

## Molecular Modeling: a Tool to Understand Reactivity of Heterocyclic Compounds Effectively

**Rupa Madyal**

Chemistry Department, S.I.W.S. College (India)  
[rupamadyal@gmail.com](mailto:rupamadyal@gmail.com)

### Abstract

'Heterocyclic chemistry' is one of the important topics in organic chemistry that are integral to any chemistry syllabus as, heterocycles make up an exceedingly important class of compounds and have a wide range of applications. They are of particular interest in medicinal chemistry as drugs and most vitamins. Many pigments and dyestuff have heterocyclic structure. Almost all the organic compounds we know are heterocycles.

The students are oblivious to the physical aspects of chemical reactions, i.e. orientation of molecules and transfer of electrons during the course of a reaction. Due to enormous diversity of structures it is difficult for the students to understand reactivity; as a consequence, students resort to memorization.

Thinking about structures in three dimensions help students to enhance their understanding of structure and reactivity of heterocyclic compounds. This paper is aimed to teach the fundamental reactivity of heterocycles to the undergraduate and post graduate students using Molecular Modeling (MM), which is computer based method. MM helps student to understand the change in the reactivity by structural variations by analysing sophisticated structural details. Visualization of geometry, orientation, atomic charge, electrostatic isosurface, etc. will be helpful in understanding theory and grasping concepts more effectively. This approach not only enhances learning reactions but also helps to hold student interest in learning difficult concepts in reaction mechanism presented in the lecture part of the course. Students can gain a more complete and correct understanding of structure, bonding and reactivity.

### 1. Introduction

Heterocyclic compounds are widely distributed in nature and this has catalyzed the discovery and development of much new heterocyclic chemistry and methods. They are used as agrochemicals, as pharmaceuticals, as optical brightening agents, as corrosion inhibitors, etc. [1] More than half of all known organic compounds are heterocycles. [2] Hence, it is imperative to have proper insight into this topic right since undergraduate level.

The idea of using Molecular Modeling (MM) is to supplement physical models which would help students to think about structures in three dimensions. Also, they would become acquainted with a technique which has many research applications and they would learn skills that would be applicable in higher-level courses. Students would develop the ability to create three-dimensional mental images. Since electron distribution affects molecular size, shape, bonding, stability, and reactivity, the introduction of computer-generated electron density models would help students to have a better understanding of the role that electronic structure plays in chemical phenomena. The combination of the classical theory with the molecular simulation can improve students' understanding about various chemistry principles and mechanisms as it unfolds a lot of interesting chemistry. [3] An additional advantage of this methodology is that it requires simple readily available software support.

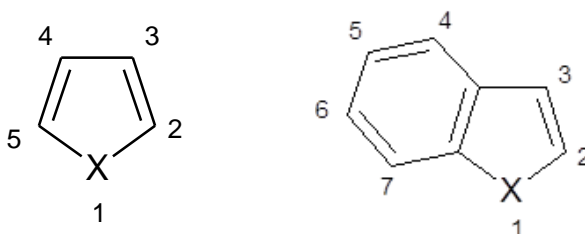
Based on my personal experience, the topic "Reactions of Heterocyclic Compounds" is somewhat challenging for a student to comprehend due to different heteroatom and their structural diversity. This paper undertakes a judicious use of five membered ring viz., pyrrole, furan and thiophene and their benzo fused analogues indole, benzofuran and benzothiophene, respectively, as a model study to demonstrate the potential of Molecular Modeling approach in prediction of electrophilic attack using electrostatic potentials maps.

## 2. Methodology

Many open softwares are freely available for geometry minimization (optimization) using approximate molecular mechanics and more accurate quantum mechanics equations. The selection of appropriate set of parameters decides the accuracy of the final structures. In the present work, all structures are optimized by Density Functional Theory (DFT) with double numerical polarization basis set and local density approximation (LDA) with VWN (Vosko, Wilk, Nusair) functional in Dmol<sup>3</sup> module of Material Studio Ver. 5.5 (Accelrys Inc.) software on a windows computer.

## 3. Results and discussion

According to Huckel's rule, pyrrole, furan and thiophene and their benzo fused analogues (Fig.1) are aromatic compounds as they satisfy  $(4n+2)$  rule and exhibit planarity. Chemical behaviour of heterocyclic compounds depends upon the electron distribution. Resonance structures are widely used to interpret the reactivity of heterocycles by locating electron density. The resonance structures of five membered heterocycles (Fig. 2) and their benzo fused analogues (Fig.3) indicate that heteroatom carries partial positive charge and carbon atoms carry partial negative charge. Experimentally, electrophilic substitution reaction in five membered heterocycles occurs preferentially at C2, whereas, their benzo-fused heterocycles prefers at C3. But resonance structures alone do not adequately explain the most likely positions of electrophilic attack.



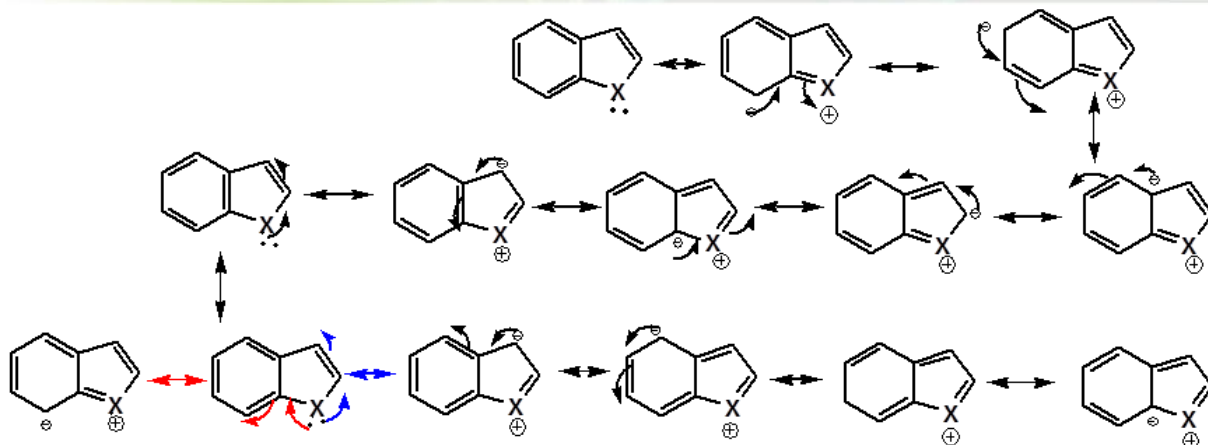
(Fig. 1 Five and six membered heterocycles where  $X = O, N$  and  $S$ )



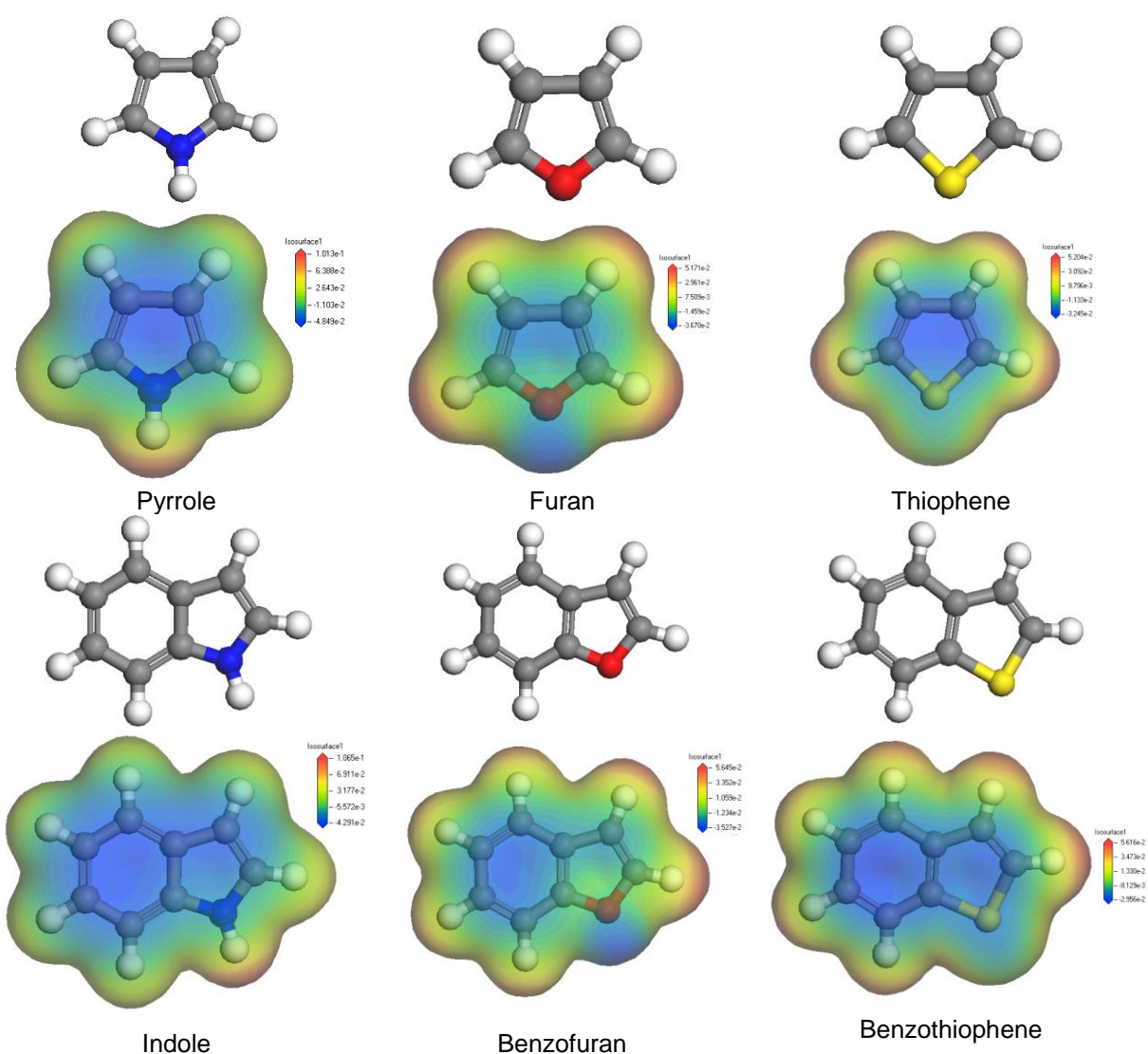
(Fig. 2 Resonance contributors of five membered heterocycles)

In order to discover reasons for their specific chemical behavior towards the electrophilic substitution reaction, one needs to choose the appropriate tool for validation of any molecules under study. Electrostatic potential (ESP) surface/map is a powerful color-coded tool which enables to visualize the charge distributions of molecules and anticipate sites of electrophilic/nucleophilic substitution. The comparative reactivity of heterocycles can be judged from the values of electrostatic potential which correctly captures the delocalized nature of electron density.[4] Electrostatic potential maps for polar molecules reveal blue colour for most electron-rich region and red colour for most electron-poor region as a user friendly visual aid. Systematic analysis of simulation results provides a clear understanding as how a molecule will react. [5]

Minimized structures of heterocycles and their electrostatic potential maps are shown in Fig.4. From the potential maps it can be seen that the pyrrole ring is more electron rich than the furan ring, which



(Fig. 3 Resonance contributors of five membered benzo-fused heterocycles)



(Fig. 4 Optimized structures of heterocycles and their electrostatic potential surfaces at LDA-VWN Level of Theory)

in turn is more electron rich than the thiophene ring. The similar trend is followed by their benzo fused analogues.

Calculated ESP charges at LDA-VWN level of theory on each atom are listed in Table 1. According to charge analysis, for pyrrole and thiophene, position 2 is preferred, whereas, in case of furan, C3 is preferred for electrophilic attack as it has higher electron density compared to other carbon atoms. But according to literature, furan is expected to give electrophilic reaction at C2. This may be attributed to the higher electronegativity of oxygen which holds lone pair more tightly. Experimental results corroborate completely with present theoretical calculations based predictions. Furan being the only exception for the reasons mentioned above.

	Heteroatom 1	C2	C3	C4	C5	C6	C7
Pyrrole	-0.159	-0.221	-0.194	-0.194	-0.221		
Furan	-0.123	-0.073	-0.200	-0.200	-0.073		
Thiophene	0.095	-0.278	-0.149	-0.149	-0.278		
Indole	-0.472	-0.016	-0.516	-0.319	-0.180	-0.130	-0.359
Benzofuran	-0.265	-0.046	-0.533	-0.327	-0.174	-0.145	-0.327
Benzothiophene	0.017	-0.220	-0.439	-0.383	-0.038	-0.240	-0.177

Table 1, *Calculated ESP charges at LDA-VWN level of theory*

After calculations and visualization of maps, it is now easy to tell them apart. Electrophilic aromatic substitution reaction in indole, benzofuran and benzothiophene takes place on the five membered ring, specifically, at C3 position, because it is more reactive toward electrophilic aromatic substitution reaction by having higher electron density than the other carbon atoms in the ring. Thus, MM helps students not only to rely less on memorization for understanding reactions but also to get involved in the learning process.

It is very clear from the charge values and maps that highly electronegative 'C' atom in heterocycle is susceptible for electrophilic substitution reactions and less electronegative for nucleophilic substitution reactions. Students can compare the resonating structures shown in literature with the calculated charges and electrostatic potential maps.

#### 4. Conclusion

Molecular modeling approach would stimulate students' curiosity by enhancing clarity about geometry at the atomic and/or molecular level and would provide opportunity to visualize why and how transformations taking place in chemical reactions. Electronic charge distribution of the heterocycles and its influence on substitution reaction could be unequivocally established. Molecular modelling approach would help the students to understand basic mechanisms of organic reactions in an interesting way. Calculated values are in good agreement with experimental reactivity. It is now possible to correlate the positions of electrophilic/nucleophilic substitution in a number of heterocyclic compounds with the ESP charges. This approach adequately corroborates laboratory experiments with theory. It holds a potential to enable students to independently envisage and design a research project.

Students would engage themselves in such exercise to understand reactivity of a molecule in a better manner without mere memorization and would be able to figure out the chemical behavior of molecules hitherto unknown to them.

#### References

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