



## Does Nature Prefer Heterocycles?

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Heterocycles make up an exceedingly important class of compounds. In fact more than half of all known organic compounds are heterocycles. Many natural drugs such as quinine, papaverine, emetine, theophylline, atropine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature.

All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, 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, such as vitamins, enzymes, coenzymes, ATP, DNA, RNA and serotonin. Why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, 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 a great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned above are good examples of nature's preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above-mentioned properties.

The following is a good example of how man learnt to imitate nature by incorporating heterocycles into drug molecules to enhance their biological activity: Red sulfanilamide and the less toxic white sulfanilamide (second generation) were the first sulfa drugs, and these contained no heterocyclic fragments. However, the intensive research work that followed their discovery demonstrated that modification of the p-aminobenzenesulfonamide structure by the introduction of heterocyclic substituents into the amide markedly enhanced their biological activity. Many derivatives of this type, including the well-known sulfathiazole, sulfadimidine, sulfadimethoxine and others, were gradually introduced into clinical treatment. Sulfa drugs are highly efficient against many bacterial species and against some protozoa. Gastrointestinal infections, meningitis, tuberculosis, scarlet fever and other diseases have been successfully treated by such preparations. With the passage of time, however, the increasing evidence of clinical toxicity of these drugs has led to a diminution in their use, and they have been replaced by penicillins, cephalosporins and, more recently, quinolone drugs which are all heterocyclic in structure.

The role played by the heterocycle imidazole in the interaction of enzymes with substrates is perhaps the most illustrative example of the importance of heterocycles in biochemical systems.

Let's consider this:

The histidine residue is a constituent of the active site in many enzymes. The imidazole ring of histidine has a series of unique properties, enabling it to show catalytic activity. Firstly, the rather high basicity enables histidine both to form strong hydrogen bonds and also to abstract a proton from the acidic groups, such as the OH group of water and alcohols. Since an RO<sup>-</sup> anion is a much stronger nucleophile than a neutral ROH molecule, the imidazole ring can catalyze a nucleophilic addition to a carbonyl group.

In a living organism, this type of catalysis is represented by the hydrolytic cleavage of protein amide bonds. The participating enzymes are called proteases. Histidine and serine residues are constituents of the protease chymotrypsin. The following is a simplified mechanism for the action of chymotrypsin. Within the enzyme, the imidazole ring of a histidine and the hydroxy group of a serine are bound by hydrogen bonding. When a protein molecule approaches, the imidazole nitrogen abstracts a proton from the OH group, thus activating the serine oxygen atom towards attack at the carbonyl carbon atom in the polypeptide. The unstable activated complex is called an "enzyme-substrate complex". Further conversion brings about cleavage of the amide bond and acylation of the enzyme at its' hydroxy group. By an analogous catalytic mechanism, subsequent hydrolysis of the ester bond occurs with elimination of acid (RCO<sub>2</sub>H) and regeneration of the enzyme.

The imidazole ring in chymotrypsin functions in an amphoteric manner, i.e., both as an NH acid and a base. Significantly, the basicity of histidine is such that it exists 50% as the neutral form and 50% as the imidazolium cation at the physiological pH of 7.4.

In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, pesticides, herbicides and drugs do not necessarily have to be heterocyclic in structure. In a similar fashion there are many common features in chemistry and physics between such related compounds as pyrrole and aniline, or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine, and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: the introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems.

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