Chapter 19

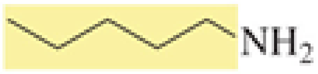
Heterocyclic compounds

Some more of amines

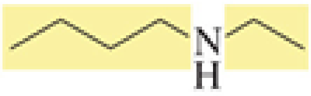
Heterocycles

Nomenclature

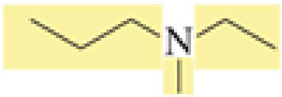
- straight chain amines ~ --amine



a primary amine
1-pentanamine
pentylamine



a secondary amine
N-ethyl-1-butanamine
butylethylamine

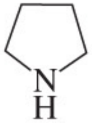


a tertiary amine
N-ethyl-*N*-methyl-1-propanamine
ethylmethylpropylamine

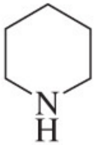
- cyclic amines ~ azacycloalkane; common more popular

azacyclopropane
aziridine

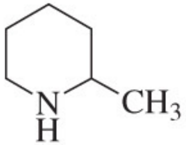
azacyclobutane
azetidine



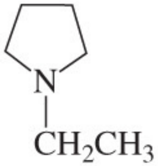
azacyclopentane
pyrrolidine



azacyclohexane
piperidine

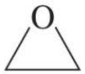


2-methylazacyclohexane
2-methylpiperidine



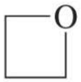
N-ethylazacyclopentane
N-ethylpyrrolidine

- O- S- heterocycles



oxacyclopropane
oxirane
ethylene oxide

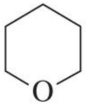
thiacyclopropane
thiirane



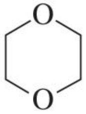
oxacyclobutane
oxetane

THF, a popular solvent

oxacyclopentane
tetrahydrofuran
oxolane



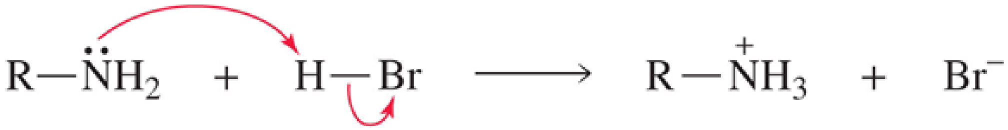
oxacyclohexane
tetrahydropyran
oxane



1,4-dioxacyclohexane
1,4-dioxane

Amine as a base

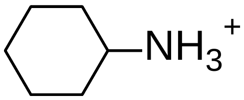
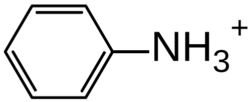
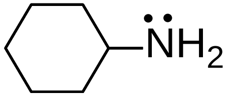
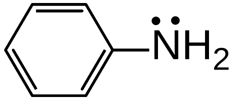
- Amines are most common organic bases.



$R-\ddot{N}H_2 + H-Br \longrightarrow R-\overset{+}{N}H_3 + Br^-$

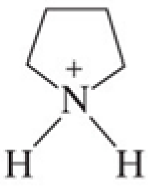
organic acids and bases §2.3 p91

- basicity ~ pK_a of conj acid

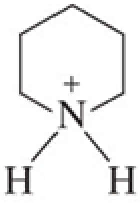
	NH_4^+	$CH_3NH_3^+$	$CH_3CH_2NH_3^+$		
pK_a =	9.4	10.6	10.8	11.2 ← +I	4.6 ← −M > +I
	$\ddot{N}H_3$	$CH_3\ddot{N}H_2$	$CH_3CH_2\ddot{N}H_2$		
pK_b =	4.6	3.4	3.2	2.8	9.6
pK_a =	~35	~40	>40	>40	~30

  - inductive and resonance ED a/o EW, steric effect
  - 1°, 2°, 3° amines ~ structure-basicity relationship complex

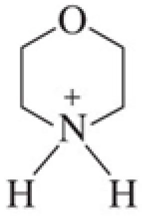
- cyclic amines



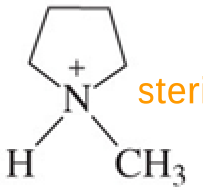
pyrrolidine
pK_a = 11.27



piperidine
pK_a = 11.12

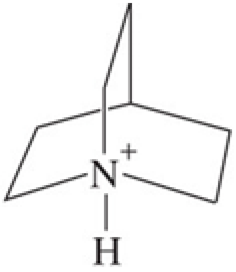


morpholine
pK_a = 9.28



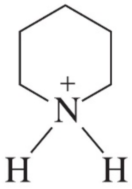
steric

N-methylpyrrolidine
pK_a = 10.32

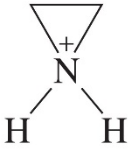


quinuclidine
pK_a = 11.38

  - properties similar to straight chain amines, when big enough
  - if not,



piperidinium ion
pK_a = 11.1

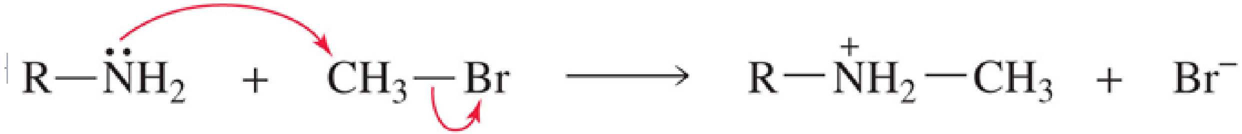


aziridinium ion
pK_a = 8.0

larger bond angle = more s character =
higher EN N = more acidic

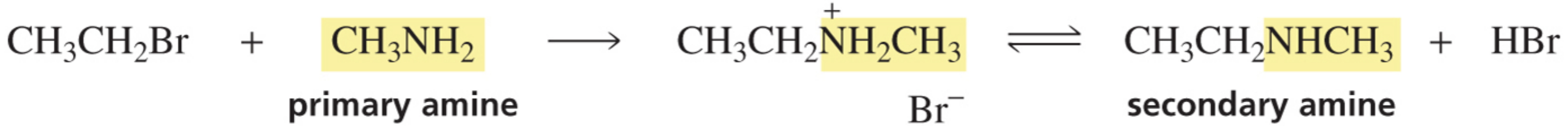
Amine as a Nu:

- Amines are Nu: awa B: (with :)



$$R-\ddot{N}H_2 + CH_3-Br \longrightarrow R-\overset{+}{N}H_2-CH_3 + Br^-$$

- Nu: in S_N rxn → amine alkylated



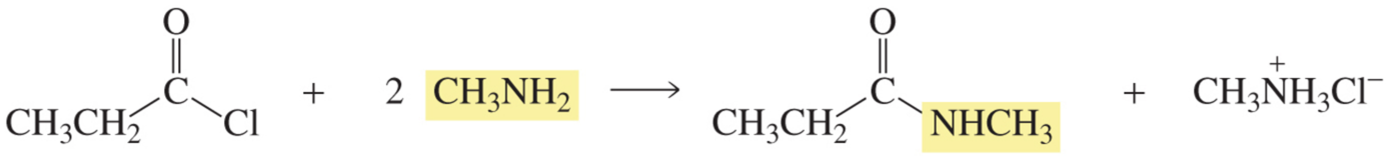
$$CH_3CH_2Br + CH_3NH_2 \longrightarrow CH_3CH_2\overset{+}{N}H_2CH_3\ Br^- \rightleftharpoons CH_3CH_2NHCH_3 + HBr$$

primary amine

secondary amine

  - NH_2 as a leaving group? (very) poor
    - X >> OH ≈ OR >> NH_2

- Nu: in add’n-elim’n [acyl subst’n] rxn → amine acylated

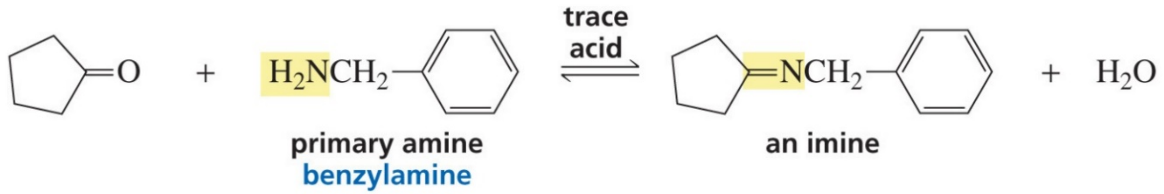


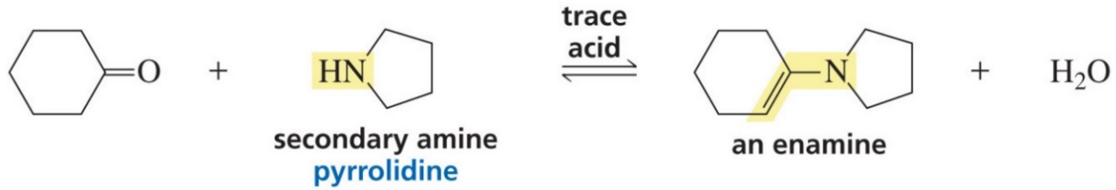
$$CH_3CH_2C(=O)Cl + 2\ CH_3NH_2 \longrightarrow CH_3CH_2C(=O)NHCH_3 + CH_3\overset{+}{N}H_3Cl^-$$

acyl chloride

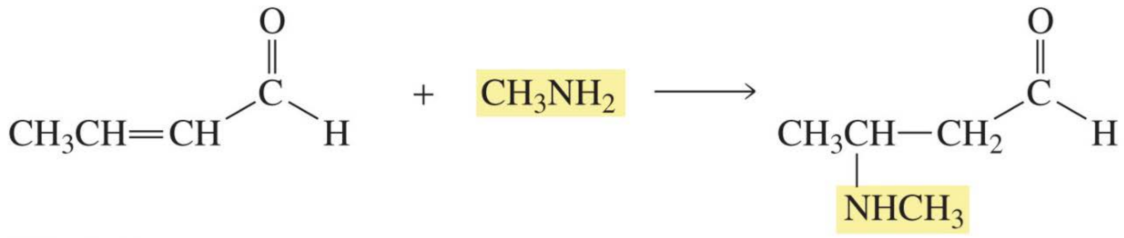
amide

- Nu: in add'n-elim'n (to A&K) → to imine or enamine

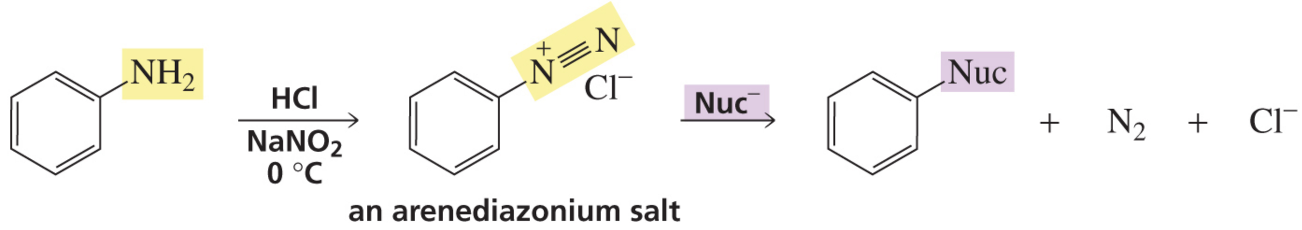




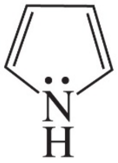
- Nu: in conjugate addition rxn



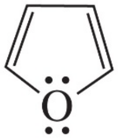
- amine to N_2Cl (to other Nu:)



Pyrrole, furan, thiophene



pyrrole

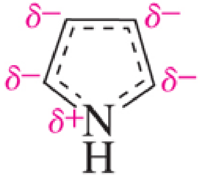


furan

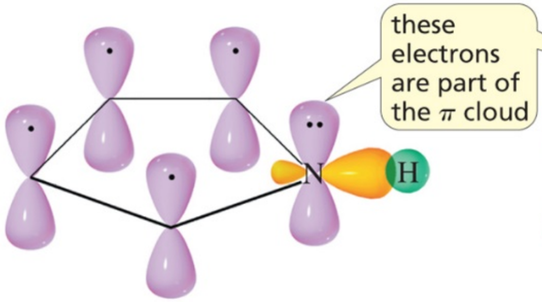
thiophene

5-membered-ring
(aromatic) heterocycles

- aromatic
  - p-orbital/cyclic/planar
  - 6 pi e’s

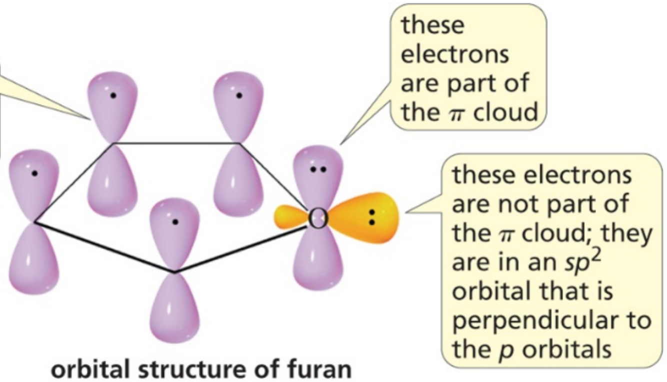


resonance hybrid



these electrons are part of the π cloud

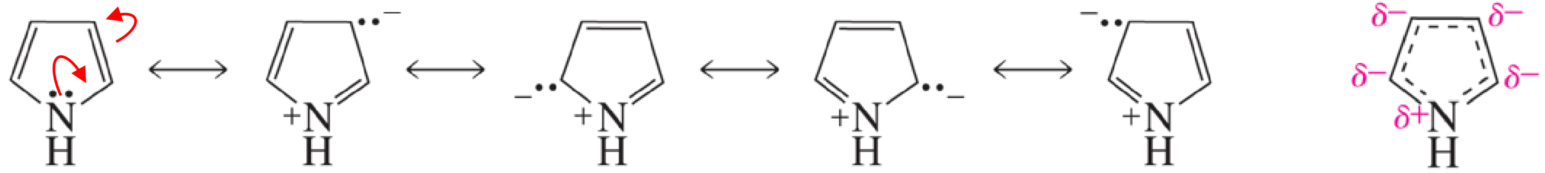
orbital structure of pyrrole



these electrons are part of the π cloud

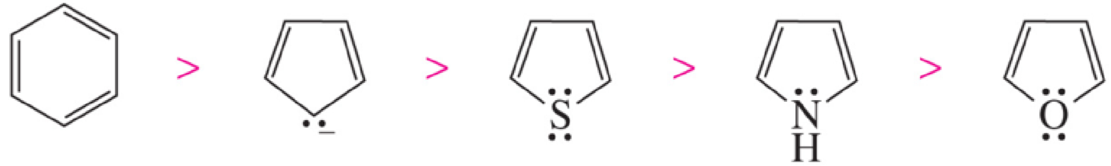
these electrons are not part of the π cloud; they are in an sp^2 orbital that is perpendicular to the *p* orbitals

orbital structure of furan



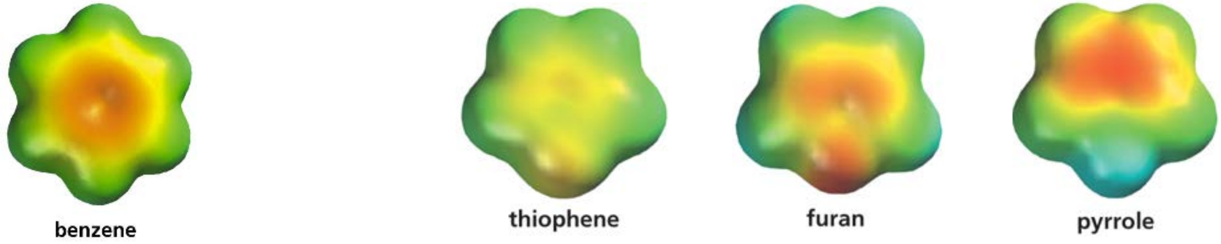
resonance hybrid

- delocalization [resonance] energy

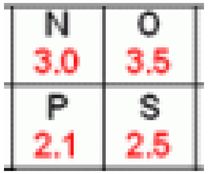


  - higher when forms are equally important [stable]
    - (+) on S > N > O [EN S < N < O]
    - effect of 3p of S < EN of S

N	O
3.0	3.5
P	S
2.1	2.5



- polarity
  - inductive and resonance effect
  - $\mu = q d$

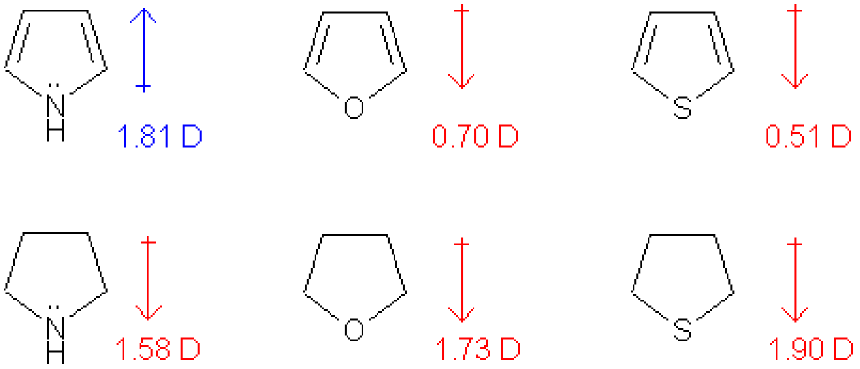


N	O
3.0	3.5
P	S
2.1	2.5

+M > –I

+M < –I

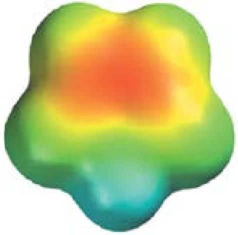
+M < –I



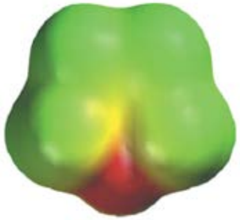
0M & –I

0M & larger –I
← larger EN

0M & larger –I
← larger d



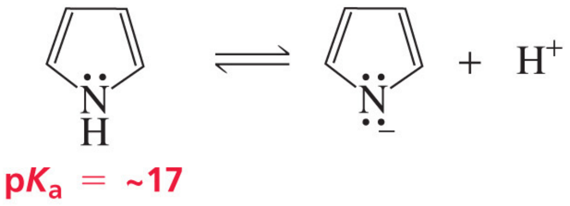
pyrrole

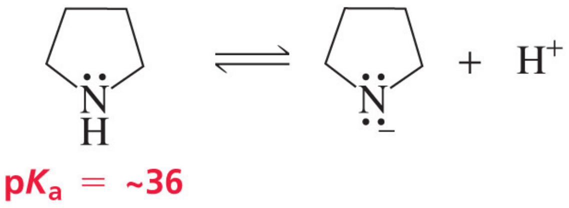


pyrrolidine

Acidity/basicity

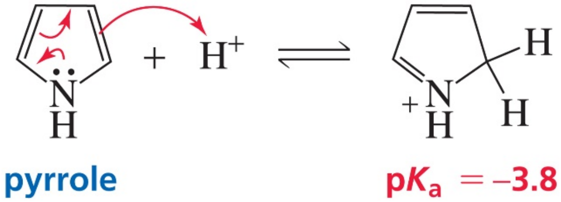
- acidity of pyrrole





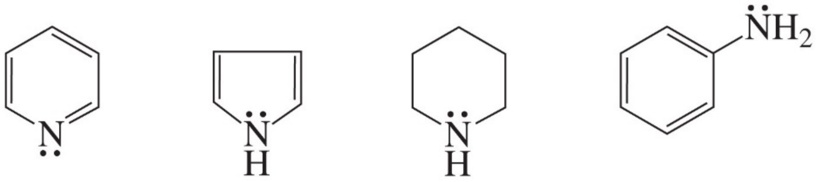
  - sp^2 [more EN] vs sp^3 N

- basicity
  - Pyrrole is a very weak base. ← : in aromaticity
  - protonation at C-2 not at N ← A-B rxn = aromatic subst’n



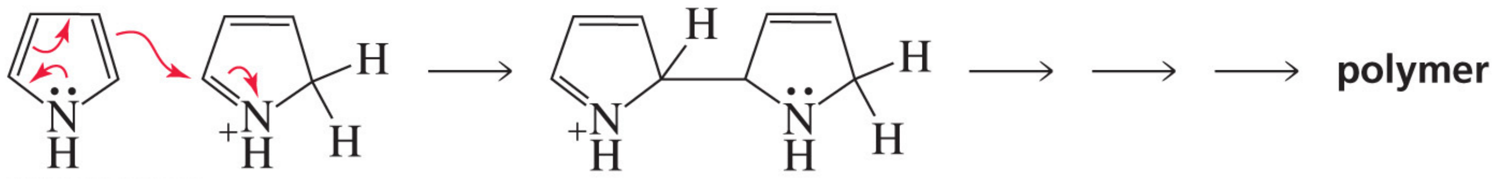
  - Problem p967. order of basicity?

  Table 19.1

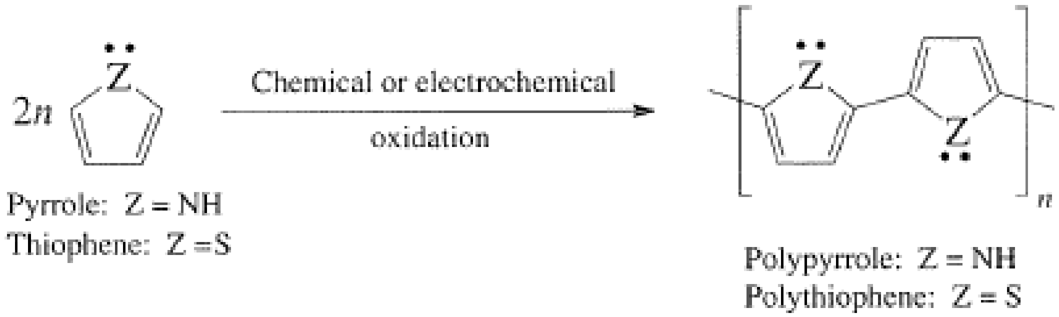


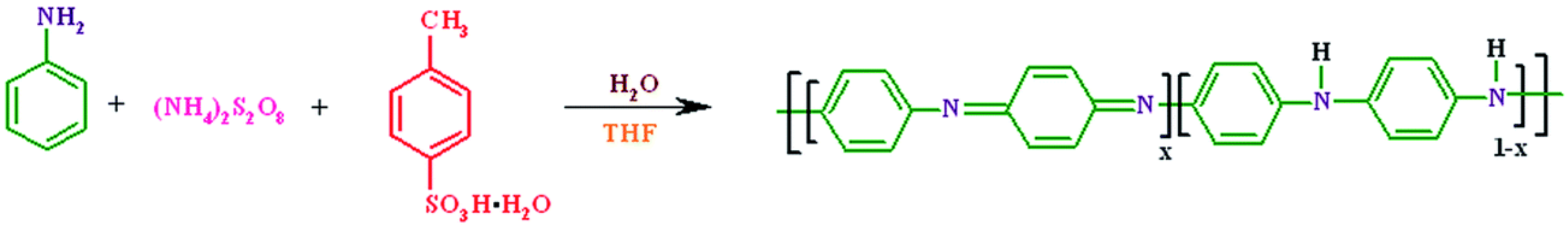
Polypyrrole

- pyrrole is unstable in acidic condition. → polymerize



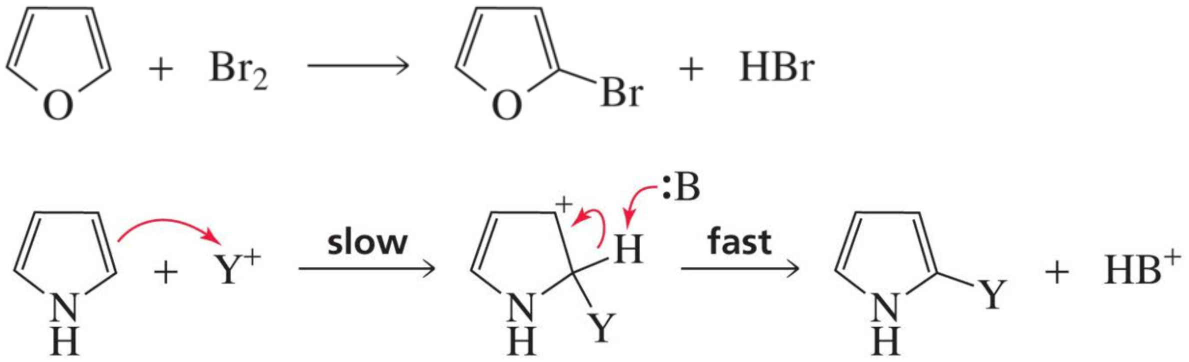
- PPy/PT/PANi ~ (common) conducting polymers



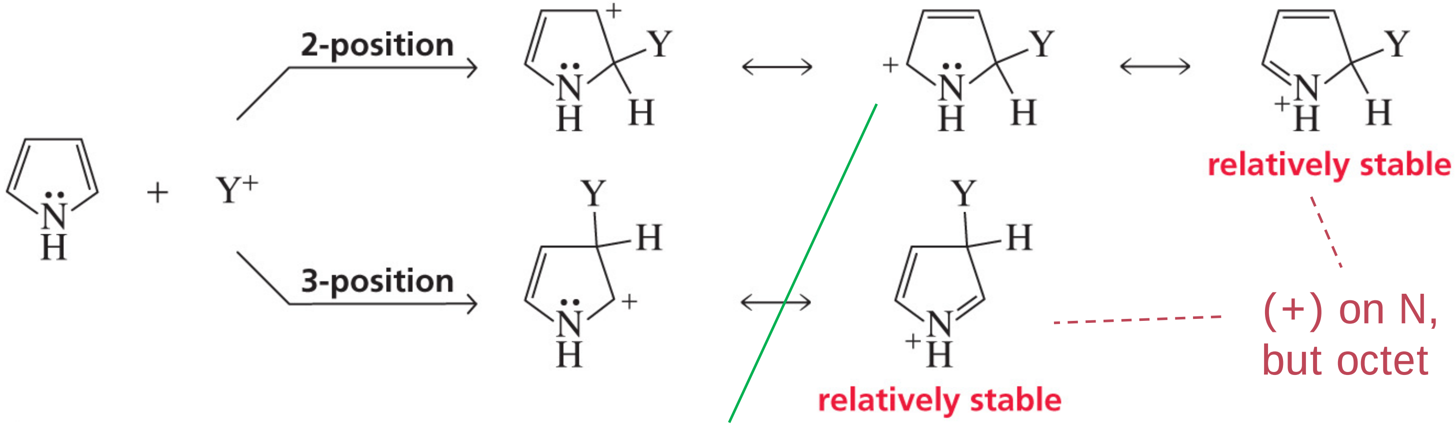


Rxns of p/f/t

- e-philic aromatic subst’n



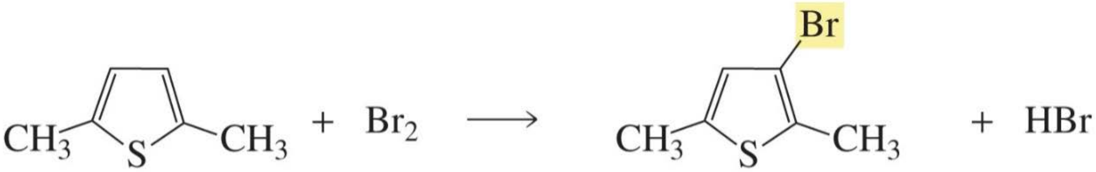
- on C-2 preferred



(+) on N,
but octet

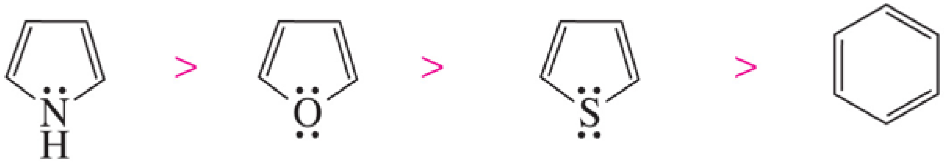
  - additional (less important) form

- when 2 C-2's occupied, on C-3

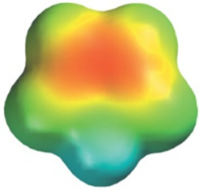


3-bromo-2,5-dimethylthiophene

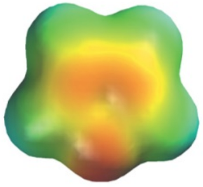
- reactivity



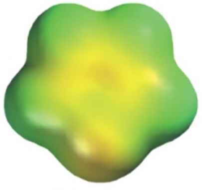
  - p/f/t all more reactive than bz
    - N, O, S resonance ED (to ring)
  - O more EN → poorer resonance
  - S 3p → poorer resonance



pyrrole

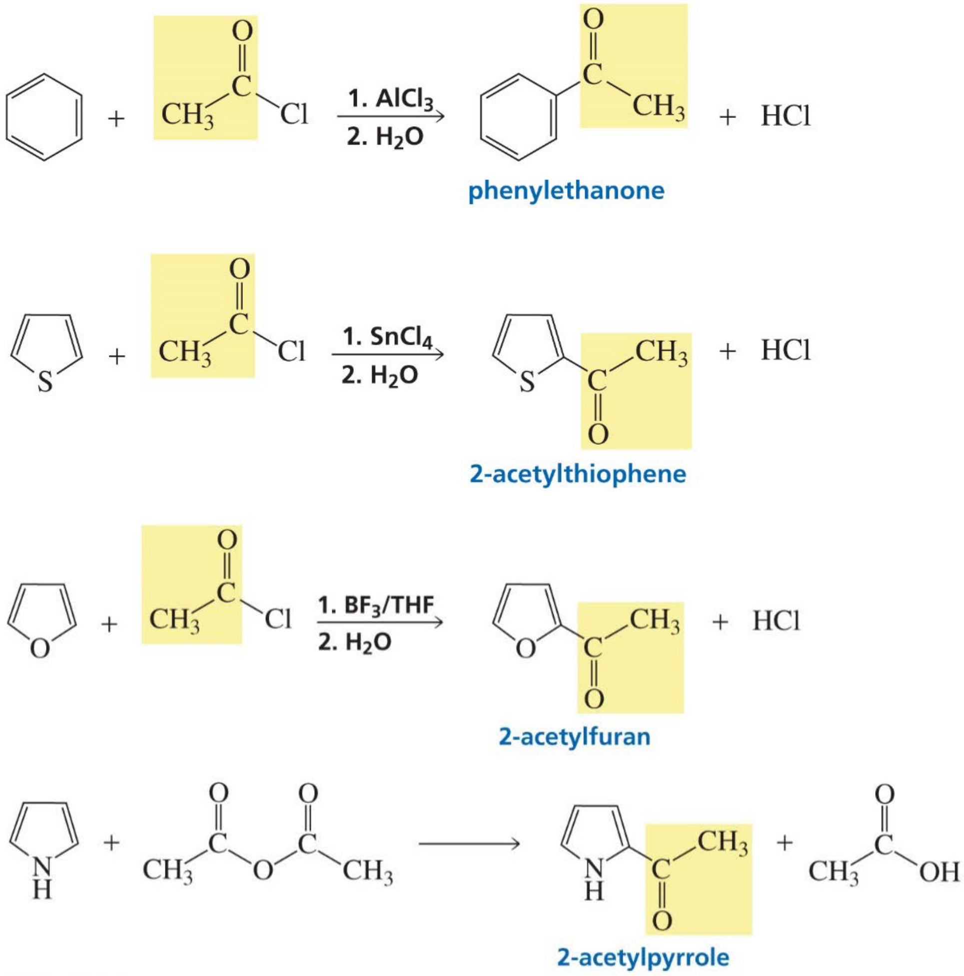


furan

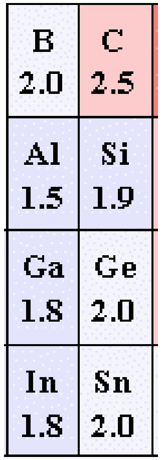


thiophene

- rxns



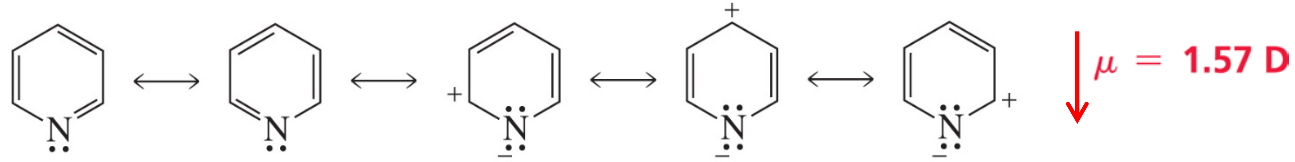
strength of LA
$AlCl_3$ > $SnCl_4$ > BF_3
The structure-strength relation is complex.



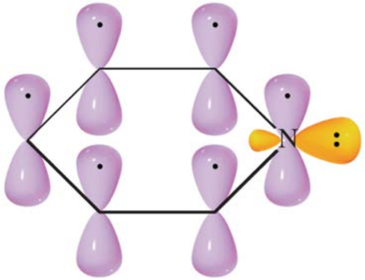
B 2.0	C 2.5
Al 1.5	Si 1.9
Ga 1.8	Ge 2.0
In 1.8	Sn 2.0

Pyridine

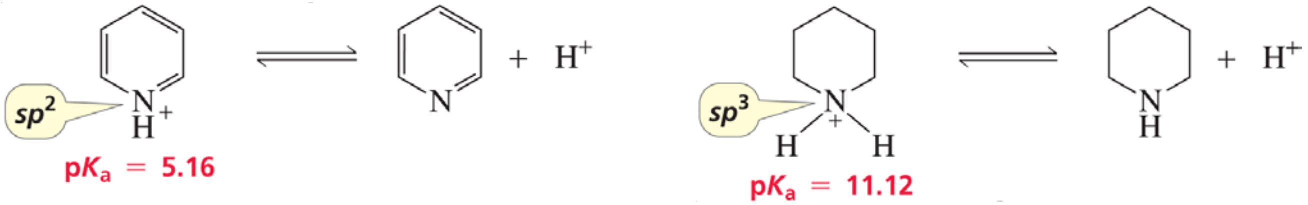
- 6-membered-ring aromatic heterocycle



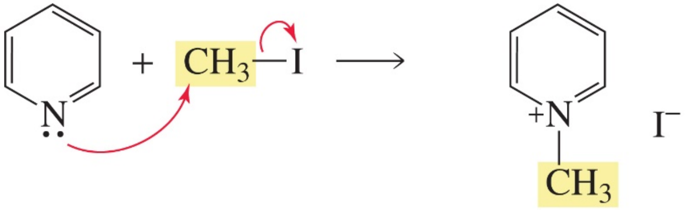
resonance contributors of pyridine



- basicity/acidity
  - much stronger base than pyrrole
  - weaker base than piperidine

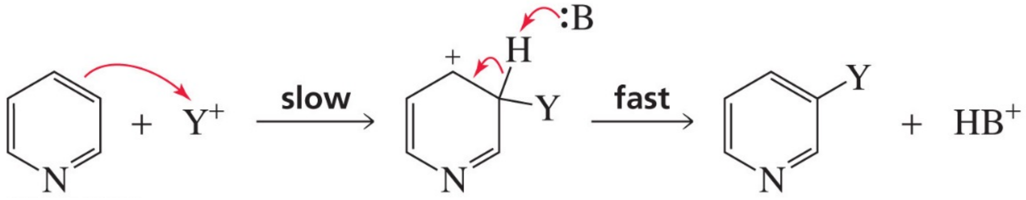


- Nu:

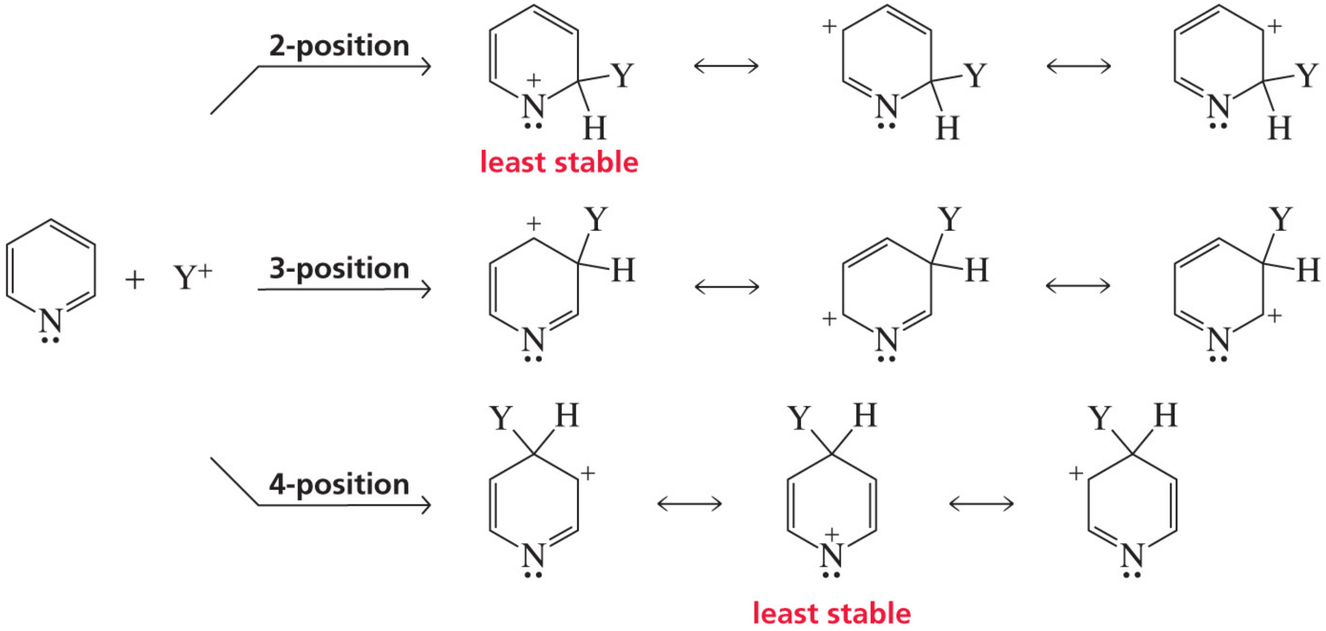


Rxn of pyridine

- e-philic aromatic substit’n

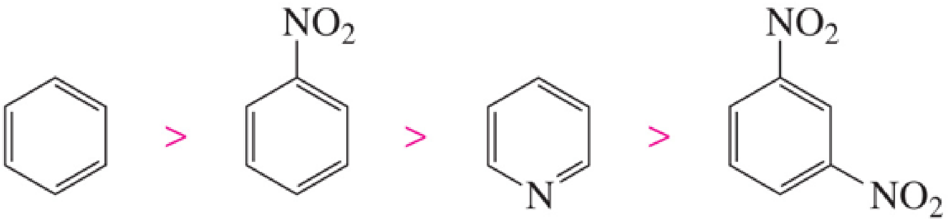


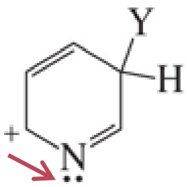
- on C-3

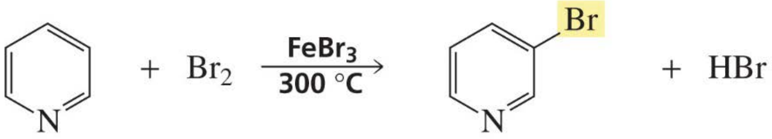


(+) on N

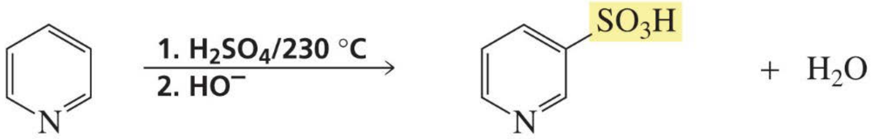
- less reactive than bz
  - EN [EW] N on the ring → nucleophilicity ↓, interm stability ↓



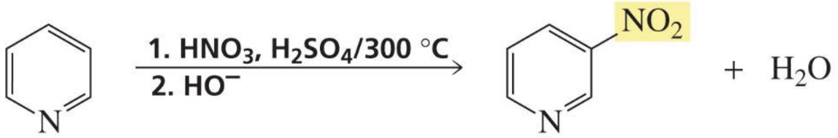




3-bromopyridine
30%



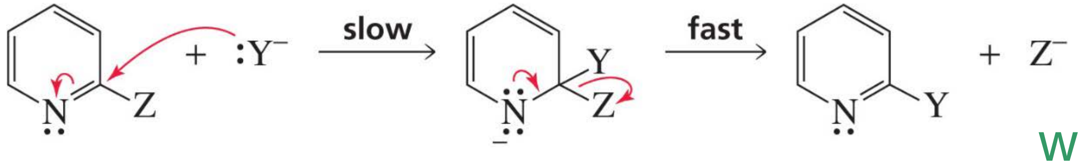
pyridine-3-sulfonic acid
71%



3-nitropyridine
22%

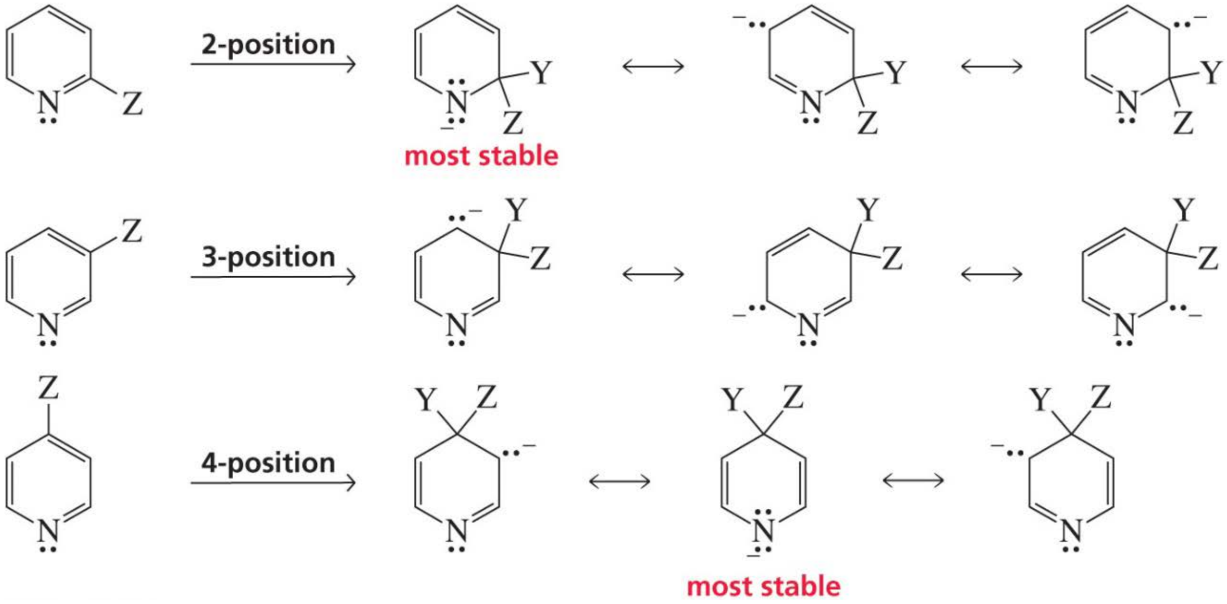
no F-C rxn either

- more reactive than bz in S_NAr
  - N stabilizes interm

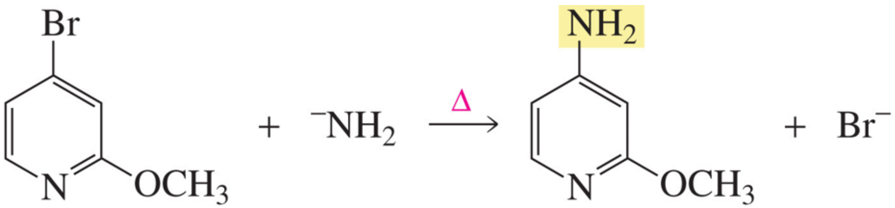


weaker B: leaving

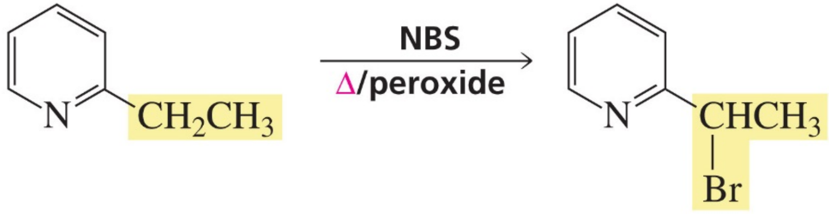
  - on C-2 and C-4

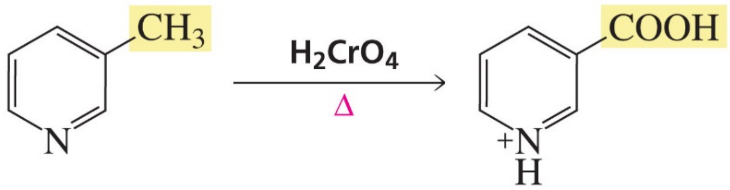


- nucleophilic aromatic substit’n (cont’d)
  - L on C-2 and C-4? weaker B: substituted

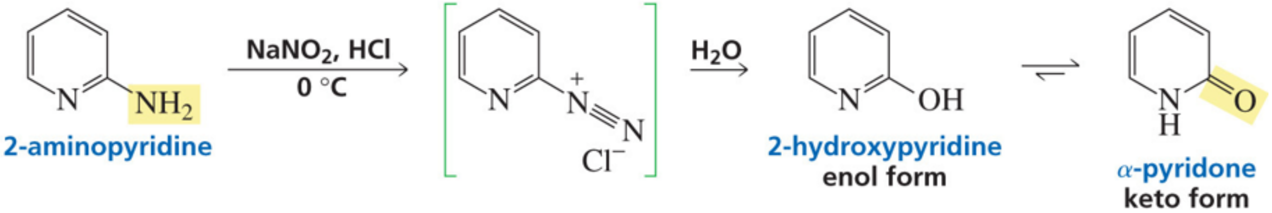


- substituted pyridine further modified

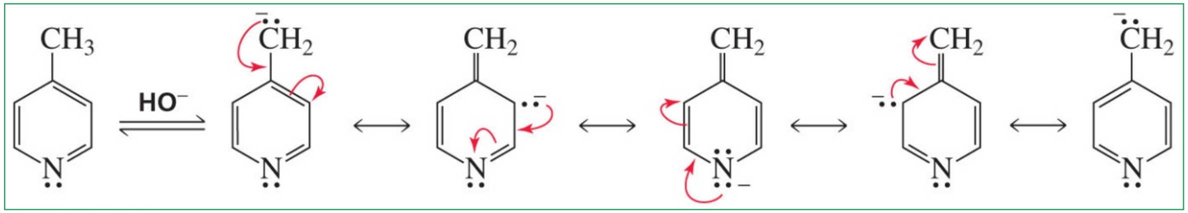




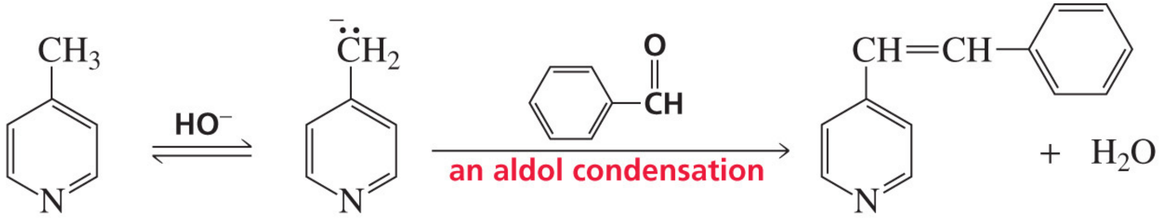
- aminopyridine diazotized to pyridone

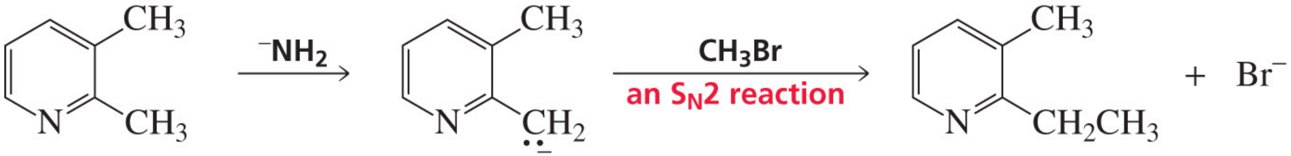


- (2- or 4-)methylpyridine to C:⁻ (by B:)



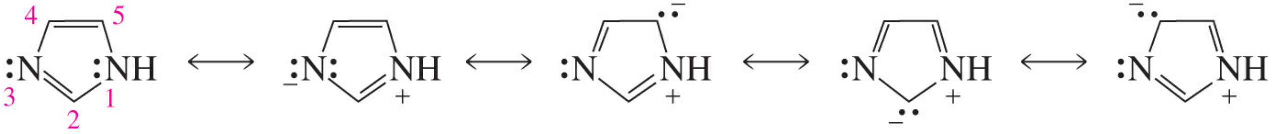
EW N and resonance
→ pK_a comparable to
that of α-C of ketone



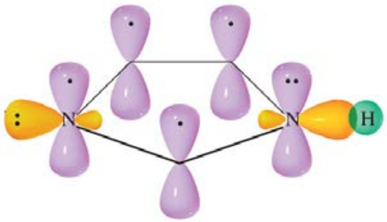


Other heterocyclic amines

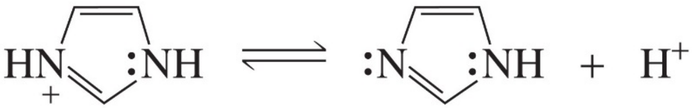
- imidazole



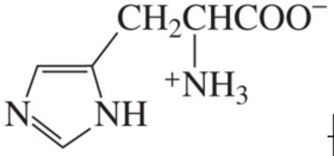
resonance contributors of imidazole



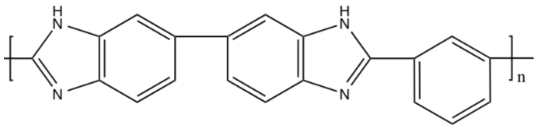
  - part of histidine, a protein
  - protonated to



$pK_a = 6.8$



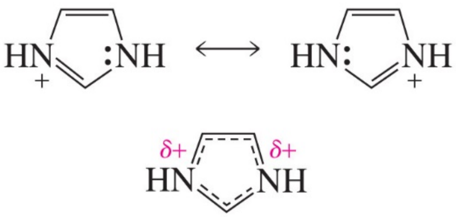
histidine



polybenzimidazole

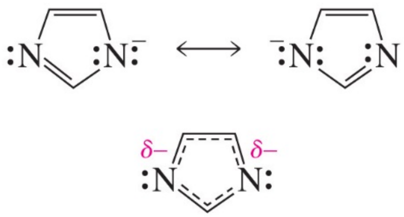
    - both present at pH of 7.4

protonated imidazole



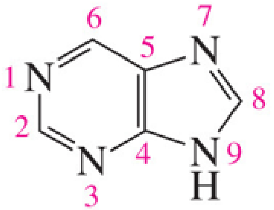
resonance hybrid

imidazole anion

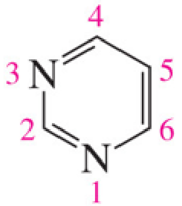


resonance hybrid

- purine and pyrimidine
  - comprise nucleic acids [RNA, DNA]
  - abundant in food

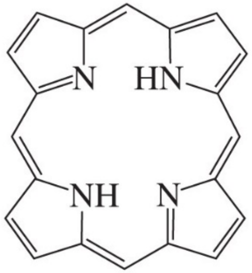


purine

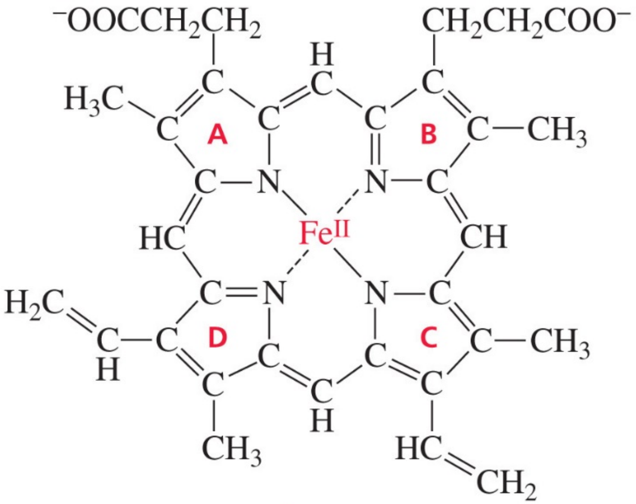


pyrimidine

- porphyrin
  - 4 pyrroles linked by C
  - heme = Fe ligand
    - hemoglobin transport O_2
    - myoglobin stores O_2
  - chlorophyll ~ Mg ligand
  - vitamin B12 ~ Co ligand



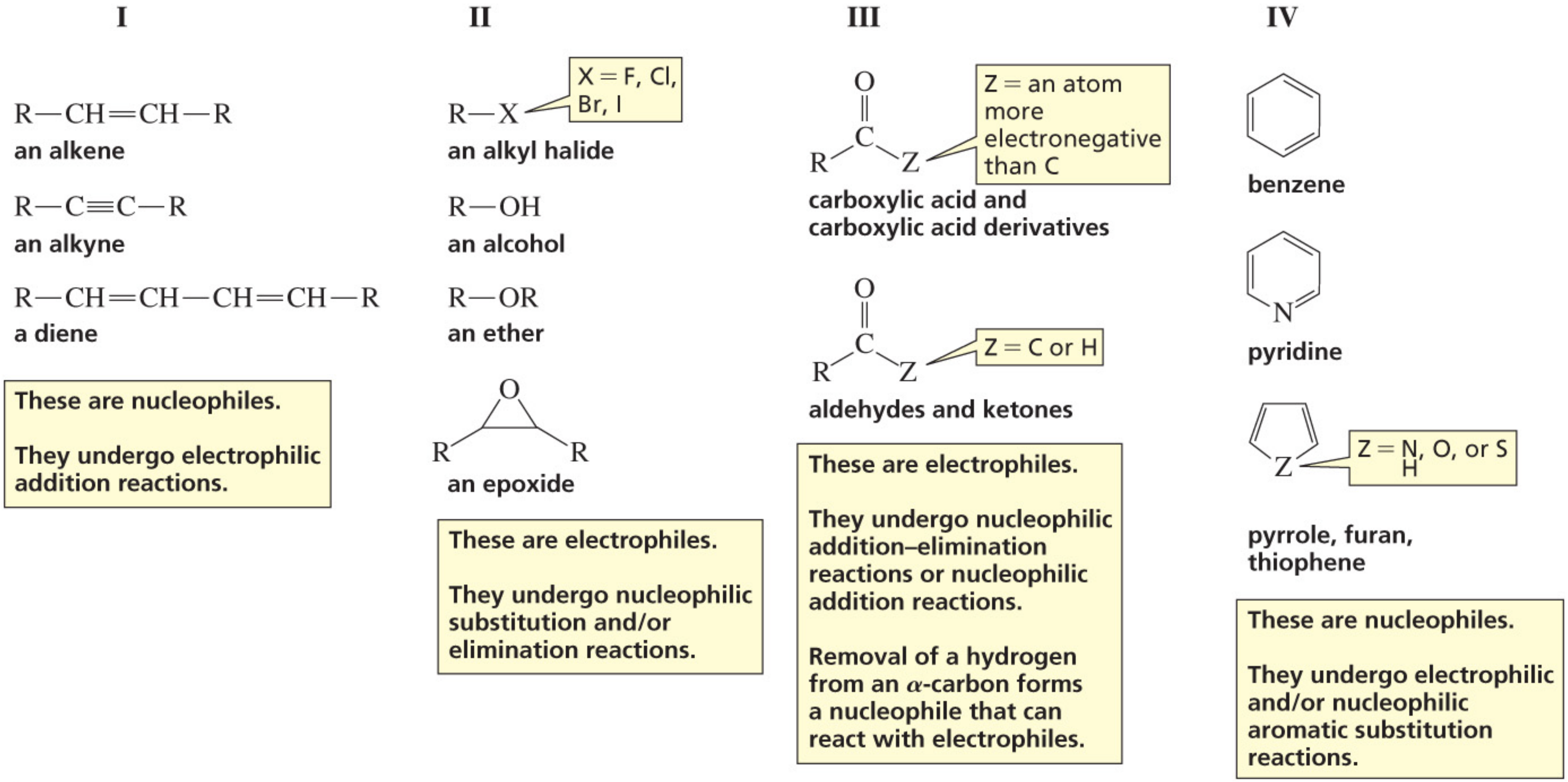
a porphyrin ring system



heme

conjugated with high absorptivity
→ why blood red

The 4 groups



I

R—CH═CH—R

an alkene

R—C≡C—R

an alkyne

R—CH═CH—CH═CH—R

a diene

These are nucleophiles.

They undergo electrophilic addition reactions.

II

R—X

X = F, Cl, Br, I

an alkyl halide

R—OH

an alcohol

R—OR

an ether

an epoxide

These are electrophiles.

They undergo nucleophilic substitution and/or elimination reactions.

III

Z = an atom more electronegative than C

carboxylic acid and carboxylic acid derivatives

Z = C or H

aldehydes and ketones

These are electrophiles.

They undergo nucleophilic addition–elimination reactions or nucleophilic addition reactions.

Removal of a hydrogen from an α-carbon forms a nucleophile that can react with electrophiles.

IV

benzene

pyridine

Z = N, O, or S
H

pyrrole, furan, thiophene

These are nucleophiles.

They undergo electrophilic and/or nucleophilic aromatic substitution reactions.

한 학기 수고 많았습니다.

Good Luck in the Final, and Happy New Year!