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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

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.

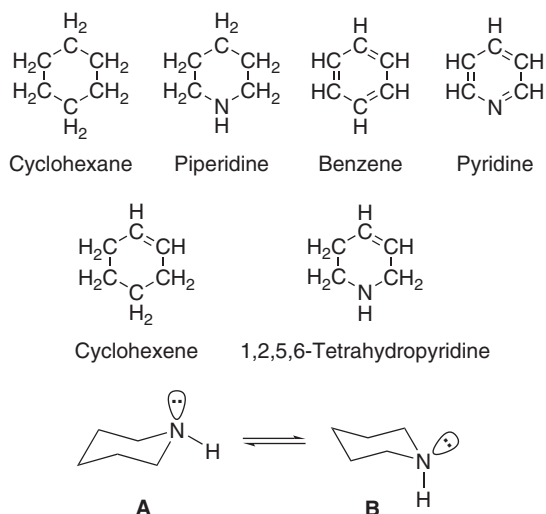


Figure 1.1 The relationship between cyclic hydrocarbons and heterocycles and the two chair conformations of piperidine.

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 ($109^\circ 28'$) 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).

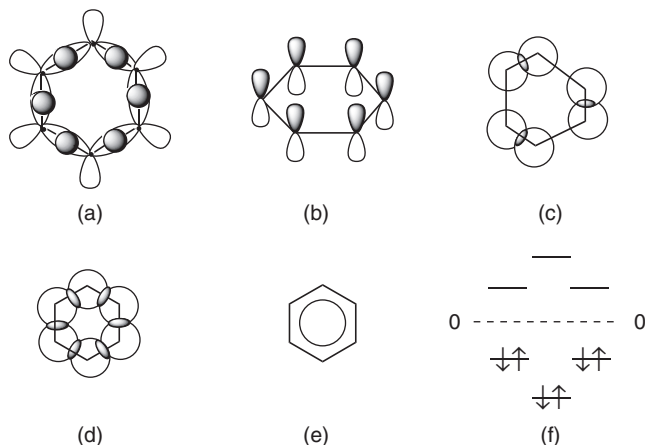


Figure 1.2 The electronic structure of the benzene molecule: (a) framework of σ -bonds, (b) p -orbital orientation, (c) overlap of p -orbitals forming localized π -bonds (view from above), (d) overlap of p -orbitals forming delocalized π -bonds, (e) representation of the benzene ring reflecting the equivalence 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).

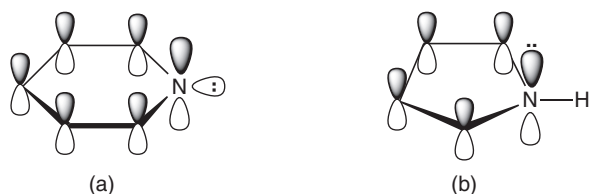


Figure 1.3 The orientation of π -electron orbitals and unshared electron pairs in (a) pyridine and (b) pyrrole (C–H bonds are omitted).

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’.

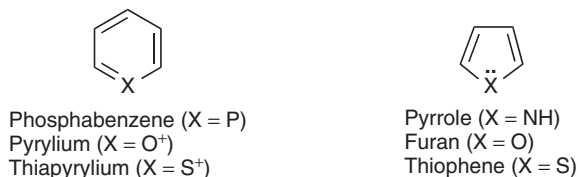


Figure 1.4 Examples of heterocycles with pyridine-like and pyrrole-like heteroatoms.

Formally, pentagonal aromatic heterocycles can also be derived from benzene by a heteroatom taking the place of one complete $\text{CH}=\text{CH}$ 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*.

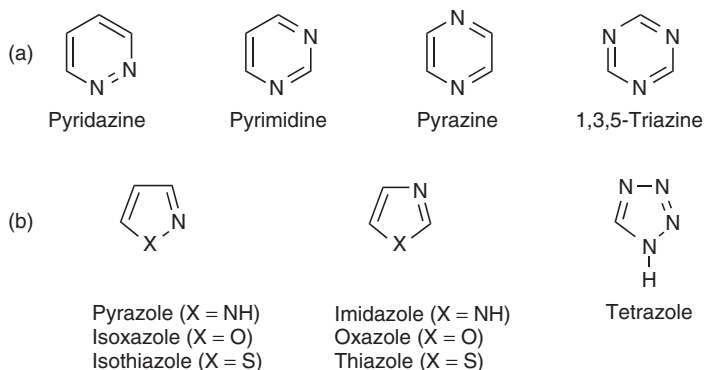


Figure 1.5 Heterocycles of (a) the azine class and (b) the azole class.

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.

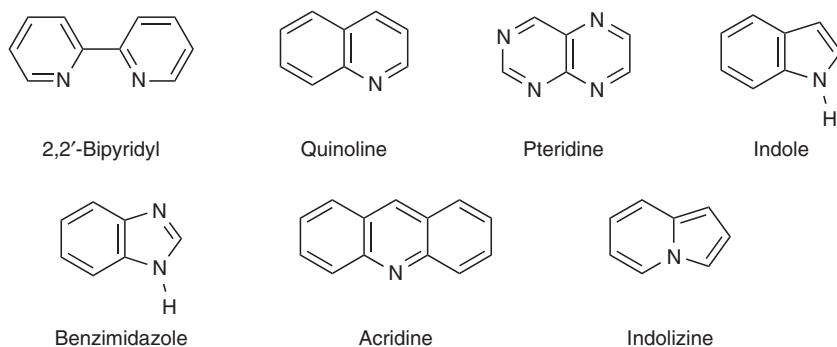


Figure 1.6 Examples of bi- and polycyclic heterocycles.

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.

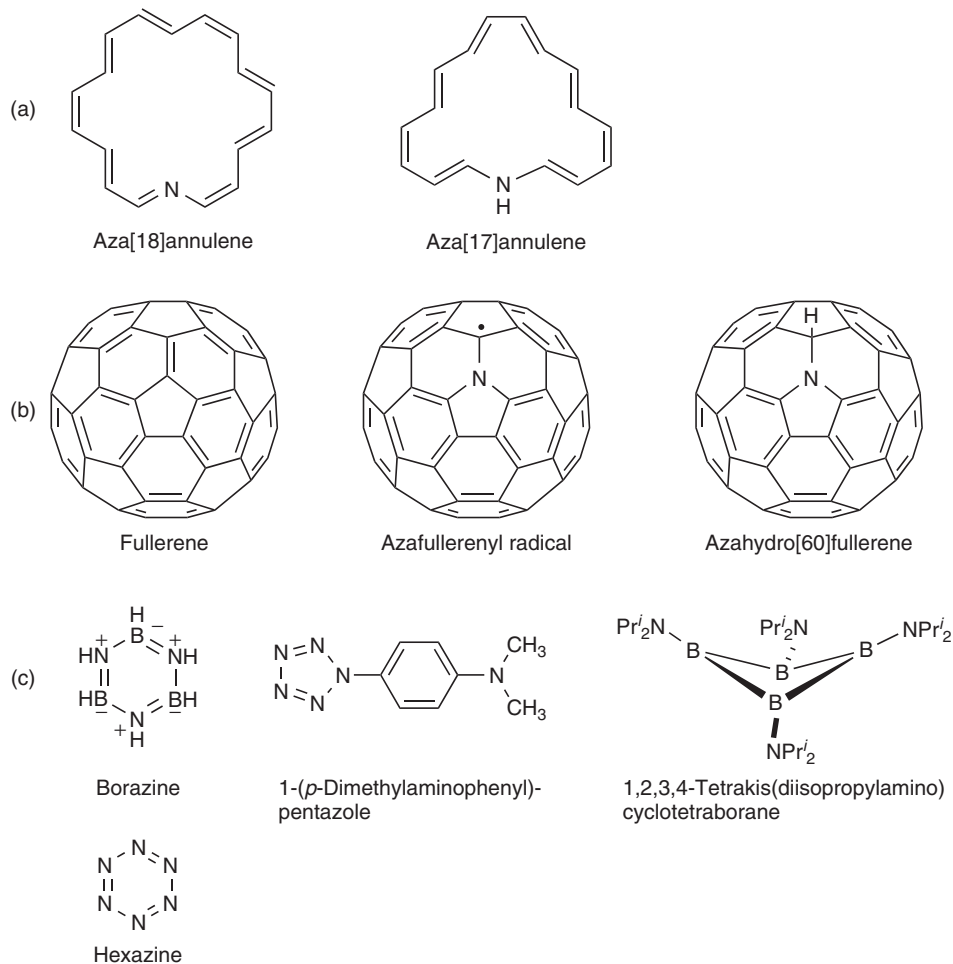


Figure 1.7 Examples of (a) macroheterocycles, (b) azafullerenes and (c) rings without cyclic carbon atoms.

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

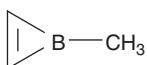
azafullerenes. The valence rules determine that, at the introduction of one nitrogen atom into the fullerene molecule C_{60} , the free radical specie $C_{59}N^{\bullet}$ should be produced. Its stabilization can be achieved either via dimerization into 2,2'-biaza[60]fullerene $(C_{59}N)_2$ or by means of hydrogen atom addition leading to green azahydro[60]fullerene $C_{59}NH$ (Figure 1.7b). Carbon nanotubes containing nitrogen or boron heteroatoms 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)cyclotetaborane 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: $N_6 \rightarrow 3N_2$.

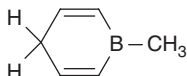
Of course, the examples given above by far do not cover all of the heterocyclic systems possible. In the following chapters we will become acquainted with many new ones.

1.4 Problems

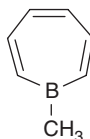
- How many chair conformations are possible for unsubstituted piperidine? How many for a 1,4-disubstituted piperidine? Draw their structures.
- The boat conformation for saturated six-membered rings is energetically unfavorable. Account for this fact. Design the structure of a substituted piperidine in which the boat conformation is fixed.
- 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.
- Indicate which of the heterocycles listed below can be formally regarded as aromatic. Explain your choices.



(a)



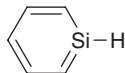
(b)



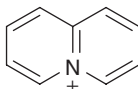
(c)



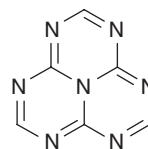
(d)



(e)



(f)



(g)

- 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.
- Draw all of the possible isomeric imidazopyridines, that is, the heterocycles which consist of fused pyridine and imidazole nuclei.
- 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.
- The relative stability (aromaticity) of five-membered heterocycles is changed in the following sequence: thiophene > pyrrole > furan. How this can be explained?
- 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

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