

# Preface

This volume of “Topics in Heterocyclic Chemistry” focuses on the aspects of structure, bonding and reactivity of heterocyclic systems. It aims at presenting a series of different state-of-the-art methods and concepts available in quantum mechanics and theoretical chemistry to probe these different important aspects of heterocyclic compounds.

In quantum chemistry, quantum mechanics is applied to problems in chemistry. An important goal in this field, among others, is to accurately solve the time-independent Schrödinger equation for molecular systems, yielding the different energy states of the system and the accompanying wave functions, from which all properties can be obtained. Unfortunately, this equation can only be solved exactly for one-electron systems; for many-electron systems, approximations have to be made. In recent decades, powerful and accurate methods have been developed. Accompanied by the ever-increasing power of computers and the availability of dedicated specialized software, accurate calculations of different properties of compounds of ever-increasing size can now be performed. These properties include, among others, molecular structures and energetics, such as reaction energies and activation barriers, both of importance to describe thermodynamic and kinetic aspects of a chemical reaction. This often requires the explicit treatment of the effect of the solvent, which can play a crucial role in determining chemical reactivity. Often, use is made of density functional theory methods, which, instead of the wave function, adopt the electron density as the basic quantity to describe all atomic and molecular properties. Another important aspect of quantum chemistry is that it serves as a source for the evaluation and computation of concepts. Chemistry has traditionally used and continues to use a series of powerful concepts in order to explain chemical behaviour. These concepts are not only invoked to provide rationalization, but they are also applied in a predictive manner. Already from the early days of quantum mechanics, a lot of attention has been devoted to the computation of these chemical concepts, which are often not experimentally measurable or, in quantum mechanical terms, correspond to non-observables. In this volume, attention will also be devoted to the use of a selected number of these concepts to rationalize the bonding and reactivity of heterocyclic compounds.

In the first chapter in this volume, Van Speybroeck et al. show how computational chemistry and molecular modelling, in synergy with experiment, can play an important role in the elucidation of various aspects related to the reactivity of aziridinium ions, important intermediates in the synthesis of functionalized amines and other nitrogen-containing organic compounds. This chapter focuses on the computation of ring strain and the role of the solvent, N- and C-substituents and nucleophile on the kinetics (through activation-free energies) of regio- and stereocontrolled ring opening of the aziridinium ions. Density functional theory-based reactivity descriptors are introduced to probe the regio- and stereochemical preferences in the ring-opening reaction. These reactivity descriptors are discussed in more detail by Morell et al. in the subsequent chapter, paying attention, among others, to the intricacies of the less frequently used selectivity descriptors for excited states. In addition, these authors describe their application, in particular of the so-called dual descriptor, to a very important series of heterocyclic ring systems, DNA bases. It is investigated how both global and local DFT-based reactivity indices can provide insights into the occurrence and formation mechanisms of DNA lesions.

The role of the electron density as a central quantity in density functional theory is already emphasized in the above chapters. However, the analysis of the topology of this function has been proven to also give important insights into the structure, bonding and reactivity. This approach is the central topic in the chapter of Popelier et al., focusing in detail on the characterization of five-membered heterocyclic ring systems through the theory of quantum chemical topology (QCT). After a short tour d'horizon of QCT, the authors show that ring atom properties can be obtained from the ring critical point (RCP) properties, and in their quest for determining a ring's net charge, they introduce the concept of ring characteristic orthogonality, with different characteristics of a ring affecting the ring's properties orthogonally. The RCP and ring atom properties of the model are finally tested against the IGPD inhibitor molecules.

The majority of quantum chemical calculations nowadays are performed within the molecular orbital (MO) framework. In this approach, molecular orbitals are constructed as a linear combination of (atom-centred) atomic orbitals. These molecular orbitals on the other hand are delocalized over the whole molecule and, thus, provide no straightforward connection to the Lewis picture of bonding often used by chemists. Valence bond (VB) theory was introduced almost at the same time as the MO approach around 1930, but received much less attention in subsequent decades due to its computational intricacies. In recent years, it regained interest as described by Havenith et al. in the chapter "[Valence Bond Theory in Heterocyclic Chemistry](#)," providing an alternative method that more closely connects to the concept of a molecule being atoms connected by bonds consisting of electron pairs. The method is subsequently discussed within the context of heterocyclic rings, leading to the conclusion that VB is a strong tool in the interpretation of the electronic structure in terms of classical chemical concepts such as bond bending, hyperconjugation and aromaticity. The last concept, of ubiquitous importance when studying unsaturated rings, is further elaborated on

in the final two chapters of the volume in the case of heterocyclic ring systems. As stated and discussed in detail in the contribution of Sola et al., this concept, related to the cyclic delocalization of electrons, cannot be defined without ambiguity, and it is often indirectly “measured” on the basis of its repercussion on various properties of the molecule. These authors discuss this concept for both organic and inorganic monocycles with special emphasis on the measures based on electron delocalization properties of aromatic rings.

In the final chapter, Nguyen et al. focus on the aromaticity of polyheterocyclic systems containing sulphur and their derivatives, such as annulated oligothiophenes (sulflower) and their O, Se, PH, PF and NH analogues. In addition, this chapter also discusses the use of the electron localization function (ELF) to probe aromaticity and to gain insight into bonding in these particular systems. The concept of disk aromaticity is thereby proposed to be an effective measure of the aromaticity of polyheterocycles.

In summary, the volume presents a broad overview of concepts and the way they can be quantified by state-of-the-art techniques to study the structure, bonding and reactivity of heterocyclic compounds.

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