The Chemistry of Heterocycles

Structure, Reactions, Syntheses, and Applications

Mohammad Jafarzadeh

Faculty of Chemistry, Razi University

The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

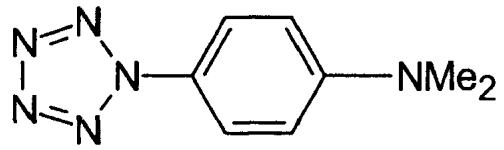
1. The Structure of Heterocyclic Compounds

- Molecules are defined by the type and number of atoms as well as by the covalent bonding within them. There are two main types of structure:

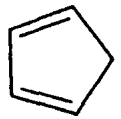
— The atoms form a chain - aliphatic (acyclic) compounds

— The atoms form a ring - cyclic compounds

Cyclic compounds in which the ring is made up of atoms of one element only are called ***isocyclic*** compounds. If the ring consists of C-atoms only, then we speak of a **carbocyclic** compound, e.g.:



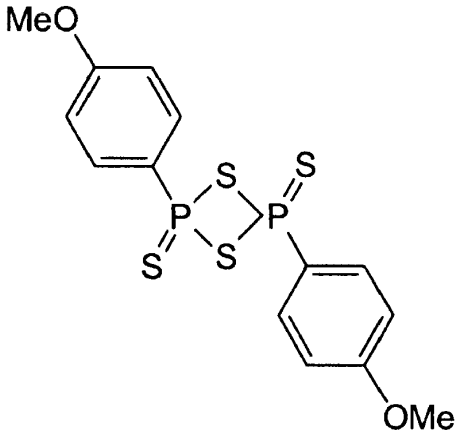
(4 - dimethylaminophenyl) pentazole
isocyclic



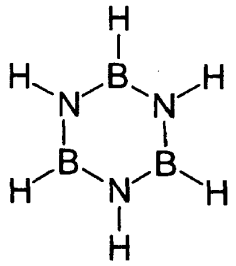
cyclopenta - 1,3 - diene
isocyclic und carbocyclic

Cyclic compounds with at least two different atoms in the ring (as ring atoms or members of the ring) are known as heterocyclic compounds. The ring itself is called a heterocycle.

If the ring contains no C-atom, then we speak of an **inorganic heterocycle**, e.g.:

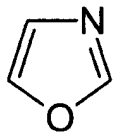


2,4 - bis (4 - methoxyphenyl) -
1,3 - dithiadiphosphetan -2,4 - disulfide
(Lawesson - Reagent)

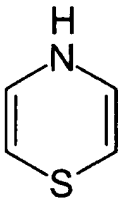


borazine

If at least one ring atom is a C-atom, then the molecule is an **organic heterocyclic compound**. In this case, all the ring atoms which are not carbon are called **heteroatoms**, e.g.:



oxazole
heteroatoms O and N



4 - *H* - 1,4 - thiazine
heteroatoms S and N

In principle, all elements except the alkali metals can act as ring atoms.

Along with the type of ring atoms, their total number is important since this determines the ring size.

The smallest possible ring is three-membered. The most important rings are the five- and six-membered heterocycles. There is no upper limit; there exist seven-, eight-, nine- and larger-membered heterocycles.

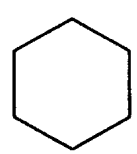
Although inorganic heterocycles have been synthesized, this book limits itself to organic compounds. In these, the N-atom is the most common heteroatom. Next in importance are O- and S-atoms.

Heterocycles with Se-, Te-, P-, As-, Sb-, Bi-, Si-, Ge-, Sn-, Pb- or B-atoms are less common.

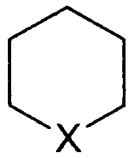
To determine the stability and reactivity of heterocyclic compounds, it is useful to compare them with their carbocyclic analogues. Heterocycles derive from a carbocyclic compound by replacing appropriate CH_2 or CH groups by heteroatoms.

Monocyclic systems can distinguish four types of heterocycles as follows:

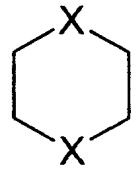
• Saturated heterocycles (heterocycloalkanes)



cyclohexane



X = O oxane
X = S thiane
X = NH piperidine

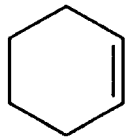


X = O 1,4 - dioxane
X = S 1,4 - dithiane
X = NH piperazine

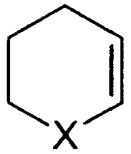
In this category, there are no multiple bonds between the ring atoms.

The compounds react largely like their aliphatic analogues, e.g. oxane (tetrahydropyran) and dioxane behave like dialkyl ethers, thiane and 1,4-dithiane like dialkyl sulfides, and piperidine and piperazine like secondary aliphatic amines.

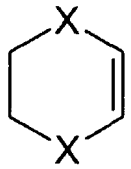
• Partially unsaturated systems (heterocycloalkenes)



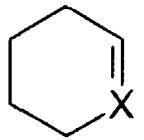
cyclohexene



X = O 3,4 - dihydro - 2*H* - pyran
X = S
X = NH



X = O 3,4 - dihydro - 1,4 - dioxin
X = S
X = NH



X = $O^{\oplus}$
X = $S^{\oplus}$
X = NH 2,3,4,5 - tetrahydropyridine

If the multiple bonds are between two C-atoms of the ring, for instance, in 3,4-dihydro-2*H*-pyran, the compounds react essentially like alkenes or alkynes.

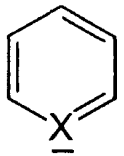
The heteroatom can also be involved in a double bond. In the case of X = O^+, the compounds behave like oxenium salts, in the case of X = S^+, like sulfenium salts, and in the case of X = N, like imines (azomethines).

• Systems with the greatest possible number of noncumulated double bonds (heteroannulenes)

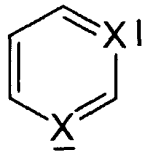
Annulenes derive two types of heterocycles:

— systems of the same ring size, if CH is replaced by X
— systems of the next lower ring size, if HC=CH is replaced by X.

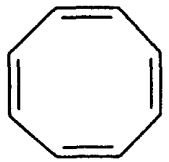
[6]annulene
benzene



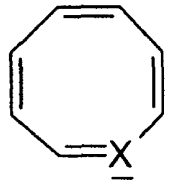
X = $O^{\oplus}$ pyryliumsalts
X = $S^{\oplus}$ thiiniumsalts
X = N pyridine,
pyridine-like N - atom



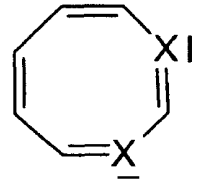
X = N pyrimidine



[8]annulene
cyclooctatetraene

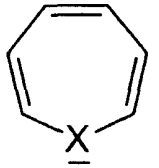


X = $O^{\oplus}$
X = $S^{\oplus}$
X = N azocine



X = N 1,3 - diazocine

X = O furan
X = S thiophene
X = NH pyrrole,
pyrrole-like N - atom



X = O oxepine
X = S thiepine
X = NH azepine

In both cases, the resulting heterocycles are iso-π-electronic with the corresponding annulenes, i.e. the number of π-electrons in the ring is the same.

This is because in the pyrylium and thiinium salts, as well as in pyridine, pyrimidine, azocine and 1,3-diazocine, each heteroatom donates one electron pair to the conjugated system and its nonbonding electron pair does not contribute.

However, with furan, thiophene, pyrrole, oxepin, thiepin and azepine, one electron pair of the heteroatom is incorporated into the conjugated system (delocalization of the electrons).

Where nitrogen is the heteroatom, this difference can be expressed by the designation *pyridine-like N-atom* or *pyrrole-like N-atom*.

• **Heteroaromatic systems**

This includes heteroannulenes, which comply with the HÜCKEL rule, i.e. which possess (4n+2) π-electrons delocalized over the ring. The most important group of these compounds derives from [6]annulene (benzene). They are known as heteroarenes, e.g. furan, thiophene, pyrrole, pyridine, and the pyrylium and thiinium ions.

As regards stability and reactivity, they can be compared to the corresponding benzenoid compounds.

The antiaromatic systems, i.e. systems possessing 4n delocalized electrons, e.g. oxepin, azepine, thiepin, azocine, and 1,3-diazocine, as well as the corresponding annulenes, are, by contrast, much less stable and very reactive.

The classification of heterocycles as heterocycloalkanes, heterocycloalkenes, heteroannulenes and heteroaromatics allows an estimation of their stability and reactivity.

In some cases, this can also be applied to inorganic heterocycles. For instance, borazine, a colourless liquid, bp 55 °C, is classified as a heteroaromatic system.