REACTIONS OF FIVE MEMBERED HETEROCYCLES
The structures of five-membered saturated heterocycles are similar to cyclopentane. Since there is little angle strain in five-membered rings, the structures adopt an envelope conformation to minimize torsional strain. The heteroatom occupies the out-of-plane position to avoid gauche interactions. See pyrrolidine below.
Reactions of Five-Membered Heterocycles

Pyrrolidines as a Bases

• Since ring strain is of little or no importance in five membered heterocycles, ring-opening reactions are rarer compared to three- or four-membered heterocycles.

• Among the saturated heterocycles only pyrrolidine has significant basic character.

• Pyrrolidine is more basic than acyclic secondary amines because the nitrogen lone pair is more exposed in the structure.
Reactions of Five-Membered Heterocycles
Perspectives

• The majority of five-membered heterocycles are aromatic compounds with a planar structure.

![Chemical structures](image)

- Azole (Pyrrole)
- Oxole (Furan)
- Thiole (Thiophene)
- Imidazole
- Oxazole
- Thiazole

• The lone pair of electrons on the heteroatom contributes to the six-electrons of the π-system to fulfil the aromaticity requirement.
Structure of Five Membered Aromatic Heterocycles

- Five-membered aromatic heterocycles have a $\pi$-electron excess (six electrons on five atoms) relative to benzene with an $\pi$-electron density of one on each ring atom.

- Although five membered heterocycles have an electronegative heteroatom, they are more electron rich compared to benzene, thus classified as $\pi$-excessive.
Aromatic Heterocycles

Classification

• Generally, other aromatic heterocycles can also be classified as either $\pi$-excessive or $\pi$-deficient.

AROMATIC HETEROCYCLES

$\pi$- EXCESSIVE $\pi$- DEFICIENT

$\mathbb{Z} = \text{O, S, NH}$

• Thus relative to benzene, pyridine in $\pi$-deficient.

• There is a vast difference between the properties of the two classes of aromatic heterocycles.

• A characteristic of $\pi$-deficient heterocyclic systems is their low reactivity with electrophilic agents.
Reactivity of Five Membered Aromatic Heterocycles

- The degree of \( \pi \)-excessivity in a five-membered ring is determined by the ease with which the lone pair is released into the delocalized system.
- This is directly related to the electronegativity of the heteroatom.
- Thus the lower the electronegativity of the heteroatom, the higher the \( \pi \)-excessivity and the higher the reactivity with electrophiles in electrophilic aromatic substitution.
Electrophilic Aromatic Substitutions in Five Membered Heterocycles

\( \pi \)-Excessive Heterocycles

- A significant feature of \( \pi \)-excessive systems like five membered heterocycles is that they undergo electrophilic aromatic reactions faster than benzene.
- The reactivity is greater than that of benzene and is in roughly the same range as found for benzenes bearing electron releasing groups as in aniline.
- The greater electron density in these rings accounts for this higher reactivity.
- The dominant reactions of the five membered aromatic heterocycles that we will look at are the electrophilic aromatic substitutions.
Reactions of Five Membered Heterocycles

Electrophilic Aromatic Substitution

- The substitution in the five membered heterocycles is regioselective to the α position.
- However, when the α-positions are occupied, the β-position becomes the target for substitution.
Reactions of Five Membered Heterocycles

Why the Regioselectivity

An inspection of the resonance structures for \( \alpha \) and \( \beta \)-substitution shows that the +ve charge is better resonance stabilized when the substitution is at the \( \alpha \)-position than at \( \beta \)-position.

Whereas a more stable intermediate cation stabilized by 3 resonance intermediates is formed in \( \alpha \)-substitution, in \( \beta \)-substitution only 2 resonance structures are formed.
Reactions of Five Membered Heterocycles
Electrophilic Aromatic Substitution

- Of the three classes of five membered heterocycles (pyrrole, furan and thiophene), pyrrole is the most susceptible to electrophilic attack.
- This susceptibility is from the greater electron-donating ability of neutral trivalent nitrogen and the greater stability of a positive charge on tetravalent nitrogen.
- Since thiophene and pyrrole have a higher degree of aromatic character, they readily undergo electrophilic aromatic substitution compared to furan.
- The common aromatic substitution reactions include halogenation, nitration, acylation and formylation.
Halogenation of Five Membered Heterocycles

- Halogenation occurs at the α-position. Bromination and iodination are easy to control compared to the more electrophilic chlorination, which requires low temperatures to control the chlorination.
- For example, furan can be chlorinated and halogenated as illustrated below
Nitration of Five Membered Heterocycles

- The reagent AcONO$_2$ is generated *in situ* from concentrated HNO$_3$ and Ac$_2$O.
- The nitration with AcONO$_2$ occurs by electrophilic aromatic substitution.
- Furan, pyrrole and thiophene can readily be nitrated using these reagents.
Mechanism of Nitration of Five Membered Heterocycles

• The nitration of furan follows the following steps:
The acylation of five membered heterocycles commonly employs an acid anhydride in the presence of an acid catalyst (e.g. phosphoric acid) or a Lewis acid (e.g. BF$_3$, ZnCl$_2$, SnCl$_4$ and AlCl$_3$).

\(-\text{Acetylation of furan can be accomplished using acetic anhydride in the presence of phosphoric acid.}\)
The acylation of furan using acetic anhydride in the presence of phosphoric acid as a catalyst follows the following steps:
Acylation of Five Membered Heterocycles

• In general, in the acylation of five membered heterocycles, position 2 (α-position) is more reactive than position 3.
• However, when position 2 is blocked, β-acylation can proceed smoothly.

![Chemical reaction diagram]

• Thiophene and pyrrole react in a similar manner..
Formylation of Five Membered Heterocycles

- Formylation of five membered heterocycles is accomplished using dimethylformamide (DMF) and phosphorus oxytrichloride (POCl$_3$).
- Furfural, an important renewable, non-petroleum based, chemical feedstock, can be prepared by the formylation of furan.
Mechanism of Formylation of Five Membered Heterocycles

- The formylation of furan follows the following steps:
Reactions of Five Membered Heterocycles

Hydrogenation

- The five membered aromatic heterocycles undergo hydrogenation in the presence of a catalyst to provide the corresponding tetrahydro derivatives.
- Using different metal catalysts (Pd, Ni, Pt or PtO₂), diverse saturated heterocycles can be accessed.
Oxidation of Thiophene

• Oxidation of thiophene with meta-chloroperoxybenzoic acid provides thiophene-1,1-dioxide (thiophene sulphone).

• Controlled oxidation to thiophene sulphoxide is possible with dimethyldioxirane.
Practice Questions
Reactions of Five Membered Heterocycles

Complete the following reactions by providing the principal organic products:

Propose a reasonable and stepwise reaction mechanism for the transformation below: