Heterocyclic Chemistry

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Introduction

This textbook is designed for the Honours student and for the advanced graduate who wishes to brush up the fundamentals of heterocyclic chemistry and obtain a better grasp of the reactivity of heteroaromatic systems, especially in the broader context of homoaromatic and general aliphatic chemistry.

The emphasis in this treatment of the subject is very much on heteroaromatic systems, for it is here that most of the lessons which are specifically heterocyclic can be learned and much that seems new can, on closer scrutiny, be seen to be already familiar and related to the reactivity of simpler systems.

In order better to drive the basic lessons home, only the simple well-known heteroaromatics are treated in depth: some of the more peripheral ones are described more or less briefly, with an emphasis on similarities and differences with the more fundamental systems.

In the one chapter on non-aromatic heterocycles we have in the main brought out those aspects in which they differ from their acyclic counterparts in aliphatic chemistry.

The book begins with a chapter on the structures of the heteroaromatics: the static picture of the molecule is given in some detail in the familiar bond-resonance terms, which in the opinion of many university teachers still is the best approach for most purposes. This is followed by a brief comment on the place of quantum mechanical molecular orbital theory in the teaching of heterocyclic chemistry.

Then there is another general chapter which explains the general principles and the main types of reaction used in the synthesis of heteroaromatic systems.

The student is strongly advised to read these initial chapters carefully, for much that is said there is subsequently assumed. In his subsequent studies, the reader will find it helpful to refer back to these sections.

The bulk of the subject matter deals with the chemistry of pyridines, quinolines, isoquinolines, the three diazines, pyrylium salts, the pyrones, benzopyrylium salts, the benzopyrones, pyrroles, furans, thiophens, indoles, 1,3-azoles, and the purines.

The systems treated more briefly are quinolizinium and thiopyrylium salts, isoindole, indolizine, benzofuran, benzothiophen, the 1,2-azoles, and the non-aromatic heterocycles.

To have included more systems would, we feel, have detracted from the value of the treatment we have worked out. A reading list at the end of each main section and at the end of the book lead to aspects which the reader may wish to study in greater depth.

In this main section of the book, the chemistry of each heterocycle is first discussed in one chapter in general terms, that is, broad mechanistic aspects are presented and the relationship of the reactivity of the system to other appropriate systems brought out; then, in a following chapter, the chemistry is discussed systematically in detail. In these detailed chapters the same sequence of reaction types is largely adhered to, so that an introduction giving general information including the main biologically and chemotherapeutically significant molecules is always followed by reactions with electrophilic reagents in a standard order: protonation, nitration, sulphonation, etc., then by reactions with oxidizing agents, with nucleophilic agents, with free radicals, with reducing agents, and with dienophiles; then come reactions of metalloderivatives, of alkyl, carbonyl, halo, oxy, and amino derivatives. Where a particular aspect has nothing of special interest to offer, it is generally left out. The chapter then ends with a discussion of synthesis: here the most important general methods for the system are examined and a number of literature syntheses are given, without detailed comment, which illustrate both ring synthesis and substituent manipulation.

It is hoped that this two-stage treatment will make for better understanding and easier assimilation of information. Repetition in this approach is inevitable, but we believe that repetition of various important facts and generalizations in different contexts is didactically valuable.

Glossary of Abbreviations and Symbols

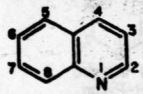
Chemical symbols are used in the text, as well as more usually on reaction arrows, since we feel that this does not detract from clarity while economizing on space.

ny = no yield given in original account.
hy = original account describes yield as 'high', 'good', or 'quantitative'.
ly = original account describes yield as 'low'.
RT = experiment carried out at room temperature.
Δ = experiment carried out at reflux.
atm = atmospheres.
aq = aqueous solution.
(liq) = in liquid phase.
c = concentrated.
f = fuming.
Me = methyl.
Et = ethyl.
Pr^n = normal propyl.
Pr^i = isopropyl.
Bu^n = normal butyl.
Bu^t = tertiary butyl.
Ph = phenyl.
Ac = acetyl (CH_3CO-).
THF = tetrahydrofuran.
DMF = dimethylformamide.
DMSO = dimethylsulphoxide.
LAH = lithium aluminium hydride.
HMPA = hexamethylphosphoramide.

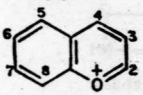
Pyridine

Pyrylium

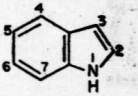
Pyrrole



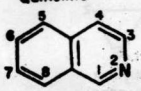
Quinoline



1-Benzopyrylium

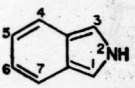


Indole

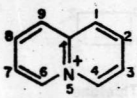


Isoquinoline

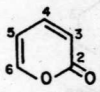
γ-Pyrone



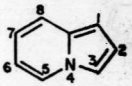
2H-Isoindole



Quinolizinium

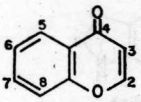


α-Pyrone



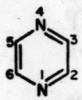
Indolizine

Pyrimidine

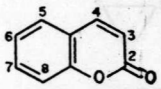


Chromone

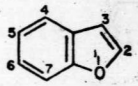
Furan



Pyrazine



Coumarin

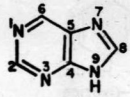


Benzofuran

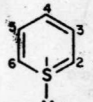
Pyridazine

Thiopyrylium

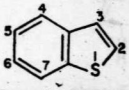
Thiophen



Purine

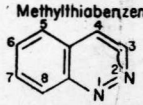


Methylthiabenzene

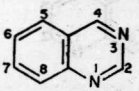


Benzothiophen

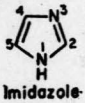
Sym-triazine



Cinnoline



Quinazoline



Imidazole

Aziridine

2H-Pyran

Thiazole

Azetidine

3,4-Dihydro 2H-Pyran

Oxazole

Pyrrolidine

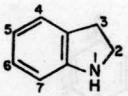
Ethylene (Thiirane) Sulphide

Pyrazole

Piperidine

Thietane

Isoxazole

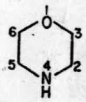


Indoline

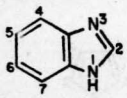
1,4-Dioxan

Isothiazole

Ethylene Oxide

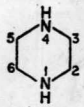


Morpholine



Benzimidazole

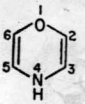
Oxetane



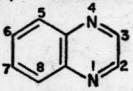
Piperazine

1,2,4-Triazole

Tetrahydro Furan

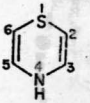


1,4-Oxazine



Quinoxaline

4H-Pyran



1,4-Thiazine

Contents

1

Structure and Main Physical Properties of the Aromatic Heterocyclic Systems

This chapter presents in simple terms the valence-bond view of the main heteroaromatic systems, and also briefly assesses the current value of molecular orbital calculations in relation to elementary teaching of heterocyclic chemistry.

Brief descriptions of benzene, naphthalene, cyclopentadienyl anion and cycloheptatrienyl cation are included in order to provide a background and to emphasize the close relationship of homo and heteroaromatic structures.

HOMOAROMATIC SYSTEMS

The concept of aromaticity as represented by benzene is a familiar and relatively simple one. We know well the difference in reactivity between benzene on the one hand and olefins like ethylene or, say, cyclohexadiene on the other: that is, that the olefins react rapidly *by addition* with electrophiles such as bromine, whereas benzene reacts only under much more forcing conditions and then nearly always *by substitution*. This difference is due to the cyclic arrangement of the six π-electrons in benzene: this forms a conjugated molecular orbital system which is thermodynamically much more stable than a corresponding non-cyclically conjugated system. This extra stabilization generally results in a diminished tendency to react by addition and a greater tendency to react by substitution, with survival of the original cyclic conjugated system of electrons in the product, and is characteristic of aromatic compounds.

A general rule proposed by Hückel in 1931 states that aromaticity is observed in cyclically conjugated systems of $4n + 2$ electrons, that is, with 2, or 6, or 10, or 14, etc., electrons.

The more recent and more fundamental molecular-orbital description of aromatic systems, which, most importantly, allows the essential aspects of their electronic absorption characteristics to be rationalized, is of course

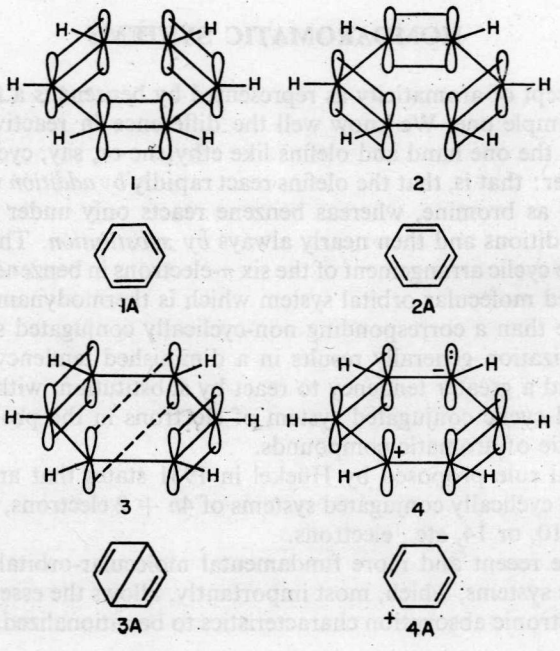
fully available. This aspect of theoretical chemistry is one of the most important present-day developments in chemical thinking. We believe, however, that it does not yet play an important part in the teaching of elementary aromatic chemistry: its fullest impact is yet to be felt in the field of reactions which proceed by so-called ionic mechanisms in solution (see also p. 22).

In this treatment of heterocyclic chemistry, therefore, we shall use the simpler and more pictorial valence-bond resonance description of structure and reactivity. Even though this treatment is far from rigorous, generations of students have found it a valuable aid to the understanding and learning of elementary organic chemistry, which at a much more advanced level gives way naturally to the much more complex quantum mechanical approach.

A brief valence-bond resonance description of benzene and of naphthalene follows in order to pave the way for a similar description of the heteroaromatic systems.

Valence-bond View of the Structure of Benzene and Naphthalene

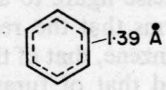
In benzene, the geometry of the ring, with angles of 120°, precisely fits the geometry of a planar trigonally hybridized carbon atom, and allows the setting-up of a σ-skeleton of six sp^2 carbon atoms in a strainless planar ring: each carbon then has one extra electron which occupies an atomic orbital orthogonal to the plane of the ring. These electrons may be combined in spin-coupled pairs to produce a 'Kekule structure', 1 (1A).



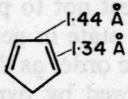
However, as has been known for over 100 years, there are two ways of combining electrons in pairs in this way, the second being 2 (2A): these two structures are entirely equivalent, and they interact, by what was known as bond resonance and more recently has been named exchange degeneracy, to lead to complete equivalence of all the C—C bonds. In more complete treatments of the structure, other modes of coupling the electrons are incorporated into the calculations, such as the six in which two electrons pair across the ring as in 3 (3A), or the six in which polarization occurs as in 4 (4A): but these are high-energy modes of coupling which make only relatively minor contributions to the overall picture.

Structures 1–4 (1A–4A) are canonical forms: they have no physical existence as such, that is, benzene is never at any time like any of them but has a hybrid structure which is intermediate between them all.

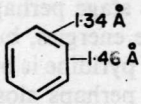
Benzene thus emerges as a regular hexagon with a measured bond-length of 1·39 Å, which is intermediate between the 1·34 Å of the alkene double bond and the 1·46 Å of a single bond between sp^2 hybridized carbons in polyenes.



benzene

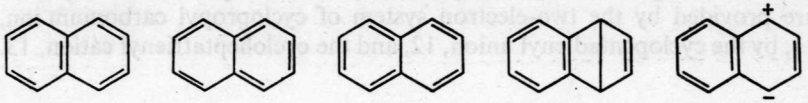


cyclopentadiene



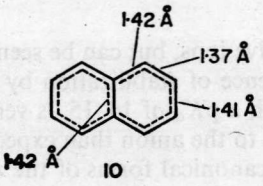
hypothetical cyclohexatriene

When naphthalene is treated likewise, one finds that simple pairing of the ten π-electrons gives three canonical structures, 5, 6, and 7, which correspond to structures 1 and 2 of benzene; canonical structures 8 and 9 are of much higher energy and contribute little to the ground state structure of naphthalene. Just by taking the geometrical average of 5, 6, and



5 6 7 8 9

7, the C1—C2 bond comes to $1\frac{2}{3}$ of a single bond; C2—C3, C1—C9, and C9—C10 each comes to $1\frac{1}{3}$ of a single bond. Now, by simple proportion, a $1\frac{1}{3}$ bond would be about 1·42 Å long, and a $1\frac{2}{3}$ bond about 1·38 Å. Over the years, actual measurements of the bond-lengths of naphthalene have given a range of values, but if one takes one of the most recent sets shown in 10, published in 1966 and determined by electron-diffraction, the closeness of the measured values to those arrived at by taking the geometric mean of canonical structures 5, 6, and 7 is striking.



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Aromatic Resonance Energy

The difference between the ground-state energy of benzene and that of a hypothetical non-aromatic 1,3,5-cyclohexatriene corresponds to the degree of stabilization conferred to benzene by special cyclic interaction of the six π-electrons. This difference is usually known as aromatic resonance energy.

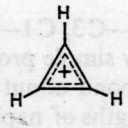
A very important point to understand is that aromatic resonance energy is a very difficult property to measure and calculate. The difficulty lies in estimating the energy of the hypothetical non-aromatic structure. This estimate is least difficult to make in the case of benzene, becomes more difficult in the case of naphthalene, and still more difficult in the case of the simple heterocyclic compounds like pyridine, pyrrole, furan, etc. This is evident in the wide range of values published for each of the main heterocycles.

The resonance energy of systems like pyrylium, pyridinium, pyridones, and pyrones are the most difficult to assess.

At this stage perhaps it is best not to put a precise figure to aromatic resonance energies, but just to state in general terms that the resonance energy of pyridine is of the same order as that of benzene, that of thiophen is lower, perhaps closely followed by pyrrole, and that of furan is the lowest of all the simple uncharged heterocycles with one heteroatom.

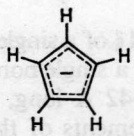
Cyclopentadienyl Anion and Cycloheptatrienyl Cations

Aromatic planar cyclic systems of 2, 6, 10, etc., π-electrons may not only be associated with a wide range of ring sizes but also with an integral positive or negative charge. Simple examples of charged aromatic systems are provided by the two-electron system of cyclopropyl carbonium ion, 11, by the cyclopentadienyl anion, 12, and the cycloheptatrienyl cation, 13.



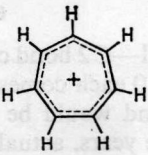
11

cyclopropyl carbonium ion
2 π electron system



12

cyclopentadienyl anion
6 π electron system

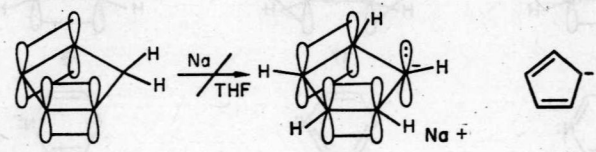


13

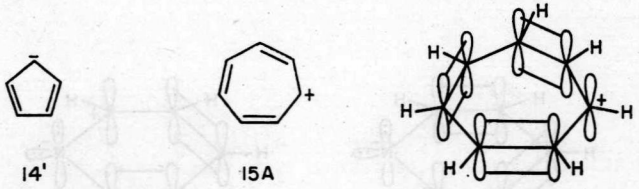
cycloheptatrienyl cation
6 π electron system

These are all highly reactive ions, but can be seen to be much less reactive than expected in the absence of stabilization by aromatic delocalization: thus cyclopentadiene, with a pK_a of 14–15, is very much more acidic and more easily deprotonated to the anion than expected of a simple diene. In the five equivalent main canonical forms of the anion, 14 (14A), 14′, etc.,

the six electrons are paired as shown and the resulting resonance hybrid is a regular pentagon. It may be noted that in the σ-ring skeleton there must be appreciable strain due to compression of the sp^2 hybrid angle of 120° to 109° of the pentagon.



cyclopentadiene 14 14A

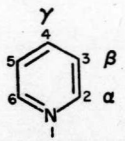


14' 15A 15

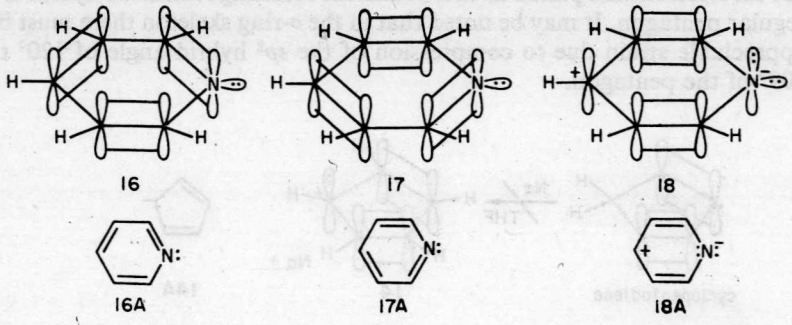
Tropylium bromide is an ionic, water-soluble compound: the cation has seven equivalent main canonical forms, the six electrons are paired as shown in 15 (15A), the seventh carbon having an empty orbital. The resonance hybrid then is a regular heptagon.

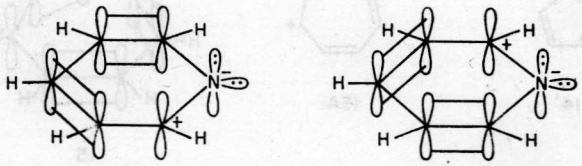
HETEROAROMATIC SYSTEMS

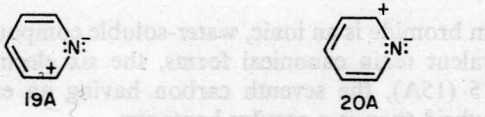
Pyridine and Related Systems

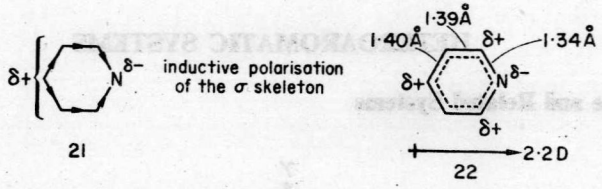


The structure of pyridine is completely analogous with that of benzene being related by replacement of =CH— by =N—. The differences are: (*a*) a departure from perfectly regular hexagonal geometry caused by the shorter C—N bond; (*b*) the replacement of a hydrogen in the plane of the ring by an unshared electron pair, likewise in the plane of the ring and in an sp^2 hybrid orbital, not at all involved in the aromatic π-electron system, and responsible for the basic properties of pyridines; (*c*) a strong permanent dipole, caused by the greater electronegativity of nitrogen compared with that of carbon.

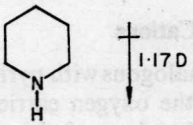




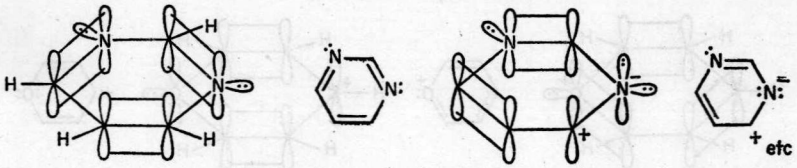




The more electronegative nitrogen causes both inductive polarization, mainly of the σ-bonds as shown in 21, and stabilizes those polarized canonical structures in which the nitrogen is negatively charged, 18, 19, and 20, which thus make a significant contribution to the hybrid structure. The main canonical forms are, as in benzene, the Kekule structures 16 and 17. Pyridine, then, is a molecule with essentially equivalent bonds in which both inductive and mesomeric effects work in the same direction and result in a dipole of 2.21 D, the negative end of which is on the nitrogen, the positive fractional charges being located mainly on C 2, C 4 and C 6. The dipole moment of piperidine gives an idea of the value of the induced polarization of the σ-skeleton of pyridine.

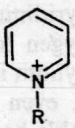


The structures of the *diazines* are analogous, thus pyrimidine can be represented by the following canonical structures:

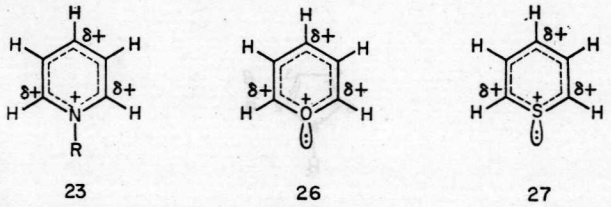


The structures of *quinoline* and *isoquinoline* bear the same relationship to pyridine as naphthalene does to benzene.

Pyridinium and Related Cations



Electrophilic addition to the pyridine nitrogen generates pyridinium ions, 23, the simplest being 1H-pyridinium (23, R=H) formed by inter-



23 26 27

change on hetero atom roughly 1-38

action with a protic acid. In fact 1H-pyridinium is isoelectronic with benzene, and the difference lies in the higher nuclear charge of N which makes the system positively charged. Thus pyridinium cations are still very much aromatic in character. The formal positive charge on the nitrogen, however, must interact quite strongly with the aromatic molecular orbital system and reduce its stabilizing effect: furthermore the positive charge is delocalized on to ring carbon both mesomerically (cf. pyridine 18, 19, 20) and inductively (cf. pyridine 21) and C 2, C 4 and C 6 carry fractional positive charges which are much higher than in pyridine.