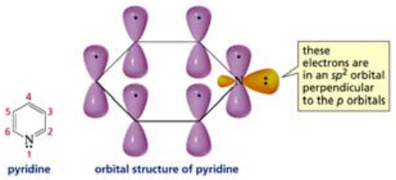
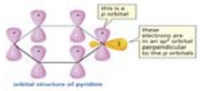
Aromatic Six-Membered-Ring Heterocycles



Pyridine

a Six-Membered Heterocycle

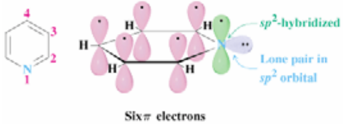
- Pyridine is a six membered heterocyclic compound with molecular formula of C_6H_5N and it is obtained from coal tar.
- It may be formally derived from the structure of benzene through the exchange of one ring carbon for a *sp*² hybridized nitrogen.
- Pyridine is an aromatic compound, however, the nitrogen's lone pair of electrons is in an *sp*² orbital orthogonal to the *p* orbitals of the ring, therefore it is not involved in maintaining aromaticity but it is available to react with protons thus pyridine is basic



Pyridine

a Six-Membered Heterocycle

- **It is a nitrogen-containing heterocyclic analog of benzene**
- **Lone pair of electrons on N occupies an sp2 orbital in the plane of the ring but is not involved in aromaticity.**

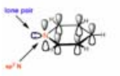


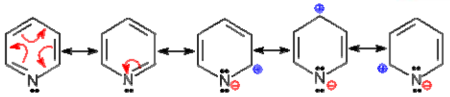
- **On the other hand all six-memeberd rings with a heteroatom other than N are not aromatic .**

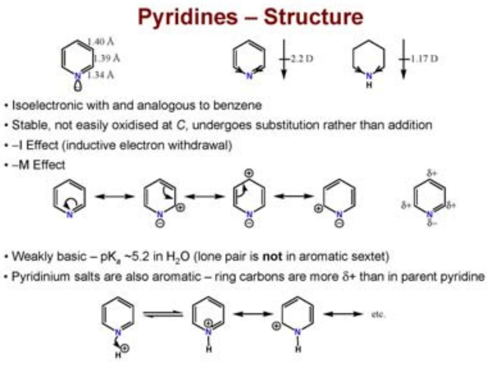
Pyridine

a Six-Membered Heterocycle

❖ Due to the greater electronegativity of nitrogen (relative to carbons) it tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge while the carbons at positions 3 and 5 remain neutral.







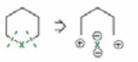
Pyridines – Structure

- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at *C*, undergoes substitution rather than addition
- –I Effect (inductive electron withdrawal)
- –M Effect

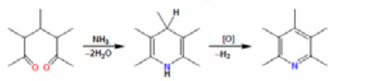
- Weakly basic – pK_a ~5.2 in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more δ+ than in parent pyridine

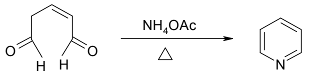
Synthesis of Pyridine

Common Strategy ''5 + 1''



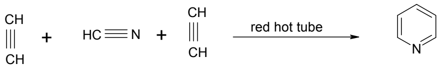
- From 1,5-dicarbonyl compounds:



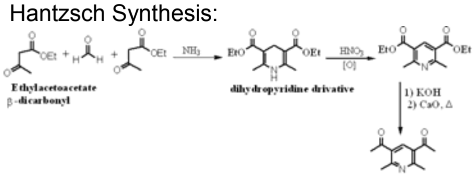


Synthesis of Pyridine

- Bönnemann cyclization:

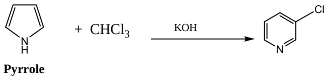


- Hantzsch Synthesis:

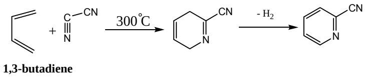


Synthesis of Pyridine

- From Pyrrole:

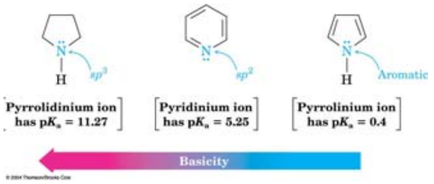


- By Diels Alder reaction



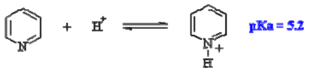
Basicity of Pyridines

- Pyridine is a stronger base than pyrrole but a weaker base than alkylamines
- The sp^2-hybridized N holds the lone-pair electrons more tightly than the sp^3-hybridized nitrogen in an alkylamine

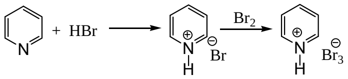


Basicity of Pyridines

- Pyridine is a weak base; since lone pair is in an sp^2 hybrid orbital.

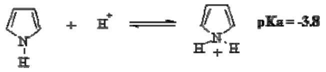


- It undergoes many reactions typical of amines such as reaction with Bronsted acids such as chromic acid and hydrobromic acid.



Basicity of Pyridines

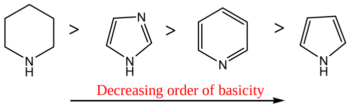
- Compared to pyrrole, pyridine is much stronger base
  - this is due to the nitrogen lone pair is not involved in maintaining the aromaticity thus it free for protonation,
  - however, in pyrrole the lone pair on the N atom is already involved in the aromatic array of p electrons.
  - Protonation of pyrrole on N atom results in loss of aromaticity and is therefore unfavorable.



- Compared to imidazole, pyridine is less basic this is due to the fact that
  - In imidazole, on protonation the + ve charge can be delocalized over two nitrogen atoms
  - While in case of pyridine it is delocalized over the ring which interrupt aromatcity.

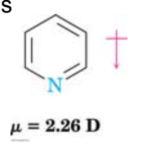
Basicity of Pyridines

- Compared to analogous aliphatic amines, pyridine is less basic
  - This is due to the nitrogen atom in pyridine is *sp*^{2} hybridized
    - more electronegative
  - The lone pair of electrons occupies an *sp2* orbital
    - thus it is held more tightly by the nucleus than the lone pair of electron in aliphatic amines with *sp3* hybridized
  - In Aliphatic Amines, N atom and the lone pair of electrons occupies an *sp3* orbital (less electronegative).



Low Reactivity of Pyridine

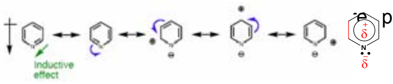
- Complex between ring nitrogen and incoming electrophile deactivates ring with positive charge
- Electron-withdrawing nitrogen atom deactivates causes a dipole making positively polarized C's poor Lewis bases



$\mu = 2.26$ D

Electrophilic Substitution of Pyridine

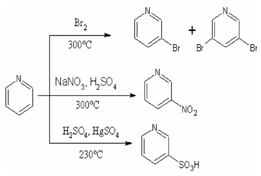
- The negative pole in pyridine ring is at N while the positive pole is at carbon skeleton which is opposite to what happens in pyrrole.
- This is due to the greater electronegativity of nitrogen (relative to carbons)
- Nitrogen tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6
  - e partial



  -
  - Carbons at positions 3 and 5 (β-position) remain

Electrophilic Substitution of Pyridine

- Also as a consequence of electron deficiency on pyridine ring , pyridine is less reactive towards electrophiles than pyrrole and benzene (it resembles highly deactivated benzene derivatives), where it does not undergo Friedel-Craft's alkylation or acylation or coupling with diazonium salts.
- Moreover, electrophilic substitution reactions of pyridine require very harsh conditions (e.g. v. high temp.) to take place and are low yielding .



Electrophilic Substitution of Pyridine

- The pyridine ring undergoes electrophilic aromatic substitution reactions with great difficulty, under drastic conditions

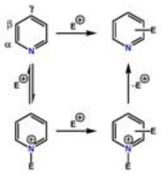
3-Bromopyridine (30%)

3-Pyridinesulfonic acid (70%)

3-Nitropyridine (5%)

Pyridines – Electrophilic Reactions

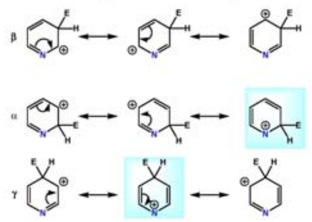
Pathways for the Electrophilic Aromatic Substitution of Pyridines



- The position of the equilibrium between the pyridine and pyridinium salt depends on the substitution pattern and nature of the substituents, but usually favours the salt

Pyridines – Electrophilic Reactions

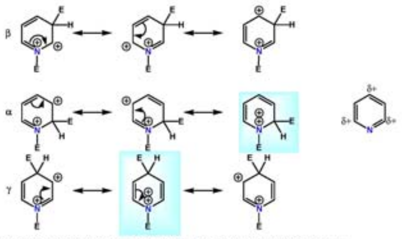
Regiochemical Outcome of Electrophilic Substitution of Pyridines



- Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable
- The β-substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the α /γ products

Pyridines – Electrophilic Reactions

Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions



- Regiochemical control is even more pronounced in the case of pyridinium ions
- In both pyridine and pyridinium systems, β substitution is favoured but the reaction is slower than that of benzene
- Reaction will usually proceed through the small amount of the free pyridine available

Pyridines – Electrophilic Reactions

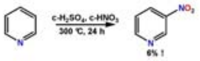
N Substitution

C Substitution

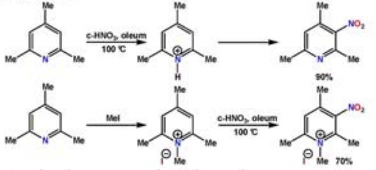
- Reaction at *C* is usually difficult and slow, requiring forcing conditions
- Friedel-Crafts reactions are not usually possible on free pyridines

Pyridines – Electrophilic Reactions

Nitration of Pyridine

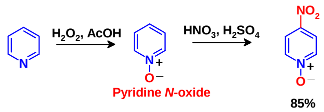


Use of Activating Groups



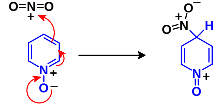
- Multiple electron-donating groups accelerate the reaction
- Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case

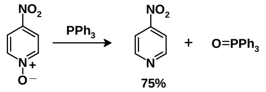
Nitration of Pyridine



We now have an activating and protecting group

Mechanism



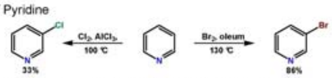


Pyridines – Electrophilic Reactions

Sulfonation of Pyridine

- Low yield from direct nitration but good yield via a mercury intermediate

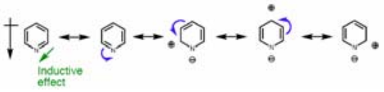
Halogenation of Pyridine



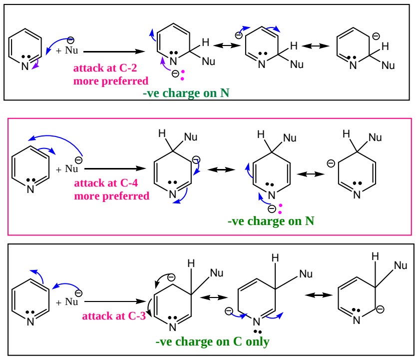
- Forcing reaction conditions are required for direct halogenation

Pyridines – Nucleophilic Reactions

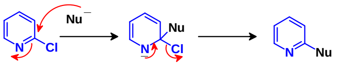
- Pyridine is very reactive towards nucleophiles than benzene
  - it resembles benzene having strong electron withdrawing group due to the withdrawing effect of the electronegative N atom .
- As appeared from the canonical structures of pyridine positions 2, 4 and 6 carry partial positive charges thus nucleophilic substitution proceeds readily at the 2-position followed by 4-position but not at the 3-position.
- Additionally, attack at positions 2, 4 or 6 results in resonance structure in which the negative charge is delocalized at N thus it is more preferred while attack at position 3 or 5 results in resonance structures in which the negative charge is delocalized over carbons only.



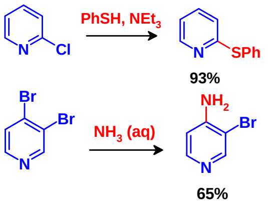
Orientation of Nucleophilic Substitution



Orientation of Substitution

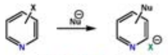


E.g.



Pyridines – Nucleophilic Reactions

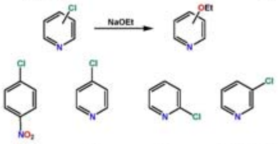
Nucleophilic Substitution



X = Cl, Br, I, (NO_2)

Nu = MeO⁻, NH_3, PhSH etc.

- Favoured by electron-withdrawing substituents that are also good leaving groups
- The position of the leaving group influences reaction rate (γ > α >> β)



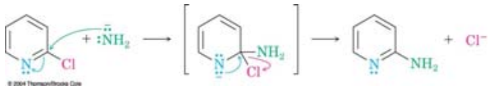
Relative rate	80	40	1	3×10^{-4}

Nucleophilic Substitution of Pyridine

- 2- and 4-substituted (but not 3-substituted) halopyridines readily undergo **nucleophilic** aromatic substitution

Mechanism of Nucleophilic Substitution on Pyridine

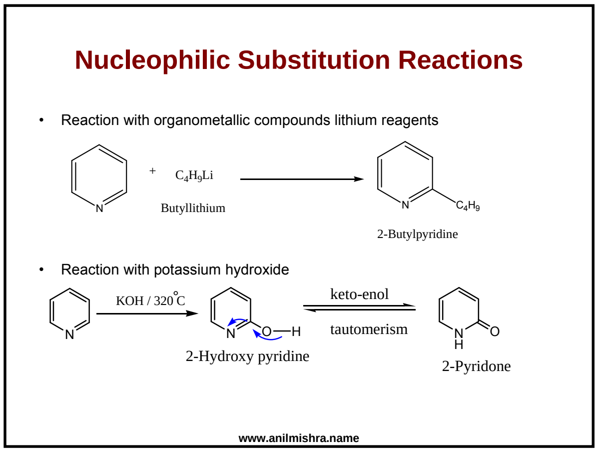
- Reaction occurs by addition of the nucleophile to the C=N bond, followed by loss of halide ion



Nucleophilic Substitution Reactions

- The Chichibabin reaction

R* can be *o-*, *m-*, *or p-* substituent



Nucleophilic Substitution Reactions

- Reaction with organometallic compounds lithium reagents

- Reaction with potassium hydroxide

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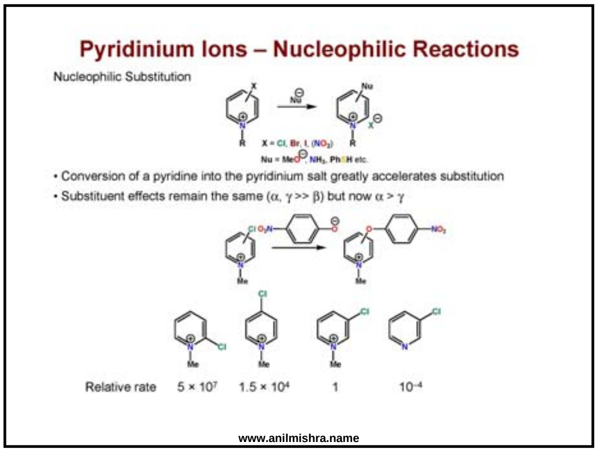

Pyridinium Ions – Nucleophilic Reactions

Nucleophilic Substitution

$X = Cl, Br, I, (NO_2)$

$Nu = MeO^{\ominus}, NH_3, PhSH$ etc.

- Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
- Substituent effects remain the same ($\alpha, \gamma >> \beta$) but now $\alpha > \gamma$

Relative rate	5×10^7	1.5×10^4	1	10^{-4}

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