Heterocyclic Chemistry at a Glance

Second Edition

John A. Joule
Keith Mills

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Heterocyclic Chemistry at a Glance

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Second Edition

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Biography

John Arthur Joule was born in Harrogate, Yorkshire, England, but grew up and attended school in Llandudno, North Wales, going on to study for BSc, MSc, and PhD (1961; with George F. Smith) degrees at The University of Manchester. Following post-doctoral periods in Princeton (Richard K. Hill) and Stanford (Carl Djerassi) he joined the academic staff of The University of Manchester where he served for 41 years, retiring and being appointed Professor Emeritus in 2004. Sabbatical periods were spent at the University of Ibadan, Nigeria, Johns Hopkins Medical School, Department of Pharmacology and Experimental Therapeutics, and the University of Maryland, Baltimore County. He was William Evans Visiting Fellow at Otago University, New Zealand.

Dr. Joule has taught many courses on heterocyclic chemistry to industry and academe in the UK and elsewhere. He is currently Associate Editor for *Tetrahedron Letters,* Scientific Editor for *Arkivoc*, and Co-Editor of the annual *Progress in Heterocyclic Chemistry.*

Keith Mills was born in Barnsley, Yorkshire, England and attended Barnsley Grammar School, going on to study for BSc, MSc and PhD (1971; with John Joule) degrees at The University of Manchester.

Following post-doctoral periods at Columbia (Gilbert Stork) and Imperial College (Derek Barton/Philip Magnus), he joined Allen and Hanburys (part of the Glaxo Group) at Ware and later Stevenage (finally as part of GSK), working in Medicinal Chemistry and Development Chemistry departments for a total of 25 years. During this time he spent a secondment at Glaxo, Verona. Since leaving GSK he has been an independent consultant to small pharmaceutical companies.

Dr. Mills has worked in several areas of medicine and many areas of organic chemistry, but with particular emphasis on heterocyclic chemistry and the applications of transition metal-catalysed reactions.

Heterocyclic Chemistry was first published in 1972, written by George Smith and John Joule, followed by a second edition in 1978. The third edition (Joule, Mills and Smith) was written in 1995 and, after the death of George Smith, a fourth edition (Joule and Mills) appeared in 2000 and a fifth edition in 2010. The first edition of *Heterocyclic Chemistry at a Glance* was published in 2007.

Contents

Abbreviations

Ac	acetyl [$CH_3C{=}O$], thus AcOH = ethanoic (acetic) acid; Ac_2O = ethanoic anhydride (acetic anhydride)
anti	on the opposite side (antonym of *syn*)
aq	aqueous – the reaction mixture contains water
Ar	general designation for a benzenoid aromatic group
[bmim][BF_4]	1-*n*-butyl-3-methylimidazolium tetrafluoroborate (an ionic liquid)
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl – ligand for palladium(0)
Bn	benzyl [$PhCH_2$] – *N*-protecting group; removed by hydrogenolysis over Pd
Boc	*t*-butyloxycarbonyl [*t*-BuOCO] – protecting group; removed with acid
Bom	benzyloxymethyl [$PhCH_2OCH_2$] – protecting group; removed by hydrogenolysis over Pd
Bt	benzotriazol-1-yl (structure page 136)
Bz	benzoyl [PhCO] as in OBz, a benzoate
c	cyclo as in *c*-C_6H_{11} = cyclohexyl
c.	concentrated, as in c. H_2SO_4 = concentrated sulfuric acid
cat	catalyst – reagent not consumed in the reaction – usually, in the case of metal catalysts, e.g. Pd, used in sub-stoichiometric quantities – 1–5 mol%
Cbz	benzyloxycarbonyl [$PhCH_2OCO$] – protecting group; removed by hydrogenolysis
CDI	1,1′-carbonyldiimidazole [$(C_3H_3N_2)_2C{=}O$] – peptide coupling reagent
Cy	cyclohexyl [*c*-C_6H_{11}]
dba	*trans,trans*-dibenzylideneacetone [$PhCH{=}CHCOCH{=}CHPh$] – ligand for palladium(0)
DCC	dicyclohexylcarbodiimide [*c*-$C_6H_{11}N{=}C{=}N$*c*-C_6H_{11}] – for coupling acid and amine to give amide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone – oxidant, often used for dehydrogenation
DMAP	4-dimethylaminopyridine [4-$Me_2NC_5H_4N$] – nucleophilic catalyst
DME	1,2-dimethoxyethane [$MeO(CH_2)_2OMe$] – ethereal solvent
DMF	dimethylformamide [$Me_2NCH{=}O$] – dipolar aprotic solvent
DMFDMA	dimethylformamide dimethyl acetal [$Me_2NCH(OMe)_2$]
DMSO	dimethylsulfoxide [$Me_2S{=}O$] – dipolar aprotic solvent
dppb	1,4-bis(diphenylphosphino)butane [$Ph_2P(CH_2)_4PPh_2$] – ligand for palladium(0)
dppe	1,2-bis(diphenylphosphino)ethane [$Ph_2P(CH_2)_2PPh_2$] – ligand for palladium(0)
dppf	1,1′-bis(diphenylphosphino)ferrocene [$(Ph_2PC_5H_4)_2Fe$] – ligand for palladium(0)
dppp	1,3-bis(diphenylphosphino)propane [$Ph_2P(CH_2)_3PPh_2$] – ligand for palladium(0)
ee	enantiomeric excess – a measure of the efficiency of an asymmetric synthesis
El^+	general designation for a positively charged electrophile
Et	ethyl [CH_3CH_2]
f.	fuming, as in f. HNO_3 = fuming nitric acid
2-Fur	furan-2-yl [C_4H_3O]
GABA	γ-aminobutyric acid (4-aminobutanoic acid) [$H_2N(CH_2)_3CO_2H$]
Hal	general designation for a halogen
Het	general designation for a heteroaryl group

i-Pr	isopropyl [Me_2CH]
LDA	lithium di-isopropylamide [$LiN(i\text{-}Pr)_2$] – hindered strong base
LiTMP	lithium 2,2,6,6-tetramethylpiperidide [$LiN(C(Me)_2(CH_2)_3C(Me)_2$] – hindered non-nucleophilic strong base
Me	methyl [CH_3]
Ms	methanesulfonyl (mesyl) [$MeSO_2$] – protecting group for azole nitrogen
NaHMDS	sodium bis(trimethylsilyl)amide [sodium hexamethyldisilazide] [$NaN(SiMe_3)_2$] – hindered non-nucleophilic strong base
NBS	*N*-bromosuccinimide [$C_4H_4BrNO_2$] – brominating agent
NCS	*N*-chlorosuccinimide [$C_4H_4ClNO_2$] – chlorinating agent
NMP	*N*-methylpyrrolidin-2-one (1-methylpyrrolidin-2-one) [C_5H_9NO] – dipolar aprotic solvent
n-Bu	normal butyl [$CH_3(CH_2)_3$]
n-Pr	normal propyl [$CH_3CH_2CH_2$]
Nu^-	general designation for a negatively charged nucleophile
Ph	phenyl [C_6H_5]
PMB	*p*-methoxybenzyl [$4\text{-}MeOC_6H_4CH_2$]
Pr	see *i*-Pr and *n*-Pr
2-Py; 3-Py; 4-Py	pyridin-2-yl; pyridin-3-yl; pyridin-4-yl [C_5H_4N]
R	general designation for an alkyl group
o-Tol	*ortho*-tolyl (2-methylphenyl) [C_7H_7]
p-Tol	*para*-tolyl (4-methylphenyl) [C_7H_7]
rt	room temperature (ca. 20 °C)
Selectfluor™	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate – electrophilic fluorinating agent
SEM	trimethylsilylethoxymethyl [$Me_3Si(CH_2)_2OCH_2$] – protecting group; removed with fluoride
SES	trimethylsilylethanesulfonyl [$Me_3Si(CH_2)_2SO_2$] – N-protecting group; removed with fluoride
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl – ligand for palladium(0)
syn	on the same side (antonym of *anti*)
TBDMS	*t*-butyldimethylsilyl [$t\text{-}Bu(CH_3)_2Si$] – bulky silyl protecting group
t-Bu	tertiary butyl [$(CH_3)_3C$]
Tf	trifluoromethanesulfonyl [CF_3SO_2], thus TfO^- = triflate [$CF_3SO_3^-$] – triflate is a good leaving group
THF	tetrahydrofuran – common ethereal solvent for dry reactions at low temperature
THP	tetrahydropyran-2-yl [C_5H_9O] – protecting group; removed with aqueous acid
TIPS	tri-isopropylsilyl [$Si(i\text{-}Pr)_3$] – protecting group for nitrogen or oxygen
TIPB	1,3,5-tri-*iso*-propylbenzene – inert high-boiling solvent
TMSCl	trimethylsilyl chloride (chlorotrimethylsilane) [Me_3SiCl] – *O*- and *N*-trimethylsilylating reagent
Tol	same as *p*-Tol
TosMIC	tosylmethyl isocyanide [$TolSO_2CH_2N^+{\equiv}C^-$]
Ts	*p*-toluenesulfonyl (tosyl) [$p\text{-}TolSO_2$] – Ts is a good protecting group for azole nitrogen and Ts^- can be a leaving group (*para*-toluensulfinate)
Tr	trityl (triphenylmethyl) [Ph_3C] – *N*-protecting group; removed with acid
TTF	tetrathiafulvalene ($C_6H_4S_4$)
X	general designation for halogen (or in palladium(0) chemistry, sometimes OTf)

Introduction to Second Edition

The material in this book comprises an introduction to, and summary of, the most important ideas and principles of heterocyclic chemistry. We have attempted to encapsulate everything that a non-specialist, or beginning student, would need to know of the subject. At the same time, we believe that this book will serve as a good starting point for further, more extensive study of the subject.

This Second Edition has been expanded by 50% compared with the First Edition (2007), allowing us to include more examples and illustrations, and exercises at the ends of the chapters (with answers available online at http://booksupport.wiley.com). The other significant difference to the First Edition is the use of colour in the schemes (for details, see below).

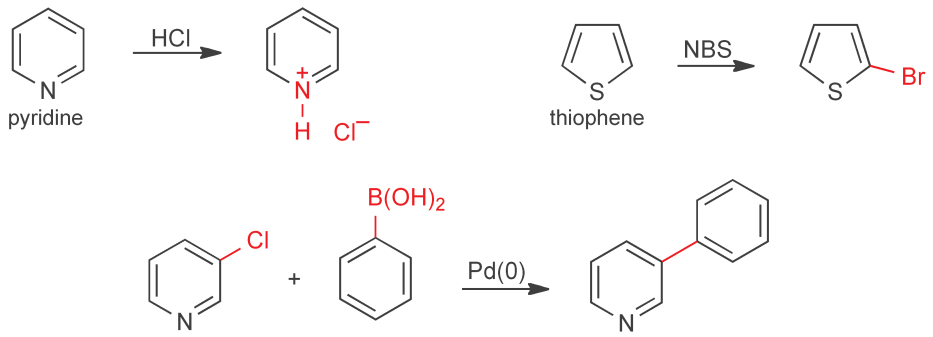
We now have three supplementary chapters dealing with the occurrence and significance of heterocycles in the world at large: Chapters 17 and 18 deal with 'Heterocycles in Nature' and 'Heterocycles in Medicine'; Chapter 19 discusses major significant heterocyclic involvements in dyes and pigments, polymers, pesticides, explosives, food and drink, and electronics.

The book is mainly concerned with aromatic heterocycles though we also include a short discussion of non-aromatic heterocycles (Chapter 16). We deal with the characteristic reactivities of the most important heteroaromatic systems and the principal routes for their ring synthesis from non-heterocyclic precursors. Thus the chemistry of pyridines, pyridazines, pyrimidines, pyrazines, quinolines, isoquinolines, pyrylium and benzopyrylium cations, pyrroles, indoles, thiophenes, furans, imidazoles, oxazoles, thiazoles, pyrazoles, isoxazoles, isothiazoles, purines, heterocycles with more than two heteroatoms in the ring (for example triazoles and triazines) and heterocycles in which a heteroatom is located at a ring junction (for example pyrrolizines and indolizines) is covered (Chapters 5–15). The book starts with a discussion of nomenclature and structures of aromatic heterocycles (Chapters 1 and 2); then follows Chapter 3, which examines in detail the typical reactions of heterocycles, except for those involving palladium-catalysis, since these are considered separately in the following Chapter 4.

The book assumes a basic knowledge of organic chemistry such as one would expect of a student at the second year level of a UK Honours Chemistry course and thus would be suitable for second/third/fourth year undergraduate and post-graduate courses in UK Universities. It is also relevant that much Inorganic Chemistry relies on maintaining metals in various (often unusual) oxidation states by surrounding them with ligands and that these are very often heterocyclic, so choosing or designing appropriate heterocyclic ligands and then being able to synthesise them, is also an integral prerequisite of Inorganic Chemistry. With this book we also target students in other disciplines – Pharmacy, Pharmacology, Medicinal Chemistry – whose subjects require them to assimilate the basics of this particular area of organic chemistry. The vital importance of a proper understanding of heterocyclic chemistry for the study of biochemistry at the molecular level and for drug design and synthesis in medicinal chemistry, is emphasised in Chapters 17 and 18, 'Heterocycles in Nature' and 'Heterocycles in Medicine'.

It is not the purpose of this book to provide guidance for the conduct of practical work: especially at the undergraduate level, all experimental work must be conducted under the supervision of an experienced teacher. For experimental details the reader must consult the original literature – many references to suitable, key papers can be found in our fuller exposition – *Heterocyclic Chemistry*, *5th Edition,* Joule and Mills, Wiley, 2010. All the examples in *Heterocyclic Chemistry at a Glance* are taken from the literature and the vast majority proceed in good yields. In the reaction schemes, so that the reader can concentrate on the chemistry in question, we have simply shown that a particular compound will react with a particular reagent or reactant to give a product, and we have omitted practical details such as solvent, reaction time, yields, and most other details, except where their inclusion makes a didactical point. Where reactions were carried out at room temperature or with gentle warming or cooling, no comment is made. Where reactions were carried out with strong heating (e.g. reflux in a high-boiling solvent) the word 'heat' is used on the reaction arrow; for transformations carried out at very low temperature, this is specified on the reaction arrow. For some of the palladium-catalysed reactions we give full experimental conditions, to illustrate what is typical for cross-couplings.

In the reaction schemes, we have highlighted in red those parts of the products (or intermediates) where a change in structure or bonding has taken place. We hope that this both facilitates comprehension of the chemical processes that are occurring and quickly focuses the reader's attention on just those parts of the molecules where structural change has occurred. For example, in the first reaction below, only changes at the pyridine nitrogen are involved; in the second example, the introduced bromine resulting from the substitution, and its new bond to the heterocycle, are highlighted. The exception to this policy is in palladium-catalysed cross-coupling processes where the functional groups in each of the coupling partners, as well as the new bond formed, are coloured red, as shown in the third example below.



Finally we acknowledge the crucial advice, support and encouragement from staff at Wiley, in bringing this project to fruition, in particular Paul Deards and Sarah Tilley. Mrs Joyce Dowle is thanked for her helpful comments during the preparation of Chapter 19 and Judith Egan-Shuttler for her careful copy editing.

Further reading

This book can act only as an introduction to heterocyclic chemistry and does not include references to original literature, or to the many reviews that are available. For further study and to go more deeply into the topics covered in this book we recommend, as a first port-of-call, our textbook *Heterocyclic Chemistry* [1] in which there are a host of leading references to the original literature and appropriate reviews.

The premier sources of regular reviews in this area are *Advances in Heterocyclic Chemistry* [2] and *Progress in Heterocyclic Chemistry* [3] and the principles of heterocyclic nomenclature are set out in one review [4] in the former series. The journal, *Heterocycles,* also carries many useful reviews specifically in the heterocyclic area. As its title implies, an exhaustive coverage of the area is provided in the three parts of *Comprehensive Heterocyclic Chemistry* (CHC), original (1984), and its two updates (1996 and 2008) [5]. Note: The three parts must be read *together* – the later parts update but do not repeat the earlier material. The *Handbook of Heterocyclic Chemistry* [6] that accompanies CHC encapsulates the key information from the series in a single volume. There is a comprehensive compilation of heterocyclic data and facts: the still-continuing and still-growing series of monographs [7] dealing with particular heterocyclic systems, edited originally by Arnold Weissberger, and latterly by Edward C. Taylor and Peter Wipf, is a vital source of information and reviews for all those working with heterocyclic compounds. The '*Science of Synthesis*' series contains authoritative discussions on the synthesis of heterocycles, organized in a hierarchical system [8]; volumes 9–17, published over the period 2000–2008, discuss aromatic heterocycles.

For further reading relating in particular to Chapters 17, 18 and 19, we recommend *Heterocycles in Life and Society* [9], *Introduction to Enzyme and Coenzyme Chemistry* [10], *Nucleic Acids in Chemistry and Biology* [11], *The Alkaloids; Chemistry and Biology* [12], *Comprehensive Medicinal Chemistry II* [13], *Molecules and Medicine* [14], *Goodman and Gilman's The Pharmacological Basis of Therapeutics* [15], *The Chemistry of Explosives* [16], *Food. The Chemistry of its Components* [17], *Perfumes: the Guide* [18], *Handbook of Conducting Polymers* [19], *Handbook of Oligo- and Polythiophenes* [20], *Tetrathiafulvalenes, Oligoacenenes, and their Buckminsterfullerene Derivatives: the Bricks and Mortar of Organic Electronics* [21].

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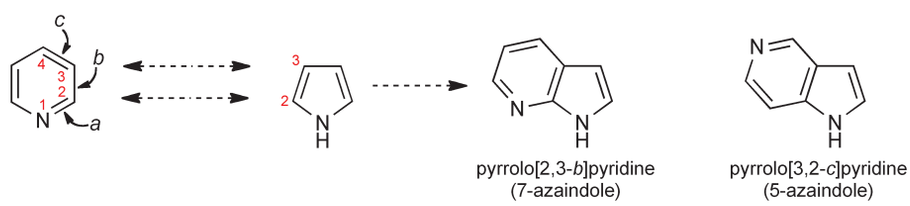
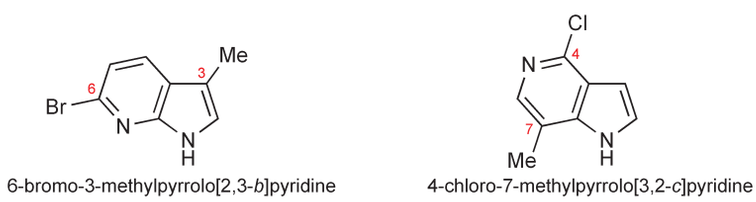
1

Heterocyclic Nomenclature

A selection of the structures, names and standard numbering of the more common heteroaromatic systems and some common non-aromatic heterocycles, are shown in this chapter. The aromatic heterocycles are grouped into those with six-membered rings and those with five-membered rings. The names of six-membered aromatic heterocycles that contain nitrogen generally end in 'ine', though note that 'purine' is the name for a very important bicyclic system which, has both a six- and a five-membered nitrogen-containing heterocycle. Five-membered heterocycles containing nitrogen generally end with 'ole'. Note the use of italic '*H*' in a name such as '9*H*-purine' to designate the location of an *N*-hydrogen in a system in which, by tautomerism, the hydrogen could reside on another nitrogen (e.g. N-7 in the case of purine). Names such as 'pyridine', 'pyrrole' and 'thiophene' are the original, and now standard, names for these heterocycles; names such as '1,2,4-triazine' for a six-membered ring with three nitrogens located as indicated by the numbers, are more logically systematic.

A detailed discussion of the systematic rules for naming polycyclic systems in which several aromatic or heteroaromatic rings are fused together, is beyond the scope of this book, however, two simple examples will serve to illustrate the principles. In the name 'pyrrolo[2,3-*b*]pyridine', the numbers signify the positions of the first named heterocycle, numbered as if it were a separate entity, which are the points of ring fusion; the italic letter, '*b*' in this case, designates the *side* of the second named heterocycle to which the other ring is fused, the lettering deriving from the numbering of that heterocycle as a separate entity, that is, side *a* is between atoms 1 and 2, side *b* is that between atoms 2 and 3, and so on. Actually, this particular heterocycle is more often referred to as '7-azaindole' – note the use of the prefix 'aza' to denote the replacement of a ring carbon by nitrogen. Similarly, '5-azaindole' is systematically called 'pyrrolo[3,2-*c*]pyridine' – note that the order of the numbers '3,2-' arises because the first atom of the pyrrole encountered in counting round from the pyridine nitrogen to determine the side of fusion, and thus the label '*c*', is C-3 of the pyrrole unit. The numbering of a bi- or polycyclic system *as a whole* is generated from a series of rules concerned with the orientation of the rings and the positions of the nitrogen(s), but we do not deal with these here – the overall numbering for these two systems is shown for two substituted examples.

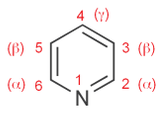


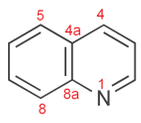


A device that is useful in discussions of reactivity is the designation of positions as 'α', 'β' or 'γ'. For example, the 2- *and* the 6-positions in pyridine are equivalent in reactivity terms, so to make discussion of such reactivity clearer, each of these positions is referred to as an 'α-position'. Comparable use of α and β is made in describing reactivity in five-membered systems. These useful designations are shown on some of the structures. Note that carbons at angular positions do not have a separate number but are designated using the number of the preceding atom followed by 'a' – as illustrated for quinoline.

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Six-membered aromatic heterocycles


pyridine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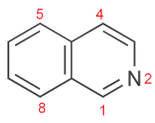
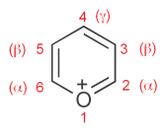
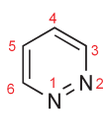

isoquinoline


pyrylium cation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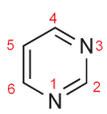
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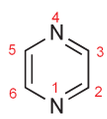
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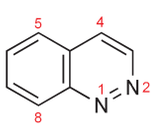
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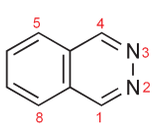
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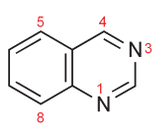
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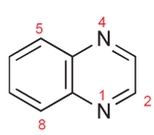
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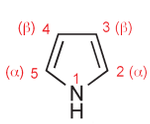
Five-membered aromatic heterocycles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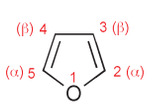
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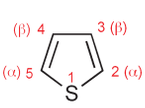
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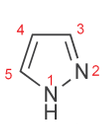
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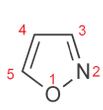
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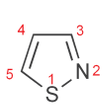
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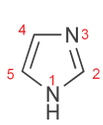
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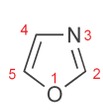
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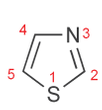
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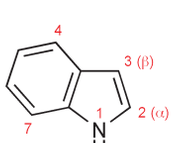
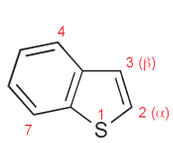
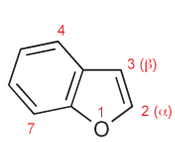

indole
[1*H*-indole]


benzothiophene
[benzo[*b*]thiophene]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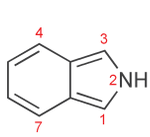
[benzo[*b*]furan]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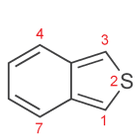
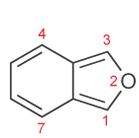

benzo[*c*]thiophene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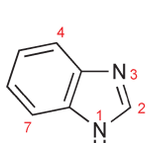
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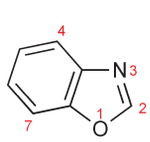
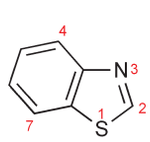

benzoxazole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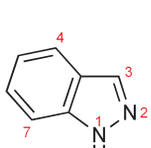
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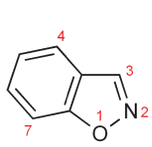
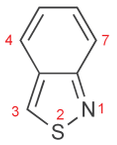
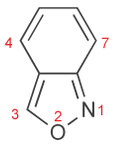

1,2-benzisoxazole

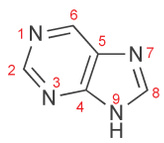

1,2-benzisothiazole



2,1-benzisothiazole

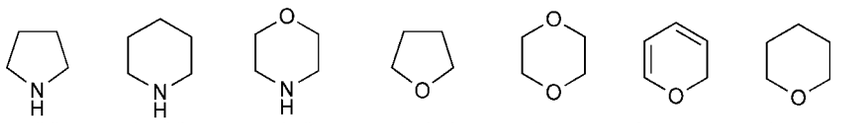


2,1-benzisoxazole
(anthranil)



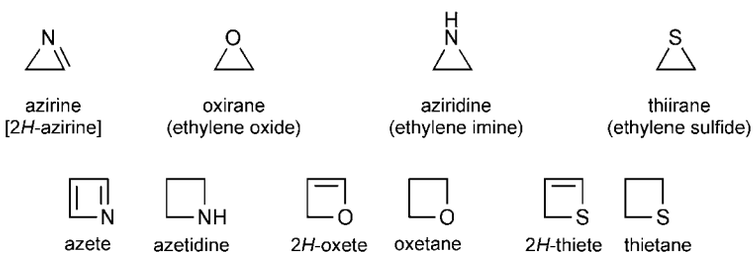
purine
[9*H*-purine]

Non-aromatic heterocycles



pyrrolidine | piperidine | morpholine | tetrahydrofuran (THF) | dioxane [1,4-dioxane] | 2*H*-pyran | tetrahydropyran

Small-ring heterocycles



azirine [2*H*-azirine] | oxirane (ethylene oxide) | aziridine (ethylene imine) | thiirane (ethylene sulfide)

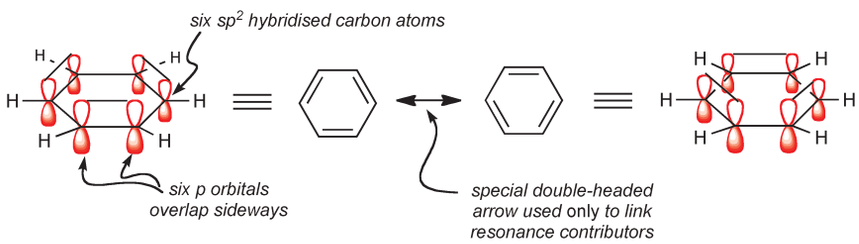
azete | azetidine | 2*H*-oxete | oxetane | 2*H*-thiete | thietane

2

Structures of Heteroaromatic Compounds

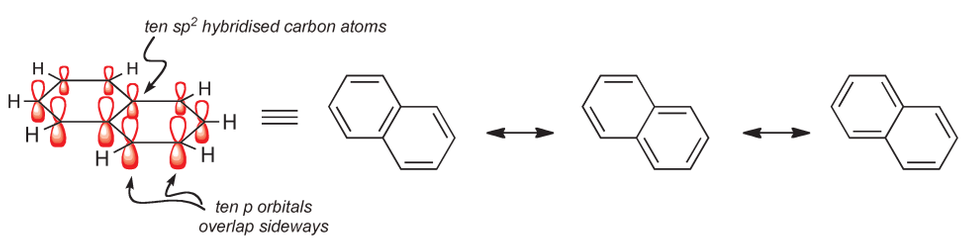
Structures of benzene and naphthalene

We start our consideration of heteroaromatic structures by recalling the prototypical structures of aromatic hydrocarbons such as benzene and naphthalene. Hückel's rule states that aromaticity is associated with fully conjugated cyclic systems of $4n+2$ π-electrons, that is with 2, 6, 10, 14 and so on, π-electrons, with 6π-electron monocyclic compounds being by far the commonest. Thus, benzene has a cyclic arrangement of six π-electrons comprising a conjugated molecular orbital system that is thermodynamically much more stable than a corresponding non-cyclically conjugated system – this additional stabilisation is called 'resonance energy' and has a value of about 152 kJ mol^{-1} for benzene. Compared with alkenes, this results in a much diminished tendency to react with electrophiles by addition and a greater tendency to react by substitution of hydrogen. Addition reactions would lead to products in which a substantial proportion of the resonance energy had been lost. As we shall remind ourselves in Chapter 3, *electrophilic substitution* is *the* prototypical reaction of benzene.



In benzene, the geometry of the ring, with angles of 120°, fits precisely the geometry of a planar trigonally hybridised carbon atom, and allows the assembly of a σ-skeleton of six sp^2 hybridised carbon atoms in a strainless planar ring. Each carbon then has one extra electron, which occupies an atomic p orbital orthogonal to the plane of the ring. The p orbitals interact sideways to generate the π-molecular orbitals associated with the aromatic system.

We shall represent the stabilising delocalisation of aromatic molecules by drawing 'mesomeric structures', thus benzene is represented as a 'resonance hybrid' of the two extreme forms. These have no existence in their own right, but are 'resonance contributors' to the 'real' structure. The use of mesomeric structures is particularly useful in representing the polarisation inherent in many heterocycles and, especially, for representing the delocalisation of charge in reaction intermediates. We shall find them invaluable in helping to understand heteroaromatic reactivity and regioselectivity.

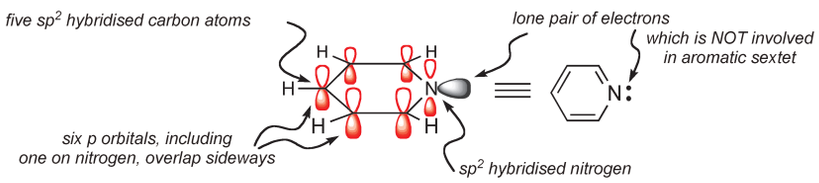


Naphthalene, with ten carbons and ten orthogonal p orbitals, has an aromatic system with ten π-electrons. Naphthalene is represented by three mesomeric structures and has a resonance energy of about 255 kJ mol^{-1}, substantially less than twice that of benzene.

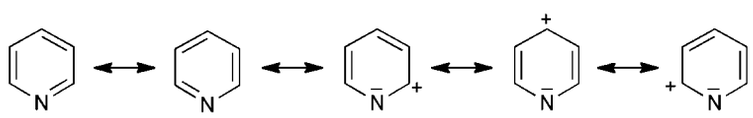
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Structures of pyridines and pyridiniums

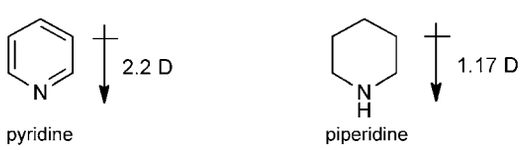
The structure of pyridine is completely analogous to that of benzene, being related through replacement of CH by N. The key differences are: (i) the departure from perfectly regular hexagonal geometry caused by the presence of the heteroatom, in particular shorter carbon–nitrogen bonds, (ii) the replacement of a hydrogen in the plane of the ring with an unshared electron pair, likewise in the plane of the ring, located in an sp^2 hybrid orbital, and *not at all involved in the aromatic π-electron sextet*, (iii) a strong permanent dipole, traceable to the greater electronegativity of nitrogen compared with carbon and (iv) the presence of a polarised imine unit (C=N). Note: It is the nitrogen lone pair, not involved in the aromatic sextet, that is responsible for the basic and nucleophilic reactivities of pyridine that we shall discuss in Chapter 5.



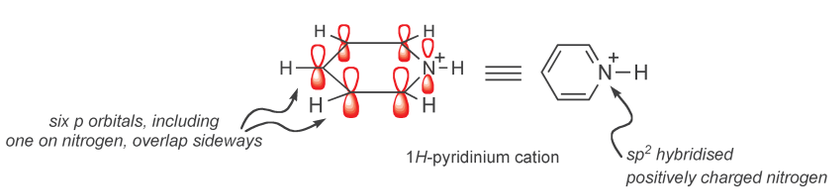
The electronegative nitrogen causes inductive polarisation, *and additionally*, stabilises polarised mesomeric structures in which nitrogen is negatively charged that, together with the two neutral contributors, represent pyridine. The polarised contributors imply a *permanent polarisation of the π-electron system*. The resonance energy of pyridine is about 117 kJ mol^{-1}.

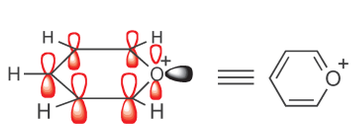


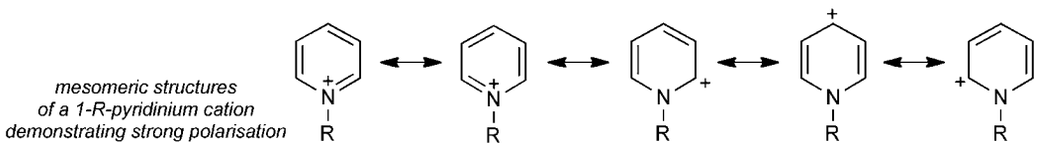
Inductive and resonance effects work in the same direction in pyridine resulting in a permanent dipole towards the nitrogen atom. A comparison with the dipole moment of piperidine, which is due wholly to the induced polarisation of the σ-skeleton, illustrates the additional π-system polarisation. The polarisation of the π-system also means that there are fractional positive charges on the carbons of the ring, mainly at the α- and γ-positions. It is because of this general electron-deficiency at carbon that pyridine and similar heterocycles are sometimes referred to as 'π-deficient'.



Addition of a positively charged electrophile to the pyridine nitrogen, utilising the lone pair of electrons to make a bond, generates pyridinium ions, the simplest being 1*H*-pyridinium formed by addition of a proton. Pyridinium cations are still aromatic – the system of six p orbitals required to generate the aromatic molecular orbitals is still present, though the formal positive charge on the nitrogen atom severely distorts the π-system, making the α- and γ-carbons in these cations carry high fractional positive charges, as indicated by the mesomeric structures. The structure of the pyrylium cation is analogous, but without a substituent on the oxygen.

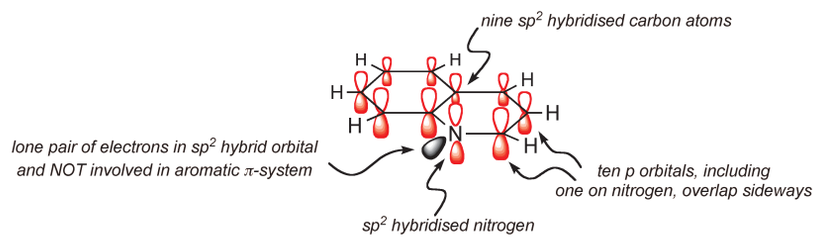






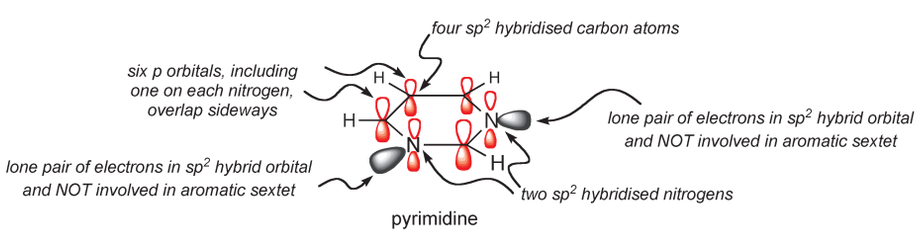
Structures of quinolines and isoquinolines

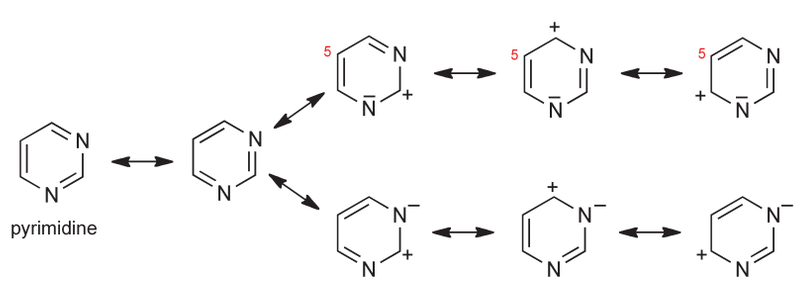
Quinoline and isoquinoline are related to pyridine exactly as naphthalene is related to benzene, that is they are 10π-electron aromatic systems. Only the heterocyclic ring is strongly polarised and, using quinoline as an example, the polarisation is represented as before by dipolar mesomeric contributors. Isoquinoline is completely analogous.



Structures of diazines (illustrated using pyrimidine)

Diazines contain two sp^2 hybridised nitrogens in a six-membered ring. The presence of the additional electron-withdrawing imine (C=N) has a major impact on the structure and chemical reactivity – the resonance contributors for pyrimidine illustrate the polarisation, which substantially increases the partial positive charges at all carbons, but to a lesser extent at C-5.





Structures of pyrroles, thiophenes and furans

We began our discussion of the structure of pyridine by reference to that of benzene and so, with pyrrole, it is useful to recall the structure of the cyclopentadienyl anion. The cyclopentadienyl anion, produced by the removal of one proton