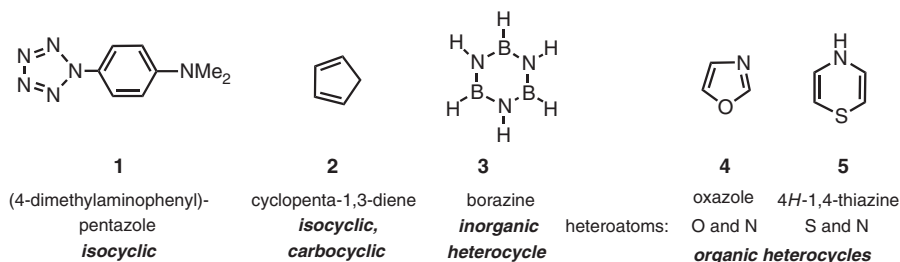


1 The Structure of Heterocyclic Compounds

Most chemical compounds consist of molecules. The classification of such chemical compounds is based on the structure of these molecules, which is 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*, for example, 1. If the ring consists of C-atoms only, then we speak of a *carbocyclic compound*, for example, 2. 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*, for example, 3. If at least one ring atom is a C-atom, then the molecule is an *organic heterocyclic compound*, for example, 4. In this case, all the ring atoms which are not carbon are called *heteroatoms*.



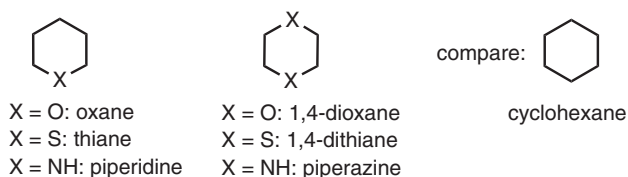
Along with the type of ring atoms, their total number is important, since this determines the ring size. The smallest possible ring is three-membered. The most important rings are the five- and six-membered heterocycles. There is no upper limit; there exist seven-, eight-, nine-, and larger-membered heterocycles.

In principle, all elements except the alkali metals can act as ring atoms. Although inorganic heterocycles have been synthesized, this book limits itself to organic ones. 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.

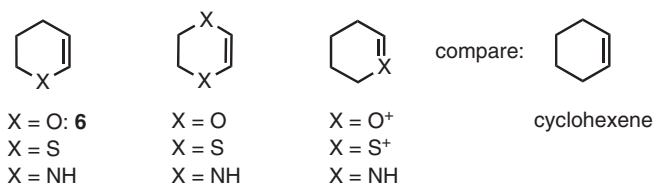
To determine the stability and reactivity of heterocyclic compounds, it is useful to compare them with their carbocyclic analogs. In principle, it is possible to derive every heterocycle from a carbocyclic compound by replacing appropriate CH₂ or CH groups by heteroatoms. If one limits oneself to monocyclic systems, one can distinguish four types of heterocycles as follows:

(1) Saturated heterocycles (heterocycloalkanes), e.g.



In this category, there are no multiple bonds between the ring atoms. The compounds react largely like their aliphatic analogs, for example, oxane (tetrahydropyran) and dioxane behave like dialkyl ethers, thiane and 1,4-dithiane like dialkyl sulfides, and piperidine and piperazine like secondary aliphatic amines.

(2) Partially unsaturated systems (heterocycloalkenes), e.g.

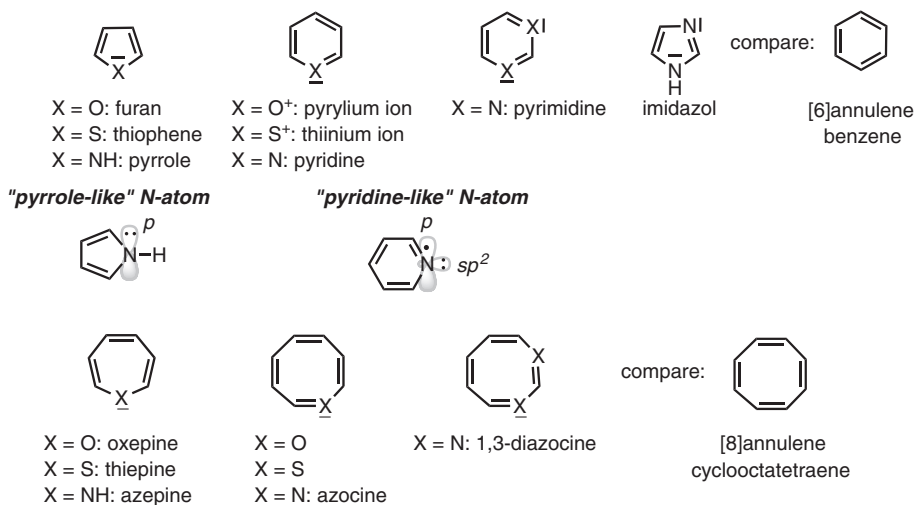


If the multiple bonds are between two C-atoms of the ring, as, for instance, in 3,4-dihydro-2*H*-pyran (**6**), the compounds react essentially like alkenes or alkynes, enolethers, enamines, and so on. The heteroatom can also be part of a double bond. In the case of X = O⁺, the compounds behave like oxenium salts, in the case of X = S⁺ like sulfenium salts, and in the case of X = N like imines (azomethines).

(3) Systems with the greatest possible number of noncumulated double bonds (heteroannulenes), e.g.

From the annulenes, one can formally 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.



In both cases, the resulting heterocycles are iso- π -electronic with the corresponding annulenes, that is, 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* 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*. In imidazole both types can be found.

(4) Heteroaromatic systems

This includes heteroannulenes, which comply with the HÜCKEL rule, that is, 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*, for example, furan, thiophene, pyrrole, pyridine, and the pyrylium and thiinium ions. As regards stability and reactivity, they can be compared to the corresponding benzenoid compounds [1a–d].

The antiaromatic systems, that is, systems possessing $4n$ delocalized electrons, for example, oxepine, azepine, thiepine, 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 (3), a colorless liquid, bp 55 °C, is classified as a heteroaromatic system.

Reference

1. (a) von Rague Schleyer, P. and Jiao, H. (1996) *Pure Appl. Chem.*, **68**, 209; (b) von Rague Schleyer, P. and Jiao, H. (2001) *Chem. Rev.*, **101**, 1115; (c) Bird, C.W. (1998) *Tetrahedron*, **54**, 10179; (d) Krygowski, T.M., Cyranski, M.K., Czarnocki, Z., Häfelinger, G., and Katritzky, A.R. (2000) *Tetrahedron*, **56**, 1783.