Chemistry II (Organic)

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

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Jan 2010
Format & scope of lectures 4 & 5

- **Bonding, aromaticity & reactivity of 5-ring heteroaromatics:**
  - cf. cyclopentadienyl anion
  - pyroles, 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 $S_{E,Ar}$ mechanism
Pyrroles, Furans & Thiophenes – Importance

- **Natural products:**
  - Furan
  - Rosefuran (component of rose oil)
  - Porphobilinogen (biosynthetic precursor to tetrapyrrole pigments)
  - Chlorophyll (green leaf pigment)

- **Pharmaceuticals:**
  - Lipitor (atorvastatin, anti-cholesterol)
  - Ranitidine (zantac, anti-ulcer)
  - Vioxx (rofecoxib, COX-II inhibitor)
  - Nitrofurazone (bactericide)
  - Duloxetine (indicated for major depressive disorders)
  - Pyrantel (anthelmintic vs. pinworm)
The cyclopentadienyl anion is a C5-symmetric aromatic 5-membered cyclic carbanion:

\[
\text{cyclopentadiene} \quad = \quad \text{cyclopentadienyl anion} \quad \text{NaOEt} \quad \text{EtOH} \quad \text{etc.} \quad \text{Na}^+ \quad \text{Na}^+ \quad \text{sp}^2 \quad \text{6π electron aromatic}
\]

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furan & thiophene can be considered as the corresponding aromatic systems where the anionic \( \text{CH}^- \) unit has been replaced by the iso-electronic \( \text{NH}, \text{O} \) and \( \text{S} \) units respectively:

\[
\text{Na}^+ \quad \text{Na}^+ \quad \text{sp}^2 \quad \text{6π electron aromatic}
\]

They are no longer C5-symmetric and do not bear a negative charge but they retain 6p electrons and are still aromatic.
The MO diagram for the cyclopentadienyl anion can be generated using the Musulin-Frost method (lecture 1). The asymmetry introduced by $\text{CH} \rightarrow \text{NH/O/S}$ ‘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 lower in energy. The larger the mismatch in energy ($\Delta E_i$) the smaller the resulting stabilisation ($\Delta E_{\text{STAB}}$) because:

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

- $S^2 = \text{overlap integral}$
- $E_{\text{STAB}} = \text{stabilisation energy}$
- $\Delta E_i = \text{interaction energy}$

Consequently, the resonance energies loosely reflect the difference in the Pauling electronegativities of S (2.6), N (3.0) & O (3.4) relative to C (2.5):

- Thiophene: 152 kJmol\(^{-1}\)
- Pyrrole: 122 kJmol\(^{-1}\)
- Furan: 90 kJmol\(^{-1}\)
- Resonance energies: thiophene $>$ pyrrole $>$ furan → increasing tendency 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 \( \pi \)-electrons distributed over 5 atoms so the carbon frameworks are *ALL* inherently *ELECTRON RICH* (relative to benzene with 6 \( \pi \)-electrons over 6 atoms).

- Additionally, the distribution of \( \pi \)-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 \( \pi \)-electron densities*
  
  - *NB.* many text books highlight dipole moments in this regard – but the sp\(^2\) lone pairs of furan and thiophene complicate this analysis.

  \[\begin{align*}
  \pi\text{-electron densities:} & \quad \text{MOST electron rich Cs} & \text{dipole moments:} & \quad \text{1.090} & \quad \text{1.087} & \quad \text{1.647} \\
  & \quad \text{1.067} & \quad \text{1.078} & \quad \text{1.710} & \quad \text{1.046} & \quad \text{1.071} & \quad \text{1.760} & \quad \text{all 1.000} \\
  \end{align*}\]

  - *dipole moment dominated by sp\(^2\) lone pair*  
  - *dipole moment is solvent dependent*

- The *calculated \( \pi \)-electron densities* reflect the relative *REACTIVITIES* of the 3 heterocycles towards *electrophiles*:

\[\begin{align*}
  \text{relative rates:} & \quad 5.3 \times 10^7 & \quad 1.4 \times 10^2 & \quad 1 & \quad \text{no reaction} \\
  \end{align*}\]
The calculated $\pi$-electron densities reflect a balance of opposing factors:

- **INDUCTIVE** withdrawal of electron density away from the carbons (via $\sigma$-bonds):
  - this mirrors Pauling electronegativities: $\text{O} (3.4) > \text{N} (3.0) > \text{S} (2.6)$ as revealed by the dipole moments of the saturated (i.e. non-aromatic) heterocycles:

\[
\begin{align*}
\text{dipole moments:} & \quad \sim 1.7 \text{ D} & \quad \sim 1.6 \text{ D} & \quad \sim 0.5 \text{ D}
\end{align*}
\]

- **RESONANCE** donation of electron density towards the carbons (via $\pi$-bonds):
  - 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:

\[
\begin{align*}
\text{pK}_a: & \quad +10.4 & \quad -2.1 & \quad -4.5
\end{align*}
\]

**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:
    - 1.42 Å
    - 1.38 Å
    - 1.37 Å
    - 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:
    - 109.2 ppm
    - 6.2 ppm
    - 118.2 ppm
    - 6.6 ppm
    - 3.4 Hz
    - 2.6 Hz

- Resonance energy: 90 kJmol⁻¹ [i.e. lower than benzene (152); intermediate cf. thiophene (122) & furan (68)] → rarely undergoes addition reactions & requires EWGs 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 ($S_{E}$Ar), unreactive towards nucleophilic substitution ($S_{N}$Ar)

- 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 $^{\pi}$-excessive

  - 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 NH₃ or 1° 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$_e$Ar) (see supplementary slides 1-2)
  - **reactivity:** extremely reactive towards many electrophiles ($E^+$); >furan, thiophene, benzene; similar to aniline
  - **regioselectivity:** the kinetic product predominates; predict by estimating the energy of the respective Wheland intermediates → 2-substitution is favoured:

  ![Reaction Mechanism Diagram]

  - **e.g. nitration:** ($E^+ = \text{NO}_2^+$)
    - **2-selective**
      - $\text{Ac}_2\text{O}, \text{c.} \text{HNO}_3, -10 \, ^\circ\text{C}$
      - $\text{Ac}_2\text{O}$, c$_\text{HNO}_3$, -10 °C
      - $\text{Ac}_2\text{O}$, Cu(NO$_3$)$_2$, 25 °C
      - $\text{Ac}_2\text{O}$, Cu(NO$_3$)$_2$, 25 °C
    - **3-selective**
      - $\text{Ac}_2\text{O}$, Cu(NO$_3$)$_2$, 25 °C
      - $\text{Ac}_2\text{O}$, Cu(NO$_3$)$_2$, 25 °C

  ![Product Ratios Diagram]

  - major product (2-subst.)
  - minor product (3-subst.)
  - 4 : 1
Electrophilic substitution (S_{EAr}) cont.

- **e.g. halogenation:** (E^{+} = \text{Hal}^{+})
  - reacts rapidly to give tetra-halopyrroles unless conditions are carefully controlled

2-selective

\[
\begin{align*}
\text{NCS (1eq), Et}_{2}O, 0 \, ^\circ\text{C} & \rightarrow \text{N} & \text{H} \rightarrow \text{Cl} \quad \text{(unstable)} & \text{cf.} \quad \text{Br}_{2} (4eq), \text{EtOH}, 0 \, ^\circ\text{C} & \rightarrow \text{N} & \text{H} \rightarrow \text{Br} \quad \text{[70\%]} \\
\end{align*}
\]

3-selective

\[
\begin{align*}
\text{NBS, THF, } -78 \, ^\circ\text{C} & \rightarrow \text{N} & \text{Si(Pr)_{3}} \rightarrow \text{N} & \text{Si(Pr)_{3}} \quad \text{[90\%]} & \text{Hal}^{+} & \text{halonium ion} \\
\end{align*}
\]

- **e.g. acylation:** (E^{+} = \text{RCO}^{+})
  - comparison with analogous reactions of furan & thiophene

\[
\begin{align*}
\text{O} & \quad \text{Nh} & \quad 5.3 \times 10^{7} & \quad \text{O} & \quad 1.4 \times 10^{2} \\
\text{S} & \quad 1 & \quad \text{S} & \quad 1 & \quad \text{S} & \quad 1 \\
\end{align*}
\]

- Vilsmeier formylation: (E^{+} = \text{chlorinium ion})

\[
\begin{align*}
\text{NHC(O)=CHOCH_{3}} (1eq) & \rightarrow \text{N} & \text{H} \rightarrow \text{Cl} & \text{H}_{2}\text{O} & \rightarrow \text{N} & \text{H} \rightarrow \text{Cl} & \text{Me}_{2}\text{NH} + \text{HCl} & \text{DMF} \\
\end{align*}
\]
**Pyrroles – Reactivity cont.**

- **Electrophilic substitution (S$_\text{E}$_Ar) cont.**
  - e.g. **Mannich reactions (aminomethylation):** ($E^+ = RCH=NR'_2^+$, iminium ion)

\[
\text{H}_2\text{NMe}_2 + \text{H}^+ \rightarrow \text{Me}_2\text{NMe}
\]

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

\[
\text{RCHO} + \text{H}_2\text{O} \rightarrow \text{RCH(OH)}_2^+
\]

**facile dehydrogenation (-6H, oxidation) to give aromatic porphyrin product**

(18π electron, i.e. 4n + 2 where n = 4)
**Pyrroles – Reactivity cont.**

- **Metallation:** \((\text{NH } \text{pK}_a = 17.5)\)

  \[ \text{NH}-\text{pyrroles:} \quad (N\text{-metallation}) \]
  \[ \begin{align*}
  \text{NH}_3 & \quad \xrightarrow{\text{NaNaNH}_2} \quad \text{ionic} \\
  \text{RMgBr} & \quad \xrightarrow{\text{RH}} \quad \text{covalent}
  \end{align*} \]

  \[ \text{metallated pyrrole is an ambident nucleophile} \]

  \[ \text{E}^+ \cdot \text{X}^- = \text{MeI, RCOCI etc.} \]

- **NR pyrroles:** \((C\text{-metallation})\)

  \[ 1) \text{lithium base (e.g. BuLi or LDA)} \]
  \[ 2) \text{E}^+ \]

  \[ \text{E}^+ \cdot \text{X}^- = \text{MeI, RCOCI etc.} \]

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

  \[ \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \]

  \[ \text{N} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \]

  \[ \text{AlCl}_3, \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C} \]

  \[ \text{hv, CH}_2\text{Cl}_2 \]

  \[ \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \]

  \[ \text{N} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \]

  \[ \text{O} \quad \text{h}, \text{CH}_2\text{Cl}_2 \]

  \[ \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \]

  \[ \text{N} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{MeO}_2\text{C} \]

  \[ \text{O} \quad \text{h}, \text{CH}_2\text{Cl}_2 \]
**Furan – Structure and Properties**

- A liquid bp 31 °C
- **Bond lengths, \(^1H\) and \(^{13}C\) NMR chemical shifts** and **coupling constants** as expected for an aromatic system:
  
  ![Bond lengths Diagram](image)

  - **Bond lengths:**
    - 1.44 Å
    - cf. ave C-C 1.48 Å
    - ave C=C 1.34 Å
    - ave C-O 1.43 Å

  - **\(^{13}C\) and \(^1H\) NMR:**
    - 110 ppm
    - 142 ppm
    - 6.2 ppm
    - 7.3 ppm
    - 3.3 Hz
    - 1.8 Hz

- **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 $\xrightarrow{H^+}$ pentoses $\xrightarrow{H^+}$ steam distill furfuraldehyde $\xrightarrow{\Delta}$ furan
**Electrophilic substitution:** via addition-elimination (S_{E}Ar) (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}^{+})

![Nitration reaction diagram]

- **e.g. sulfonylation:** (E^{+} = SO_{3}^{+})

![Sulfonylation reaction diagram]

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

![Halogenation reaction diagram]

- **e.g. acylation:** Vilsmeyer formylation (E^{+} = chloriminium ion) as for pyrrole
Furans – Reactivity cont.

- **Metallation:**

  \[
  \text{Furane} \xrightarrow{^6\text{BuLi, Et}_2\text{O}} \text{Furane}_2^{\text{Li}} \xrightarrow{\text{E}^+} \text{Furane}_E
  \]

  \(\text{E}^+X^- = \text{MeI, RCOCl etc.}\)

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

  \[
  \text{Furane} + \text{Maleic anhydride} \quad \xrightarrow{\text{NOT}} \quad \text{exo thermodynamic product}
  \]

- **Reaction as an enol ether – electrophilic addition:**

  - usually achieved by use of an electrophile in a nucleophilic solvent at low temperature

  \[
  \text{Furane} \xrightarrow{\text{Br}_2, \text{MeOH}} \text{Bromo furane} \xrightarrow{\text{MeOH, HBr}} \text{Addition product}
  \]

  \[
  \text{Addition product} \xrightarrow{\text{MeOH, HBr}} \text{Addition product} \xrightarrow{\text{MeOH, HBr}} \text{Oxygenated product} \xrightarrow{\text{H}_3\text{O}^+} \text{Oxygenated product}
  \]
**Thiophene – Structure and Properties**

- A liquid bp 84 °C
- **Bond lengths**, $^1H$ and $^{13}C$ NMR chemical shifts and coupling constants as expected for an aromatic system:
  
  **Bond lengths:**
  - $1.37 \, \text{Å}$
  - $1.42 \, \text{Å}$
  - $1.71 \, \text{Å}$

  **$^{13}C$ and $^1H$ NMR:**
  - $127 \, \text{ppm}$
  - $126 \, \text{ppm}$
  - $6.9 \, \text{ppm}$
  - $7.0 \, \text{ppm}$

- **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 ($S_E\text{Ar}$), unreactive towards nucleophilic substitution ($S_N\text{Ar}$)

![Thiophene resonance structure](image)
**Thiophenes – Syntheses**

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

  \[
  \text{R} \text{O} = \text{O} + \text{P}_2\text{S}_5 \quad \text{or} \quad \text{Lawesson's reagent} \rightarrow \text{R}' \text{S} \text{R} \quad \text{pt} \quad \text{R} \text{S} \text{R}' \quad \text{pt} \quad \text{R} \text{S} \text{R}' \quad \text{pt} \quad \text{R} \text{S} \text{R}' \text{H}^+ \]

- **Hinsberg:** 1,2-dicarbonyl with thiodiacetate

  - NB. $Z = \text{CO}_2\text{R}''$

  \[
  \text{R} \text{O} = \text{O} \quad \text{tBuO} \quad \text{H}^+ \quad \text{tBuOH} \rightarrow \text{R} \text{S} \text{R} \quad \text{H}_2\text{S} \quad \text{pt} \quad \text{R} \text{S} \text{R}' \text{H}^+ \]

- **Commercial synthesis of thiophene:**

  \[
  \text{S}_8 \quad \text{600 °C} \rightarrow \text{S} \]
**Thiophenes – Reactivity**

- **Electrophilic substitution:** via addition-elimination (SEAr) (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:** \((E^+ = \text{Hal}^+)\) like pyrrole/furan – mild conditions to avoid poly-halogenation

  \[
  \text{I}_2, \text{aq HNO}_3 \quad 90 \, ^\circ\text{C} \quad \text{I}_2
  \]

- **Metallation:** as for furan but \(\alpha\)-protons more acidic – easier to deprotonate

  \[
  \text{S} \quad \overset{\text{BuLi, Et}_2\text{O}}{\text{H}} \quad \text{S} \quad \overset{\text{Li}}{\text{2Li}} \quad \text{S} \quad \overset{E^\ominus}{\text{E}} \quad \text{E}^{\ominus}\text{X}^{\ominus} = \text{MeI, RCOCl etc.}
  \]

- **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\textsubscript{E}Ar**

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

<table>
<thead>
<tr>
<th><img src="image" alt="Diagram" /></th>
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<td>Wheland intermediate (sigma complex, arenium ion)</td>
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**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 SEAr**

- ** nitration:**
  - c.HNO₃:c.H₂SO₄ (1:1) or c.HNO₃ in Ac₂O

  $\text{HNO}_3^- + \text{H}_2\text{SO}_4^- \rightarrow \text{NO}_3^- + \text{HSO}_4^- + \text{H}_2\text{O}$

  Nitronium ion = $\text{E}^+$

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

  $\text{Br}_2 + \text{FeBr}_3 \rightarrow \text{Br}^+\text{...FeBr}_4^-$

  Halogen-Lewis acid complex = $\text{E}^+$

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

  $\text{R}^+\text{Cl}^- + \text{AlCl}_3 \rightarrow \text{AlCl}_4^- + \text{RCO}^+$

  Acylium ion = $\text{E}^+$

- ** sulfonylation:**
  - oleum (c.H₂SO₄ saturated with SO₃)

  $\text{SO}_3^+ + \text{H}_2\text{SO}_4^- \rightarrow \text{HSO}_4^- + \text{H}_2\text{SO}_7^-$

  Protonated sulfur trioxide = $\text{E}^+$