-electron system



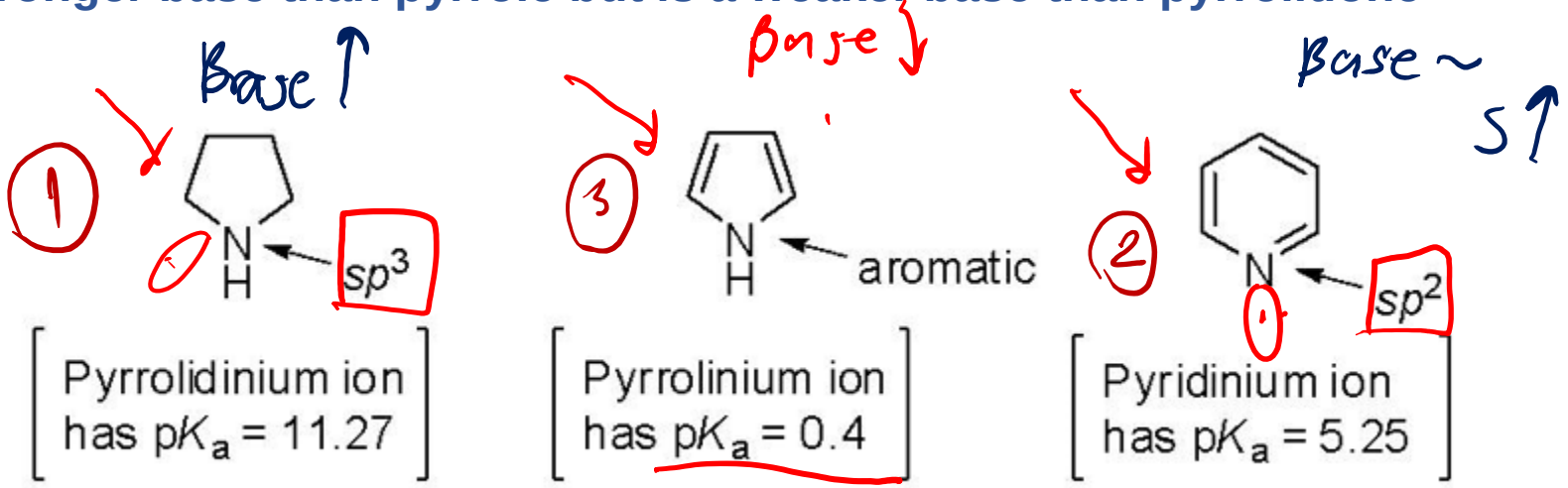


Heteroaromaticity – Basicity

- Protonation on N of pyrrole destroys the aromaticity, giving its conjugate acid a very low pK_a (strong acid); **Pyrrole is a much weaker base than pyrrolidone**



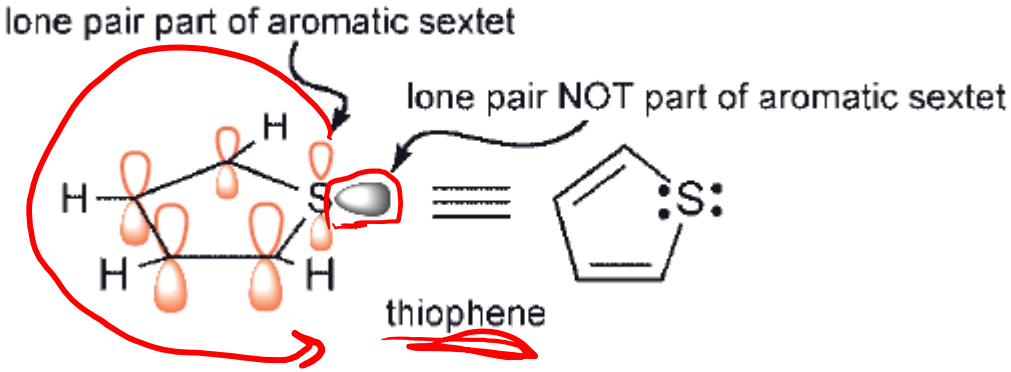
- Protonation on N of pyridine does not affect aromaticity; however, the **sp^2**-hybridized N holds lone-pair electrons more tightly than the sp^3; **Pyridine is a stronger base than pyrrole but is a weaker base than pyrrolidone**

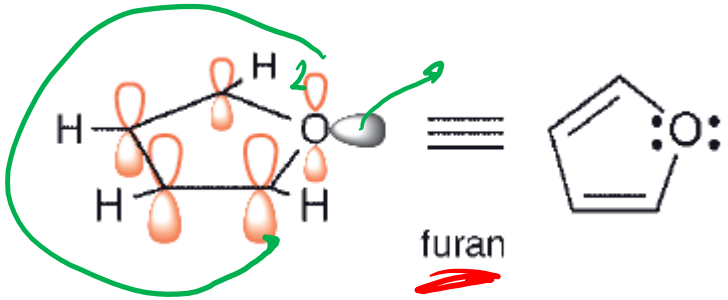


Heteroaromaticity – Five-Membered

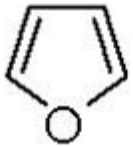
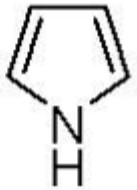
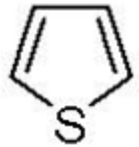
Thiophene and Furan

- NH in pyrrole is replaced by S and O, respectively
- Heteroatom in each has one lone pair as part of the aromatic sextet, as in pyrrole, but also has a second lone pair that is not involved





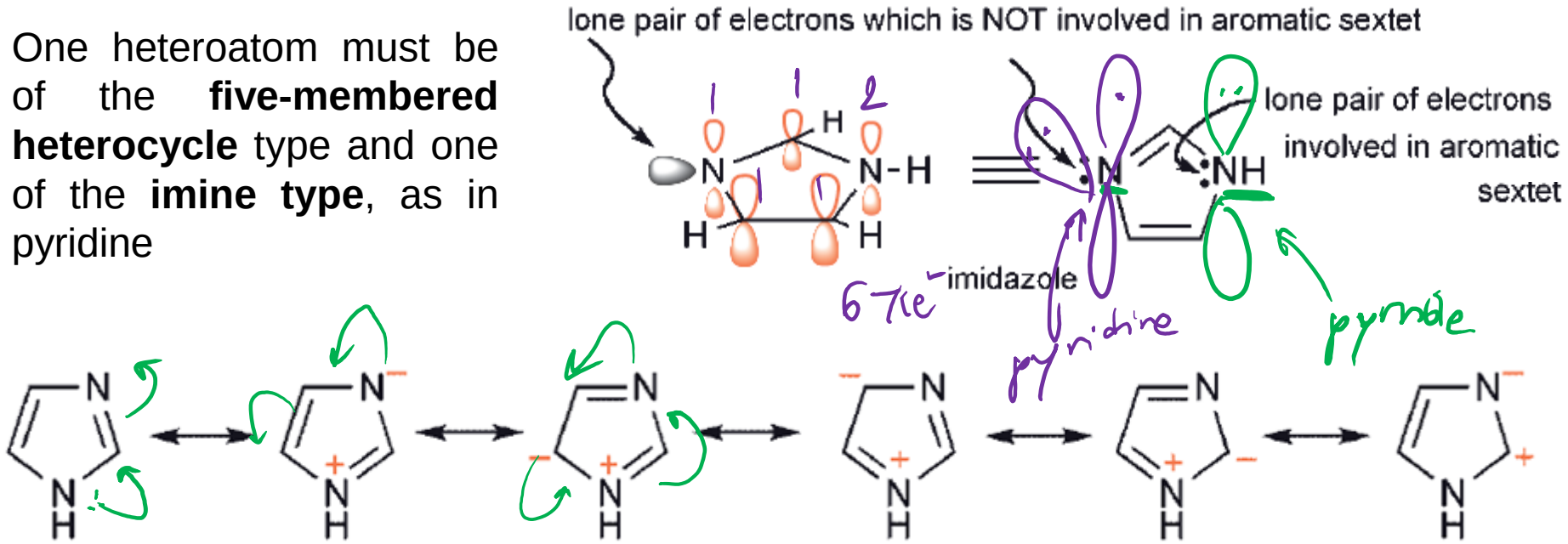
- **Degree of aromaticity** depends on the electronegativity of the heteroatom

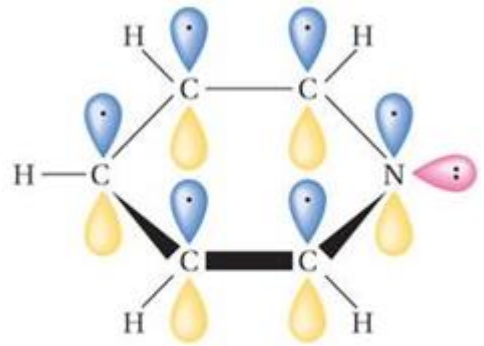
Electronegativity	O = 3.5	>	N = 3.0	>	S = 2.5
Aromaticity		<		<	

Heteroaromaticity – Five-Membered

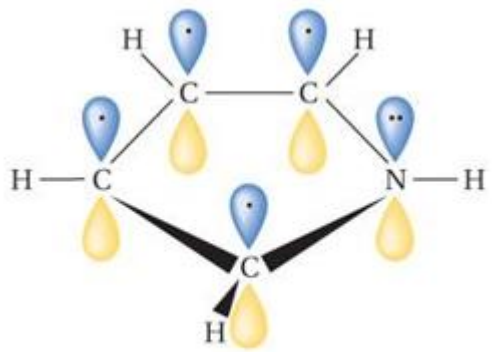
Imidazole

One heteroatom must be of the **five-membered heterocycle** type and one of the **imine type**, as in pyridine

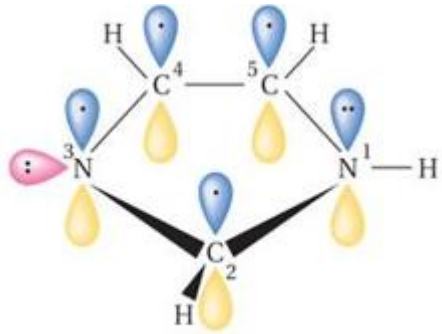




Bonding in pyridine



Bonding in pyrrole

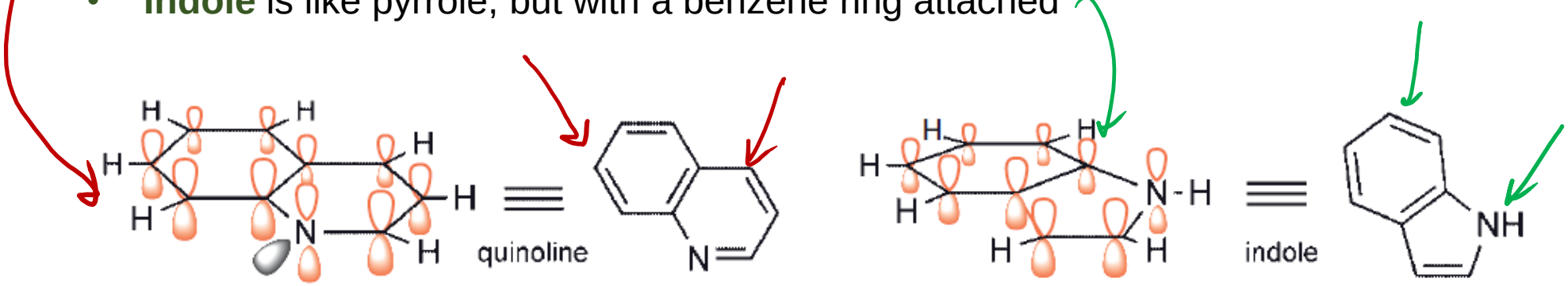


Bonding in imidazole

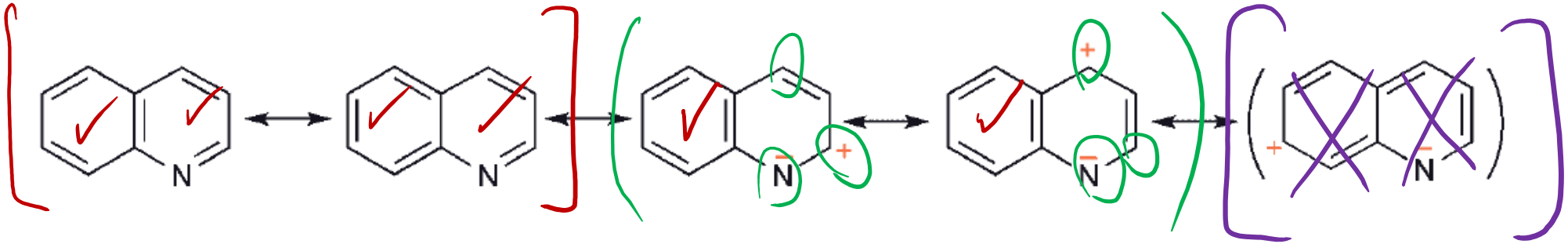
Heteroaromaticity – Bicyclic Compounds

- It is straightforward to extrapolate to those systems which combine two (or more) of aromatics/heteroaromatics

- **Quinoline** is like naphthalene, only with one of the rings a pyridine
- **Indole** is like pyrrole, but with a benzene ring attached



- Contributors in which **both aromatic rings are disrupted** make a very much **smaller contribution** and are shown in parentheses

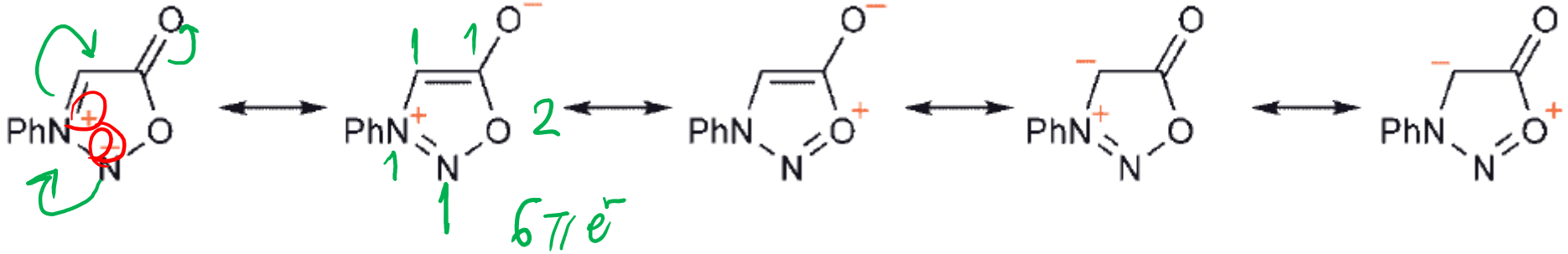


Heteroaromaticity – Mesoionic Systems

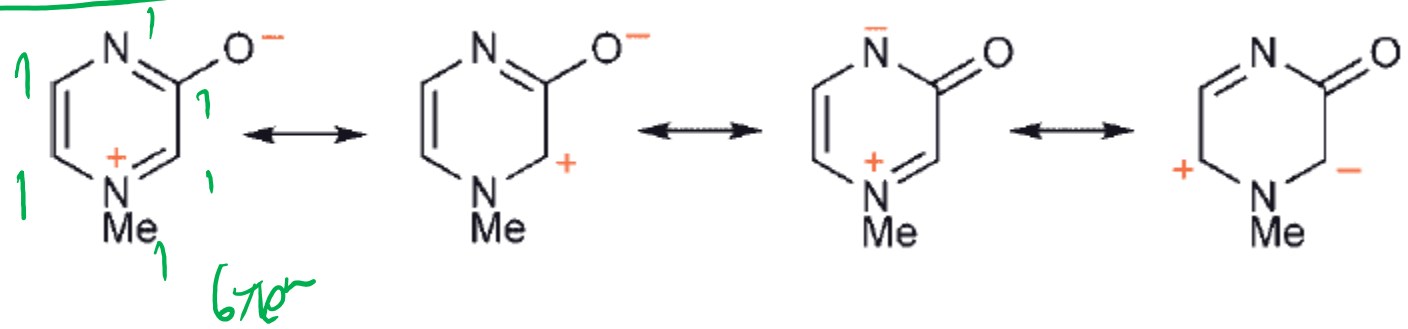
- Heterocyclic substances for which no plausible, unpolarised mesomeric structure can be written

- Despite the presence of a nominal positive and negative charge in all resonance contributors to such compounds, they are not salt-like, are of course **overall neutral**, and behave like '**organic**' substances, dissolving in the usual solvents

Syndone

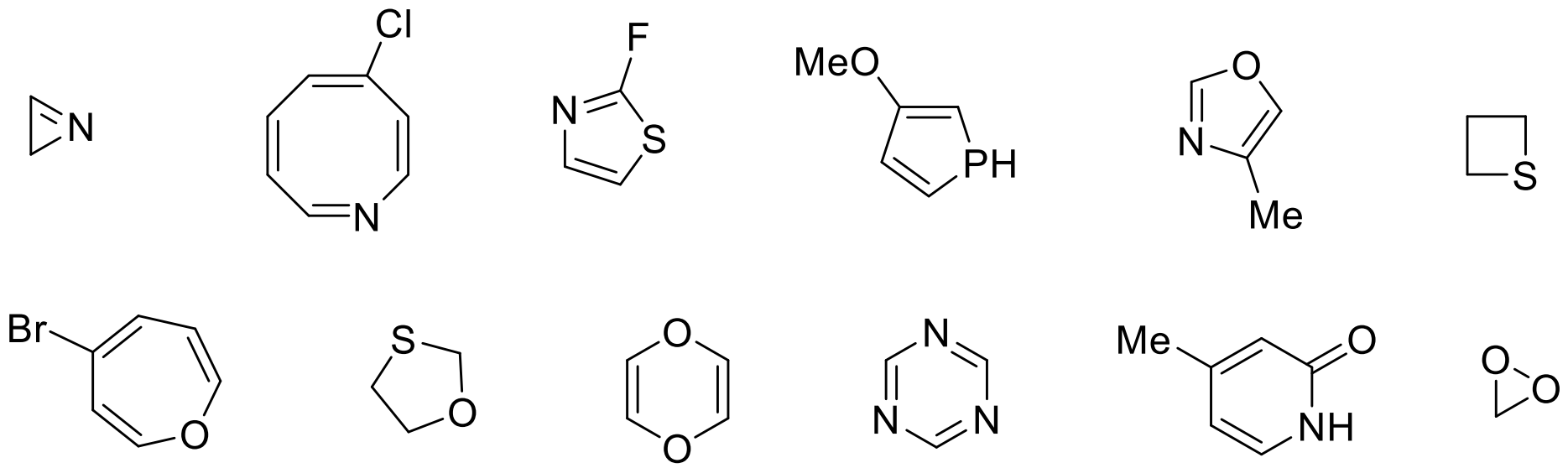


Pyrazinium-3-olate



Homework # 1

Provide the Hantzsch – Widman name for each structure and state whether it is *aromatic*, *nonaromatic* or *antiaromatic*



- Take a photo / capture screen of your answer

- Upload PDF/JPEG file into the “Assignment for Week 1” in the Blackboard

Homework # 2

2 minute presentation on the applications of heterocycles

Such as:

- **Natural Products**
- **Drugs**
- **Agrochemicals**
- **Conducting Polymer**
- **Metal complexes**

The example must contain at least **2 heterocycles** in the molecule

Focus on **Nomenclature** and its **Applications**

Upload in Youtube

Copy the URL and paste in the “Assignment for Week 1” in the Blackboard

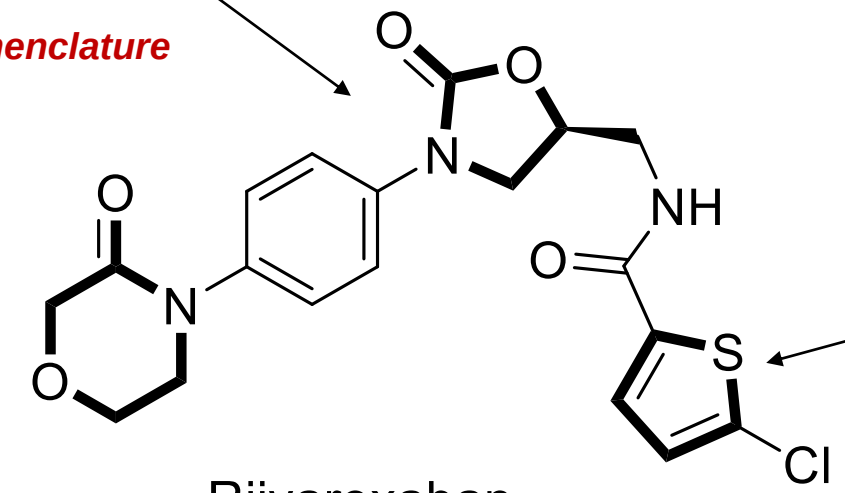
Example

Rivaroxaban

- **Anticoagulant** medication (blood thinner) commonly used to prevent blood clots

1,3-Oxazolidin-2-one

Explain briefly about the nomenclature



Riivaroxaban

Thiole
(Thiophene)

Tetrahydro-1,4-oxazin-3-one
(Morpholin-3-one)