II. THEORY AND METHODS

“In so far as quantum mechanics is correct, chemical questions are problems in applied mathematics.”
Henry Eyring

II.1. Computational chemistry

Quantum Mechanics (QM) was born at the beginning of the XX century with the introduction of Max Planck’s idea that the energy was quantized. QM describes mathematically the movement of electrons by a simple postulate, which establishes that the energy can be transferred between particles in specific quantities. With this idea, in conjunction with other ones from many physicists such as Einstein, Schrödinger, Bohr, Heisenberg, Dirac, and so on; and with a series of experiments that questioned the foundations of Classical Physics, one of the most complete and predictive theories was conceived, and which has been most tested throughout history. In the years that followed, this theoretical basis slowly began to be applied to small molecules, reactions and chemical bonds; thus, QM applied to chemistry is known as theoretical chemistry.1,2

On the other hand, from the decade of the 50s, the development of computers introduced a third methodology to scientific research: computational simulation. This is commonly known as numerical experiments. Thus, computational chemistry (CC) can be defined as a branch of chemistry that makes use of mathematical models (of the QM and also of classical mechanics) to simulate the interactions between the atoms and molecules of substances and matter in general, and thus be able to solve problems of a chemical nature, making intensive use of computers. Additionally, CC offers useful information to rationalize or interpret trends and to enunciate structure-activity relationships, so it has a powerful predictive power.

Nowadays, thanks to the accelerated development of technology, computational simulation has become an essential calculation tool, both for experimentalists and for theorists. In this context, Professor Dominic Tildesley, who is one of the presidents of the Royal Society of Chemistry (RSC), a former chief scientist at
Unilever and a current director of the European Center for Atomic and Molecular Calculus, has said:

“The speed and development of computers is now so rapid, and the advances in modelling and informatics are so dramatic that in 15 years' time, no chemist will be doing any experiments at the bench without trying to model them first.”

II.2. Electronic structure methods

Electronic structure methods are based on QM principles, which were developed to study small molecular systems in gas phase. However, their expansion to biochemical systems and materials has required the development of approximations and other methodologies that can consider systems that are more complex.

Within the formalism of the QM, a system is described by its wave function $\Psi(x,y,z,t)$, since it includes all its information. This wave function can be obtained by the corresponding solution of the time-dependent Schrödinger equation or, more commonly, by time-independent equation (Equation II.1). This equation represents, in simple words, an energetic quantum-mechanic balance, and it is solved by obtaining the eigenfunctions of the Hamiltonian operator $\hat{H}$.

$$\hat{H}\Psi(x,y,z,t) = E\Psi(x,y,z,t)$$  \hspace{1cm} (II.1)

The $\hat{H}$ operator describes the potential and kinetic energy of an electron, and $E$ is the total energy of the electron.

All the electronic-structure methods are characterized by the different mathematical approaches that are used in the $\hat{H}$ operator to solve Eq. II.1. All the calculations performed in this thesis were carried out with Density Functional Theory (DFT) Hamiltonians.

The popular B3LYP (Becke, three-parameter, Lee-Yang-Parr) exchange-correlation functional, was used as a test in almost all the systems. However, this
functional cannot describe long-range dispersion interactions, which are important in hydrogen-bonded systems. Therefore, three functionals that include dispersion correction were used:

- **ω-B97XD**: this functional was developed by Head-Gordon et al., and it includes a version of Grimme’s D2 dispersion. Within their versions (D, D2 and D3), the Grimme’s dispersion method simply add a correction term to the original DFT Hamiltonian.

- **B3LYP-D3**: this functional includes the refined version of Grimme dispersion, which has more accuracy, broader range of applicability, and less empiricism.

- **BLYP-D3(BJ)**: this is the hybrid Becke, one-parameter, Lee-Yang-Parr with the improvement D3(BJ). This includes Grimme’s D3 dispersion and embodies the Becke-Johnson damping function.

### II.2.1. Basis sets

A basis set is defined as a set of monoelectronic functions in which the molecular orbitals (MO) are expanded. These are the basis functions $\chi$, conventionally called atomic orbitals (MO = LCAO, Linear Combination of Atomic Orbitals),

All the calculations begin with the selection of the basis set, and after the Hamiltonian, it is one of the most important factors for obtaining good results.

In this thesis, two types of basis set were used:

- **Slater type functions** (STO, Slater type orbital): these functions are more accurate, since they mirror the exact orbitals for the hydrogen atom. In this thesis, two STOs were used: first, *Triple Zeta plus Double Polarization* (TZ2P), which contains six $s$-functions and three $p$-functions for the first row elements and contains two set of polarization functions. Secondly, a *Double Zeta plus Polarization* (DZP) type basis.
**Gaussian type functions** (GTO, Gaussian type orbital): These basis sets have some problems, i.e. in representing the proper behavior near the nucleus; therefore, more GTOs are necessary for achieving a certain accuracy compared with STOs. However, in terms of computational efficiency, GTOs are generally more preferred. In chapters III, IV and V, the split valence 6-311++G(d,p) basis set is applied. In this GTO, the core is described by one contracted GTO (CGTO) composed of six primitive GTOs; three GTOs for contracted valence orbitals and two different sizes of GTOs for extended valence orbitals; two diffuse basis functions (s- and p-type for heavy atoms and s for H); and, two polarization functions (d-type orbitals for heavy atoms and p-type orbitals for hydrogen).

II.2.2. Analysis of molecular properties:

**II.2.2.1. Energetic analysis**

Electronic structure methods allow the calculation of the electronic energy of a molecular system given, with a specific nuclear configuration.

In supramolecular systems, the energetic analysis of molecular aggregates is vitally important. In order to obtain the interaction energy of a system, a chemical reaction is defined according **Equation II.2**.

\[ A + B \rightarrow [A \cdots B]_{\text{complex}} \] (II.2)

**Figure II.1** represents **equation II.2** and displays the interaction between monomers A and B. When the isolated monomers are brought together to interact, they undergo geometrical deformations (bond distances, angles, dihedrals) which go along with energy changes. When the adduct is formed, three types of energies can be defined.
Figure II.1. Scheme of a bimolecular complex formation and the associated energy changes.

Deformation energy: or preparation energy, is the energy needed to deform the monomers from their isolated structures to that they acquire within the complex (see also Fig. II.1).

\[ \Delta E_{\text{def}}^A = E_{AB}^A - E_A^A \]  
\[ \Delta E_{\text{def}}^B = E_{AB}^B - E_B^B \]  

In this equation, the subscripts indicate the system and the superscripts the considered geometry.

Interaction energy: is the difference between the energy of the complex and the energy of the monomers with the same structures they have in the complex. In other words, the interaction energy is the actual energy of the complex.

\[ \Delta E_{\text{int}} = E_{AB} - E_A^A - E_B^B \]  

Bonding energy: is the difference between the energy of the complex and the energy of the isolated monomers (Equation II.4). That is, the energy change produced when two isolated molecules are brought together from the infinite in order to form a stable complex.

\[ \Delta E_{\text{bond}} = E_{AB} - E_A^A - E_B^B \]
This equation can be obtained by adding up equations II.3-5:

\[
\Delta E_{\text{bond}} = \Delta E_{\text{int}} - \sum \Delta E_{\text{def}} \tag{II.7}
\]

Cooperativity – synergy

As was mentioned in Chapter I, hydrogen bonds show what is called cooperative or synergetic effect. Strictly speaking, this implies that the whole is greater than the sum of the parts. In simple words, 1 + 1 is more than 2.

The cooperativity in supramolecules can be evaluated by what is commonly known as many body energy analysis. This analysis is performed by subtracting the sum of energies of all the possible pairs to the total interaction energy:

\[
\Delta E_{\text{coop}} = \Delta E_{\text{int}} - \sum_{j} \sum_{i<j} \Delta E_{ij} \tag{II.8}
\]

Therefore, if \( \Delta E_{\text{coop}} < 0 \), the synergy is present and the cooperativity is positive. In the opposite case, \( \Delta E_{\text{coop}} > 0 \), the cooperative effect is negative. For instance, in order to study the effect of adding a monomer \( C \) to the dimer \( AB \) to form a complex \( ABC \), the cooperativity can be calculated as:

\[
\Delta E_{\text{coop}} = E_{\text{AB}} - E_{\text{A}} - E_{\text{B}} - \left( \Delta E_{\text{AB}} + \Delta E_{\text{AC}} + \Delta E_{\text{BC}} \right) \tag{II.7}
\]

Energy correction

As the use of ab-initio calculations progressed to improve accuracy and to address problems such as weak van der Waals interactions or hydrogen bond interactions, it became clear that the use of an incomplete basis set results in significant errors in the calculation of potential energy curves.

The so-called basis set superposition error (BSSE) is caused by the tendency of electrons, which are associated with a given atom, to use the basis functions of a neighboring atom to decrease its energy. Consequently, the interaction energy is
overestimated. In addition, the weaker the interaction the more dramatic is the error.

The counterpoise (CP) method of Boys and Bernardi\textsuperscript{5} is one of the most used techniques to remove the BSSE. There is controversy in the literature regarding the effectiveness of the CP method to correct the BSSE. For example, there are situations in which CP correction over-corrects energy, especially when using small basis sets.\textsuperscript{6,7} On the other hand, in systems dominated by dispersion it was found that the corrected values are higher. Contrarily, van Duijneveldt \textit{et al.}\textsuperscript{8} have pointed out that the CP correction does not over-correct, and that the poor agreement with experimental values or high levels calculations is a reflection of the basis set incompleteness error (BSIE). At the limit of the complete base set, the BSSE and BSIE would be reduced to zero. However, Schwenke and Truhlar,\textsuperscript{9,10} found that the reliability of the CP correction does not increase with increasing the size of the base, and concluded that the extra cost required by the correction method does not guarantee obtaining a more accurate result. Frisch \textit{et al.}\textsuperscript{11} came to a similar conclusion in a later study.

In this thesis, the BSSE was computed for B3LYP, \(\omega\)-B97XD and B3LYP-D3 calculations. For the BLYP-D3(BJ) functional, the BSSE was not calculated because the dispersion correction was developed such that small BSSE effects were absorbed into the empirical potential.\textsuperscript{12}

\textit{Energy Decomposition Analysis (EDA)}

The EDA is a theoretical method that partitions the intermolecular interaction energy into energy components such as electrostatic, polarization, charge transfer, exchange and correlation contributions and dispersion. Many possible ways exist in which the interaction energy can be decomposed. In this thesis, the EDA scheme implemented in the Amsterdam Density Functional (ADF) program was used.

Within this approach, the interaction energy, which is examined in the framework of the Kohn–Sham Molecular Orbital model, is quantitatively decomposed into physically meaningful terms: electrostatic interaction, Pauli-
repulsive orbital interactions, and attractive orbital interactions:

$$\Delta E_{\text{int}} = \Delta V_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$$ (II.8)

The term $\Delta V_{\text{elstat}}$ corresponds to the classical electrostatic interaction between the unperturbed charge distributions of the prepared (that is, deformed) units and it is usually attractive. The Pauli repulsion $\Delta E_{\text{Pauli}}$ comprises the destabilizing interactions between occupied orbitals and is responsible for any steric repulsion. The orbital interaction $\Delta E_{\text{oi}}$ accounts for charge transfer (that is, donor–acceptor interactions between occupied orbitals on one moiety with unoccupied orbitals of the other, including the HOMO–LUMO interactions) and polarization (empty/occupied orbital mixing on one fragment due to the presence of another fragment). The term $\Delta E_{\text{disp}}$ accounts for the dispersion corrections. For planar systems with $C_3$ symmetry, the orbital interaction energy was further decomposed into the contributions from each irreducible representation $\Gamma$ of the interacting system.

$$\Delta E_{\text{oi}} = \Delta E_{\sigma} + \Delta E_{\pi}$$ (II.9)

**II.2.2.2. Quantum Theory of Atoms in Molecules.**

The *Atoms in Molecules Theory* (AIM) developed by Bader et al.\textsuperscript{13–15} provides the theoretical basis of the molecular structure hypothesis, which recognizes the molecule as a group of atoms hold together by a bond network.

AIM is an interpretive theory that helps to recover chemical concepts through a topological and rigorous study of the electron density $\rho(\mathbf{r})$. The theory is almost independent on any method of calculation or experimental, and as a starting point only needs the electronic density of the system, which can be obtained by quantum chemical calculations or experimental techniques. Over the years, the AIM theory
has evolved into a program that establishes a bridge between modern *ab initio* wave functions and chemical knowledge.\textsuperscript{16}

The approach of the AIM theory is a quantum chemical model that characterizes the bond of a system based only on the *topology of the electronic charge density*. The first step is to compute the critical points of the $\rho(r)$ function (nuclear, bond, ring and cage critical points). The analysis of these points reveals that the properties of the density at the critical point contain information about the characteristics of the interaction between two atoms, which also are of great physical-chemical interest.\textsuperscript{17} The pair of gradient paths that originate in the BCP and end in the neighboring nuclei define a line, called the atomic interaction line, through which the electronic density $\rho(r)$ is a maximum with respect to any neighboring line. The network of link paths in a molecule, in a given nuclear configuration, defines a *molecular graph*. A molecular graph of the cyanuric acid molecule is shown in Figure II.2.

![Molecular graph of cyanuric acid. BCP: bond critical point, RCP: ring critical point.](image)

**Figure II.2.** Molecular graph of cyanuric acid. BCP: bond critical point, RCP: ring critical point.

\textbf{II.2.2.3. Natural Bond Orbital (NBO) analysis.}

The NBO approach\textsuperscript{18,19} is a population analysis technique, which provides a localized representation of the electron density in a molecule, from electronic wave functions. The localized orbitals can be identified with bonds, lone pairs and antibonds. The strength or energy of the delocalization interactions between orbitals $E^{(2)}$ is estimated by the second order perturbation theory and depend on the relative
orientation of the orbitals and the energy difference between the donor and acceptor orbitals. This energy represents the estimation of the non-diagonal elements of the Fock NBO matrix. It can be deduced from the second-order perturbation approach:

\[ E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\epsilon_j - \epsilon_i} \]  

(II.10)

where \( q_i \) is the donor orbital population; \( \epsilon_i, \epsilon_j \), are the elements of the diagonal (orbital energies) and \( F(i,j) \) is the Fock NBO matrix of non-diagonal elements.

Despite that NBO analysis overestimate charge-transfer energies,\(^{20}\) is not itself a method to quantify these magnitudes as those obtained by a decomposition analysis. The NBO approach is implemented in Chapters 3 – 5.

II.4. References


DC, United States) 1988, 88 (6), 899–926.
