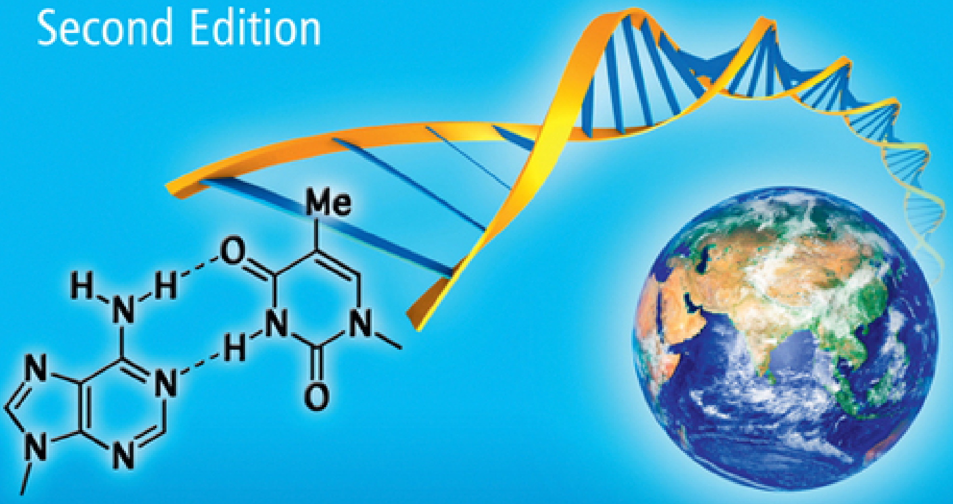
Heterocycles in Life and Society

An Introduction to Heterocyclic Chemistry, Biochemistry and Applications

Second Edition



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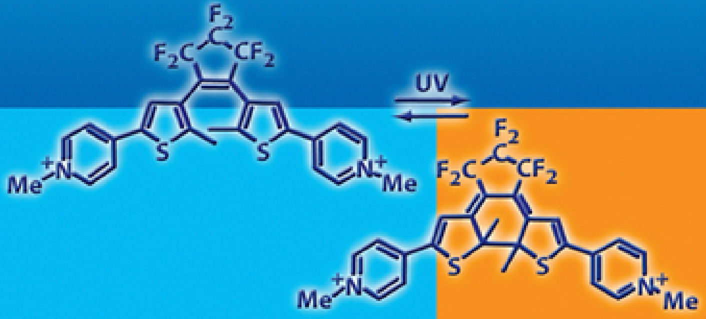

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Heterocycles in Life and Society

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An Introduction to Heterocyclic Chemistry, Biochemistry and Applications

Second Edition

by

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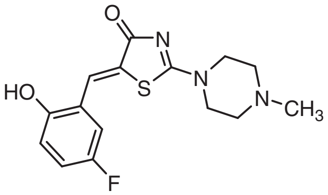
Contents

Preface to Second English Edition

On 7 September 2009, Chemical Abstracts Service registered its 50-millionth chemical substance – a heterocyclic compound of the following structure:



Hardly a casual coincidence: heterocyclic compounds form the largest and one of the most important classes of organic compounds and some 55% of organic chemistry publications include the field. They include not only the many thousands of original articles and conference materials published annually but a great number of scientific monographs such as the multivolume *Comprehensive Heterocyclic Chemistry*, covering all fields of heterocyclic chemistry. Heterocyclic chemistry is taught worldwide at most universities and its scope is reflected in many fine text compendia and reference sources. It is therefore very strange that many general chemistry (and even organic chemistry) texts fail to include heterocycles and discuss the significance of their chemistry, or at most only in a nonsystematic manner. Furthermore, time constraints often prevent teachers of chemistry from elaborating on the manifold applications of heterocycles. This is why from the very beginning the main goal of the present book and its predecessor was to bridge this gap and to emphasize not so much the innumerable reactions of the different classes of heterocycles as their practical importance in life and society, especially their scientific applications in various branches of technology, medicine and agriculture. Our hope was, and is, that this approach will inspire the student to become involved in an immensely important and exciting field of modern chemical science and technology. The 14 years that have passed since the first edition have justified this approach. Indeed, human society, in addition to chronic old problems, now faces acute, newly recognized dangers such as climate change and ecology degradation, energy shortages, depletion of mineral resources, population growth, pandemic illnesses and so on. These challenges have forced science to become more applied and expensive but at the same time more productive and useful. This productivity results from the appearance of new powerful physical methods, apparatus as well as fundamental developments in computational techniques.

The past 10 years have been marked in biochemistry by such milestone achievements as genome decoding, clarification of ribosome structure and its activity mechanism, and wide applications of imaging techniques. Further progress has been made in medicinal chemistry where new methods of biological screening, drug delivery and drug targeting in combination with innovative chemotherapy have been elaborated. An epochal event in science is the creation of nanotechnology which, via new materials and electronic devices, is leading to revolutionary changes in our future life. In the energy sector the growing production of biofuels, progress in development of hydrogen as a fuel, artificial photosynthesis and dye-sensitized solar cells all look very encouraging. These and other lines of development would be impossible without organic chemistry and often without heterocyclic compounds. The discussion of these themes lies at the focus of this second edition: most chapters have been substantially revised and updated, and chapter 11 is completely new.

While this book is intended for university level chemistry and biochemistry students and their instructors, it should be of interest to researchers over the whole of the chemical, biological, medical and agricultural sciences as well as in adjacent branches of science and technology. These assertions are well founded because the majority of known pharmaceutical preparations (antibiotic, neurotropic, cardiovascular, anticarcinogenic) are heterocyclic in nature; because the agricultural use of new plant development regulators and pesticides based on heterocyclic structures becomes more widespread each year; and because great attention is being paid to the synthesis and production of new kinds of thermostable polymers, highly durable fibers, fast pigments, colorants and functional dyes and of organic conductors containing heterocyclic fragments.

This book consists of 12 chapters. First, chapters (1) and (2) present the elements of the structure and properties of heterocycles and are a useful introduction to the fundamentals of their chemistry. Next, four chapters deal in a general way with the key role of heterocyclic molecules in life processes, including the transfer of hereditary information (3), the manner in which enzymes function (4), the storage and transfer of bioenergy (5) and photosynthesis (6). Chapters (7)–(9) consider the applications of heterocycles in medicine, agriculture, and industry, respectively. We have now dedicated chapter (10) to supramolecular chemistry in view of its significance. Finally, chapter (11) considers the future contribution of heterocyclic chemistry to modern trends of applied science, the latest discoveries and the prospects of finding new spheres of use for heterocycles. Chapter (12) deals with the past: specifically the emergence of heterocyclic molecules on primordial Earth, which is tightly connected with the far-reaching achievements of astrophysics. Due to modern orbital telescopes and space stations our knowledge about the origin of the Universe and its evolution has been significantly widened and deepened. On this basis new scientific disciplines are arising and strongly developing. In two of these, perhaps the most fascinating (prebiotic chemistry, synthetic biology), the role of heterocyclic compounds is especially important. In fact, a test-tube recreation of the process of molecular evolution up to synthesis of biological cells and live organisms is put forward as a not so distant perspective. It is not necessary to possess a rich imagination to foresee that the consequences of such a development of events could be even more dramatic then that of nanotechnology.

Throughout this text the student will learn to apply the knowledge gained by working on problems related to the topics covered in each chapter. Many of the 100 problems have been chosen from scientific journals and represent areas of recent significant interest. The scientists who solved these mysteries were yesterday’s students. Thus, the approach to the problems will give today’s students further insight into nature and a preview of what is scientifically possible. Each chapter also contains suggested further reading.

The authors have tried to organize this book in as simplified a form as possible, in as far as the scientific language is concerned. Each chapter is preceded by a piece written by a Russian poet (translated into English by E. N. Sokolyuk) or (in one case) an American poet. The selected verses may suggest subtle links with the concepts and contents of each chapter and were introduced with the hope of fruitful cross-pollination between the natural sciences and humanities, so much needed in our modern world.

In conclusion, we would like to express our warm acknowledgements to many people who helped us during the preparation of the second edition of this book. We are most grateful for helpful discussion and technical assistance from Dr Anna Gulevskaya, Dr Valery Ozeryanskii (for reading Chapter 11), Dr Vladimir Sorokin (who kindly supplied us with some fresh literature sources) and Dr John Zoltewicz.

A. F. Pozharskii
A. T. Soldatenkov
A. R. Katritzky

Preface to First English Edition

The book presents an updated translation of the Russian original ‘*MoJIekyJIbI-IIepcTHИ*’ by A. F. Pozharskii and A. T. Soldatenkov, published in 1993 by Khimiya. It has been a great pleasure to accept the invitation of my long-standing friend Sasha Pozharskii to join him and Professor Soldatenkov in producing the present English version, which follows closely the concepts and objectives of the original. We hope that this book may ignite for its readers some of the passion for heterocyclic chemistry which we the authors possess and help to repair the neglect of heterocyclic chemistry on the US academic scene. This neglect contrasts with the high importance awarded to heterocyclic chemistry and biochemistry by American industry, as well as by academic and industrial chemists alike in Europe, Japan and all over the world.

This volume could not have been produced without the help of many people. Dr Daniel Brown (Cambridge) read the whole text and made very helpful suggestions. Among many other colleagues who read parts of the work, I would like to acknowledge particularly Dr Phil Cote, Dr Alastair Monro, Dr Emil Pop, Dr Nigel Richards, Dr Eric Scriven and Dr John Zoltewicz. It is a pleasure to thank also Ms Jacqui Wells, Dr Olga Denisko and Ms Cynthia Lee for all the help they gave me in producing and finalizing the manuscript.

Alan R. Katritzky
Gainesville, Florida
April 1996

1

Molecular Rings Studded With Jewels

> Fortune Goddess, in your glory, in your honor, stern Kama,
> Bangles, finger-rings and bracelets I will lay before your Temple.
>
> *V. Bryusov*

Readers of this book, whether or not they are students of organic chemistry, will all be aware of the vital role of proteins, fats and carbohydrates in life processes. Experience has shown that considerably less is usually known about another class of compounds which have a similar importance in the chemistry of life, namely the heterocyclic compounds or, in short, heterocycles. What are heterocycles?

1.1 From Homocycle to Heterocycle

It is rumored that the Russian scientist Beketov once compared heterocyclic molecules to jewelry rings studded with precious stones. Several carbon atoms thus make up the setting of the molecular ring, while the role of the jewel is played by an atom of another element, a heteroatom. In general, it is the heteroatom which imparts to a heterocycle its distinctive and sometimes striking properties. For example, if we change one carbon atom in cyclohexane for one nitrogen atom, we obtain a heterocyclic ring, piperidine, from a homocyclic molecule. In the same way, we can derive pyridine from benzene, or 1,2,5,6-tetrahydropyridine from cyclohexene (Figure 1.1).

A great many heterocyclic compounds are known. They differ in the size and number of their rings, in the type and number of heteroatoms, in the positions of the heteroatoms and so on. The rules of their classification help to orient us in this area.

Cyclic hydrocarbons are divided into cycloalkanes (cyclopentane, cyclohexane, etc.), cycloalkenes (e.g., cyclohexene) and aromatic hydrocarbons (with benzene as the main representative). The most basic general classification of heterocycles is similarly divided into heterocycloalkanes (e.g., piperidine), heterocycloalkenes (e.g., 1,2,5,6-tetrahydropyridine) and heteroaromatic systems (e.g., pyridine, etc.). Subsequent classification is based on the type of heteroatom. On the whole, heterocycloalkanes and heterocycloalkenes show comparatively small differences when compared with related noncyclic compounds. Thus, piperidine possesses chemical

Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, Second Edition. Alexander F. Pozharskii, Anatoly T. Soldatenkov and Alan R. Katritzky.

properties very similar to those of aliphatic secondary amines, such as diethylamine, and 1,2,5,6-tetrahydropyridine resembles both a secondary amine and an alkene.

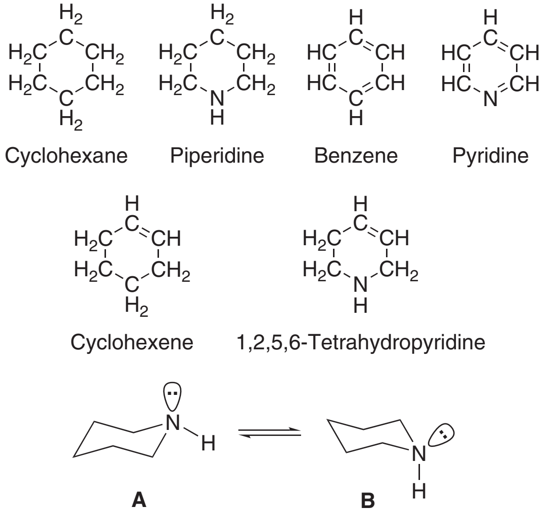


Figure 1.1 *The relationship between cyclic hydrocarbons and heterocycles and the two chair conformations of piperidine.*

An interesting feature of heterocycloalkanes and heterocycloalkenes is the possibility of their existence in several geometrically distinct nonplanar forms which can quite easily (without bond cleavage) equilibrate with each other. Such forms are called conformations. For instance, piperidine exists mainly in a pair of chair conformations in which the internal angle between any pair of bonds is close to tetrahedral (109° 28′) to minimize steric strain. In these two chair conformations (Figure 1.1), the N—H proton is in either the equatorial (A) or axial (B) position, the first being slightly preferred.

By contrast, the heteroaromatic compounds, as the most important group of heterocycles, possess highly specific features. Historically, the name 'aromatic' for derivatives of benzene, naphthalene and their numerous analogues came from their characteristic physical and chemical properties. Aromatic compounds differ from other groups in possessing thermodynamic stability. Thus, they are resistant to heating and tend to be oxidized and reduced with difficulty. On treatment with electrophilic, nucleophilic and radical agents, they mainly undergo substitution of hydrogen atoms rather than the addition reactions to multiple bonds which are typical for ethylene and other alkenes. Such behavior results from the peculiar electronic configuration of the aromatic ring. We consider in the next section the structure of benzene and some parent heteroaromatic molecules.

1.2 Building Heterocycles From Benzene

Each carbon atom in the benzene molecule formally participates in bond formation with its four atomic orbitals, each occupied by one electron. Three of these orbitals are hybridized and are called sp^2-orbitals. Their axes lie in the same plane and are directed from each other at an angle of 120°. These atomic orbitals overlap similar orbitals of adjacent carbon atoms or the s-orbitals of hydrogen atoms, thereby forming the ring framework of six carbon–carbon bonds and six carbon–hydrogen bonds (Figure 1.2a). The molecular orbitals and bonds thus formed are called σ-orbitals and σ-bonds, respectively. The fourth electron of the carbon atom is located in an atomic *p*-orbital, which is dumbbell shaped and has an axis perpendicular to the ring plane (Figure 1.2b). If the *p*-orbitals merely overlapped in pairs, the benzene molecule would possess the cyclohexatriene structure with three single and three conjugated double bonds, as reflected in the classic representation of benzene – the Kekulé structure (Figure 1.2c). However, in reality, the benzene ring is a regular hexagon, which indicates equal overlap of each *p*-orbital with its two neighboring *p*-orbitals, resulting in the formation of a completely delocalized π-electron cloud (Figure 1.2d, e).

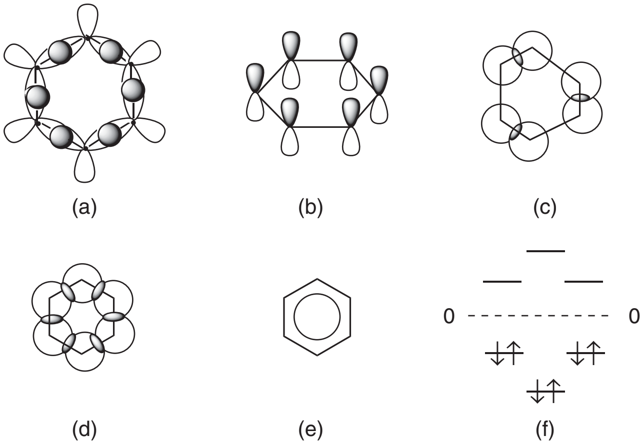


Figure 1.2 *The electronic structure of the benzene molecule: (a) framework of σ-bonds, (b) p-orbital orientation, (c) overlap of p-orbitals forming localized π-bonds (view from above), (d) overlap of p-orbitals forming delocalized π-bonds, (e) representation of the benzene ring reflecting the equivalence of all carbon-carbon bonds and the equal distribution of π-electrons, (f) energy levels of molecular π-orbitals showing electron occupation of the three orbitals of lower energy.*

Thus, in the benzene molecule as well as in the molecules of other aromatic compounds, we observe a new type of carbon–carbon bond called ‘aromatic’, which is intermediate in length between a single and a double bond. Standard aromatic C—C bond lengths are close to 1.40 Å, whereas the C—C distance is 1.54 Å in ethane and 1.34 Å in ethylene.

The high stability of the benzene molecule is explained by the energetic picture available from quantum mechanics. Benzene has six molecular π-orbitals. Three of these π-orbitals (bonding orbitals) lie below the nonbonding energy level and are occupied by six electrons with a large energy stabilization. The remaining three are above the nonbonding level (antibonding orbitals). Occupation of the bonding orbitals leads to the formation of strong bonds and stabilizes the molecule as a whole. Incomplete occupation of bonding orbitals, and especially the occupation of antibonding orbitals, results in considerable destabilization. Figure 1.2f shows that all three bonding orbitals in benzene are completely occupied. Hence, it is often said that benzene has a stable aromatic π-electron sextet, a concept that can be compared in its importance to the inert octet cloud of neon or the F^- anion.

In addition to the π-electron sextet, stable aromatic arrangements can also be formed by 2, 10, 14, 18 or 22 π-electrons. Such molecules contain cyclic sets of delocalized π-electrons. For example, the aromatic molecule naphthalene possesses 10 π-electrons. The number of electrons required for a stable aromatic configuration can be calculated by the $4n + 2$ 'Hückel rule', where $n = 0, 1, 2, 3$ and so on, which was suggested by the German scientist Hückel in the early 1930s.[1]

The electronic configuration of the pyridine molecule is very similar to that of benzene (Figure 1.3a). Both compounds contain an aromatic π-electron sextet. However, the presence of the nitrogen heteroatom in the case of pyridine results in significant changes in the cyclic molecular structure. First, the nitrogen atom has five valence electrons in the outer shell, in contrast with the carbon atom which has only four. Two take part in the formation of the skeletal carbon–nitrogen σ-bonds, and a third electron is utilized in the aromatic π-cloud. The two remaining electrons are unshared, their sp^2-orbitals lying in the plane of the ring. Owing to the availability of this unshared pair of electrons, the pyridine molecule undergoes many additional reactions over and above those which are characteristic of benzene or other aromatic hydrocarbons. Second, nitrogen is a more electronegative element than carbon and therefore attracts electron density. The distribution of the π-electron cloud in the pyridine ring is thus distorted (see Chapter 2).

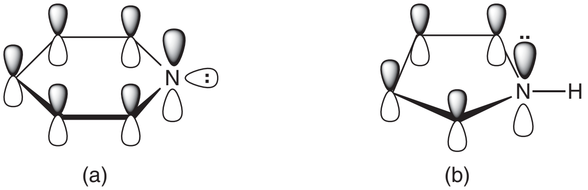


Figure 1.3 *The orientation of π-electron orbitals and unshared electron pairs in (a) pyridine and (b) pyrrole (C—H bonds are omitted).*

Heterocyclic compounds include examples containing many other heteroatoms such as phosphorus, oxygen, sulfur and so on. By substitution of a ring carbon atom we may formally transform benzene into phosphabenzene or pyrylium and thiapyrylium cations (Figure 1.4). Note that a six-membered ring which includes oxygen or another group VI element can only be aromatic if the heteroatom bears a formal positive charge (+1). Such cationic rings exist only in association with counterions like ClO_4^- or BF_4^-. Just like the nitrogen atom in pyridine, the phosphorus, oxygen and sulfur atoms donate one π-electron to the aromatic electron cloud. Such heteroatoms are often called 'pyridine-like'.

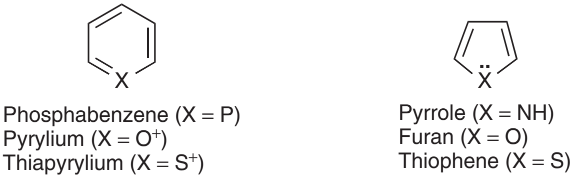


Figure 1.4 *Examples of heterocycles with pyridine-like and pyrrole-like heteroatoms.*

Formally, pentagonal aromatic heterocycles can also be derived from benzene by a heteroatom taking the place of one complete CH═CH group. Two electrons of the heteroatom p-orbital must

---

[1] For monocyclic fully conjugated compounds, the Hückel rule stops working with 26 and larger π-electron systems ($n \geq 6$). This is explained by a strong increase of inter-electron repulsion that outweighs the gain of aromatic stabilization.

now be involved in the π-system in order to obtain an aromatic sextet (Figure 1.3b). This type of heteroatom is called 'pyrrole-like' in contrast to the 'pyridine-like' nitrogen which donates only one electron to the sextet. The corresponding five-membered heterocycles containing nitrogen, oxygen or sulfur atoms are named pyrrole, furan and thiophene, respectively (Figure 1.4). One more difference between a pyridine-like heteroatom and a pyrrole-like heteroatom is obvious: the first participates with one double bond in the Kekulé structure, while the second is involved with single bonds only.

A heterocycle can contain several heteroatoms. Pyridazine, pyrimidine, pyrazine and 1,3,5-triazine are heterocyclic compounds with a single ring but two or three identical heteroatoms (Figure 1.5a). Together with pyridine and many other analogues they form the family of *azines*.

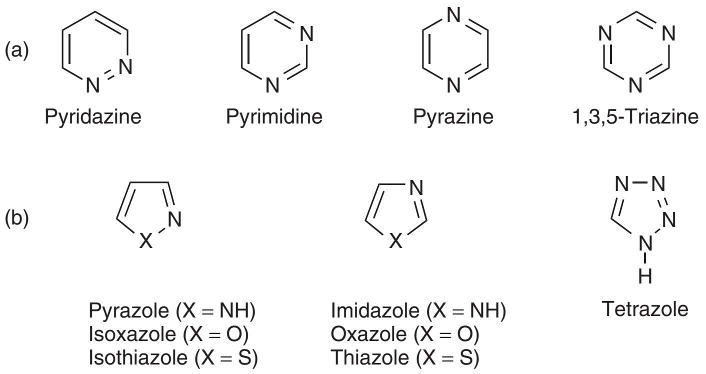


Figure 1.5 *Heterocycles of (a) the azine class and (b) the azole class.*

Five-membered heterocyclic compounds containing both pyridine-like and pyrrole-like nitrogen or other heteroatoms are called *azoles*. Pyrazole, imidazole and their oxygen and sulfur analogues belong to the azole series (Figure 1.5b).

Two or more rings are encountered in many heterocyclic compounds. The rings may be connected to each other by a single bond (as in the case of 2,2′-bipyridyl) or may be fused as shown in Figure 1.6 to form condensed systems. For example, two fused rings exist in quinoline, pteridine, indole and benzimidazole and three fused rings in acridine. In some cases a heteroatom may belong simultaneously to two (e.g., indolizine) or even three rings. Such a heteroatom is denoted a 'bridgehead' atom.

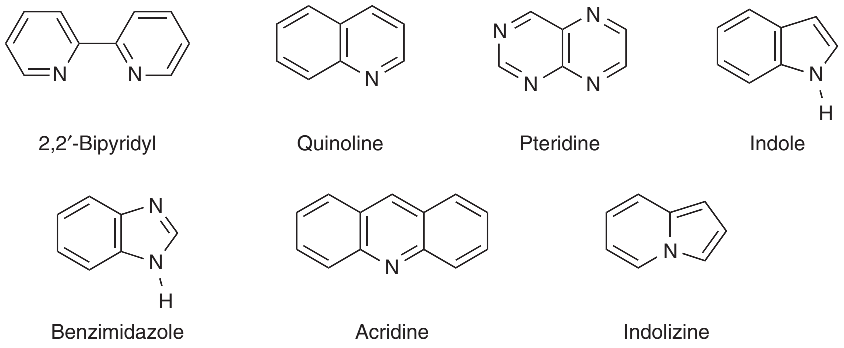
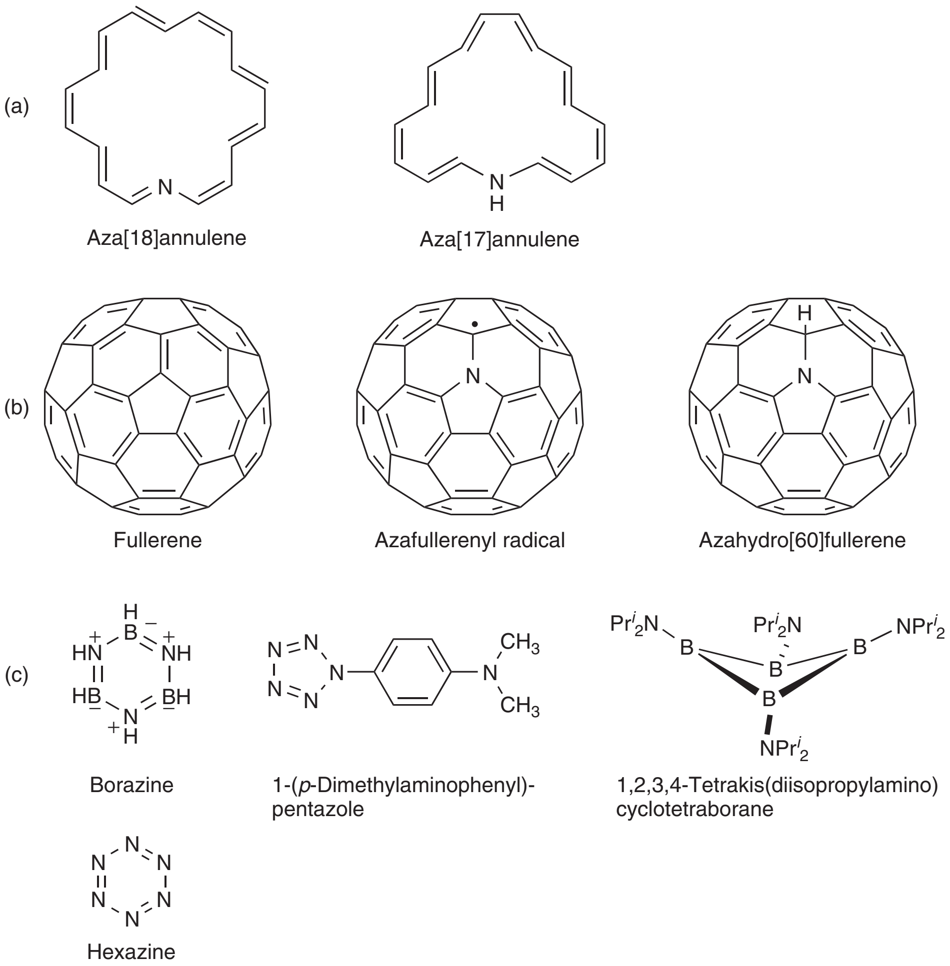


Figure 1.6 *Examples of bi- and polycyclic heterocycles.*

1.3 Some More Kinds of Heterocycles

The comparison of heterocycles with jewel-studded rings is most appropriate for five- and six-membered systems which are frequently natural products and which have become commonplace in many research laboratories. However, polymembered cycles or macrocycles have recently drawn much attention. They resemble not so much finger-rings but rather molecular bracelets or bangles. For example, aza[18]annulene is an 18-membered analogue of pyridine, and aza[17]annulene is a 17-membered analogue of pyrrole (Figure 1.7a). We focus our attention on macrocycles in subsequent chapters, especially Chapter 10.



Aza[18]annulene

Aza[17]annulene

Fullerene

Azafullerenyl radical

Azahydro[60]fullerene

Borazine

1-(*p*-Dimethylaminophenyl)-pentazole

1,2,3,4-Tetrakis(diisopropylamino) cyclotetraborane

Hexazine

Figure 1.7 *Examples of (a) macroheterocycles, (b) azafullerenes and (c) rings without cyclic carbon atoms.*

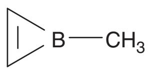
Another recently arisen area is the chemistry of heterofullerenes – compounds in which one or more cage carbon atoms are substituted by heteroatoms. The most stable among them are azafullerenes. The valence rules determine that, at the introduction of one nitrogen atom into the fullerene molecule C_{60}, the free radical specie $C_{59}N^{\bullet}$ should be produced. Its stabilization can be achieved either via dimerization into 2,2′-biaza[60]fullerene $(C_{59}N)_2$ or by means of hydrogen atom addition leading to green azahydro[60]fullerene $C_{59}NH$ (Figure 1.7b). Carbon nanotubes containing nitrogen or boron heteroaatoms are also known.

How many heteroatoms may be included in one ring? As many as one can imagine. A ring may, in principle, be completely constructed from noncarbon atoms (Figure 1.7c). Borazine, a well known example of such a compound, was designated 'inorganic benzene' because of its high stability. 1-(*p*-Dimethylaminophenyl)pentazole and blue-colored 1,2,3,4-tetrakis (diisopropylamino)cyclotetraborane contain five- and four-membered heterocycles composed only of nitrogen or boron atoms. The curiosity of many chemists has long been excited by a theoretical substance named 'hexazabenzene' or 'hexazine'. Numerous attempts to prepare this compound have so far ended in failure, supposedly because of its great instability and tendency to decompose to give nitrogen: $N_6 \rightarrow 3N_2$.

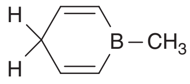
Of course, the examples given above by far do not cover all of the heterocyclic systems possible. In the following chapters we will become acquainted with many new ones.

1.4 Problems

1. How many chair conformations are possible for unsubstituted piperidine? How many for a 1,4-disubstituted piperidine? Draw their structures.
2. The boat conformation for saturated six-membered rings is energetically unfavorable. Account for this fact. Design the structure of a substituted piperidine in which the boat conformation is fixed.
3. Phosphacyclohexane (phosphorinane) exists almost completely in a chair conformation with the P—H bond axial. Discuss possible reasons for the stabilization of this conformation compared with the analogous piperidine conformation.
4. Indicate which of the heterocycles listed below can be formally regarded as aromatic. Explain your choices.



(a)



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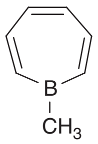

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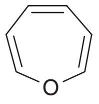

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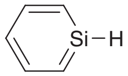
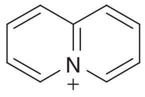
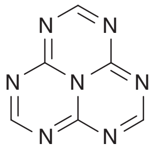


(e)



(f)



(g)

5. Historically, the first synthetic homocyclic aromatic system not containing carbon atoms was the golden-orange salt P_5^- Na^+. Draw its structure and explain the following facts: (i) the salt is stable only in tetrahydrofuran solution in the presence of 18-crown-6 (see Section 10.1.1), (ii) all phosphorus atoms in the anion P_5^- in solution are equivalent.
6. Draw all of the possible isomeric imidazopyridines, that is, the heterocycles which consist of fused pyridine and imidazole nuclei.
7. What is the orientation of the nitrogen lone pair of electrons in aza[18]annulene (Figure 1.7)? Is any alternative orientation possible? Discuss the orientation of the N—H bond in aza[17]annulene.
8. The relative stability (aromaticity) of five-membered heterocycles is changed in the following sequence: thiophene> pyrrole> furan. How this can be explained?
9. To avoid the formation of a free radical by placing one nitrogen atom into fullerene, one can simultaneously introduce into the molecule two heteroatoms. Draw the simplest structures of such a type.

1.5 Suggested Reading

1. Joule, J. A., *Heterocyclic Chemistry*, 4th edn, Wiley-Blackwell, Chichester, 2000.
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4. Katritzky, A. R., Ramsden C., Scriven E. and Taylor, R. (eds), *Comprehensive Heterocyclic Chemistry III*, vols 1–15, Elsevier, New York, 2008.
5. Katritzky, A. R., Rees, C. W. and Scriven E. (eds), *Comprehensive Heterocyclic Chemistry II*, vols 1–12, Pergamon Press, Oxford, 1995.
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7. Elguero, J., Marzin, C., Katritzky, A. R. and Linda, P. The tautomerism of heterocycles, in *Advances in Heterocyclic Chemistry*, *Suppl. 1*, Academic Press, New York, 1976.
8. Pozharskii, A. F., *Theoretical Basis of Heterocyclic Chemistry* (in Russian), Khimia, Moscow, 1985.
9. Katritzky, A. R. (ed.) Special issue on heterocyclic chemistry, *Chem. Rev*., 2004, **104** (5).

2

Why Nature Prefers Heterocycles

Ties subtle, full of power exist
Between the shape and flavor of a flower.
So is a brilliant unseen, until comes hour
To facet it from diamond mist.

V. Bryusov

All biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds. Why does nature utilize heterocycles? To answer this question we first describe the basic physical and physicochemical properties of the fundamental heterocyclic types.

2.1 Reactions for all Tastes

Heterocycles are involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may form anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles and yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Let us consider pyridine.

We have already seen that the nitrogen atom in pyridine induces π-electron withdrawal from the carbon atoms. As a result of this electronic shift, the carbon atoms in the *ortho* and *para* positions (relative to the nitrogen atom) acquire a partial positive charge (Figure 2.1). Thus, a π-electron deficit on the carbon skeleton is characteristic of all heterocycles containing pyridine-like heteroatoms. Such heterocycles are called π-deficient.

Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, Second Edition. Alexander F. Pozharskii, Anatoly T. Soldatenkov and Alan R. Katritzky.

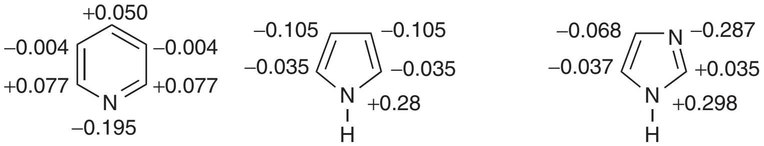
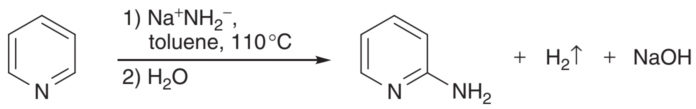
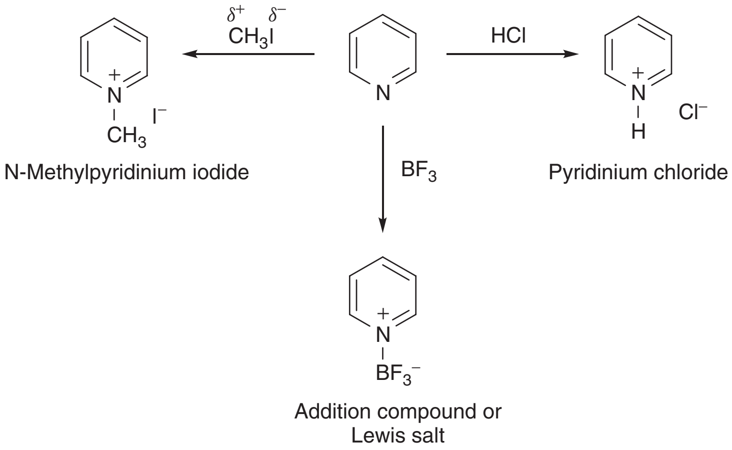


Figure 2.1 *The π-electron charges in pyridine, pyrrole and imidazole.*

A unique feature of π-deficient heterocycles is their facile interaction with negatively charged nucleophilic reagents. As a typical example, the reaction of pyridine with sodamide gives 2-aminopyridine in good yield:

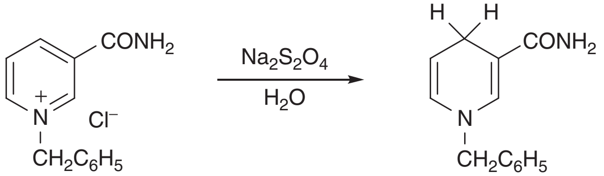


Substitution of the hydrogen atom under the action of positively charged (electrophilic) agents proceeds with difficulty or does not occur at all in π-deficient heterocycles. However, electrophiles add readily to the pyridine nitrogen owing to its unshared pair of electrons. Pyridine thus forms pyridinium and *N*-alkylpyridinium salts with acids and alkyl halides, respectively, and a zwitterionic addition compound or Lewis salt with BF_3:



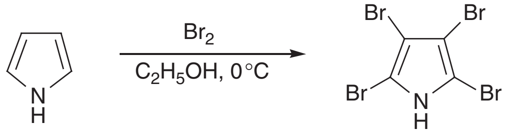
Pyridine and other heterocycles containing a pyridine-like nitrogen atom behave as bases in these and similar reactions (see Section 2.2).

The introduction of electron-accepting groups into an organic compound lowers the energy of all molecular orbitals. Hence, such compounds donate electrons with difficulty and are thus poorly oxidized. By contrast, their ability to accept additional electrons enables such compounds to be readily reduced. Pyridine-like heteroatoms are electron acceptors, and hence π-deficient heterocycles are reduced with ease. This is found to be the case, especially in relation to compounds which have a positively charged heteroatom, like salts of pyrylium, pyridinium and so on. For example, 1-benzyl-3-carbamoylpyridinium chloride is reduced by sodium dithionite to the corresponding 1,4-dihydropyridine derivative:

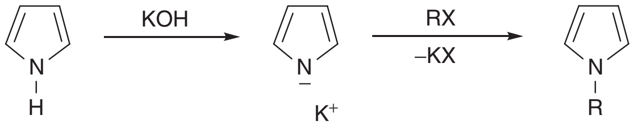


We shall see elsewhere (Sections 4.2.1 and 5.2) that nature uses this apparently simple reaction to drive a great many biologically important processes.

Quite a different situation is encountered in the case of pyrrole, furan and thiophene. Since the heteroatoms of these compounds each contribute two electrons to the π-aromatic ensemble, the cyclic system of five atoms formally has six π-electrons. As a result, in spite of the higher intrinsic electronegativity of the heteroatom, all of the carbon atoms possess excess negative charge (Figure 2.1). Such compounds are named π-excessive heterocycles. Reactions with nucleophiles agents are not common but they readily interact with electrophiles. Thus, pyrrole is almost instantly halogenated even under very mild conditions to give the tetrahalogenopyrrole, and these reactions cannot be stopped at the monosubstitution stage:



Two-electron donation to the aromatic system by the pyrrole-like heteroatom imparts a partial positive charge to the heteroatom (Figure 2.1). In the case of pyrrole and related NH-heterocycles, the N—H bond reactivity increases. N-Anions, which are readily alkylated, acylated and arylated, are thus formed under the action of bases. Such reactions are commonly used for the synthesis of various N-derivatives (note that a nonionized NH group does not, as a rule, undergo these conversions):



The molecular orbitals in π-excessive heterocycles are of high energy, and consequently these compounds are reduced with difficulty but are readily oxidized. Compounds with both pyridine-like and pyrrole-like heteroatoms, as expected, can show both π-deficient and π-excessive properties with one or the other dominant. Thus, imidazole contains two carbon atoms with a partial negative and a third with a partial positive π-charge (Figure 2.1). Its high reactivity towards halogenation is attributed to the dominant π-excessive character of the neutral molecule and especially of the imidazole anion.

2.2 Heterocycles as Acids and Bases

In the preceding section we noted the capability of nitrogen heterocycles to behave as acids or bases, the acidic properties being inherent to heterocyclic compounds containing a pyrrole-like NH group, whereas the basic properties are characteristic for those with pyridine-like nitrogen. We describe this in more detail because acid–base properties play a vital role not only in general reactivity but in many biochemical processes as well.

The acid dissociation constant (K_a) is universally used as the quantitative measure of acidity. Dissociation constants are obtained by application of the law of mass action to the acid–base equilibrium:

$$\mathrm{H{-}A} \leftrightarrows \mathrm{H^+} + \mathrm{A^-}$$

The dissociation constant K_a is equal to the anion concentration multiplied by the proton concentration, divided by the concentration of the nondissociated acid:

$$K_a = [\mathrm{A^-}][\mathrm{H^+}]/[\mathrm{HA}] \tag{2.1}$$

In practice, following the analogous use of pH, it is more convenient to use the negative logarithm of K_a, the so-called acidity index pK_a:

$$\mathrm{p}K_a = -\log K_a = -\log[\mathrm{A^-}] - \log[\mathrm{H^+}] + \log[\mathrm{HA}]$$

as the value of $-\log[\mathrm{H^+}] = \mathrm{pH}$, then:

$$\mathrm{p}K_a = \log\{[\mathrm{HA}]/[\mathrm{A^-}]\} + \mathrm{pH} \tag{2.2}$$

It is clear from Equation (2.2) that the value of the pK_a is equal to the value of the pH when the nondissociated acid (HA) content and the anion ($\mathrm{A^-}$) content are equal, that is, when the degree of dissociation is 50%.

We see that the stronger the acid, the greater the numerator and, consequently, the larger the K_a value; a larger K_a value corresponds to a smaller pK_a. Vice versa, in a series of compounds, the pK_a increases as the acidity decreases. It should be emphasized that pK_a values, which are essentially acid ionization constants, are also employed for the measurement of basicity. As a consequence of the reversibility of the dissociation process, any acid which donates its proton is thus converted to the conjugate base; similarly, a base which accepts a proton becomes the conjugate acid. Stronger acids obviously correspond to weaker conjugate bases and vice versa. Thus, for bases, the order of the pK_a changes in the opposite sense: the larger the pK_a of the conjugate acid, the stronger the base, and the weaker bases have correspondingly lower pK_a values.

The acid dissociations of pyrrole and imidazole (Figure 2.2a) are used as an example. The corresponding pK_a values are 17.5 and 14.2, respectively.[1] As pK_a is a logarithmic scale, pyrrole is a weaker acid than imidazole by a factor of $10^{3.3}$ (i.e., by a factor of 2000). This also indicates that the pyrrole anion is a stronger base than the imidazole anion by the same factor.

Whereas both pyrrole and imidazole are very weak acids, some heterocycles have pK_a values close to those of conventional acids. Tetrazole (Figure 1.5) has a pK_a of 4.89, almost equal to that of acetic acid (pK_a 4.76).

Under ordinary conditions a neutral pyrrole-like nitrogen is unlikely to add a proton because of the tendency to preserve the aromaticity of the heterocycle. In contrast, the lone electron pair of

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[1] Standardized conditions must be used for the determination of ionization constants as the latter depend on solvent and temperature. The pK_a values given here were determined in aqueous solutions at 20 °C.