Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURES 4 & 5
Pyrroles, furans & thiophenes – properties, syntheses & reactivity

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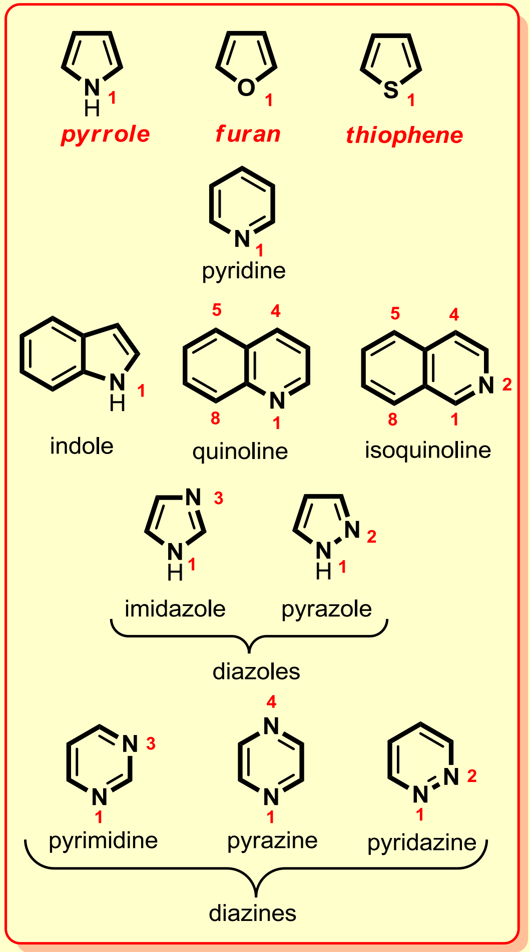
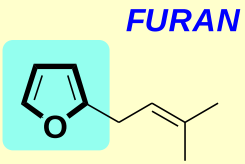
Format & scope of lectures 4 & 5

- ***Bonding, aromaticity & reactivity of 5-ring heteroaromatics:***
  - *cf.* cyclopentadienyl anion
  - pyrroles, furans & thiophenes:
    - MO and valence bond descriptions
    - resonance energies
    - electron densities
- ***Pyrroles:***
  - structure & properties
  - syntheses
  - reactivity
- ***Furans:***
  - structure & properties
  - syntheses
  - reactivity
- ***Thiophenes:***
  - structure & properties
  - syntheses
  - reactivity
- ***Supplementary slides 1-2***
  - revision of S_EAr mechanism

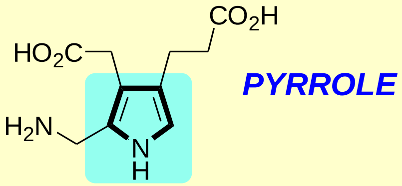


Pyrroles, Furans & Thiophenes *– Importance*

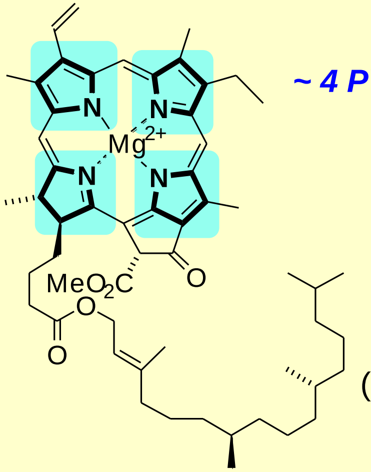
- ***Natural products*:**



rosefuran
(component of rose oil)



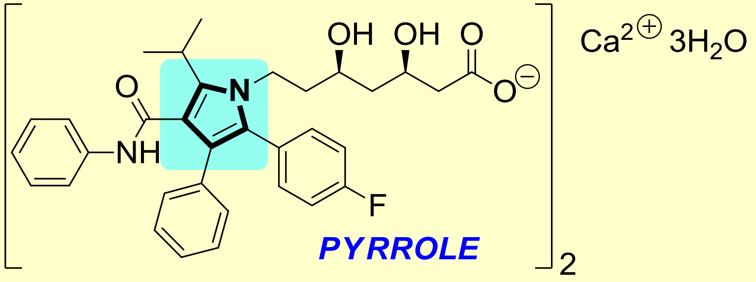
porphobilinogen
(biosynthetic precursor to
tetrapyrrole pigments)



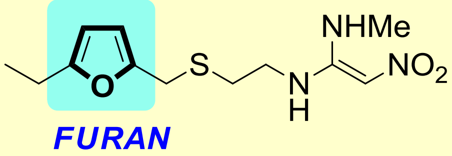
~ 4 PYRROLES

chlorophyll
(green leaf pigment)

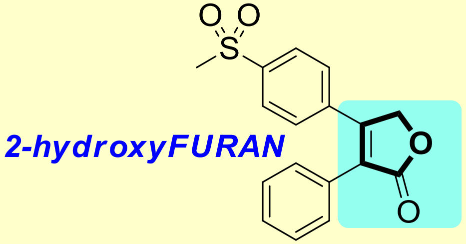
- ***Pharmaceuticals:***



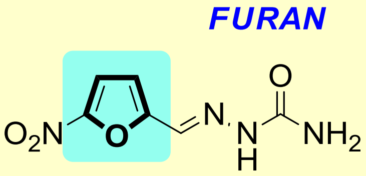
atorvastatin calcium
(Lipitor^{TM}, anti-cholesterol)



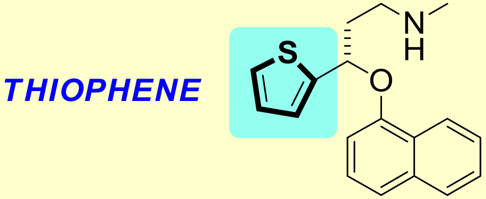
ranitidine
(Zantac^{TM}, anti-ulcer)



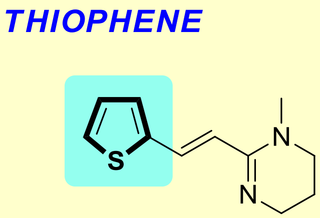
rofecoxib
(Vioxx^{TM}, anti-inflammatory)



nitrofurazone
(Furacilin^{TM}, bactericide)



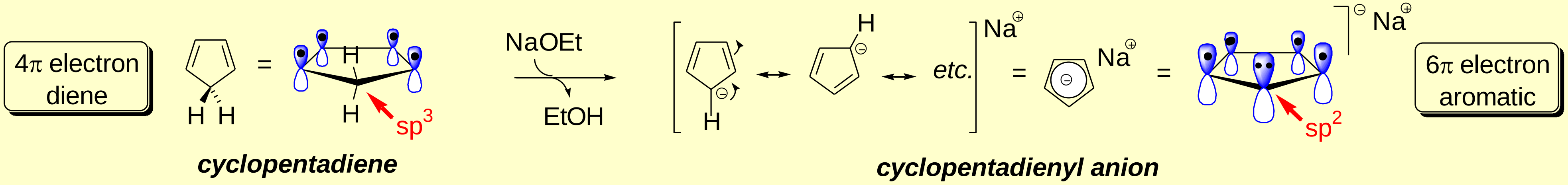
duloxetine
(Cymbalta^{TM}, anti-depressive)



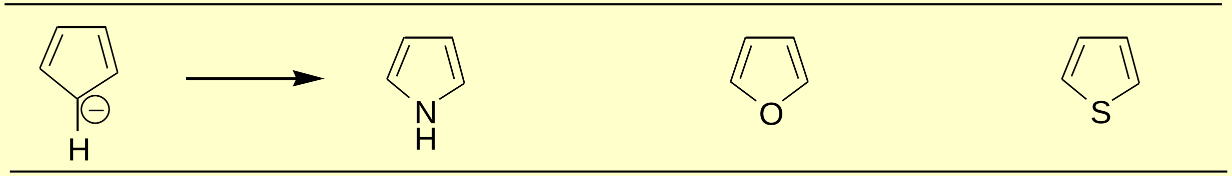
pyrantel
(anthelmintic *vs.* pinworm)

Cyclopentadienyl anion → pyrrole, furan & thiophene

- The ***cyclopentadienyl anion*** is a *C5*-symmetric aromatic 5-membered cyclic carbanion:



- ***Pyrrole***, ***furan*** & ***thiophene*** can be considered as the corresponding aromatic systems where the anionic ***CH***$^{\ominus}$ unit has been replaced by the iso-electronic ***NH***, ***O*** and ***S*** units respectively:

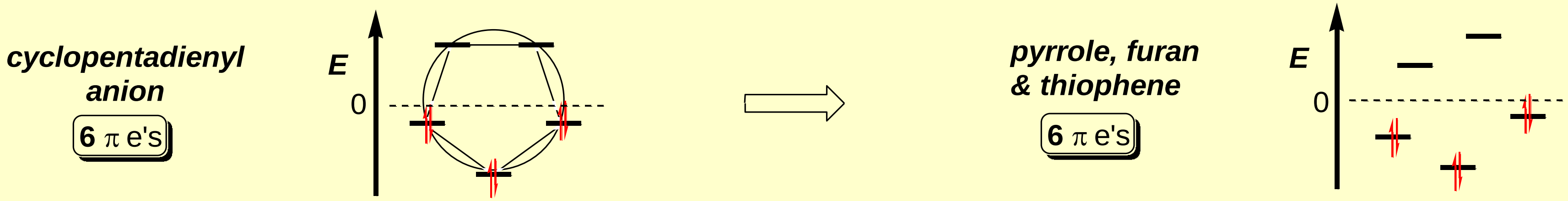


sp^2 hybrid **CH**$^{\ominus}$ sp^2 hybrid **NH** sp^2 hybrid **O** sp^2 hybrid **S**

- They are no longer *C5*-symmetric and do not bear a negative charge but they retain 6p electrons and are still aromatic

MO Description* ↔ *Resonance Energies: *pyrrole, furan & thiophene*

- The MO diagram for the ***cyclopentadienyl anion*** can be generated using the ***Musulin-Frost*** method (lecture 1). The asymmetry introduced by ***CH*** → ***NH***/***O***/***S*** 'replacement' → non-degenerate MOs for pyrrole, furan & thiophene:

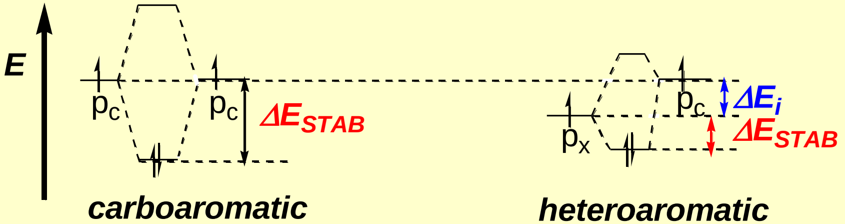


- Moreover, the energy match and orbital overlap between the heteroatom-centered p-orbital and the adjacent C-centered p-orbitals is less good and so the ***resonance energies are lower***:

Heteroatoms are more electronegative than carbon and so their p-orbitals are <u>lower</u> in energy. The larger the mismatch in energy (ΔE_i) the smaller the resulting stabilisation (ΔE_{STAB}) because:

$$\boxed{E_{STAB} \propto \frac{S^2}{\Delta E_i}}$$

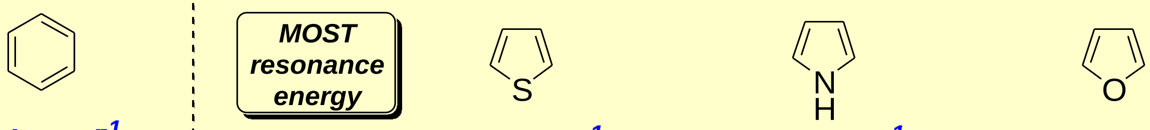
S^2 = overlap integral
E_{STAB} = stabilisation energy
ΔE_i = interaction energy



carboaromatic
$\Delta E_i = 0$; E_{STAB} = ***'BIG'***

heteroaromatic
$\Delta E_i > 0$; E_{STAB} = ***'SMALL'***

- Consequently, the ***resonance energies*** (~ ground state thermodynamic stabilities) loosely reflect the difference in the Pauling ***electronegativities*** of ***S*** (2.6), ***N*** (3.0) & ***O*** (3.4) relative to ***C*** (2.5):



MOST resonance energy

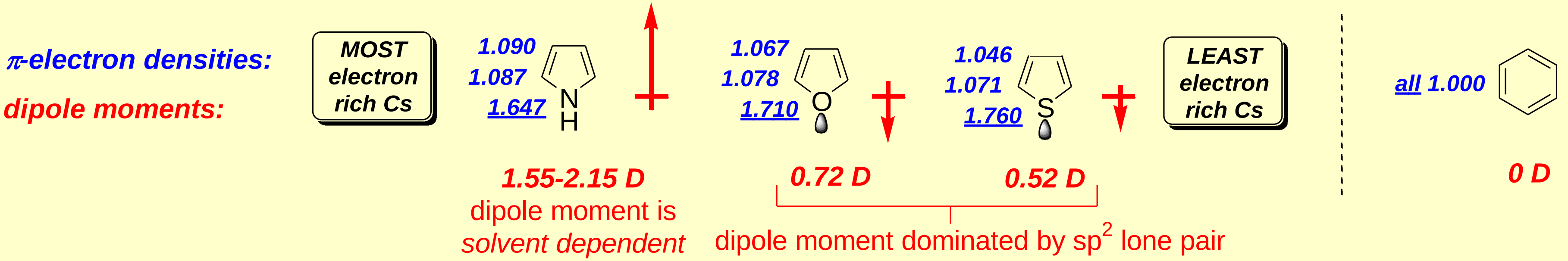
LEAST resonance energy

resonance energies: ***152 kJmol^{-1}*** ***122 kJmol^{-1}*** ***90 kJmol^{-1}*** ***68 kJmol^{-1}***

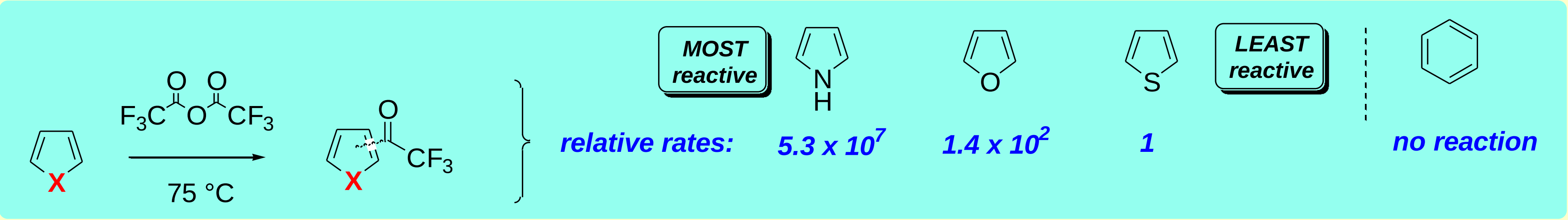
- The ***decreasing resonance energies*** in the series: thiophene > pyrrole > furan → ***increasing tendancy*** to react as ***dienes*** in ***Diels-Alder reactions*** and to undergo ***electrophilic addition*** (*cf.* ***substitution***) reactions (see later)

Calculated Electron Densities ↔ Reactivities: *pyrrole, furan & thiophene*

- ***However***, relative resonance energies are NOT the main factor affecting relative reactivities with ***electrophiles***...
- Pyrrole, furan & thiophene have 6 π-electrons distributed over 5 atoms so the carbon frameworks are ***ALL*** inherently ***ELECTRON RICH*** (relative to benzene with 6 π-electrons over 6 atoms) – all react quicker than benzene with E^+
- Additionally, the distribution of π-electron density between the heteroatom and the carbons varies considerably between the 3 ring-systems. The overall differences are manifested most clearly in their ***calculated π-electron densities***
  - ❑ *NB*. many text books highlight dipole moments in this regard – but the sp^2 lone pairs of furan and thiophene (*cf*. N-H of pyrrole) complicate this analysis

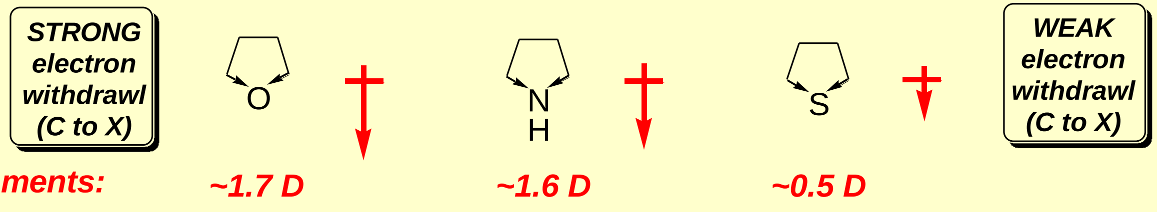


- The ***calculated π-electron densities*** reflect the relative ***REACTIVITIES*** of the 3 heterocycles towards ***electrophiles***:



Valence Bond Description ↔ ***Electron Densities:*** *pyrrole, furan & thiophene*

- The ***calculated π-electron densities*** reflect a balance of ~opposing factors:
  - ***INDUCTIVE*** <u>withdrawl</u> of electron density ***away from the carbons*** (*via* σ-bonds):
    - this mirrors Pauling ***electronegativities***: ***O*** (3.4) > ***N*** (3.0) > ***S*** (2.6) as revealed by the dipole moments of the <u>saturated</u> (*i.e.* non-aromatic) heterocycles:

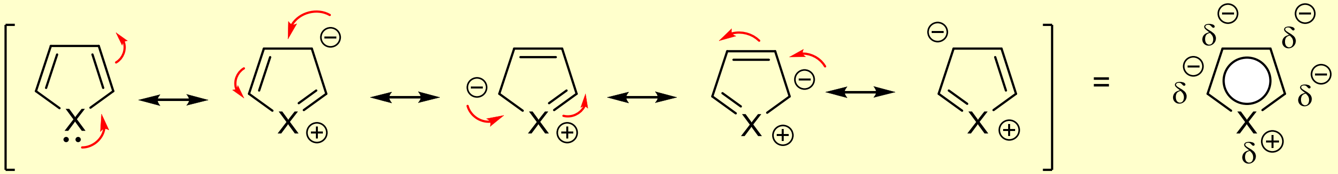


STRONG electron withdrawl (C to X)

WEAK electron withdrawl (C to X)

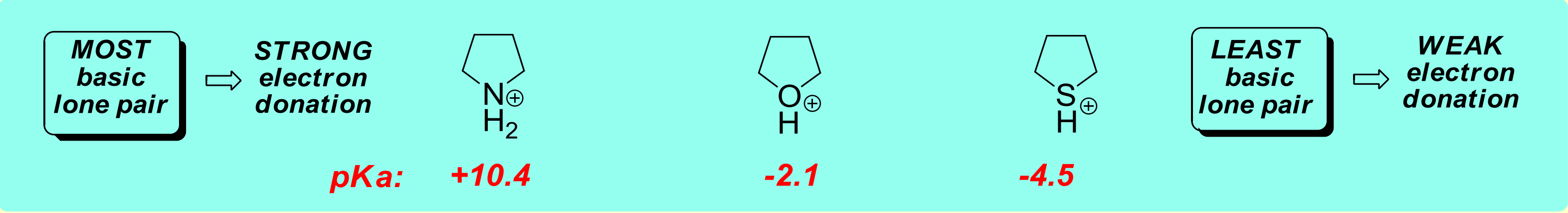
dipole moments: ***~1.7 D*** ***~1.6 D*** ***~0.5 D***

  - ***RESONANCE*** <u>donation</u> of electron density ***towards the carbons*** (*via* π-bonds):



electron DONATION (X to C)

    - the importance of this depends on the ability of the heteroatom to delocalise its p-lone pair
    - this mirrors the basicities of the protonated saturated heterocycles (i.e. ability of X atom to accommodate +ive charge:



MOST basic lone pair ⇨ ***STRONG electron donation***

LEAST basic lone pair ⇨ ***WEAK electron donation***

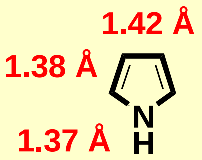
pKa: ***+10.4*** ***-2.1*** ***-4.5***

- ***RESONANCE*** is the ***dominant factor*** pushing electron density onto the carbons and hence affecting ***REACTIVITY***

Pyrrole – *Structure and Properties*

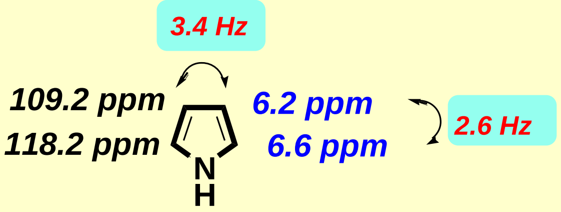
- A liquid bp 139 °C
- ***Bond lengths***, ***^{1}H*** and ***^{13}C NMR chemical shifts*** and ***coupling constants*** as expected for an aromatic system:

bond lengths:



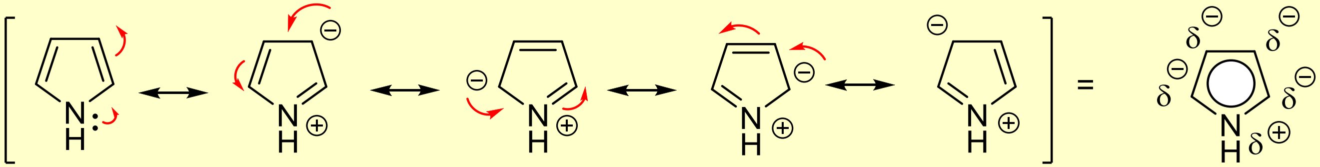
***cf.* ave C-C 1.48 Å**
ave C=C 1.34 Å
ave C-N 1.45 Å

^{13}C and ^{1}H NMR:

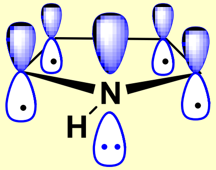


- ***Resonance energy:*** 90 kJmol^{-1} [*i.e.* lower than benzene (152); *intermediate cf.* thiophene (122) & furan (68)]
  - → rarely undergoes addition reactions & requires EWG on N to act as diene in Diels-Alder reactions

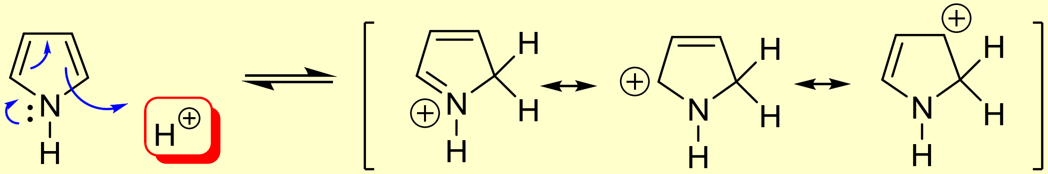
- ***Electron density:*** ***electron rich*** *cf.* benzene & higher than furan & thiophene
  - → ***very reactive towards electrophilic substitution (S_EAr)***, unreactive towards nucleophilic substitution (S_NAr)



- ***NH-acidic*** (pK_a 17.5). ***Non-basic*** because the N lone pair is part of the aromatic sextet of electrons & protonation leads to a non-aromatic *C*-protonated species:



p-orbital lone-pair part of aromatic sextet 'π-excessive'

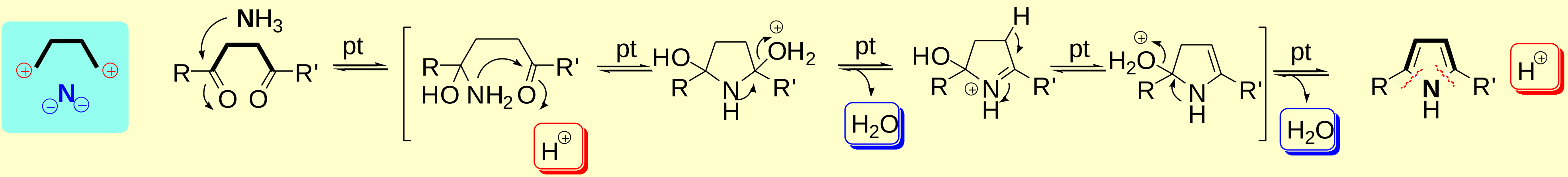


pK_a -3.8

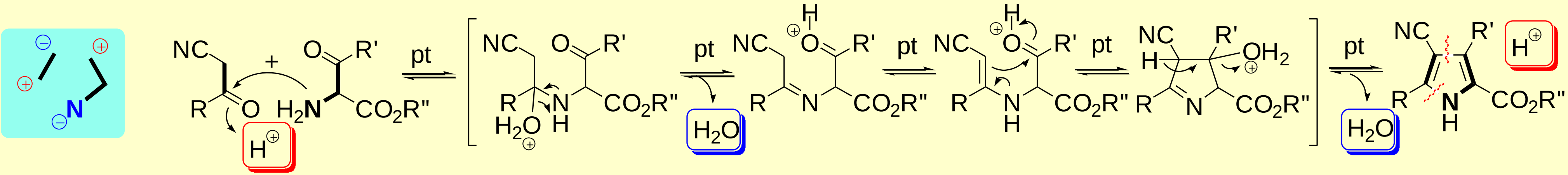
N.B. protonates on ***C2*** (resulting cation is delocalised) NOT on ***N*** (would not be delocalised)

Pyrroles *– Syntheses*

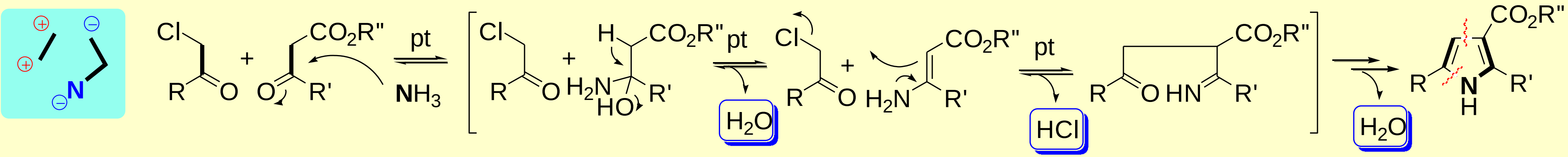
- ***Paal-Knorr (Type I):*** 1,4-dicarbonyl with NH_3 or 1º amine



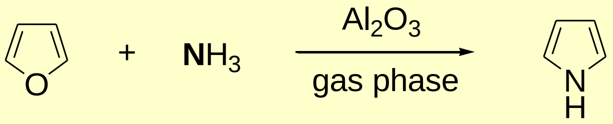
- ***Knorr (Type II):*** β-ketoester or β-ketonitrile with α-aminoketone



- ***Hantzsch (Type II):*** α-chloroketone with enaminoester

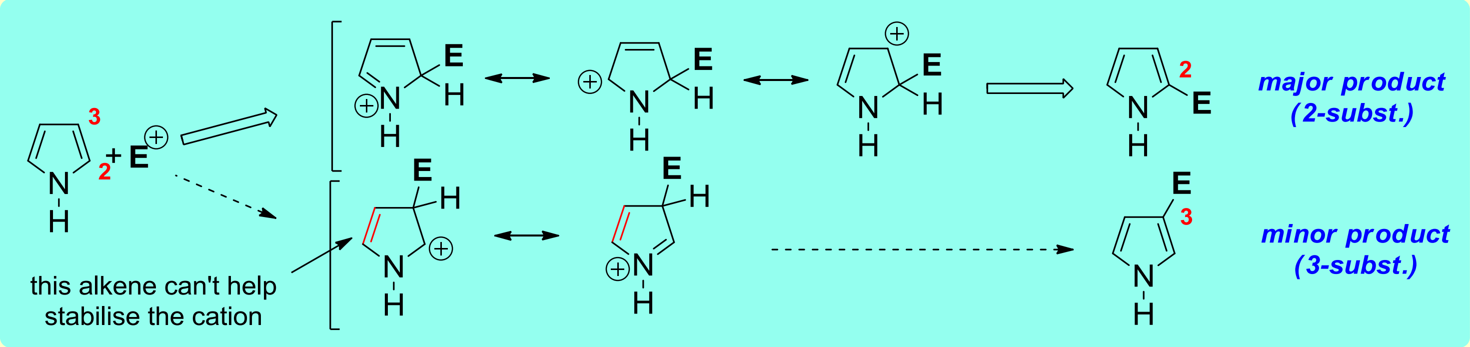


- ***Commercial synthesis of pyrrole:***



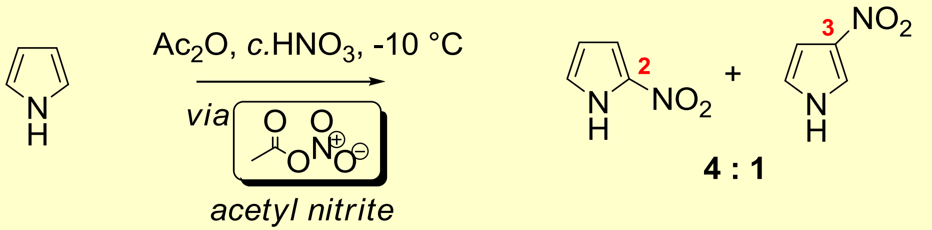
***Pyrroles** – Reactivity*

- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr) (see supplementary slides 1-2)
  - **<u>reactivity:</u>** extremely reactive towards many electrophiles (**E^+**); >furan, thiophene, benzene; similar to aniline
  - **<u>regioselectivity:</u>** the kinetic product predominates; predict by estimating the energy of the respective Wheland intermediates → 2-substitution is favoured:



  - ***e.g.* <u>nitration:</u>** (**E**$^+$ = NO_2^+)

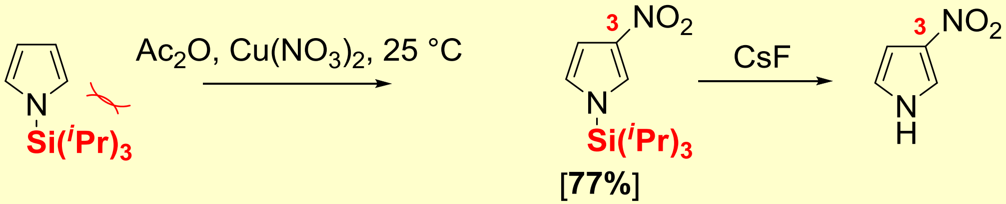
2-selective



$NO_2^{\oplus}$

nitronium ion

3-selective

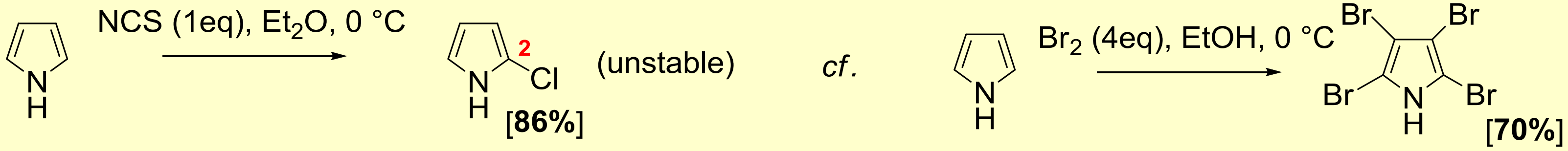


lateral protection (steric shielding of 2-/5-positions)

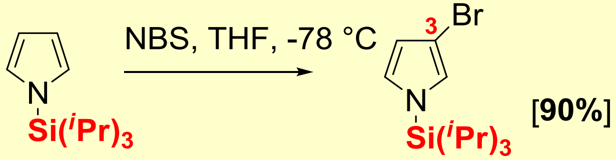
Pyrroles *– Reactivity cont.*

- ***Electrophilic substitution (S_EAr) cont.***
  - ***e.g.* <u>halogenation:</u>** (**E**$^+$ = Hal$^+$)
    - reacts rapidly to give tetra-halopyrroles unless conditions are carefully controlled

2-selective



3-selective

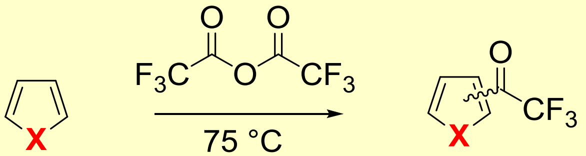


lateral protection

Hal$^\oplus$

halonium ion

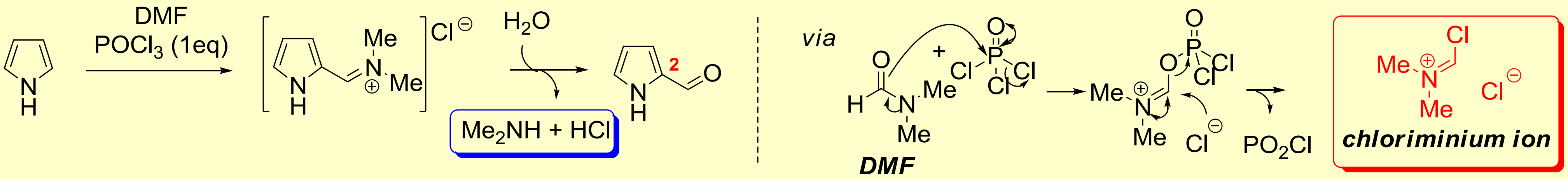
  - ***e.g.* <u>acylation:</u>** (**E**$^+$ = RCO$^+$)
    - comparison with analogous reactions of furan & thiophene



relative rate: **X** =	
NH	5.3 x 10^7
O	1.4 x 10^2
S	1

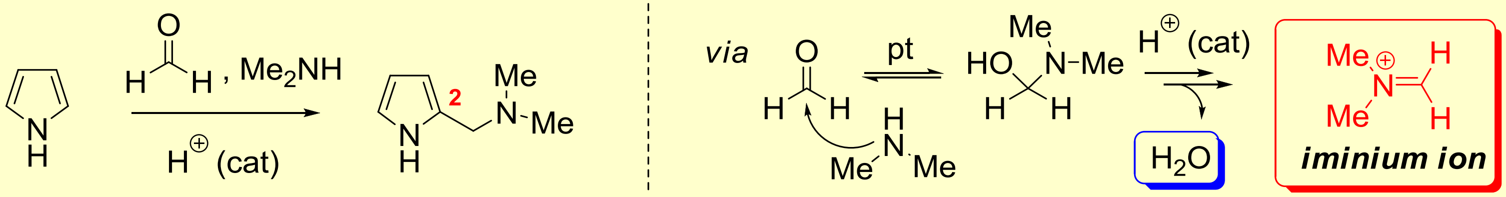
ratio of 2-acyl to 3-acyl: **X** =	
NH	6:1
O	6000:1
S	exclusively 2-acyl

    - Vilsmeyer formylation: (**E**$^+$ = chloriminium ion)

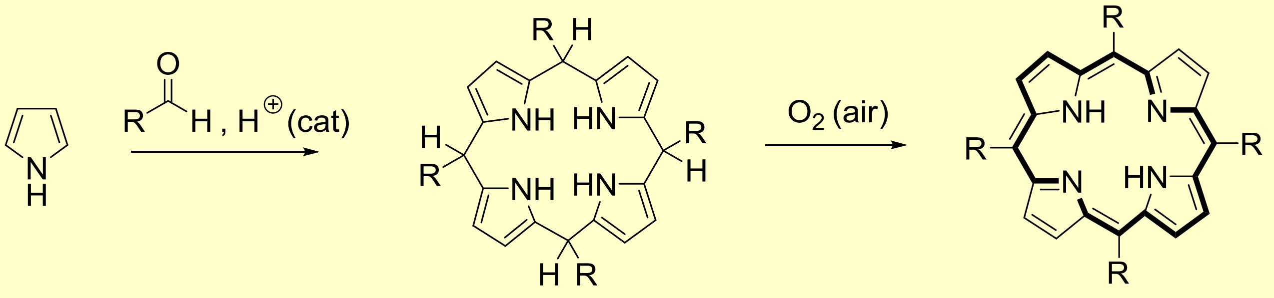


Pyrroles *– Reactivity cont.*

- ***Electrophilic substitution (S_EAr) cont.***
  - ***e.g. <u>Mannich reactions (aminomethylation):</u>*** (**E**$^+$ = RCH=NR'$_2^+$, iminium ion)



  - ***e.g. <u>acid catalysed condensation with aldehydes & ketones:</u>*** (**E**$^+$ = RCH=OH$^+$, protonated carbonyl compound)
    - → tetrapyrroles & porphyrins

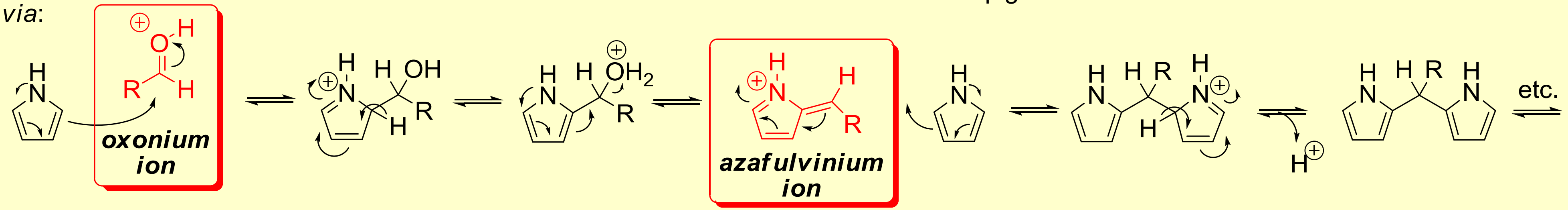


porphyrinogen

porphyrin
coloured pigment!

facile dehydrogenation (-6H, oxidation)
to give aromatic porphyrin product
(18π electron, i.e. 4n + 2 where n = 4)

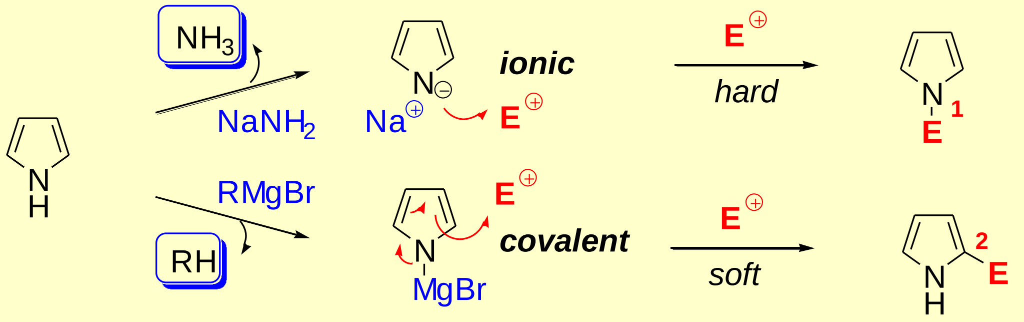
via:



Pyrroles – *Reactivity cont.*

- ***Metallation:*** (NH $pK_a = 17.5$) *NB*. For an overview & mechanistic discussion see ***LECTURE 7*** (also: Joule & Smith (5th Ed) chapter 4).

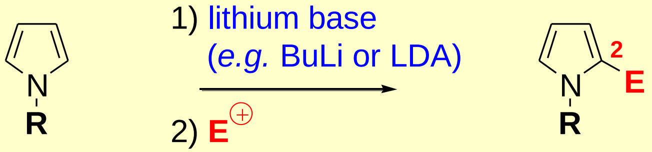
NH-pyrroles:
(N-metallation)



metallated pyrrole is an ambident nucleophile

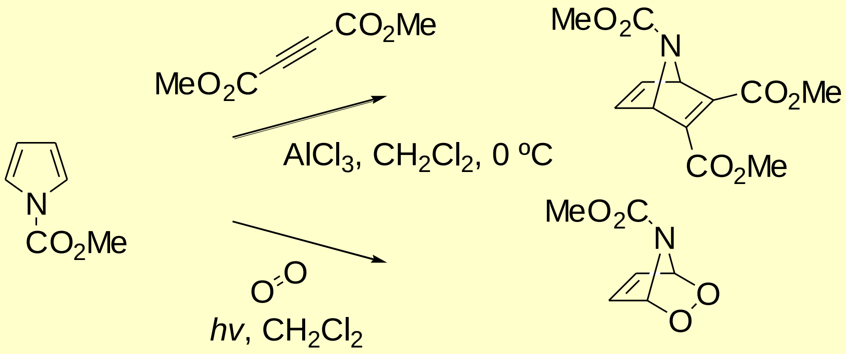
$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

NR pyrroles:
(C-metallation)



$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

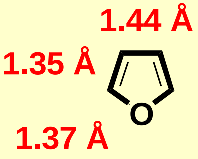
- ***Reaction as a Diels-Alder diene:***
    - only possible with EWG on N to reduce aromatic character (*i.e.* reduce resonance energy):



Furan *– Structure and Properties*

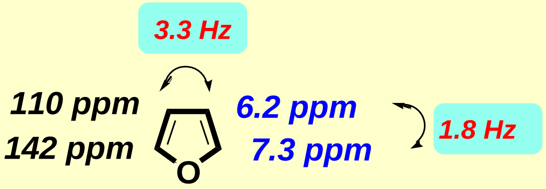
- A liquid bp 31 °C
- ***Bond lengths***, ***^{1}H*** and ***^{13}C NMR chemical shifts*** and ***coupling constants*** as expected for an aromatic system:

bond lengths:



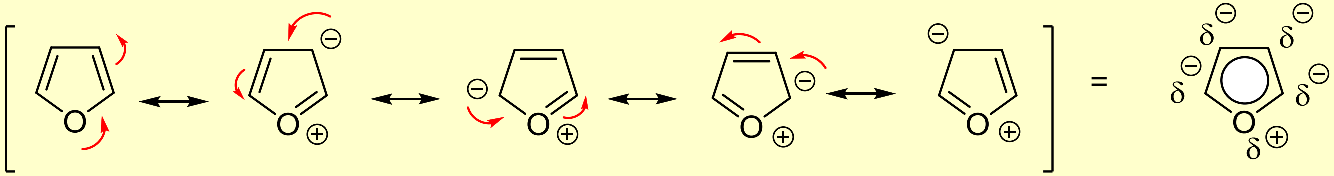
cf. ave C-C 1.48 Å
ave C=C 1.34 Å
ave C-O 1.43 Å

^{13}C and ^{1}H NMR:



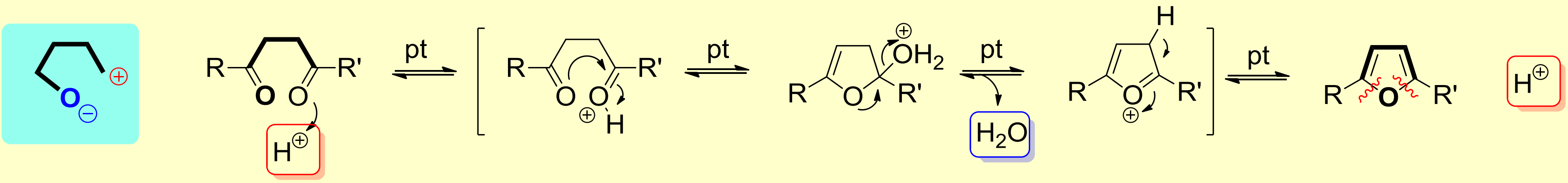
- ***Resonance energy:*** 68 kJmol^{-1} [*i.e.* lower than benzene (152), thiophene (122) & pyrrole (90)]
  - → tendency to undergo ***electrophilic addition*** as well as substitution
  - → a good ***diene*** in ***Diels-Alder reactions***

- ***Electron density:*** ***electron rich*** *cf.* benzene (& thiophene) but less so than pyrrole
  - → fairly reactive towards ***electrophilic substitution*** (**S$_E$Ar**), unreactive towards nucleophilic substitution (S$_N$Ar)

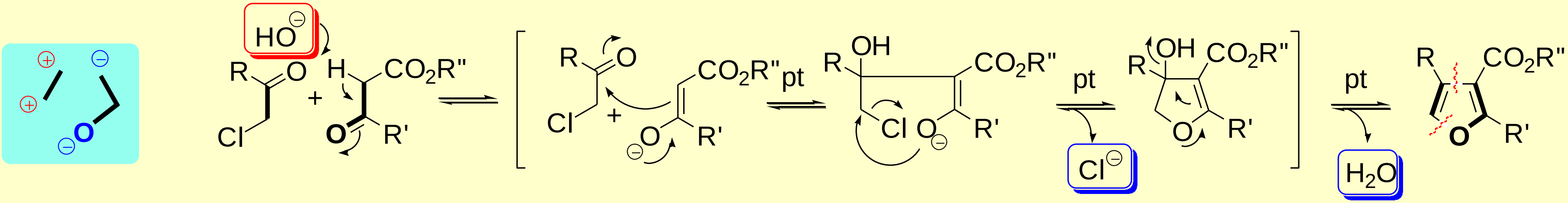


***Furans** – Syntheses*

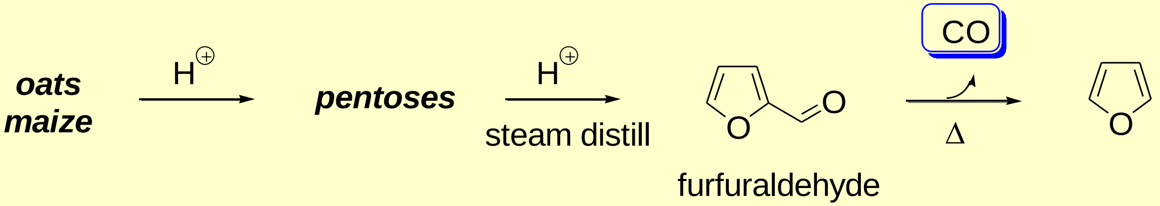
- ***Paal-Knorr (Type I):*** dehydration of 1,4-dicarbonyl



- ***Feist-Benary (Type II):*** 1,3-dicarbonyl with α-haloketone



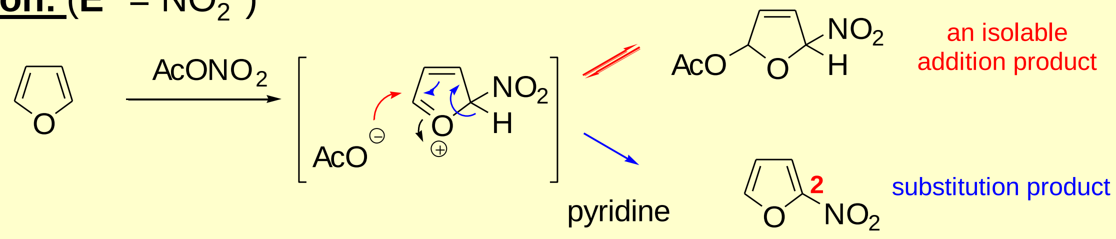
- ***Commercial synthesis of furan:***



oats maize $\xrightarrow{H^{\oplus}}$ ***pentoses*** $\xrightarrow[\text{steam distill}]{H^{\oplus}}$ furfuraldehyde $\xrightarrow[\Delta]{-CO}$ furan

***Furans** – Reactivity*

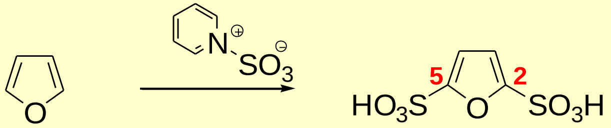
- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr) (see supplementary slides 1-2)
  - **reactivity:** reactive towards many electrophiles (**E**$^+$); <pyrrole, but >thiophene & benzene
  - **regioselectivity:** as for pyrrole the kinetic 2-substituted product predominates
  - ***e.g.*** **nitration:** (**E**$^+$ = NO_2^+)



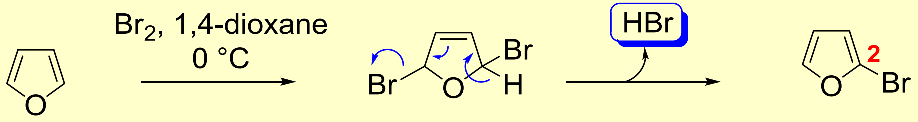
an isolable addition product

substitution product

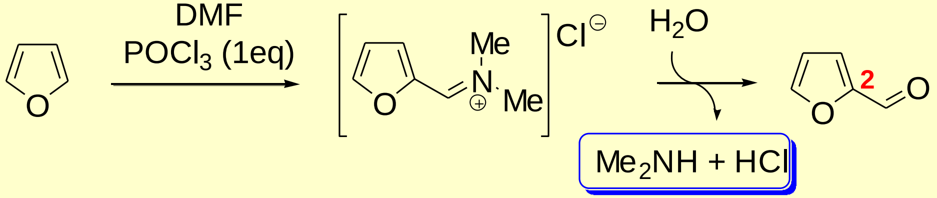
  - ***e.g.*** **sulfonylation:** (**E**$^+$ = SO_3)



  - ***e.g.*** **halogenation:** (**E**$^+$ = Hal$^+$) like pyrrole – mild conditions to avoid poly-halogenation

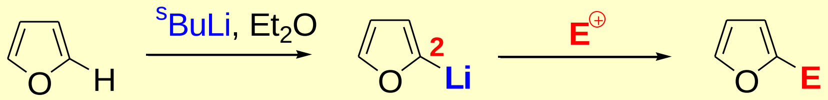


  - ***e.g.*** **acylation:** Vilsmeyer formylation (**E**$^+$ = chloriminium ion) as for pyrrole



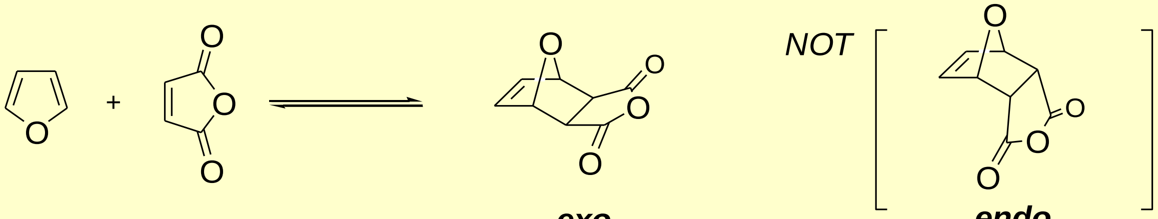
Furans *– Reactivity cont.*

- ***Metallation:*** *NB*. For an overview & mechanistic discussion see ***LECTURE 7*** (also: Joule & Smith (5th Ed) chapter 4).



$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

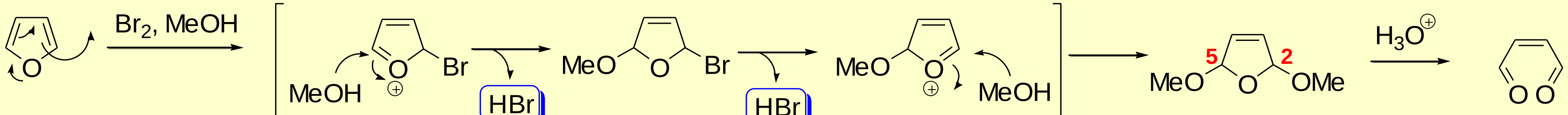
- ***Reaction as a Diels-Alder diene:*** *NB.* reversible reactions → *exo* (NOT *endo*) products



exo
thermodynamic product

endo
kinetic product

- ***Reaction as an enol ether – electrophilic <u>addition</u>:***
  - ❑ usually achieved by use of an electrophile in a nucleophilic solvent at low temperature

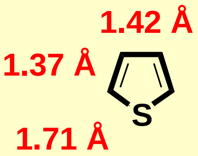


addition product

Thiophene *– Structure and Properties*

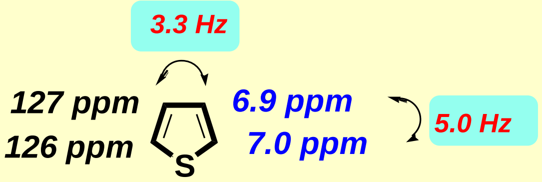
- A liquid bp 84 °C
- ***Bond lengths***, ^{1}***H*** and ^{13}***C NMR chemical shifts*** and ***coupling constants*** as expected for an aromatic system:

bond lengths:



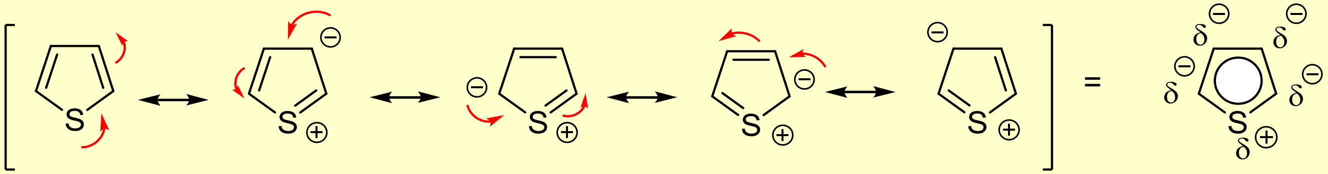
cf. **ave C-C 1.48 Å**
ave C=C 1.34 Å
ave C-S 1.82 Å

^{13}C and ^{1}H NMR:



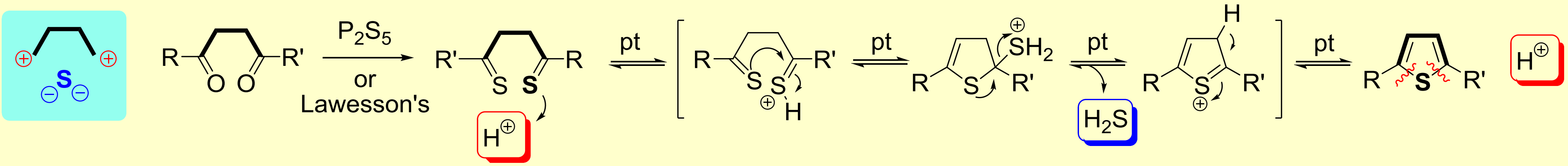
- ***Resonance energy:*** 122 kJmol^{-1} [*i.e.* lower than benzene (152); but *high cf.* pyrrole (90) & furan (68)]
  - → rarely undergoes addition reactions
  - → does not act as a diene in Diels-Alder reactions

- ***Electron density:*** ***electron rich*** *cf.* benzene but less so than pyrrole & furan
  - → fairly reactive towards ***electrophilic substitution*** (**S$_E$Ar**), unreactive towards nucleophilic substitution (S$_N$Ar)

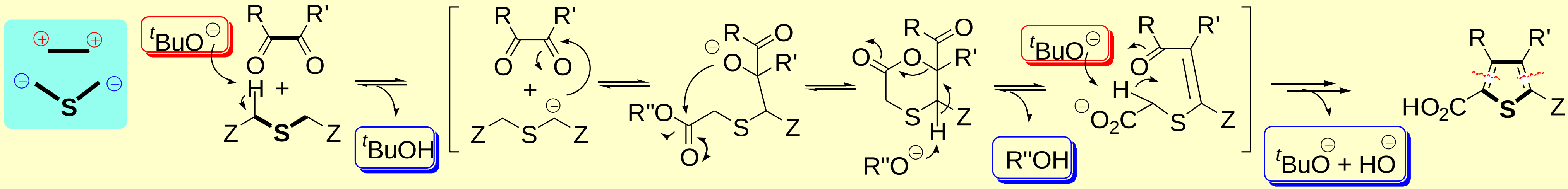


Thiophenes – *Syntheses*

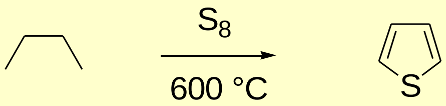
- ***Paal-Knorr (Type I):*** 1,4-dicarbonyl with P_2S_5 or Lawesson's reagent (lecture 1)



- ***Hinsberg:*** 1,2-dicarbonyl with thiodiacetate
    - *NB.* Z = CO_2R''



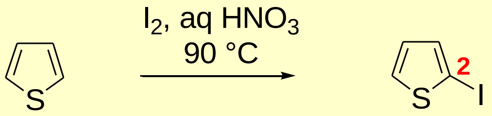
- ***Commercial synthesis of thiophene:***



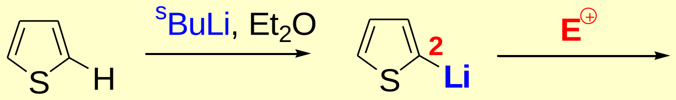
Thiophenes *– Reactivity*

- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr) (see supplementary slides 1-2)
  - **reactivity:** reactive towards many electrophiles (**E**$^+$); <<pyrrole & <furan, but >benzene
  - **regioselectivity:** as for pyrrole/furan the kinetic 2-substituted product predominates

  - ***e.g.*** **halogenation:** (**E**$^+$ = Hal$^+$) like pyrrole/furan – mild conditions to avoid poly-halogenation

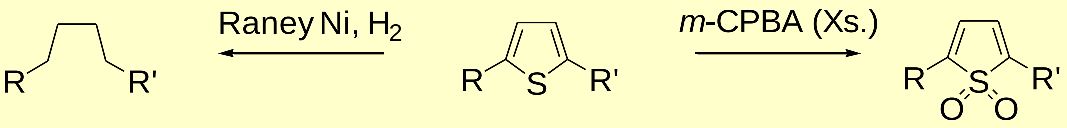


- ***Metallation:*** as for furan but α-protons more acidic – easier to deprotonate
  - *NB*. For an overview & mechanistic discussion see ***LECTURE 7*** (also: Joule & Smith (5th Ed) chapter 4).



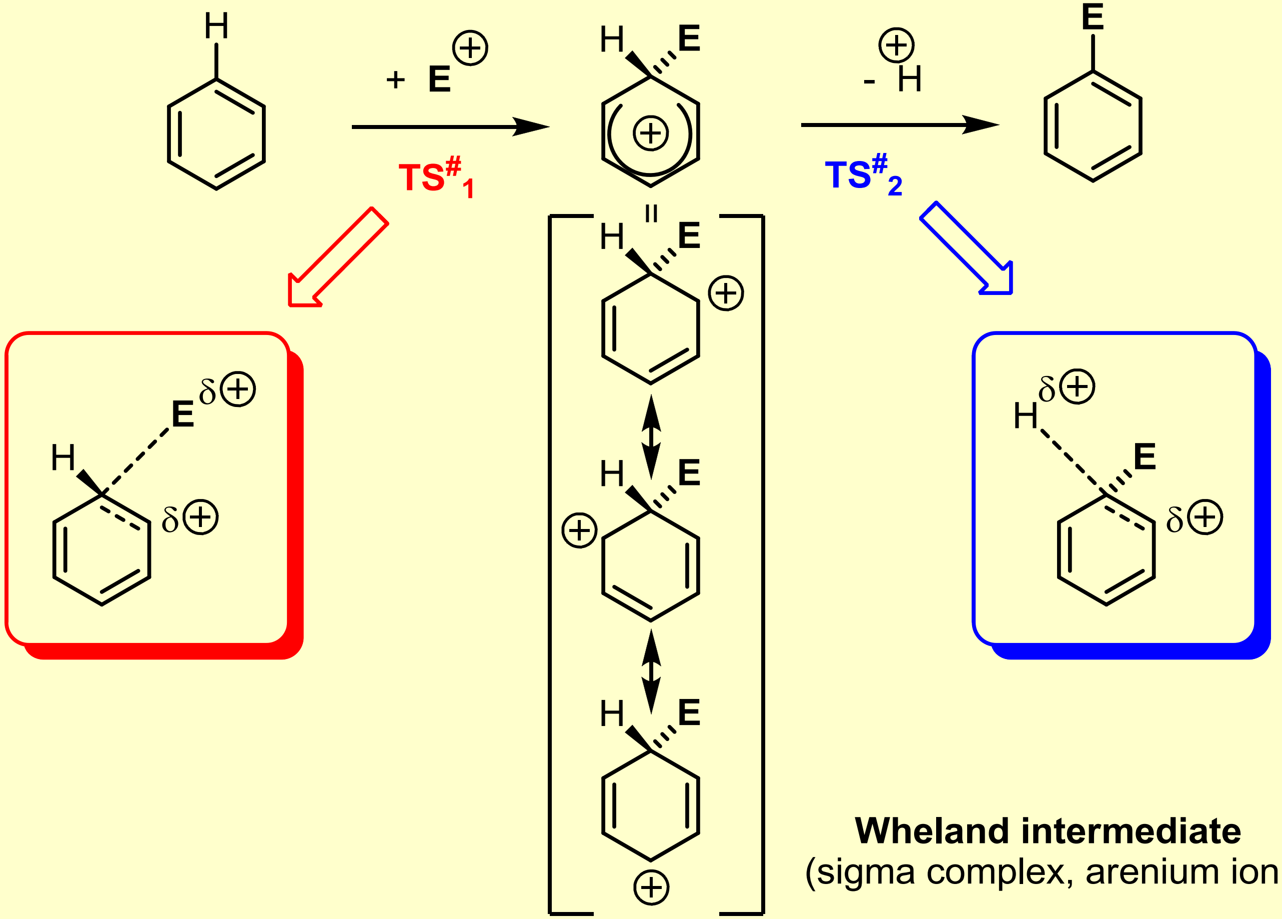
$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

- ***NO reactivity as a Diels-Alder diene*** – high resonance energy
- ***NO reactivity as a thioenol ether (i.e. addition reactions, cf. furan)*** – high resonance energy
- ***Reactions at sulfur:***
  - oxidation/reduction chemistry:



Supplementary Slide 1 – *Electrophilic Aromatic Substitution: S_EAr*

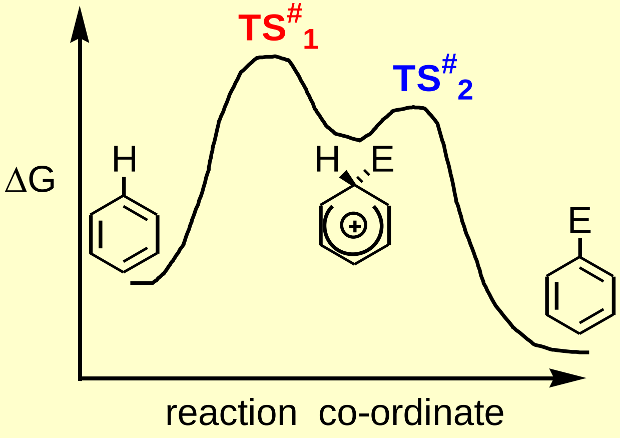
- ***Mechanism:*** addition-elimination
  - *e.g.* for benzene:



Wheland intermediate
(sigma complex, arenium ion)

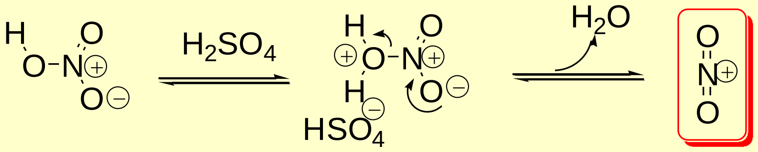
notes

- *Intermediates*: energy minima
- *Transition states*: energy maxima
- Wheland intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control



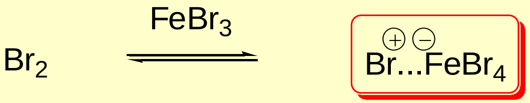
Supplementary Slide 2 – *Electrophiles for S_EAr*

- ***nitration:***
  - *c*.HNO_3:*c*.H_2SO_4 (1:1) or *c*.HNO_3 in Ac_2O



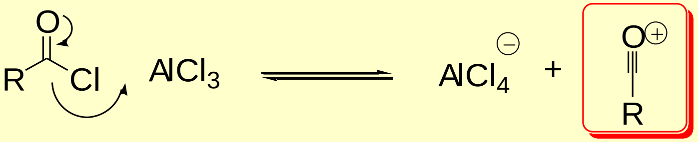
nitronium ion = **E**$^{\oplus}$

- ***halogenation:***
  - molecular halide ± Lewis acid (LA) catalyst in the dark



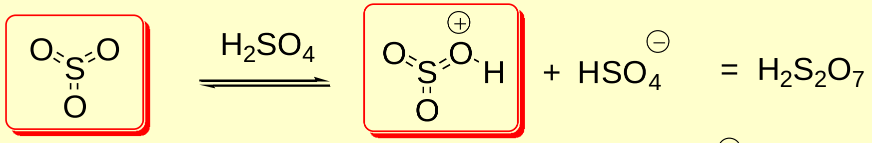
Halogen-Lewis acid complex = **E**$^{\oplus}$

- ***acylation:***
  - acid chloride or anhydride ± LA promoter:



acylium ion = **E**$^{\oplus}$

- ***sulfonylation:***
  - oleum (*c*.H_2SO_4 saturated with SO_3)



sulfur trioxide

protonated sulfur trioxide = **E**$^{\oplus}$