Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURE 1
Introduction & overview

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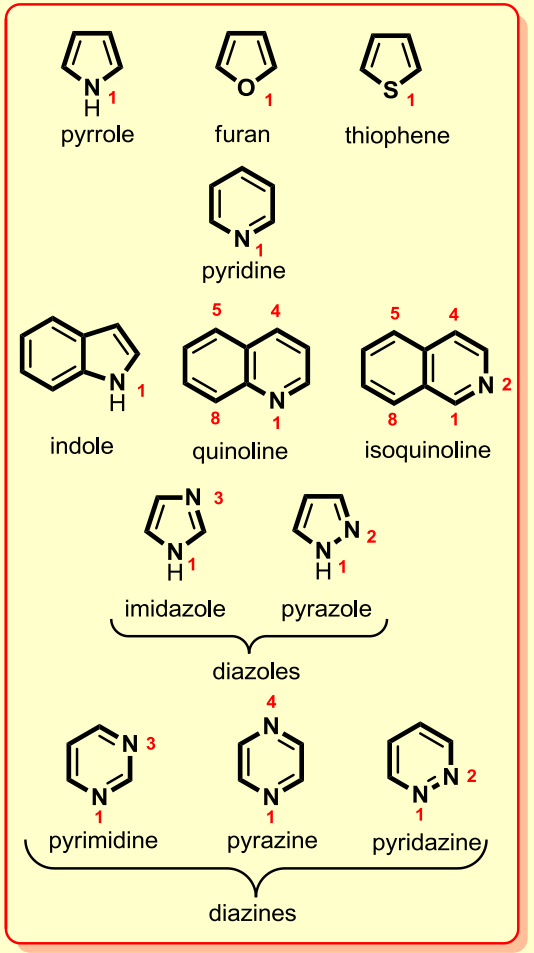
Format & scope of lecture 1

- ***Definitions of structural types***
  - heterocyclic compounds
  - aromatic heterocycles (heteroaromatics)

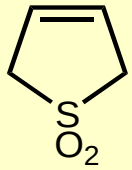
- ***Occurrence and relevance***
  - seratonin & histamine
  - LSD
  - cimetidine (Tagamet™) & ranitidine (Zantac™)
  - atorvastatin calcium (Lipitor™) & torcetrapib
  - sildenafil citrate (Viagra™) & vardenafil citrate (Levitra™)
  - celecoxib (Celebrex™) & rofecoxib (Vioxx™)
  - natural products & chiral auxiliaries/catalysts
  - agrochemicals & ‘smart’ materials

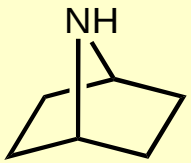
- ***Physical, chemical & spectroscopic properties***
  - recap of structure of benzene and aromaticity
  - valence bond and molecular orbital representations
  - Hückel’s rule
  - resonance energies and symmetry

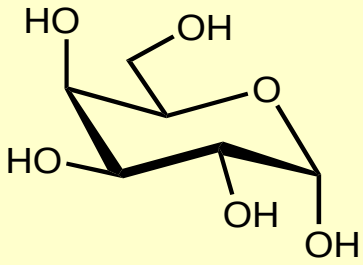


Definitions of Structural Types

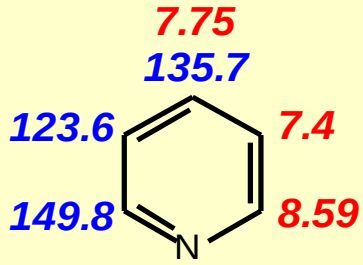
- ***Heterocyclic Compounds***
  - composed of primarily carbon atoms
  - contain at least one other element
  - ***nitrogen***, ***oxygen*** and ***sulphur***
  - ***half*** the known organic compounds
  - present in almost ALL ***pharmaceuticals*** and ***agrochemicals***

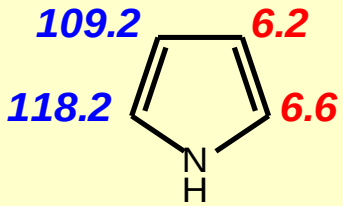






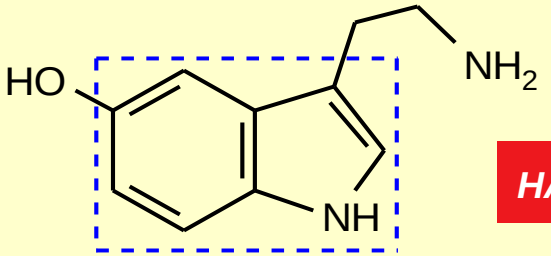
- ***AROMATIC heterocycles (HETEROAROMATICS)***
  - obey ***HÜCKEL's RULE (see later)***
    - ***~planar***
    - ***contiguous, cyclic array of p-orbitals (delocalised electrons)***
    - ***4n+2*** electrons delocalised (n is an integer)
  - possess characteristics of arenes
    - 'anomalous' chemical properties
    - ***unusual NMR chemical shifts***
    - occur widely in nature





^{13}C and ^{1}H chemical shifts (δ/ppm)

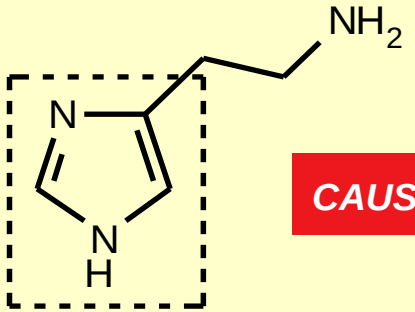
- ***5-HYDROXYTRYTPTAMINE (SEROTONIN)***
  - *first isolated in 1948*
  - *possesses wide range of pharmacological activity:*
    - *induces arterial constriction*
    - *affects mood and appetite*
    - *induces blood platelet aggregation*



INDOLE subunit

HALLUCINOGEN

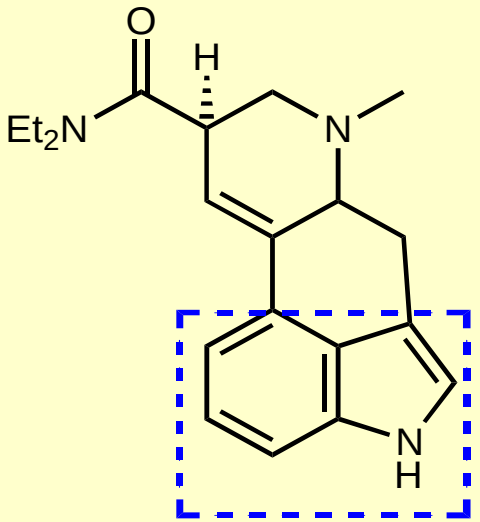
- ***HISTAMINE***
  - *isolated in 1927*
  - *derived* in vivo *from decarboxylation of amino acid histidine*
    - *liberated from cells upon injury*
    - *lowers blood pressure*
    - *directly involved in allergic reactions*
  - ***ANTIHISTAMINES*** *widely used therapeutically (see later)*



IMIDAZOLE subunit

CAUSES INFLAMMATION

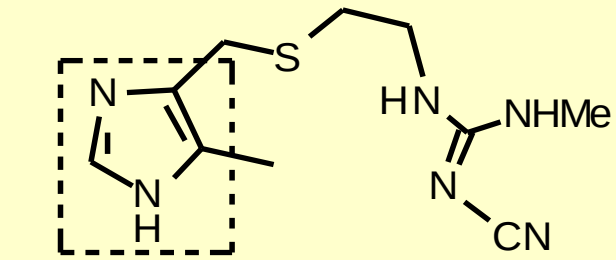
- ***LYSERGIC ACID DIETHYLAMIDE (LSD)***
  - derivative of Lysergic Acid
    - found in **ergot**, a common grain fungus
  - many potent physiological effects documented
  - LSD 1st made in 1938 by Dr. Albert Hoffmann (Sandoz, Basel, Switzerland)
    - spring 1943, Hofmann resynthesized ‘LSD-25’
    - cycled home after self-dosing: suffered ‘trip’
  - known as ‘acid’
  - strongly hallucinogenic/psychedelic
    - induces enhanced sensory perception
  - many adverse reactions
    - ‘bad trip’
    - flashbacks may occur years later
    - can induce permanent psychosis
    - has serotonin-blocking effect
    - interferes with dopamine action



INDOLE subunit

Prof. Albert Hofmann 100th birthday in 2006
I. Amato 'Trip of a century' *Chem. Eng. News.* **2006**, Feb, 43 (DOI)
D. Nichols 'LSD: cultural revolution & medical advances' *Chem. World* **2006**, Jan, 30 (DOI)

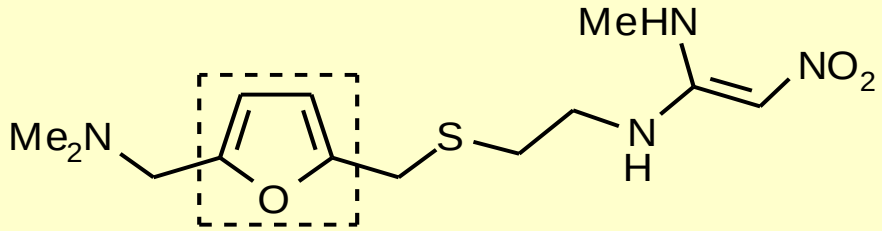
- ***CIMETIDINE (Tagamet®)***



IMIDAZOLE subunit

- SmithKlineFrench (now GSK) ***histamine H_2-receptor antagonist***
- blocks acid secretions
- Indicated for:
  - Treatment & prevention of stomach ulcers
  - gastrocœsophagal reflux disorder (GERD)
- World Health Organization: *"one of world's most essential drugs"*

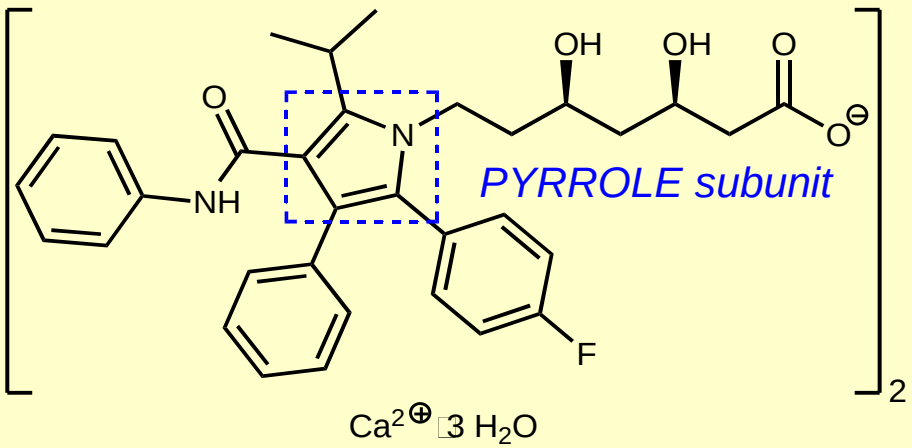
- ***RANITIDINE (Zantac®)***



FURAN subunit

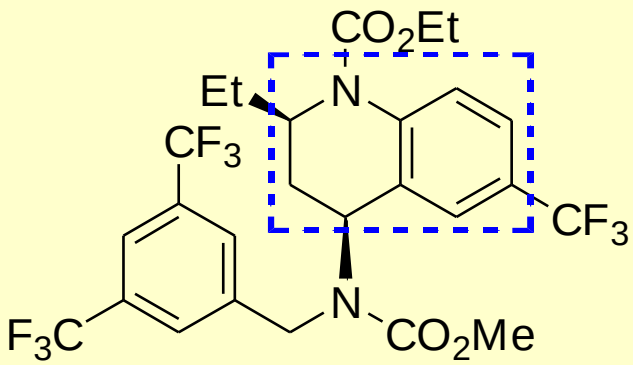
- GlaxoWellcome (now GSK) ***histamine H_2-receptor antagonist***
- blocks acid secretions
- Indicated for:
  - Treatment & prevention of stomach ulcers
  - gastrocœsophagal reflux disorder (GERD)
- World Health Organization: *"one of world's most essential drugs"*

ATORVASTATIN CALCIUM (Lipitor®)



- Pfizer ***cholesterol-lowering statin***
- HMGCoA inhibitor (see next slide)
- indicated for stroke and heart-attack prevention
- first drug to reach **>$10 billion** annual sales (2004: $10.8 bn)
- *"the most popular drug ever sold ever in the history of the world"*

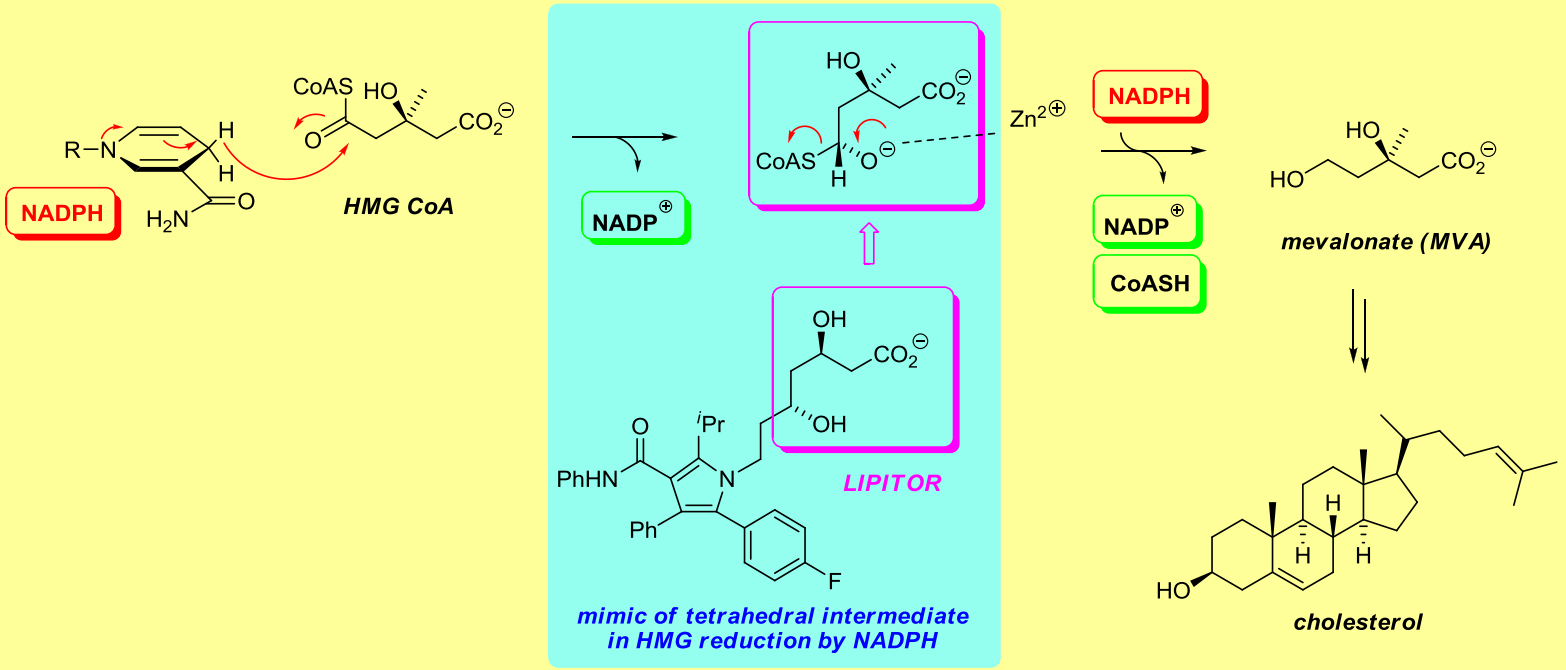
TORCETRAPIB (CP-529414)



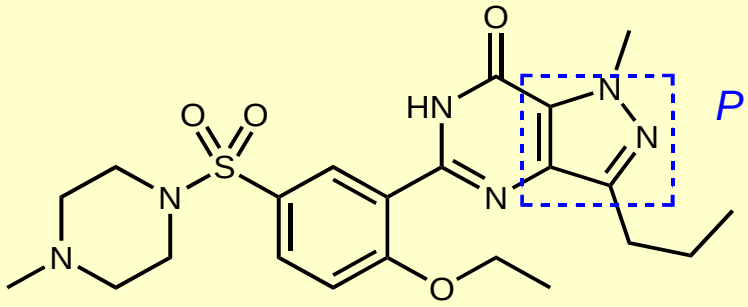
- Pfizer ***cholesteryl ester transfer protein (CETP) inhibitor***
- designed to reduce build-up of low-density lipoproteins (LDLs) 'bad cholesterol' as a co-therapy with Lipitor for cardiovascular protection
- ***Nov 30th 2006:*** Pfizer's chief executive "*This will be one of the most important compounds of our generation.*"
- ***Dec 2nd 2006:*** phase III trials abandoned (DOI)

HMG CoA reductase inhibitors - Statins

- ***HMG CoA → MVA*** is the ***rate determining step*** in the biosynthetic pathway to ***cholesterol***
  - 33 enzyme mediated steps are required to biosynthesise cholesterol from acetyl CoA & in principle the inhibition of any one of these will serve to break the chain. In practice, control rests with HMG-CoA reductase as the result of a variety of biochemical feedback mechanisms
- '***Statins***' inhibit HMG CoA reductase and are used clinically to treat ***hypercholesteraemia*** - a causative factor in ***heart disease***
  - *e.g.* ***Lipitor™*** (Pfizer) - *a* competitive inhibitior of HMG-CoA reductase



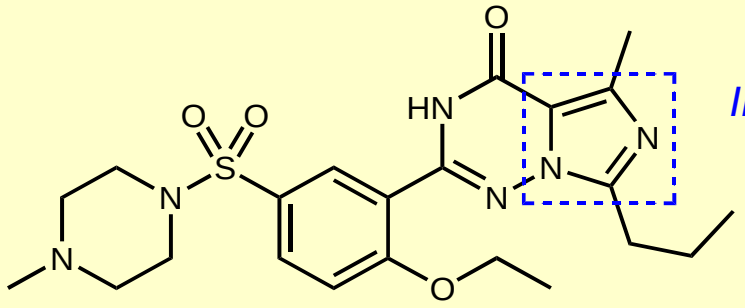
- ***SILDENAFIL CITRATE (Viagra ®)***



PYRAZOLE subunit

- Pfizer ***type 5 phosphodiesterase (PDE) inhibitor***
- prevents breakdown of cyclic GMP & originally designed for treatment of hypertension (high blood pressure)
- indicated for treatment for erectile dysfunction
- annual sales: **$1.7 bn**

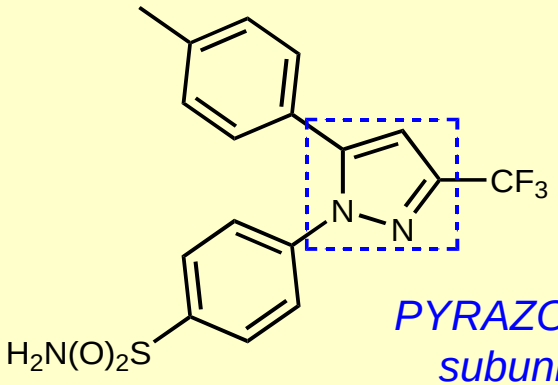
- ***VARDENAFIL CITRATE (Levitra®)***



IMIDAZOLE subunit

- Bayer ***type 5 phosphodiesterase (PDE) inhibitor***
- prevents breakdown of cyclic GMP
- Indicated for treatment for erectile dysfunction
- annual sales: **$0.25 bn**

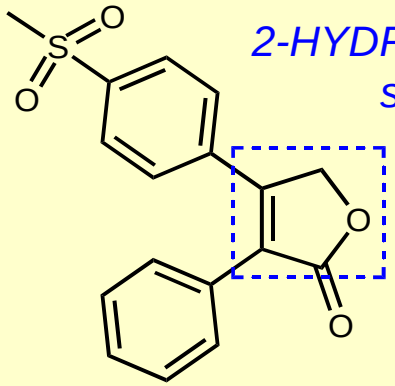
CELECOXIB (Celebrex®)



PYRAZOLE subunit

- Pfizer ***non-steroidal anti-inflammatory drug (NSAID)***
- selective COX-2 inhibitor (see next slide)
- indicated for:
  - osteoarthritis
  - rheumatoid arthritis
  - acute pain
- US sales 2004: **$2.1 bn**

ROFECOXIB (Vioxx ®)

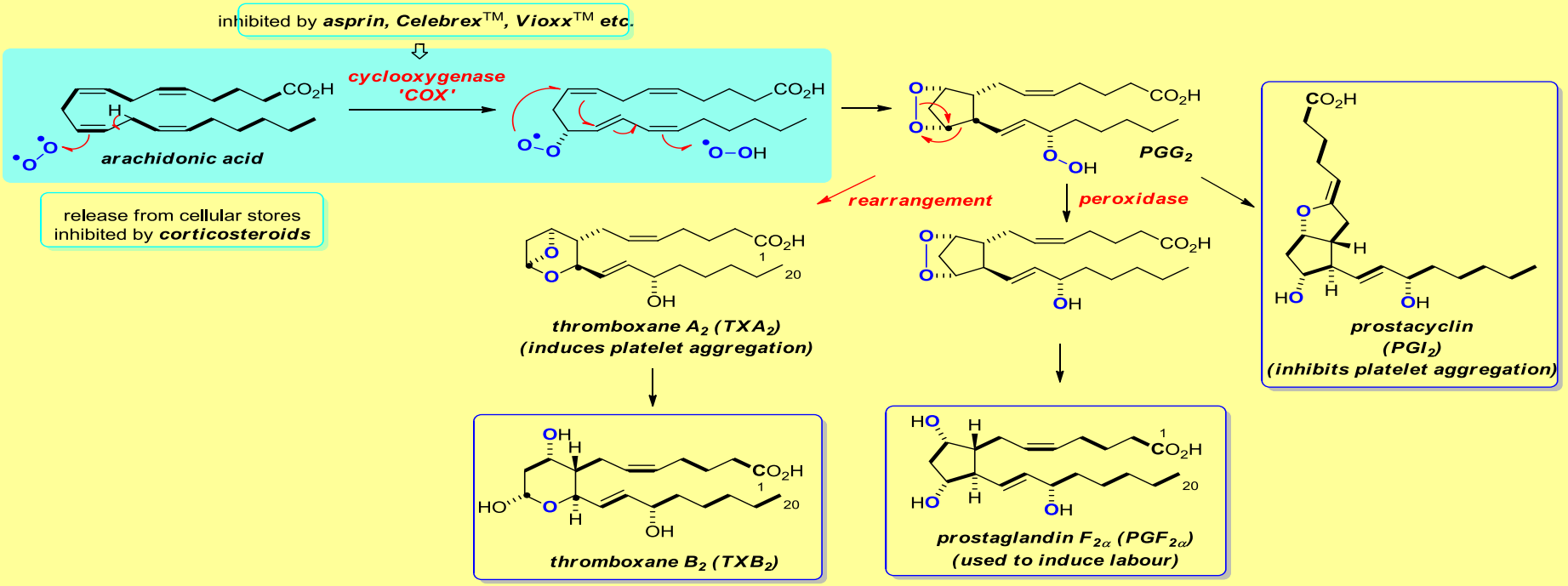


2-HYDROXYFURAN subunit

- Merck ***non-steroidal anti-inflammatory drug (NSAID)***
- selective COX-2 inhibitor (see next slide)
- indicated for:
  - osteoarthritis
  - rheumatoid arthritis
  - acute pain
- US sales 2004: **$0.9 bn**
- withdrawn from market December 2004 due to cases of heart attack

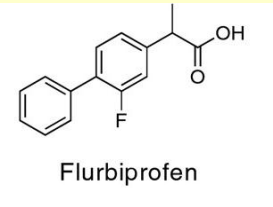
Biosynthesis of Prostaglandins & Thromboxanes

- prostaglandins ***&*** thromboxanes ***are derived from further oxidative processing of arachiodonic acid***
- ***both are important*** hormones ***which control*** **e.g.** ***smooth*** muscle contractility ***(blood pressure),*** gastric secretion***,*** platelet aggregation ***&*** inflammation ***(<nM activity)***
  - various pharmaceuticals including ***corticosteroids***, ***NSAIDs*** & ***asprin*** inhibit biosynthethetic steps in these pathways

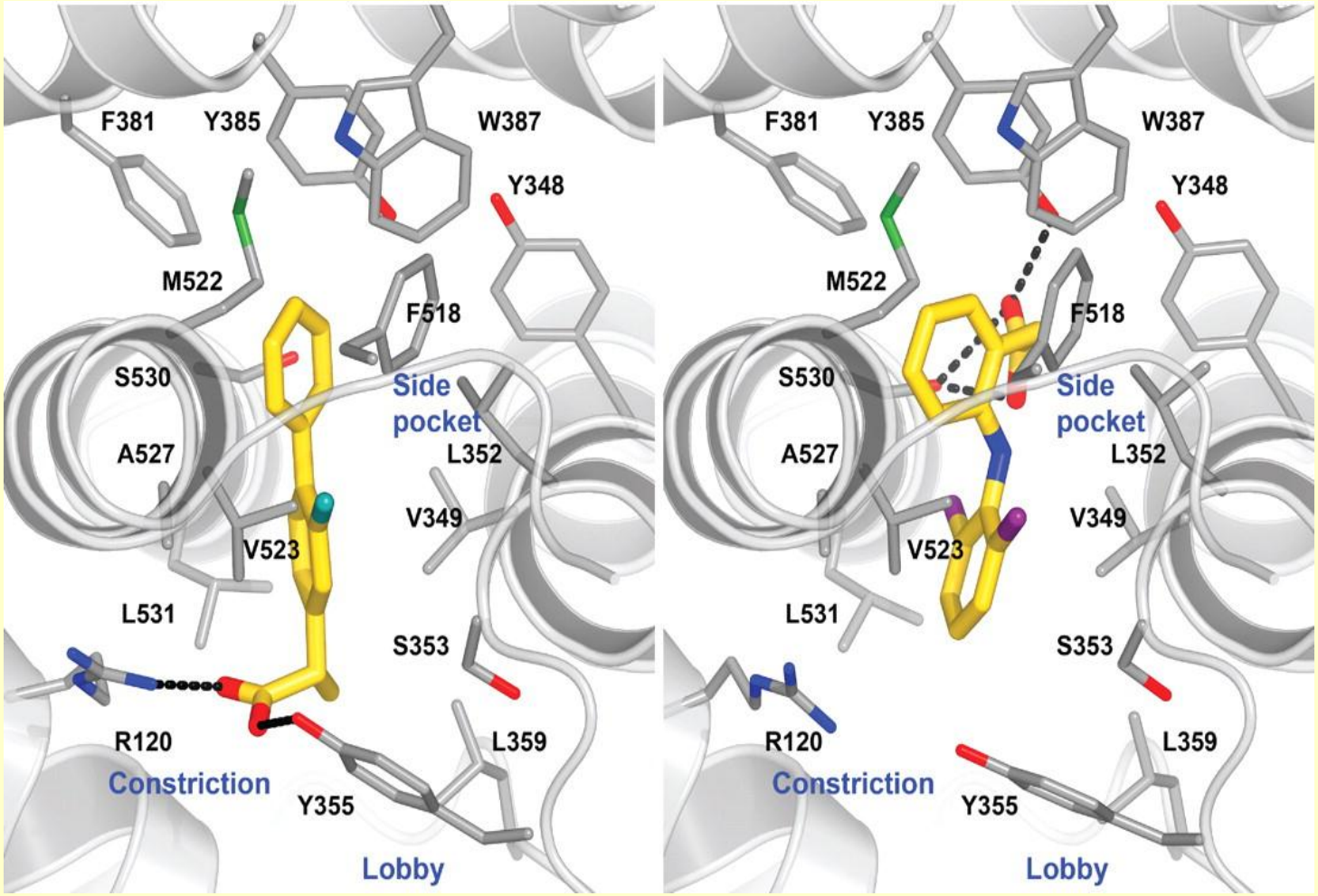


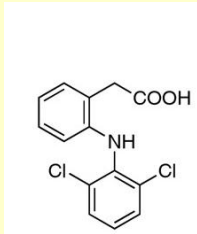
Crystal structures of flurbiprofen (Ansaid®) & diclofenac (Zolterol®) bound in mCOX-2 active site

- Duggan *et al. J. Biol. Chem.* **2010**, *285*, 34950-34959 (DOI)



Flurbiprofen

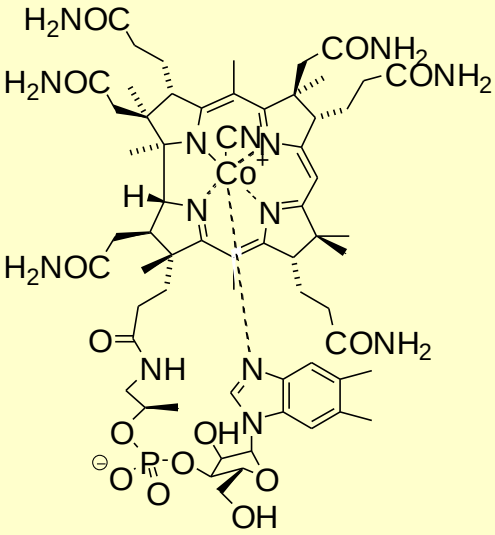




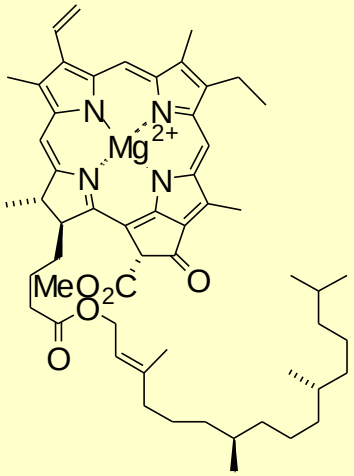
Diclofenac

Other Examples of Important Heterocyclic Compounds

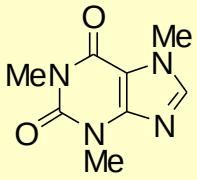
- ***More bioactive natural products***



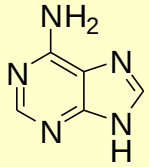
vitamin B_{12}



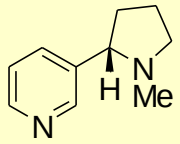
chlorophyll



caffeine

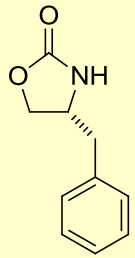


adenine (ATP, DNA..)

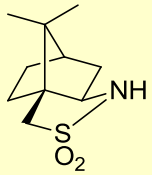


nicotine

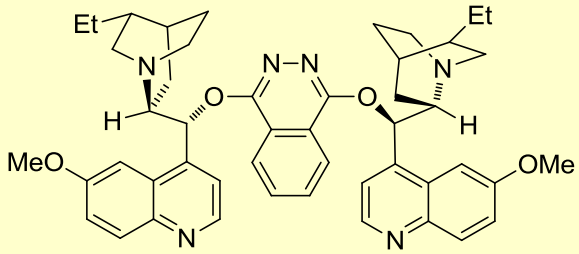
- ***Chiral auxiliaries and catalysts***



Evans' oxazolidinone



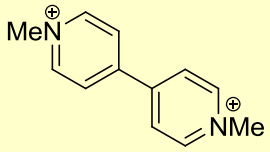
Oppolzer's camphor sultam



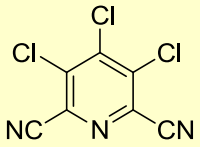
$(DHQ)_2PHAL$ (Sharpless' AD catalyst)

Other Examples of Important Heterocyclic Compounds

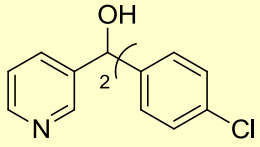
- ***Agrochemicals***



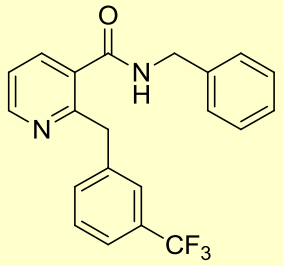
paraquat (weed-killer)



dowco 263 (fungicide)

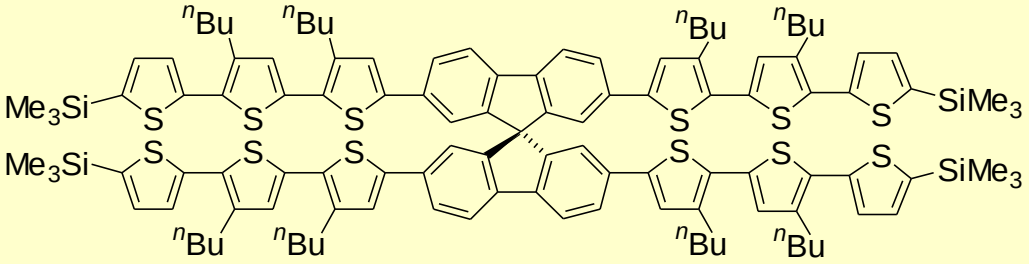


parinol (fungicide)

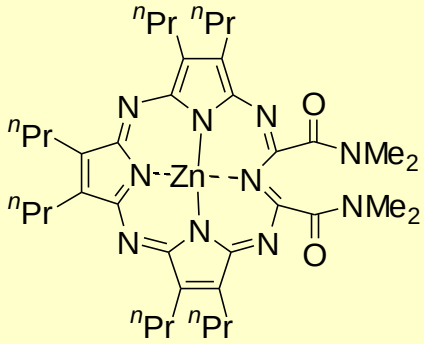


phenoxynicotinamide (herbicide)

- ***'Smart' materials***



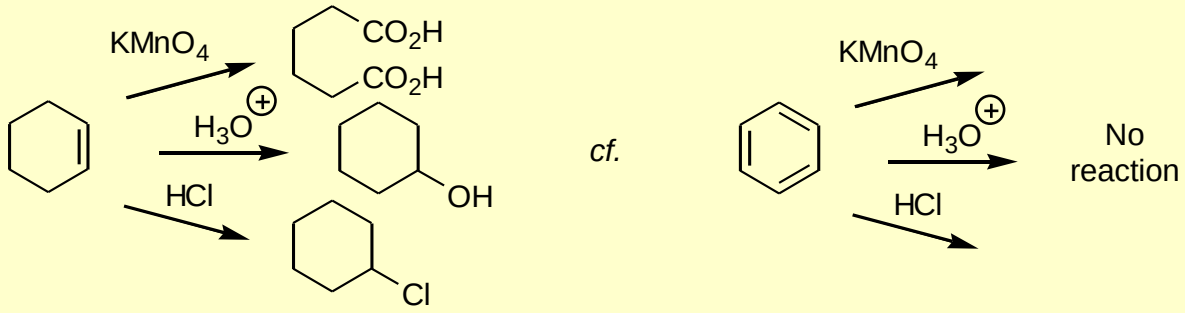
An orthogonally fused conjugated oligomer comprised of thiophene units (a potential molecular-scale electronic device)



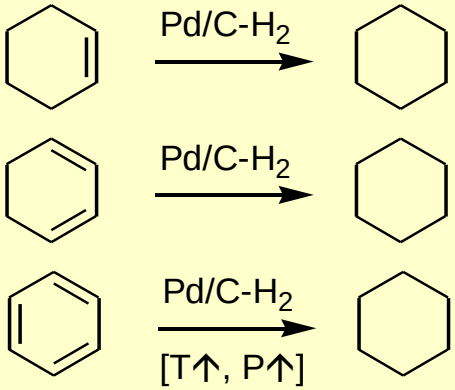
***seco*-porphyrazine**
($^1O_2$ photosensitiser for photodynamic chemotherapy)

Benzene – Stability and Resonance Energy

- Benzene is unusually unreactive (*i.e.* stable) *cf.* alkenes



- A direct estimate of resonance energy can be made by consideration of heats of hydrogenation of cyclohexenes



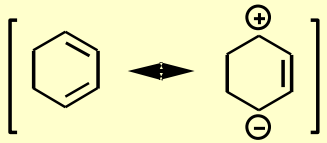
$\Delta H° = -120$ kJmol^{-1}

$\Delta H° = -232$ kJmol^{-1}

$\Delta H° = -208$ kJmol^{-1}

N.B. 1 kcal = 4.18 kJ

i.e. resonance 'worth' ~**8 kJmol^{-1}**
[(2x120)-232]

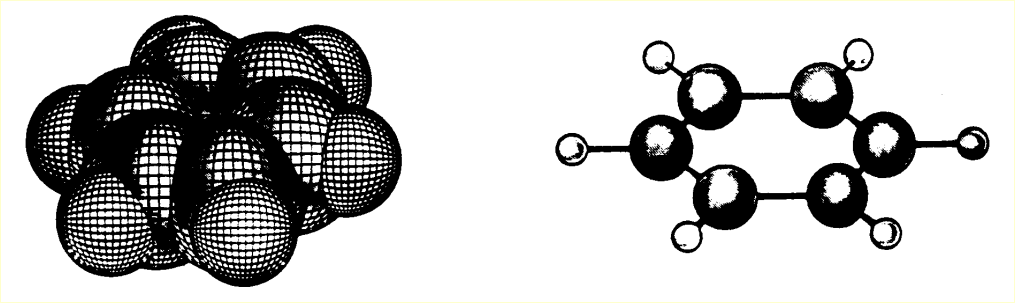


i.e. aromatic stabilisation 'worth' ~**152 kJmol^{-1}**
[(3x120)-208]

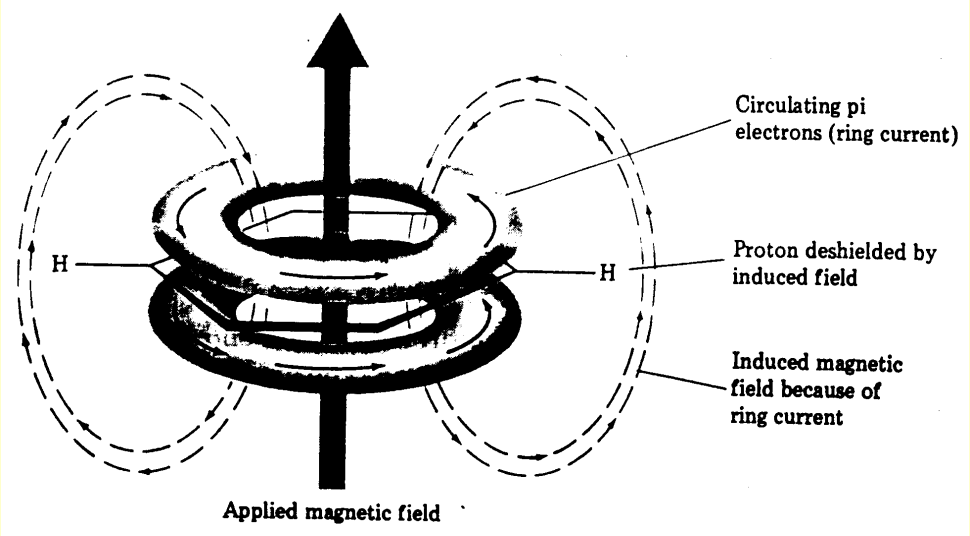
- see: K.P.C.Vollhardt *J. Am. Chem. Soc.* **2000**, *122*, 7819 (DOI)

Benzene – Structure and NMR Properties

- X-ray data show all bond lengths to be the same (1.39 Å *cf.* average C-C 1.54 Å & average C=C 1.34 Å)

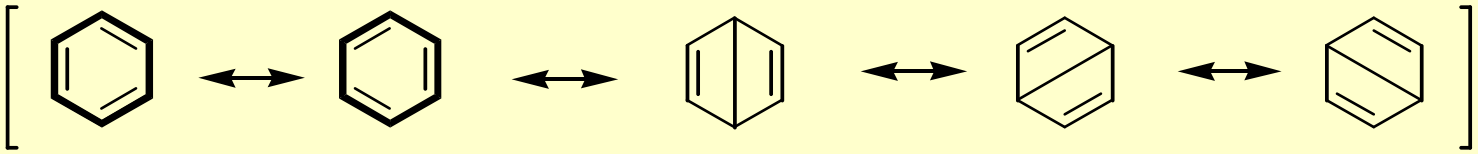


- ^{1}H NMR reveals aryl protons experience deshielding (*i.e.* → low field) – due to induced ring current:



Benzene – Valence Bond and Molecular Orbital Representations of Aromaticity

- ***VALENCE BOND (VB) THEORY***
  - resonance hybrids - imaginary structures which differ only in position of electrons (atoms/nuclei do not move)
  - Not all resonance structures contribute equally - 'real' structure is weighted average of resonance structures



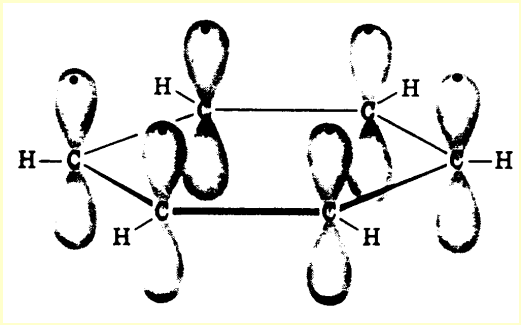
VB structure

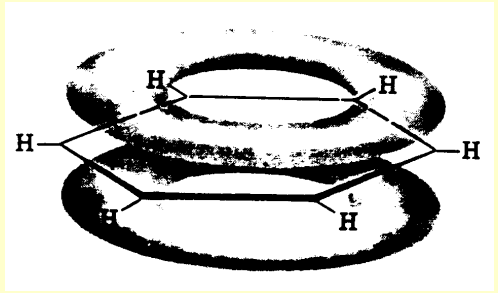
- ***MOLECULAR ORBITAL (MO) THEORY***
  - ***L***inear ***C***ombination of ***A***tomic ***O***rbitals (LCAO)
  - σ-bonding framework formed from sp^2 hybridised carbons
  - leaves p-orbital on each C atom *orthogonal* to ring
  - 6 atomic p-orbitals (AOs) → [LCAO maths] → 6 MOs
  - each MO capable of containing 2 electrons
  - 6 electrons available to occupy the 6 MOs
  - placed in 3 molecular orbitals of lowest energy: **bonding orbitals**
  - 3 **anti-bonding orbitals** remain vacant

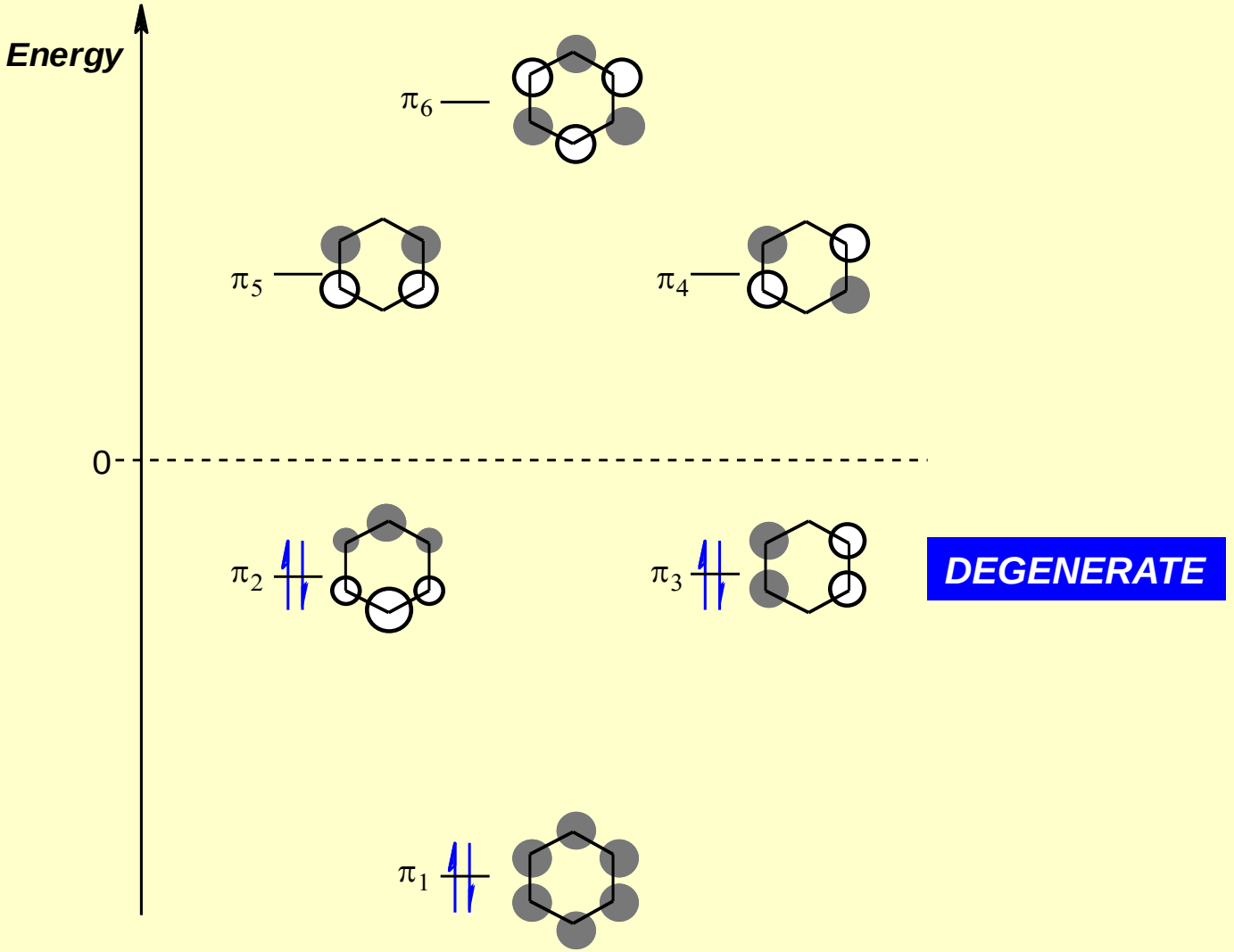
MO structure

Benzene - Molecular Orbital Description

- Molecular orbital theory rationalises reactions and properties of benzene:

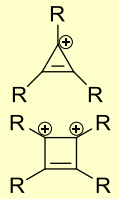
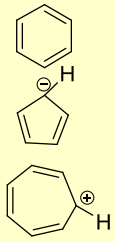
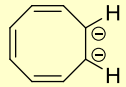
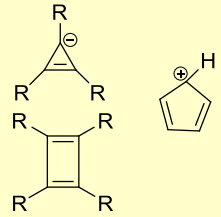
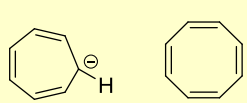




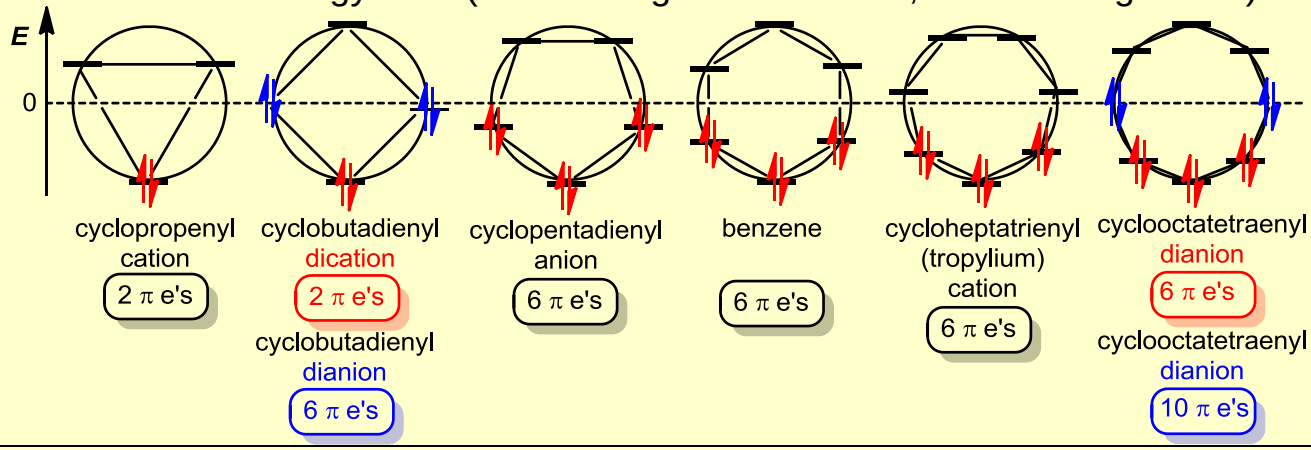


Benzene – Hückel's Rule and Musulin-Frost Diagrams

- Hückel *Z. Phys*. **1931**, *70*, 204; ***empirical rule for aromaticity***
  - For compounds which are planar & have a contiguous, cyclic array of p-orbitals perpendicular to plane of ring:
    - Those with 4n+2 p electrons display special stabilisation: *i.e.* **aromatic**
    - Those with 4n p electrons display special instability: *i.e.* **anti-aromatic**

4n+2 π electrons (aromatic)			**4n π electrons (anti- or non-aromatic)**	
n = 0	**n = 1**	**n = 2**	**n = 1**	**n = 2**
				

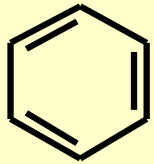
- Frost & Musulin *J. Chem. Phys.* **1953**, *21*, 572 (DOI); ***graphical device for constructing MO energy diagrams***
  - Draw appropriate regular polygon within a circle (with atoms touching circumference)
  - Ensure one atom is at lowest point → ring atom positions represent energy levels
  - Centre of circle is zero energy level (*i.e.* bonding orbitals below, anti-bonding above)



Other Aromatic Compounds - Resonance Energies

- The anomalous stability of benzene and other aromatic compounds is due primarily to the resonance stabilization gained by the highly symmetric electron delocalisation
  - A large energy input is required to disrupt the cyclically-arranged electrons
  - Consequently, aromatic compounds react slowly with electrophiles

- Other ***carboaromatic*** compounds show ***<u>similar</u> resonance energies (in kJ/mol)***



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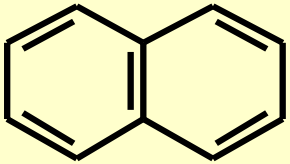

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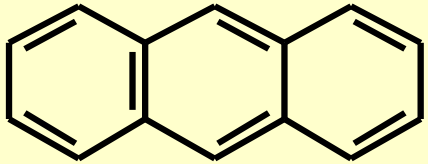

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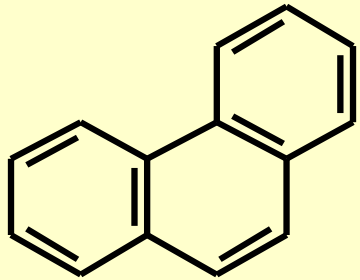
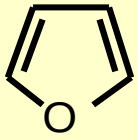


392.1

- ***Heteroaromatic*** compounds usually have ***<u>lower</u> resonance energies (in kJ/mol)***



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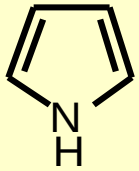

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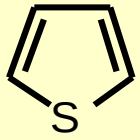

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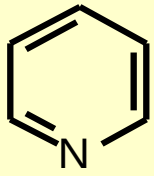

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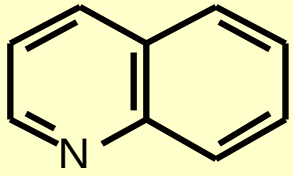

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