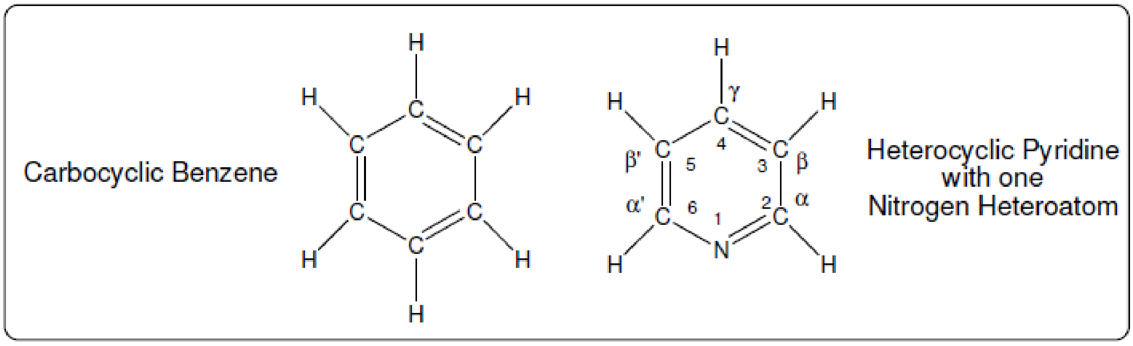
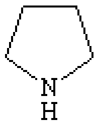
An Introduction to Heterocyclic Chemistry

Cyclic compound having only carbons as the ring members, such as benzene are called carbocyclic compounds. As only carbon forms the backbone of the ring, it is also a homocyclic compound.

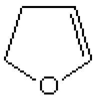
In contrast, cyclic compounds having at least one atom other than carbon as ring members, (e.g. Pyridine with nitrogen replacing one of the carbon atom) may be termed as heterocyclic compounds. These atoms are termed as heteroatoms. The structure of benzene and pyridine are provided in the figure below.



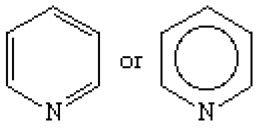
Some examples are:-



pyrrolidine



4,5-dihydrofuran



pyridine

The most common heterocycles are those having five- or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. A molecule of pyridine contains a ring of six atoms—five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively.

Uses and Importances

Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics.

Pyridine and pyrrole are both nitrogen heterocycles—their molecules contain nitrogen atoms along with carbon atoms in the rings. The molecules of many biological materials consist in part of pyridine and pyrrole rings, and such materials yield small amounts of pyridine and pyrrole upon strong heating. In fact, both of these substances were discovered in the 1850s in an oily mixture formed by strong heating of bones. Today, pyridine and pyrrole are prepared by synthetic reactions. Their chief commercial interest lies in their conversion to other substances, chiefly dyestuffs and drugs. Pyridine is used also as a solvent, a waterproofing agent, a rubber additive, an alcohol denaturant, and a dyeing adjunct.

Furan is an oxygen-containing heterocycle employed primarily for conversion to other substances (including pyrrole). Furfural, a close chemical relative of furan, is obtained from oat hulls and corncobs and is used in the production of intermediates for nylon. Thiophene, a sulfur heterocycle, resembles benzene in its chemical and physical properties. It is a frequent contaminant of the benzene obtained from natural sources and was first discovered during the purification of benzene. Like the other compounds, it is used primarily for conversion to other substances. Furan and thiophene were both discovered in the latter part of the 19th century.

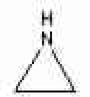
Nomenclature

Naming heterocyclic compounds is complicated because of the existence of many common names in addition to the internationally agreed-upon systematic nomenclature. (A brief account of systematic nomenclature is given here; for more information, *see below* Major classes of heterocyclic compounds.)

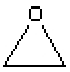
The types of heteroatoms present in a ring are indicated by prefixes; in particular, oxa-, thia-, and aza- denote oxygen, sulfur, and nitrogen atoms, respectively. The numbers of heteroatoms of a particular kind are indicated by number prefixes joined to the heteroatom prefixes, as dioxa- and triaza-. The presence of different kinds of heteroatoms is indicated by combining the above prefixes, using the following order of preference: oxa- first, followed by thia- and then aza-.

In addition, partially saturated rings are indicated by the prefixes dihydro-, tetrahydro-, and so on, according to the number of “extra” hydrogen atoms bonded to the ring atoms. The positions of heteroatoms, extra hydrogen atoms, and substituents are indicated by Arabic numerals, for which the numbering starts at an oxygen atom, if one is present, or at a sulfur or nitrogen atom and continues in such a way that the heteroatoms are assigned the lowest possible numbers. Other things being equal, numbering starts at a nitrogen atom that carries a substituent rather than at a multiply bonded nitrogen. In compounds with maximum unsaturation, if the double bonds can be arranged in more than one way, their positions are defined by indicating the nitrogen or carbon atoms that are not multiply bonded and that consequently carry an extra hydrogen atom (or substituent), as follows: 1*H*-, 2*H*-, and so on.

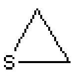
3-membered rings



Aziridine

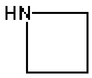


Ethylene Oxide, Oxirane

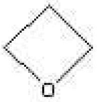


Ethylene Sulfide, Thiirane

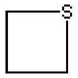
4-membered rings



Trimethylene Imine,
Azetidine

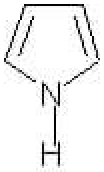


1,3-Epoxypropane, Oxetane

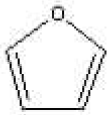


Trimethylene Sulfide,
Thietane

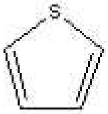
5-membered rings



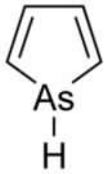
Pyrrole



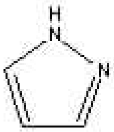
Furan



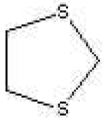
Thiophene



Arsole

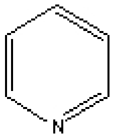


1,2-Diazole, Pyrazole

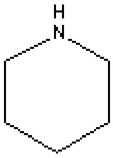


1,3-Dithiolane

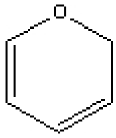
6-membered rings



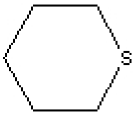
Pyridine



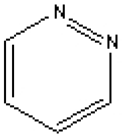
Piperidine



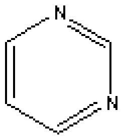
Pyran



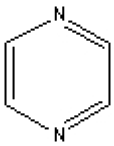
Tetrahydrothiopyran, Thiane



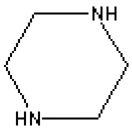
1,2-Diazine, Pyridazine



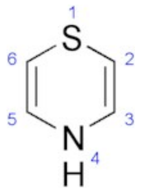
1,3-Diazine, Pyrimidine



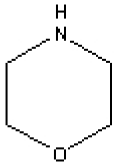
1,4-Diazine,
Pyrazine



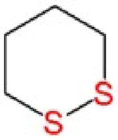
Piperazine



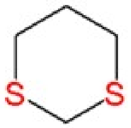
Thiazine



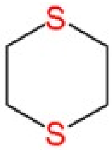
Morpholine, Oxazine



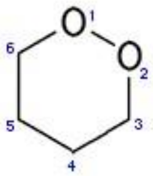
1,2-dithiane



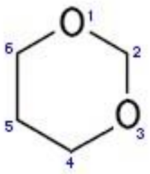
1,3-dithiane



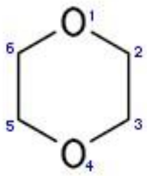
1,4-dithiane



1,2-dioxane



1,3-dioxane



1,4-dioxane

The Nature Of Heteroaromaticity

Aromaticity denotes the significant stabilization of a ring compound by a system of alternating single and double bonds—called a cyclic conjugated system—in which six π electrons generally participate. A nitrogen atom in a ring can carry a positive or a negative charge, or it can be in the neutral form. An oxygen or sulfur atom in a ring can either be in the neutral form or carry a positive charge. A fundamental distinction is usually made between (1) those heteroatoms that participate in a cyclic conjugated system by means of a lone, or unshared, pair of electrons that are in an orbital perpendicular to the plane of the ring and (2) those heteroatoms that do so because they are connected to another atom by means of a double bond.

An example of an atom of the first type is the nitrogen atom in pyrrole, which is linked by single covalent bonds to two carbon atoms and one hydrogen atom. Nitrogen has an outermost shell of five electrons, three of which can enter into three covalent bonds with other atoms. After the bonds are formed, as in the case of pyrrole, there remains an unshared electron pair that can engage in cyclic conjugation. The aromatic sextet in pyrrole is made up of two electrons from each of the two carbon-carbon double bonds and the two electrons that compose the unshared electron pair of the nitrogen atom. As a consequence, there tends to be a net flow of electron density from the nitrogen atom to the carbon atoms as the nitrogen's electrons are drawn into the aromatic sextet. Alternatively, the pyrrole molecule may be described as a resonance hybrid—that is, a molecule whose true structure can only be approximated by two or more different forms, called resonance forms.

An example of a heteroatom of the second type is the nitrogen atom in pyridine, which is linked by covalent bonds to only two carbon atoms. Pyridine also has a π-electron sextet, but the nitrogen atom contributes only one electron to it, one additional electron being contributed by each of the five carbon atoms in the ring. In particular, the unshared electron pair of the nitrogen atom is not involved.

Moreover, because nitrogen’s attraction for electrons (its electronegativity) is greater than that of carbon, electrons tend to move toward the nitrogen atom rather than away from it, as in pyrrole.

Chemical reactivity can provide a certain qualitative insight into aromaticity. The reactivity of an aromatic compound is affected by the extra stability of the conjugated system that it contains; the extra stability in turn determines the tendency of the compound to react by substitution of hydrogen—i.e., replacement of a singly bonded hydrogen atom with another singly bonded atom or group—rather than by addition of one or more atoms to the molecule via the breaking of a double bond (*see* substitution reaction; addition reaction). In terms of reactivity, therefore, the degree of aromaticity is measured by the relative tendency toward substitution rather than addition. By this criterion, pyridine is more aromatic than furan, but it is difficult to say just how much more aromatic.

Reactivity order

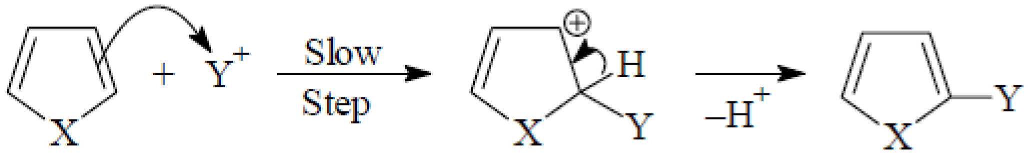
These compounds Furan, Pyrrole and Thiophene are certainly more reactive than Benzene. Out of these, Pyrrole being most aromatic, followed by Furan. Furan is comparatively less reactive because O-atom (in Furan) can accommodate a positive charge less readily at N-atom (in Pyrrole).
Thiophene is being followed by these two and is least reactive. It is so because +M-effect of sulphur is weaker than that of oxygen because overlap of 2p-orbitals of carbon and 3-p orbitals of sulphur is less than 2p -orbitals of C and O -atoms.
That's why order of reactivity is something like that, as you mentioned.
Pyrrole>Furan> Thiophene>Benzene.

In case of reactivity order, you have to see first how much stability is lost due to attaining of the T.S. The electronegativity order, is, S<N<O, so the +R effect will be S>N>O, and the resonance stabilisation(which is shown by their resonance energy)by the heteroatom in the compounds will be like this,Thiophene(29Kcal/mol)>Pyrrole(21Kcal/mol)>Furan(17Kcal/mol). In case of thiophene, p to d π-back bonding and lack of ring strain due to longer C-S bond also plays a factor in its stability.

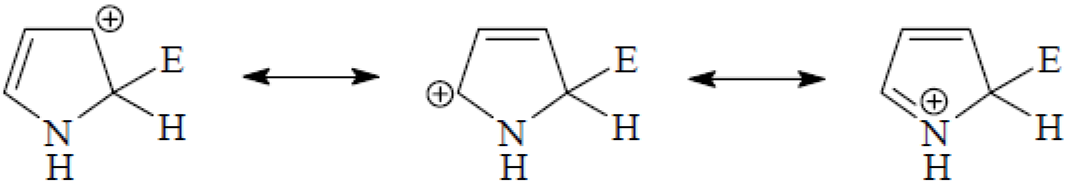
So, when they reach the transition state, this stability is nearly all lost due to lack of resonance in the T.S. Obviously, the greater the loss in stability the weaker would be its tendency to react due to the greater value of the activation energy.

Reactivity order of Pyrrole, Furan and Thiophene towards Electrophilic substitution:

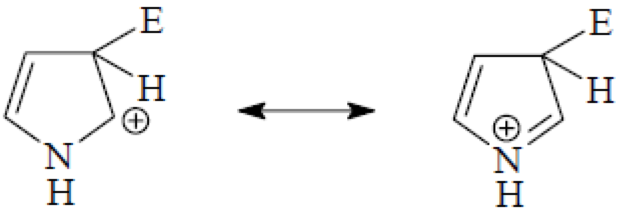
Pyrrole, furan and thiophene undergo electrophilic substitution reactions like nitration, sulphonation, halogenation etc. characteristic of aromatic rings. That carbons in 5-membered heterocyclic rings have higher electron density compared to benzene and hence undergo electrophilic substitution more readily than benzene. Electrophilic substitution takes place preferentially at 2-position (C-2).



The attack of an electrophile on pyrrole, for example, will lead to formation of 2- and 3-substitution products by way of carbocations **(1)** and **(2)** respectively. The substitution occurs preferably at C-2 position because the intermediate obtained by attack at this position is more stable than the intermediate obtained by attack at C-3. The positive charge in intermediate **(1)** is more delocalized than intermediate **(2)** and hence is more stable and preferred intermediate.



(1)



(2)

The electrophilic substitution at C-2 in furan and thiophene can also be accounted in the same manner. Furan is not as reactive as pyrrole in electrophilic substitution reactions because the oxygen in furan is more electronegative than nitrogen in pyrrole and therefore does not enhance the electron density of carbons as much as pyrrole. Thiophene is less reactive than furan towards electrophilic substitution because the p-electrons of sulphur are in 3p orbital which overlaps less effectively than the 2p orbital of nitrogen or oxygen with 2p orbitals of carbon. The relative reactivities towards electrophilic substitution follows the order: