

CHAPTER 2
METHODOLOGY

2.1 Computational Details

All computational works were performed using Gaussian 03W Revision E.01 with GaussView Revision 3.7 and Gaussian(R)09W Revision A.02 with GaussView(R)W Revision 5.0 software packages. Computational study of tetrazoles (**Chapter 3**) was carried out under the support of Department of Science and Technology, Govt. of India within DST-NER-FIST programmed, and all calculations of tetrazole was done at Molecular Modeling Group, Indian Institute of Chemical Technology (IICT), Hyderabad, Andhra Pradesh. Rest of computational works (**Chapter 4 & Chapter 5**) were completed at the Department of Chemistry, Mizoram University. All calculations in these works were done with normal desktop computer with low price hardware configuration other than any sophisticated expensive machine.

Ground state isomers and transition state species of tetrazole and triazole were fully optimised at Hartree-Fock and Density Functional Theory of methods. Harmonic vibrational frequencies are computed via analytic energy second derivatives at different levels of calculations. Influence of substituents on energies, geometries and aromaticities were investigated and discussed according to different indices. Equilibrium properties of tetrazole was evaluated from the Gibb's free energies in order to explain tautomerisation feasibility. Enthalpy differences, singlet-triplet energy differences and HOMO-LUMO energy gaps of tautomers were compared for tetrazole and triazole isomers respectively. Triazole derivatives (letrozole and vorozole) were investigated with ONIOM method in connection to the energetic properties and geometries.

Computational works in **Chapter 3** (tetrazoles) were performed using Gaussian03 program and GaussView 3.7 packages. All the structures are fully optimized at the B3LYP (three-parameter hybrid functional of Becke using Lee-Yang-Parr correlation

functional) method using the standard 6-31G, 6-31+G*, 6-31**G++ and cc-pVTZ basis sets to obtain a comparable geometries as well as to ensure reliable energy predictions. Single point frequency calculations were performed at the B3lyp/6-31G and B3lyp/6-31+G* to identify the transition state geometries. Diffuse functions have long been known to be extremely important in the description of systems having lone pair of electrons. However, many previous theoretical studies showed that the total energies calculated at B3lyp methods are as good as high level ab initio (QCISD) results, though tetrazoles are systems involving lone pair of electrons.

In order to examine the influence of basis sets with respect to their degree of consistency and reliability in terms of various parameters, comparisons of the total energies, relative energies, activation energies and degrees of aromaticity arising from the calculated result on various selected theoretical levels with standard basis sets was carried out. The purpose of this work is to obtain computational data relating to substituent effects on the structures and chemical properties of the tetrazole through the investigation of its substituted tautomers. The studies mainly focused on the chemical properties relating to the electronic structures and detailed calculations was performed up to the B3lyp/6-31++G** level.

All the Quantum-chemical calculations in **Chapter 4** (triazole) were performed using Gaussian09 suit of program and all the structures were fully optimized with Hartree-Fock and Density Functional Theory using the standard basis sets starting from 6-31g(d) up to as large as 'aug-cc-pVTZ' basis. The reasons behind the particular choice of the two methods, i.e., HF and DFT, and the specific use of different basis sets such as, 6-31g(d), 6-311g(d), 6-311++g(d,p), cc-pvdz, cc-pvtz, aug-cc-pvdz and aug-cc-pvtz mainly based on the idea to obtain comparable good results for making perfect choice of basis set in the

studies of azoles and their derivatives for future studies, and also to minimize discrepancies on the calculated results. These mentioned methods are incorporated computationally to the choices of interested triazole systems, viz., 1H-1,2,3-Triazole, 2H-1,2,3-Triazole, 1H-1,2,4-Triazole and 2H-1,2,4-Triazole respectively. The results obtained from the corresponding basis sets are tabulated in the following tables and schemes. Hybrid QM/MM method was incorporated in **Chapter 5** (Letrozole and Vorozole) for structural and energetic studies. Calculations involving larger basis sets do proof more time consumption and thus, results in slow progress all over the whole works, but all calculations have been completed successfully.

2.2 Quantum Chemistry and Schrodinger Equation

The term theoretical chemistry may be defined as the mathematical description of chemistry. The term computational chemistry is generally used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer [Young, 2001]. In the late seventeenth century, Isaac Newton discovered classical mechanics. In the early twentieth century, physicists found that classical mechanics does not correctly describe the behavior of very small particles such as electrons and nuclei of atoms and molecules. The behavior of such particles is described by a set of laws called quantum mechanics [Levine, 2000]. Quantum mechanics have been developed continuously from the time of Newton and applied to a wide range of dynamical systems, including the electromagnetic field in interaction with matter. But, it has been found possible to set up a new scheme, the quantum mechanics, which is more suitable for the description of phenomena on the atomic scale and which is in some respects more elegant and satisfying than the classical scheme. The necessity for departure from classical mechanics is clearly shown by experimental results. In the first

place, the forces known in classical electrodynamics are inadequate for the explanation of the remarkably stability of atoms and molecules, which is necessary in order that materials may have any definite physical and chemical properties at all. Another illustration of the failure of classical mechanics lies within the behavior of light, which can be explained only on the basis of a wave theory [Dirac, 1958]. Therefore, it is clear that departure from classical ideas and establishment of quantum mechanics is extremely necessary.

Quantum chemistry is the field in which solutions to the Schrodinger equation are used to predict the properties of molecules and solve chemical problems. Chemistry applies quantum mechanics to problems in chemistry. Quantum Mechanic is the correct mathematical description of the behavior of electrons and thus of chemistry. In theory, Quantum Mechanic can predict any individual atom or molecule exactly [Young, 2001]. The organic chemist utilize quantum mechanics to estimate relative stabilities of molecules, to calculate properties of reaction intermediates, to investigate the mechanism of chemical reactions, and to analyze NMR spectra.

The ultimate goal of quantum chemical approaches is the-approximate –solution of the time-dependent, non-relativistic Schrodinger equation [Young, 2001; Koch and Holthausen 2001],

$$\hat{H}\Psi_i(\vec{X}_1, \vec{X}_2, \dots, \vec{X}_N, \vec{R}_1, \vec{R}_2, \dots, \vec{R}_M) = E_i \Psi_i(\vec{X}_1, \vec{X}_2, \dots, \vec{X}_N, \vec{R}_1, \vec{R}_2, \dots, \vec{R}_M) \quad (1)$$

where \hat{H} is the Hamiltonian operator for a molecular systems consisting of M nuclei and N electrons in the absence of magnetic or electric fields. \hat{H} is a differential operator representing the total energy:

$$\hat{H} = -\frac{1}{2} \sum_{i=1}^N \nabla_i^2 - \frac{1}{2} \sum_{A=1}^M \frac{1}{M_A} \nabla_A^2 - \sum_{i=1}^N \sum_{A=1}^M \frac{Z_A}{r_{iA}} + \sum_{i=1}^N \sum_{j>i}^N \frac{1}{r_{ij}} + \sum_{A=1}^M \sum_{B>A}^M \frac{Z_A Z_B}{R_{AB}} \quad (2)$$

Here, A and B run over the M nuclei while i and j denote the N electrons in the system. The first two terms describe the kinetic energy of the electrons and nuclei respectively, where the Laplacian operator $\nabla_{\mathbf{q}}^2$ is defined as a sum of differential operators (in cartesian coordinates) [Young, 2001; Jensen, 2007; Koch and Holthausen, 2001] and,

$$\nabla_{\mathbf{q}}^2 = \frac{\partial^2}{\partial X_{\mathbf{q}}^2} + \frac{\partial^2}{\partial Y_{\mathbf{q}}^2} + \frac{\partial^2}{\partial Z_{\mathbf{q}}^2} \quad (3)$$

and M_A is the mass of nucleus A in multiples of the mass of an electron (in atomic units). The remaining three terms define the potential part of the Hamiltonian and represent the attractive electrostatic interaction between the nuclei and the electrons and the repulsive potential due to the electron-electron and nucleus-nucleus interactions, respectively. E_i is the numerical value of energy of the state described by Ψ_i . The wave function Ψ_i contains all information that can be possibly being known about the quantum system under consideration. This concept of wave function and the equation governing its change with time were discovered in 1926 by the Austrian physicist Erwin Schrodinger (1887-1961) [Levine, 2000]. The time-independent Schrodinger equation, which is the basis for nearly all computational chemistry method is always written in short form as [Thomas, 2007; Young, 2001, Dyall *et al.*, 2007; Jensen, 2007; Carloni and Alber, 2003; Barden and Schaefer, 2000; Mueller, 2006],

$$\hat{H}\Psi = E\Psi \quad (4)$$

where \hat{H} is the Hamiltonian operator, Ψ a wave function of the electron and nuclear positions, and E the energy. The equation of this form is called an eigen equation. Ψ is then called an eigenfunction and E an eigenvalue. The Schrodinger Equation is the key equation of quantum mechanics and the basic foundation of modern computational technique. This second order, partial differential equation determines the spatial shape and the temporal evolvment of a wave function in a given potential and for given

boundary conditions. The one-dimensional Schrodinger equation is often used when the particle of interest is confined to one spatial dimension. For x axis, one-dimensional Schrodinger equation is [Dyall *et al.*, 2007; Levine, 2000; Sarma, 2010; McMahon, 2006; Fitts, 2002; Fitzpatrick, 2013; Rae, 2002; Griffiths, 1995],

$$-\frac{\hbar^2}{2m} \frac{\partial^2}{\partial x^2} \psi(x, t) + U(x)\psi(x, t) = -\frac{\hbar}{i} \frac{\partial}{\partial t} \Psi(x, t) \quad (5)$$

Most applications of quantum mechanics in chemistry do not use this time-dependent equation; instead, the simpler time-independent equation derived from the time-dependent equation is used [Levine, 2000; Rae, 2002; Zettili, 2009],

$$-\frac{\hbar^2}{2m} \frac{d^2 \psi(x)}{dx^2} + V(x)\psi(x) = E\psi(x) \quad (6)$$

Among computational chemistry methods, quantum mechanics calculates geometries and electronic structures with accuracy especially for systems with electronic delocalization. Recent years have witnessed an increasing number of researchers using computational chemistry. This has been facilitated by the development of easy-to-use computer software. If very few aspects of chemistry can be computed exactly, almost one has been described in a qualitative or approximately quantitative manner. Many aspects of molecular structure and dynamics can be modelled using classical methods in the form of molecular mechanics and dynamics. A classical force field is based on empirical results, averaged over a large number of molecules. Because of this extensive averaging, the results can be good for standard systems, but there are many important questions in chemistry that cannot be addressed by means of this empirical approach. If one wants to know more than just the structure or other properties that are only derived from the potential energy surface (especially properties that depend directly on the electron density distribution), one has to resort to a more fundamental and general approach and use

quantum chemistry. Quantum chemical calculations are thus an attractive source of molecular descriptors, which can express all electronic and geometric properties of molecules.

In quantum chemistry the system is described by a wavefunction which can be obtained by solving the Schrodinger equation. This equation relates the stationary states of the system and their energies to the Hamiltonian operator. It can be viewed as the recipe for obtaining the energy associated with a wavefunction describing the positions of the nuclei and electrons in the system. In practice the Schrodinger equation cannot be solved exactly and approximations have to be made. A brief account on approximation methods have been describe in the following part to support the technique and concept of computational chemistry that have been implemented in this particular work.

2.3 Implemented Quantum Mechanical Methods

There are four main approaches in quantum mechanics for calculating molecular properties; namely, ab initio methods, semiempirical methods, density functional methods and molecular mechanics methods, and these are all incorporated in this study.

Semiempirical molecular quantum-mechanical methods use a simpler Hamiltonian than the correct molecular Hamiltonian and use parameters whose values are adjusted to fit experimental data or the results of ab initio calculations. In contrast, an ab initio calculation uses the correct Hamiltonian and does not use experimental data other than the values of the fundamental physical constants. The density functional method does not attempt to calculate the molecular wave function but calculates the molecular probability density ρ and calculates the molecular electronic energy from ρ [Levine, 2000]. The molecular mechanics method is not a quantum mechanical method and does not use a molecular Hamiltonian operator or wave function. Instead, it views the molecule as a

collection of atoms held together by bonds and expresses the molecular energy in terms of force constant for bond bending and stretching and other parameters.

2.3.1 *Ab initio* method

The term *ab initio* is Latin for “from the beginning.” This name is given to computations that are derived directly from theoretical principles with no inclusion of experimental data, i.e. if solutions are generated without reference to experimental data, the methods are usually called *ab initio*. An essential part of solving the Schrödinger equation is the Born–Oppenheimer approximation, where the coupling between the nuclei and electronic motion is neglected [Jensen, 2007]. This allows the electronic part to be solved with the nuclear positions as parameters, and the resulting potential energy surface (PES) forms the basis for solving the nuclear motion. The major computational effort is in solving the electronic Schrödinger equation for a given set of nuclear coordinates.

In *ab initio* methods an attempt is made to evaluate all integrals that appear in the secular determinant. Approximations are still employed, but these are mainly associated with the construction of the wavefunctions involved in the integrals. In semi-empirical methods, many of the integrals are expressed in terms of spectroscopic data or physical properties. Semi-empirical methods exist at several levels. At some levels, in order to simplify the calculations, many of the integrals are set equal to zero. The Hartree-Fock and DFT methods are similar in that they are both regarded as *ab initio* methods. In HF the central focus is the wavefunction whereas in DFT it is the electron density. They are both iterative self-consistent methods in that the process are repeated until the energy and wavefunctions (HF) or energy and electron density (DFT) are unchanged to within some acceptable tolerance [Atkins and Paula, 2002].

An important distinguishing feature among *ab initio* calculations is the extent to which they deal with electron correlation. Correlation is defined as the difference between the exact energy of a molecular system and the best energy obtainable by a SCF calculation in which the wave function is represented by a single determinant. In single-determinant calculations, we consider that each electron experiences an averaged electrostatic repulsion defined by the total charge distribution, a mean field approximation. These are called *Hartree-Fock* (HF) calculations [Carey and Sundberg, 2007].

Generally speaking, methods that do not include any empirical or semi-empirical parameters in their equations being derived directly from theoretical principles, with no inclusion of experimental data are called *ab initio* methods. In the *ab initio* methods, an attempt is made to calculate all the integrals that appear in the secular determinant. The most common type of *ab initio* calculation is a Hartree–Fock (HF) calculation, in which the primary approximation is the central field approximation. One of the advantages of this method is that it splits the multi-electron Schrödinger equation into many simplest one-electron equations [Geneste and Carpy 2004]. Each one-electron equation is solved to yield a single-electron wavefunction, called orbital and energy. This orbital describes the behaviour of an electron in the net field of all the others.

Ab initio methods try to derive information by solving the Schrödinger equation without fitting parameters to experimental data. Actually, *ab initio* methods also make use of experimental data, but in a somewhat more subtle fashion. Many different approximate methods exist for solving the Schrodinger equation, and which one to use for a specific problem is usually chosen by comparing the performance against known experimental data. Experimental data thus guides the selection of the computational

model, rather than directly entering into the computational procedure. One of the approximations inherent in essentially all *ab initio* methods is the introduction of a basis set [Jensen, 2007]. Expanding an unknown function, such as a molecular orbital, in a set of known functions is not an approximation if the basis set is complete. However, a complete basis set means that an infinite number of functions must be used, which is impossible in actual calculations. An unknown MO can be thought of as a function in the infinite coordinate system spanned by the complete basis set. When a finite basis set is used, only the components of the MO along those coordinate axes corresponding to the selected basis functions can be represented. The smaller the basis set, the poorer the representation. The type of basis functions used also influence the accuracy. The better a single basis function is able to reproduce the unknown function, the fewer basis functions are necessary for achieving a given level of accuracy. It is of course of prime importance to make the basis set as small as possible, without compromising the accuracy. The expansion of the molecular orbitals leads to integrals of quantum mechanical operators over basis functions, and the ease with which these integrals can be calculated also depends on the type of basis function. In some cases the accuracy-per-function criterion produces a different optimum function type than the efficiency-per-function criterion.

This is an approximate quantum mechanical calculation. The approximations made are usually mathematical approximations, such as using a simpler functional form for a function or finding an approximate solution to a differential equation.

2.3.2 Hartree-Fock Method

The most common type of *ab initio* calculation is called a Hartree-Fock calculation (abbreviated HF), in which the primary approximation is the central field approximation. This means that the Coulombic electron-electron repulsion is taken into account by

integrating the repulsion term. This gives the average effect of the repulsion, but not the explicit repulsion interaction. This is a variational calculation, meaning that the approximate energies calculated are all equal to or greater than the exact energy. The energies are calculated in units called Hartrees (1 Hartree = 27.2116 eV). Because of the central field approximation, the energies from HF calculations are always greater than the exact energy and tend to a limiting value called the Hartree-Fock limit as the basis set is improved [Young, 2001]. One of the advantages of this method is that it breaks the many-electron Schrodinger equation into many simpler one-electron equations. Each one electron equation is solved to yield a single-electron wave function, called an orbital, and an energy, called an orbital energy. The orbital describes the behavior of an electron in the net field of all the other electrons. The second approximation in HF calculations is due to the fact that the wave function must be described by some mathematical function, which is known exactly for only a few one-electron systems. The technique was originally introduced by D.R.Hartree and then modified by V.Fock to take into account the Pauli principle correctly [Atkins and Paula, 2002].

In the HF model, each electron is described by an orbital, and the total wave function is given as a product of orbitals. Since electrons are indistinguishable fermions (particles with a spin of 1/2), the overall wave function must be antisymmetric (change sign upon interchanging any two electrons), which is conveniently achieved by arranging the orbitals in a Slater determinant [Jensen, 2007]. The best set of orbitals is determined by the variational principle, i.e. the HF orbitals give the lowest energy within the restriction of the wave function being a single Slater determinant. The shape of a given molecular orbital describes the probability of finding an electron, where the attraction to all the nuclei and the average repulsion to all the other electrons are included. Since the other

electrons are described by their respective orbitals, the HF equations depend on their own solutions, and must therefore be solved iteratively.

In a HF calculation, the wavefunction is formed from the linear combination of basis functions. A HF calculation starts with an initial guess for the orbital coefficients which are used to calculate an energy and a new set of orbital coefficients and so on. This procedure continues iteratively until the energies and coefficients remain constant (i.e. converge) from one iteration to the next one [Geneste and Carpy, 2004]. If the system has unpaired electrons, two separate sets of orbitals for the a and b electrons can be used to construct the HF wavefunctions (UHF method) but this leads to spin contamination. When the molecular orbitals are expanded in a basis set, the resulting equations can be written as a matrix eigenvalue problem. The elements in the Fock matrix correspond to integrals of one and two-electron operators over basis functions, multiplied by density matrix elements. The HF equations in a basis set can thus be obtained by repeated diagonalizations of a Fock matrix [Jensen, 2007]. The HF model is a kind of branching point, where either additional approximations can be invoked, leading to semi-empirical methods, or it can be improved by adding additional determinants, thereby generating models that can be made to converge towards the exact solution of the electronic Schrodinger equation.

The case of interacting fermions has considerable practical importance because it represents the situation applying in many-electron atoms and molecules as well as in nuclei and in the case of electrons in solids. Since exact solutions are rarely possible, various approximations have been developed. As mentioned before, one of the most important of these is known as the self-consistent field or Hartree-Fock method. In Hartree-Fock method of approximation, the single-particle eigenfunctions are calculated

assuming that each particle is subject to a potential equivalent to the average of its interaction with all the others. This interaction potential is taken to be that from a continuous charge distribution whose magnitude is proportional to the sum of the squared moduli of some approximate set of one-electron eigenfunctions. The resulting eigenvalue equations are then solved to give new one-electron eigenfunctions which, in turn, are used to construct new potentials. This iterative process is continued until no further significant changes occur, when the system is said to be self-consistent [Rae, 2002]. More accurate results can be obtained if the eigenfunction is represented by a linear combination of determinants, each of which is constructed from a different set of one-electron functions. Nowadays, such calculations are quite straightforward for all but the heaviest atoms and for moderately sized molecules. Computations of this kind now form part of the routine armoury of the theoretical chemist and are particularly powerful for the study of short-lived chemical species, which often cannot be studied experimentally.

If the cyclic calculation of the HF method is continued, the changes in the wave functions and energy become smaller with every cycle until, within the limits of accuracy required for that particular calculation, there is no further change in them. When this point is reached the electronic wave functions are said to be consistent with the electrostatic field from which they were calculated and which the electrons themselves produce. The process is known as a *self-consistent field* (SCF) calculation [Grinter, 2005]. Nowadays, computers make this task rather easy, but the first calculations of the type were done the hard way by the Hartrees, father and son, in the 1930's. Notable contributions to the subject were also made by Vladimir A. Fock (1898–1974) and wave functions calculated by this method are often called Hartree–Fock functions. However, even an SCF calculation does not provide an exact radial wavefunction. Because the

electrons repel each other their motions are *correlated*, i.e. they keep out of each other's way, and this effect is not fully allowed for in the Hartree-Fock method which assumes that the electrons produce a static, spherical field and fails to allow for the dynamic effects of the inter-electronic repulsion which is known as electron correlation. The difference in energy between the HF and the lowest possible energy in the given basis set is called the Electron Correlation (EC) energy [Jensen, 2007].

The Hartree-Fock approach is based on the assumption that a molecular or atomic wave function may be approximated as an antisymmetrized product of one-electron orbitals in the case of a closed-shell configuration or as a number of antisymmetrized products in other cases. The goal of the Hartree-Fock method or the Self-Consistent Field (SCF) method is the subsequent derivation of the best possible one-electron orbitals by making use of the variational principle [Hameka, 2004]. Rather than vary each orbital at a time, the Hartree-Fock equations have been designed in such a way that all orbitals may be obtained at the same time as the eigenfunctions of an effective one-electron operator, the Hartree-Fock operator. The latter operator contains the average Coulomb repulsion between the electrons. The Hartree-Fock equations for most atoms may be solved exactly in numerical form, but in the case of molecules it is usually necessary to introduce additional approximations.

The functions used most often are linear combinations of Gaussian-type orbitals $\exp(-ar^2)$, abbreviated GTO. The wave function is formed from linear combinations of atomic orbitals or, stated more correctly, from linear combinations of basis functions. Because of this approximation, most HF calculations give a computed energy greater than the Hartree-Fock limit. The exact set of basis functions used is often specified by an abbreviation, such as STO-3G or 6-311++g**. The Gaussian functions are multiplied by

an angular function in order to give the orbital the symmetry of a s , p , d , and so on. A constant angular term yields s symmetry. Angular terms of x , y , z give p symmetry. Angular terms of xy , xz , yz , x^2-y^2 , $4z^2-2x^2-2y^2$ yield d symmetry. This pattern can be continued for the other orbitals. These orbitals are then combined into a determinant. This is done to satisfy two requirements of quantum mechanics. One is that the electrons must be indistinguishable. By having a linear combination of orbitals in which each electron appears in each orbital, it is only possible to say that an electron was put in a particular orbital but not which electron it is. The second requirement is that the wave function for fermions (an electron is a fermion) must be antisymmetric with respect to interchanging two particles. Thus, if electron 1 and electron 2 are switched, the sign of the total wave function must change and only the sign can change. This is satisfied by a determinant because switching two electrons is equivalent to interchanging two columns of the determinant, which changes its sign. The functions put into the determinant do not need to be individual GTO functions, called Gaussian primitives [Young, 2001]. They can be a weighted sum of basis functions on the same atom or different atoms. Sums of functions on the same atom are often used to make the calculation run faster. Sums of basis functions on different atoms are used to give the orbital a particular symmetry. For example, a water molecule with C_{2v} symmetry will have orbitals that transform as A_1 , A_2 , B_1 , B_2 , which are the irreducible representations of the C_{2v} point group. The resulting orbitals that use functions from multiple atoms are called molecular orbitals. This is done to make the calculation run much faster. Any overlap integral over orbitals of different symmetry does not need to be computed because it is zero by symmetry.

The steps in a Hartree-Fock calculation start with an initial guess for the orbital coefficients, usually using a semiempirical method. This function is used to calculate an

energy and a new set of orbital coefficients, which can then be used to obtain a new set, and so on. This procedure continues iteratively until the energies and orbital coefficients remain constant from one iteration to the next. This is called having the calculation converge. There is no guarantee the calculation will converge. In cases where it does not, some technical expertise is required to fix the problem. This iterative procedure is called a self-consistent field procedure (SCF) [Young, 2001]. Some researchers refer to these as SCF calculations to distinguish them from the earlier method created by Hartree, but HF is used more widely.

The Hartree-Fock equation, which determine the best spin orbitals for which the energy attain its lowest value is [Koch and Holthausen, 2001],

$$\hat{f} \chi_i = \epsilon_i \chi_i, i = 1, 2, \dots, N \quad (7)$$

Where the Lagrangian multipliers ϵ_i are the eigen values of operator \hat{f} . The ϵ_i have the physical interpretation of orbital energies. The Fock operator is an effective one-electron operator defined as

$$\hat{f}_i = -\frac{1}{2} \nabla_i^2 - \sum_A^M \frac{Z_A}{r_{iA}} + V_{HF}(i) \quad (8)$$

The first two terms are the kinetic energy and the potential energy due to the electron-nucleus attraction. $V_{HF}(i)$ is the Hartree-Fock potential. It is the average repulsive potential experienced by the i 'th electron due to the remaining $N-1$ electrons. Thus, the complicated two-electron repulsion operator $1/r_{ij}$ in the Hamiltonian is replaced by the simple one electron operator $V_{HF}(i)$ where the electron-electron repulsion is taken into account only in an average way. Explicitly, VHF has the following two components:-

$$V_{HF}(\vec{X}_1) = \sum_j^n (\hat{J}_j(\vec{X}_1) - \hat{K}_j(\vec{X}_1)) \quad (9)$$

The coulomb operator \hat{J} is defined as

$$\hat{J}_j(\vec{X}_1) = \int |\chi_j(\vec{X}_2)|^2 \frac{1}{r_{12}} d\vec{X}_2 \quad (10)$$

and it represent potential that an electron at position \vec{X}_1 experiences due to the average charge distribution of another electron in spin orbital χ_j . The Coulomb repulsion corresponding to a particular distance between the reference electron at \vec{X}_1 and another one at position \vec{X}_2 is weighted by the probability that the other electron is at this point in space. Finally, this interaction is integrated over all space and spin coordinates. Since the result of application of \hat{J}_j on a spin orbital χ depends solely on the value of χ_i at position \vec{X}_1 , this operator and the corresponding potential are called local [Koch and Holthausen, 2001]. The Hartree–Fock equation is ordinarily used in quantum chemistry in connection with a basis set of AOs, and it is possible to carry through a derivation of the Hartree-Fock equation for this type of basis [Lowe and Peterson, 2006]. If one is doing a Hartree–Fock calculation then all the electrons are simultaneously in all the orbitals of a particular chosen configuration [Scerri, 2004]. In a HF calculation, the wavefunction is formed from the linear combination of basis functions. A HF calculation starts with an initial guess for the orbital coefficients which are used to calculate energy and a new set of orbital coefficients and so on. Fock operator actually depends on the wavefunctions of all the electrons. To proceed, one has to guess the initial form of the wavefunction and solve the Hartree-Fock equations. That process is then continued using the newly found wavefunctions until each cycle of calculation leaves the energies and wavefunctions unchanged to within a chosen criterion. Then, this point is called self-consistent field (SCF). This procedure continues iteratively until the energies and coefficients remain constant (i.e. converge) from one iteration to the next one [Atkins and Paula, 2002].

In general, *ab initio* calculations give very good qualitative results and can yield increasingly accurate quantitative results as the molecules in question become smaller. The use of the Hartree–Fock approximation reduces computer time and reduces the cost without losing too much in the way of accuracy [Thomas, 2003]. The advantage of *ab initio* methods is that they eventually converge to the exact solution once all the approximations are made sufficiently small in magnitude. However, this convergence is not monotonic. Sometimes, the smallest calculation gives a very accurate result for a given property. There are four sources of error in *ab initio* calculations [Young, 2001]:-

1. The Born-Oppenheimer approximation
2. The use of an incomplete basis set
3. Incomplete correlation
4. The omission of relativistic effects

The disadvantage of *ab initio* methods is that they are expensive. These methods often take enormous amounts of computer CPU time, memory, and disk space. The HF method scales as N^4 , where N is the number of basis functions. This means that a calculation twice as big takes 16 times as long (2^4) to complete. One of the limitations of HF calculations is that they do not include electron correlation. Several approaches try to calculate the correlation energy after HF calculations (post-HF methods) such as Moller–Plesset perturbation theory (MP n , where n = order of correction), configuration interaction (CI), multi-configurational self-consistent field (MCSCF), the generalized valence bond (GVB) method and the coupled cluster theory (CC) [Geneste and Carpy, 2004]. But these post HF-methods were not used in this research because of limited time for the calculations of each and every species of the titled compound.

2.3.3 Density functional theory method (*DFT*)

Density functional theory (DFT) has become very popular in recent years. This is justified based on the pragmatic observation that it is less computationally intensive than

other methods with similar accuracy [Young, 2001]. This theory has been developed more recently than other ab initio methods. Because of this, there are classes of problems not yet explored with this theory, making it all the more crucial to test the accuracy of the method before applying it to unknown systems. Over the past decade, DFT has become one of the most widely used tools of the computational chemist, and in particular for systems of some size. This success has come despite complaints about arbitrary parametrization of potentials, and laments about the absence of a universal principle (other than comparison with experiment) that can guide improvements in the way the variational principle has led the development of wave-function-based methods [Dyall *et al.*, 2007].

DFT has emerged as an alternative to the ab initio and semi-empirical approaches for studying the ground state properties of molecular systems. A technique that has gained considerable ground in recent years to become one of the most widely used technique for the calculation of molecular structures is density functional theory. Its advantages include less demanding computational effort, less computer time, and better agreement with experimental values than is obtained from Hartree-Fock procedures [Young, 2001].

Modern DFT is founded on the Hohenberg–Kohn theorems and the Kohn–Sham equations [Dyall *et al.*, 2007]. The basis for Density Functional Theory is the proof by Hohenberg and Kohn that the ground state electronic energy is determined completely by the electron density ρ . The Hohenberg–Kohn theorem, which states that the energy is uniquely determined by the one-electron density ρ , forms the basis for what is commonly called density functional theory [Jensen, 2007]. In other words, there exists a one-to-one correspondence between the electron density of a system and the energy. Density functional theory as we know it today was born in 1964 when a landmark paper by Pierre

Hohenberg and Walter Kohn appeared in the Physical Review. The theorems proven in this report represent the major theoretical pillars on which all modern day density functional theories are erected. The proof originally given by Hohenberg and Kohn in their 1964 paper is disarmingly simple, almost trivial and one may wonder why it took about 40 years after Thomas and Fermi first used the density as a basic variable before their approach was put onto a firm physical foundation. Quoting directly from the Hohenberg/Kohn paper, this first theorem states that *'the external potential $V_{\text{ext}}(\vec{r})$ is (to within a constant) a unique functional of $\rho(\vec{r})$; since, in turn $V_{\text{ext}}(\vec{r})$ fixes \hat{H} we see that the full many particle ground state is a unique functional of $\rho(\vec{r})$ '* [Koch and Holthausen, 2001; Levine, 2000; Carloni and Alber, 2003; Lowe and Peterson, 2006; Carey and Sundberg, 2007].

DFT represents somewhat of a departure from conventional *ab initio* quantum chemical methods in that it does not formally deal with wavefunctions, but rather with the electron density since Kohn and co-workers discovered that all ground-state properties of a molecular system could be completely described using only the electron density and the (fixed) nuclear positions [Barden and Schaefer, 2000]. All *ab initio* methods start with Hartree-Fock (HF) approximation that results in the spin orbitals, and then electron correlation is taken into account. Though the results of such calculations are reliable, the major disadvantage is that they are computationally intensive and cannot be readily applied to large molecules of interest. Density functional (DF) methods provide an alternative route that, in general, provides results comparable to CI and MP2 computational results; however, the difference is that DF computations can be done on molecules with 100 or more heavy atoms [Mueller, 2002].

The first Hohenberg–Kohn theorem proved the existence of a unique functional relationship between the electron density and the electronic Hamiltonian. Thus, if the exact relationship were known we could compute all of the molecular properties using only the electron density (which depends on only three coordinates) and avoid the building of a wavefunction (which depends on $3n$ coordinates). Much of the development work in modern-day quantum chemistry is directed toward discovering the true nature of this functional relationship. Density Functional Theory in the Kohn–Sham version can be considered as an improvement on HF theory, where the many-body effect of electron correlation is modelled by a function of the electron density. DFT is analogously to HF, an independent-particle model, and is comparable to HF computationally, but provides significantly better results. The main disadvantage of DFT is that there is no systematic approach to improving the results towards the exact solution [Jensen, 2007].

Early DFT-related methods such as Thomas–Fermi theory, $X\alpha$, and the local density approximation (LDA) were in large part based upon fitting the functionals to the theoretical electron gas. The first truly successful DFT functionals, the generalized gradient approximation (GGA) functionals, were of the KS-DFT variety and relied on XC terms designed using density gradient corrections [Barden, and Schaefer, 2000]. Some of the most popular functionals are of this type, including the Becke-88 (B88) exchange functional and the Lee–Yang–Parr (LYP) and Perdew-86 (P86) correlation functionals. These functionals were still found to be lacking for nonlocal molecular phenomena, and so hybrid functionals were built that contained some proportion of exact (i.e., HF) exchange. Of this type, the Becke three-parameter exchange functional (B3) is still the most common. If exchange and correlation functionals are combined, modern DFT functionals (B3LYP, BP86, etc.) are the result [Barden and Schaefer, 2000].

Currently, DFT enjoys an enormous amount of acceptance for predicting molecular structures and properties due to its relative accuracy and increased speed over other quantum chemical methods. However, systems involving bond-breaking or weak bonds are still problematic. In recent years, density-functional theory (DFT) has emerged as one of the most commonly used quantum-mechanical methods for studying a wide range of molecular properties. Both local density approximation (LDA) and generalized gradient approximation (GGA) functionals have been developed. In particular, GGA functionals such as the Becke–Lee–Yang–Parr functional (BLYP) and the hybrid Becke-3-parameter-Lee–Yang–Parr functional (B3LYP) often describe electron correlation effects of molecular properties with an accuracy comparable to that of MP2 and CCSD theories [Sabin and Brandas, 2005].

DFT has emerged as an alternative to the *ab initio* and semi-empirical approaches for studying the ground state properties of molecular systems. The DFT theory is an approach to the electronic structure of atoms and molecules which has enjoyed a dramatic surge of interest since the late 1980s and in the 1990s. Whereas the HF theory does calculate the full N -electron wavefunction, the DFT theory only attempts to calculate the total electron energy and the overall electronic density distribution. The central idea of DFT is that there is a relationship between the total electronic energy and the overall electronic density. Hohenberg and Kohn showed that the ground state energy and other properties of a system were uniquely defined by the electron density. A practical application of this theory was developed by Kohn and Sham who formulated the electron density as a linear combination of basis functions similar in mathematical form to HF orbitals. A determinant is then formed from these functions (Kohn and Sham orbitals) [Geneste and Carpy, 2004]. The DFT methods compute the electron correlation via

general functionals of the electron density. The DFT functionals partition the electronic energy into several components which are computed separately: the kinetic energy, the electron nuclear interaction, the Coulomb repulsion and an exchange correlation term accounting for the remainder of the electron–electron interaction. The Kohn-Sham equation is represented as follows [Levine, 2001; Carloni and Alber, 2003; Mueller, 2002] :-

$$\left[-\frac{\nabla^2}{2} + V(r) + \int dr' \frac{\rho(r')}{|r-r'|} + V_{xc}(r)\right]\psi_i(r) = \epsilon_i \psi_i(r) \quad (11)$$

Here, $V_{xc} = \frac{\delta E_{xc}[\rho]}{\delta \rho(r)}$ is a local potential called the exchange and correlation potential.

The ϵ_i are eigenvalues of the matrix of Lagrange multipliers and are called the Kohn-Sham eigenvalues. The Kohn-Sham equations have the form of self-consistent-field equations of the Hartree type, but, in contrast with the Hartree equations, which are approximate, are formally exact. The self-consistent potential acting on the electrons in the above equation is given by a sum of the external potential, the Hartree potential, and the exchange and correlation potential [Carloni and Alber, 2003]. The final DFT energy expression is written as [Lowe and Peterson, 2006],

$$E_{\text{DFT}}[\rho] = T_s[\rho] + E_{\text{ne}}[\rho] + J[\rho] + E_{\text{xc}}[\rho] \quad (12)$$

where the exchange correlation functional $E_{\text{xc}}[\rho]$ contains the difference between the exact kinetic energy and T_s , the non-classical (exchange) part of electron-electron repulsions, $K[\rho]$, and correlation contributions to both $K[\rho]$ and $J[\rho]$. The Kohn–Sham orbitals are eigenfunctions of an effective one-electron hamiltonian that is nearly identical in form to the Fock operator in the SCF equations. In the Kohn–Sham case, however, the HF exchange operators are replaced by the functional derivative of the

exchange correlation energy. Assuming the existence of $E_{xc}[\rho]$ and an initial guess for the electron density, one then solves the Kohn–Sham eigenvalue equations for the orbitals, which can then be used to define a new electron density and effective hamiltonian. These iterations continue until the density is converged to within a specified threshold. The DFT methods compute the electron correlation via general functionals of the electron density. The DFT functionals partition the electronic energy into several components which are computed separately: the kinetic energy, the electron nuclear interaction, the Coulomb repulsion and an exchange correlation term accounting for the remainder of the electron–electron interaction [Young, 2001]. In a true density functional theory, one would deal with only the electron density (a function of three variables) and not with the orbitals [Young, 2000].

The premise behind DFT is that the energy of a molecule can be determined from the electron density instead of a wave function. The original theorem applied only to finding the ground-state electronic energy of a molecule. The method is similar in structure to the Hartree-Fock method where the electron density is expressed as a linear combination of basis functions similar in mathematical form to HF orbitals. A determinant is then formed from these functions, called Kohn-Sham orbitals. It is the electron density from this determinant of orbitals that is used to compute the energy. This procedure is necessary because Fermion systems can only have electron densities that arise from an antisymmetric wave function [Young, 2001]. A density functional is then used to obtain the energy for the electron density. The exact density functional is not known. Therefore, there is a whole list of different functionals that may have advantages or disadvantages. Some of these functionals were developed from fundamental quantum mechanics and some were developed by parameterizing functions to best reproduce experimental results.

Thus, there are in essence ab initio and semiempirical versions of DFT. DFT tend to be classified either as an ab initio method or in a class by itself. The advantage of using electron density is that the integrals for Coulomb repulsion need be done only over the electron density, which is a three-dimensional function, thus scaling as N^3 . Furthermore, at least some electron correlation can be included in the calculation. This result in faster calculations than HF calculations (which scale as N^4) and computations that is a bit more accurate as well [Young, 2001].

The better DFT functionals give results with an accuracy similar to that of an MP2 calculation. Density functionals can be broken down into several classes. The simplest is called the X_α method [Geneste and Carpy, 2004]. This type of calculation includes electron exchange but not correlation. It was introduced by J. C. Slater, who in attempting to make an approximation to Hartree-Fock unwittingly discovered the simplest form of DFT. The X_α method is similar in accuracy to HF and sometimes better. The simplest approximation to the complete problem is one based only on the electron density, called a local density approximation (LDA). For high-spin systems, this is called the local spin density approximation (LSDA). LDA calculations have been widely used for band structure calculations. Their performance is less impressive for molecular calculations, where both qualitative and quantitative errors are encountered. For example, bonds tend to be too short and too strong. In recent years, LDA, LSDA, and VWN (the Vosko, Wilks, and Nusair functional) [Young, 2001; Geneste and Carpy, 2004] have become synonymous in the literature. A more complex set of functionals used the electron density and its gradient. They are called gradient-corrected methods- BLYP (which stands for Becke, Lee, Yang and Parr), P86(which stands for Perdew 1986) and PW91(which stands for Perdew and Wang 1991). There are also hybrid methods that are a linear combination

of HF, local and gradient-corrected exchange terms. This exchange functional is then combined with a local and a gradient corrected correlation functional. The widely used hybrid functionals are B3LYP, B3P86 and B3PW91. In general, gradient-corrected or hybrid functionals give the most accurate results [Young, 2001; Geneste and Carpy, 2004]. The advantages of the method are its high accuracy and efficiency which make it particularly well suited for the realistic study of large molecular systems. It describes with consistent reliability organic systems but also inorganic, metallic systems, etc. However, there are a few cases where X_α and LDA do quite well. LDA is known to give less accurate geometries and predicts binding energies significantly too large. The current generations of hybrid functionals are a bit more accurate than the present gradient-corrected techniques. One recent development in DFT is the advent of linear scaling algorithms [Young, 2001]. These algorithms replace the Coulomb terms for distant regions of the molecule with multipole expansions. This results in a method with a time complexity of N for sufficiently large molecules. The most common linear scaling techniques are the fast multipole method (FMM) and the continuous fast multipole method (CFMM). DFT is generally faster than Hartree-Fock for systems with more than 10-15 non-hydrogen atoms, depending on the numeric integral accuracy and basis set. Linear scaling algorithms do not become advantageous until the number of heavy atoms exceeds 30 or more, depending on the general shape of the molecule [Young, 2001].

DFT calculations must use a basis set. This raises the question of whether DFT-optimized or typical HF-optimized basis sets should be used. Studies using DFT-optimized basis sets have shown little or no improvement over the use of a similar-size conventional basis set. Most DFT calculations today are being done with HF-optimized GTO basis sets. The accuracy of results tends to degrade significantly with the use of

very small basis sets. For accuracy considerations, the smallest basis set used is generally 6-31G* or the equivalent. Interestingly, there is only a small increase in accuracy obtained by using very large basis sets. This is probably due to the fact that the density functional is limiting accuracy more than the basis set limitations. Since DFT calculations use numerical integrals, calculations using GTO basis sets are no faster than those using other types of basis sets. It is reasonable to expect that STO basis sets or numeric basis sets would be more accurate due to the correct representation of the nuclear cusp and exponential decay at long distances. The fact that so many DFT studies use GTO basis sets is not a reflection of accuracy or computation time advantages. It is because there were a large number of programs written for GTO HF calculations. HF programs can be easily turned into DFT programs, so it is very common to find programs that do both. There are programs that use cubic spline basis sets (e.g., the dMol and Spartan programs) and STO basis sets (e.g., ADF) [Young, 2001].

The accuracy of results from DFT calculations can be poor to fairly good, depending on the choice of basis set and density functional. The choice of density functional is made more difficult because creating new functionals is still an active area of research. At the time of this book's publication, the B3LYP hybrid functional (also called Becke3LYP) was the most widely used for molecular calculations by a fairly large margin. This is due to the accuracy of the B3LYP results obtained for a large range of compounds, particularly organic molecules. However, it would not be surprising if this functional's dominance changed within a few years. Due to the newness of DFT, its performance is not completely known and continues to change with the development of new functionals. The bibliography at the end of this chapter includes references for studies comparing the accuracy of results. At the present time, DFT results have been very good for organic

molecules, particularly those with closed shells. Results have not been so encouraging for heavy elements, highly charged systems, or systems known to be very sensitive to electron correlation. DFT's recent heavy usage has been due to the often optimal accuracy versus CPU time [Young, 2001].

The advantages of the methods are its high accuracy and efficiency which make it particularly well suited for the realistic study of large molecular systems. It describes with consistent reliability organic systems but also inorganic, metallic systems, etc. The DFT methodology is increasingly used in pharmaceutical, agrochemical and biotechnology research [Geneste and Carpy, 2004]. It is clear that DFT methods have many advantages; they scale well with system size, implicitly include electron correlation effects and the accuracy of DFT methods is comparable to correlated ab initio methods, such as MP2, which do not scale as well. DFT methods can, therefore, be applied to larger molecular systems than traditional ab initio methods. However, despite much work to understand the form of the exchange-correlation energy functional, there is, as yet, no clear approach to improve the quality of the density functional in a systematic fashion and so it is important to test the performance of existing functional. DFT computations can be done with less computer time than the most advanced ab initio MO methods and it can be extended to considerably larger molecules than advanced ab initio methods and are being used extensively in the prediction and calculation of molecular properties [Carey and Sundberg, 2007]. Good correlations with experimental values were observed and predictions were made for several cases that have not been measured experimentally. As a result, there has been extensive use of B3LYP and other DFT methods in organic chemistry, as with MO calculations, the minimum energy geometry and total energy are

calculated. Also other properties that depend on electronic distribution, such as molecular dipoles, can also be calculated.

Recent publications and latest literatures in the field of computational chemistry showed a lot of activity in the prediction of DFT molecular energies and properties in comparison to accurate experimental results, if available, or high level calculations using traditional correlated methods [Sabin and Brandas, 2005]. It is clear that quantum mechanical methods are an important tool in chemical investigations. In particular, despite some problems, non-local hybrid DFT methods generally give reliable results for a remarkable range of chemical problems. The B3LYP Density functional theory (DFT) is then supposed to be the most reliable method for the calculation of geometries and energies of the compounds of our interest in this research work.

2.3.4 ONIOM method

Various computational methods have strengths and weaknesses. Quantum mechanics (QM) can compute many properties and model chemical reactions. Molecular mechanics (MM) is able to model very large compounds quickly. It is possible to combine these two methods into one calculation, which models a very large compound using MM and one crucial section of the molecule with QM. This calculation is designed to give results that have very good speed when only one region needs to be modeled quantum mechanically. It can also be used to model a molecule surrounded by solvent molecules. This type of calculation is called a QM/MM calculation [Young, 2001].

The earliest combined calculations were done simply by modeling different parts of the system with different techniques. For example, some crucial part of the system could be modeled by using an ab initio geometry-optimized calculation. The complete system could then be modeled using MM, by holding the geometry of the initial region fixed and

optimizing the rest of the molecule. This procedure yields geometry for the whole system, although there is no energy expression that reflects non-bonded interactions between the regions. One use is to compute the conformational strain in ligands around a metal atom, which is important in determining the possibility of binding. In order to do this, the metal atom is removed from the calculation, leaving just the ligands in the geometry from the complete system. Two energy calculations on these ligands are then performed: one without geometry optimization and one with geometry optimization. The difference between these two energies is the conformational strain that must be introduced into the ligands in order to form the compound. Another technique is to use an ab initio method to parameterize force field terms specific to a single system. For example, an ab initio method can be used to compute the reaction coordinate for a model system. An analytic function can then be fitted to this reaction coordinate. A MM calculation can then be performed, with this analytic function describing the appropriate bonds, and so on [Young, 2001].

Quantitative energy values are one of the most useful results from computational techniques. In order to develop a reasonable energy expression when two calculations are combined, it is necessary to know not only the energy of the two regions, but also the energy of interaction between those regions. There has been a number of energy computation schemes proposed. Most of these schemes can be expressed generally as [Young, 2001],

$$E = E_{QM} + E_{MM} + E_{QM/MM} + E_{pol} + E_{boundary} \quad (13)$$

The first two terms are the energies of the individual computations. The $E_{QM/MM}$ term is the energy of interaction between these regions, if we assume that both regions remain fixed. It may include van der Waals terms, electrostatic interactions, or any term in the

force field being used. E_{pol} is the effect of either region changing as a result of the presence of the other region, such as electron density polarization or solvent reorganization. E_{boundary} is a way of representing the effect of the rest of the surroundings, such as the bulk solvent.

An alternative formulation of QM/MM is the energy subtraction method. In this method, calculations are done on various regions of the molecule with various levels of theory. Then the energies are added and subtracted to give suitable corrections. This results in computing an energy for the correct number of atoms and bonds analogous to an isodesmic strategy. Three such methods have been proposed by Morokuma and coworkers [Young, 2001]. The integrated MO+MM (IMOMM) method combines an orbital-based technique with an MM technique. The integrated MO+MO method (IMOMO) integrates two different orbital-based techniques. *The our own n-layered integrated MO and MM method* (ONIOM) allows for three or more different techniques to be used in successive layers. The acronym ONIOM is often used to refer to all three of these methods since it is a generalization of the technique. The IMOHC (Integrated molecular orbital method with harmonic cap) method is a modification of IMOMO and IMOMM in which the bond distances to the link atom in the real system and the capping atom in the model system are not frozen, but are allowed to vary in the optimization [Levine, 2000]. The ONIOM method is an extension of IMOMO and IMOMM that performs calculations on n different systems using n layers of calculation. Each system and calculation level constitutes a layer. The IMOMO and IMOMM methods are versions of ONIOM with $n=2$. ONIOM3 is the three-layered version of ONIOM and uses a real system calculated at low level, an intermediate model system calculated at medium level, and a small model system calculated at high level [Levine, 2000].

This technique can be used to model a complete system as a small model system and the complete system. The complete system would be computed using only the lower level of theory. The model system would be computed with both levels of theory [Young, 2001]. The energy for the complete system, combining both levels of theory, would then be,

$$E = E_{\text{low,complete}} + E_{\text{high,model}} - E_{\text{low,model}} \quad (14)$$

Likewise, a three-layer system could be broken down into small, medium, and large regions, to be computed with low, medium, and high levels of theory (L, M, and H respectively). The energy expression would then be

$$E = E_{\text{H,small}} + E_{\text{M,medium}} - E_{\text{M,small}} + E_{\text{L,large}} - E_{\text{L,medium}} \quad (15)$$

This method has the advantage of not requiring a parameterized expression to describe the interaction of various regions. Any systematic errors in the way that the lower levels of theory describe the inner regions will be canceled out. QM/MM methods do not allow for charge transfer between different regions of the system. Thus, partitioning should not divide sections expected to have a charge separation. The geometry of one region will affect the geometry of the other because interaction between regions is not a systematic effect. If we assume transferability of parameters, this method avoids any over counting of the non-bonded interactions. One disadvantage is that the lower levels of theory must be able to describe all atoms in the inner regions of the molecule. Thus, this method cannot be used to incorporate a metal atom into a force field that is not parameterized for it. The effect of one region of the molecule causing polarization of the electron density in the other region of the molecule is incorporated only to the extent that the lower levels of theory describe polarization. This method requires more CPU time than most of the others mentioned. However, the extra time

should be minimal since it is due to lower-level calculations on smaller sections of the system [Young, 2001].

The concept of mixing methods of different accuracy has been generalized in the ONIOM method to include several (usually two or three) layers, for example using relatively high-level theory in the central part, a lower level electronic structure theory in an intermediate layer and force field to treat the outer layer. The original ONIOM method only employed mechanical embedding for the QM/MM interface, but more recent extensions have also included electronic embedding. The ONIOM method employs an extrapolation scheme based on assumed additivity, in analogy to the CBS, G_n and W_n methods [Jensen, 2007]. For a two-layer scheme, the small (model) system is calculated at both the low and high levels of theory, while the large (real) system is calculated at the low level of theory. The result for the real system at the high theoretical level is estimated by adding the change between the high and low levels of theory for the model system to the low level results for the real system.

Extrapolation can be done for multi-level ONIOM models, although it requires several intermediate calculations. It should be noted that derivatives of the ONIOM model can be constructed straightforwardly from the corresponding derivative of the underlying methods, and it is thus possible to perform geometry optimizations and vibrational analysis using the ONIOM energy function. QM/MM methods are often used for modelling solvent effects, with the solvent treated by MM methods, but in some cases the first solvation shell is included in the QM region. If such methods are used in connection with dynamical sampling of the configurational space, it is possible that MM solvent molecules can enter the QM regions, or QM solvent molecules can drift into the MM region [Jensen, 2007]. In order to handle such situations, there must be a procedure

for allowing solvent molecules to switch between a QM and MM description. In order to ensure a smooth transition, a transition region can be defined between the two parts, where a switching function is employed to make a continuous transition between the two descriptions.

The ONIOM method developed by Keiji Morokuma and his colleagues is an onion-skin-like extrapolation method that allows us to combine a variety of QM methods as well as an MM method in multiple layers [Carloni and Alber, 2003 ; Morokuma, 2002 ; Vreven *et al.*, 2012]. The concept of ONIOM is extremely simple. The target calculation is the *high* level calculation for a large *real* system, $E(\text{high,real})$, which is prohibitively expensive. We can perform for the *real* system an inexpensive *low* level calculation, $E(\text{low,real})$, that may not be sufficiently accurate for the property we want to calculate. We can also carry out an accurate *high* level calculation for a smaller *model* system, $E(\text{high,model})$. Starting from $E(\text{low,model})$, if one assumes that the correction for the *high* level, $E(\text{high,model}) - E(\text{low,model})$, and the correction for the *real* system, $E(\text{low,real}) - E(\text{low,model})$, to be additive, the energy of the *real* system at the *high* level can be estimated extrapolatively from three independent calculations as [Morokuma, 2002 ; Vreven *et al.*, 2012 ; Tao and Schlegel, 2010],

$$E(\text{ONIOM,real}) = E(\text{high,model}) + E(\text{low,real}) - E(\text{low,model}) \quad (16)$$

The definition of the model system is rather straightforward when there is no covalent bond between the layers. If one considers a solute molecule complexed with one solvent molecule as the real system, the solute will be the model system, and the solute{solvent interaction is naturally included at the low-level calculation of the real system. The situation becomes more complicated when a covalent bond exists between the layers. ONIOM adopts the most straightforward way of ensuring that the model system is

representative of the real system, i.e. saturating the dangling bonds at the end of the model layer with link atoms. For example, if a methyl group is in the low-level layer, this group is substituted by a hydrogen atom in the model system [Morokuma, 2002].

From the ONIOM energy in the above equation, we can calculate the energy gradient with respect to nuclear coordinates, $\partial E(\text{ONIOM,real})/\mathbf{R}_{\text{real}}$, which can be used to optimize the geometry of the real system on the $E(\text{ONIOM,real})$ potential surface. The Hessian or higher-order derivatives can also be calculated. One can also calculate various properties, such as the dipole moment and nuclear magnetic resonance shielding, as ONIOM expectation values of the corresponding operator. The most important question when using the ONIOM scheme is how to select the methods that will be combined, and the partitioning of the system into high- and low-level layers. These two factors are closely related. An arbitrary choice of model and method combination does not usually work. The S-value, $S(\text{level})$, is the difference between the *real* and the *model* systems, or the effect of the substituent (second layer) evaluated at a given level.

The main problem with QM/MM methods is that there is no unique way of deciding which part should be treated by force field and which by quantum mechanics. The stitching together of the two regions is certainly not unique, and the many possible combinations of force field and QM methods make QM/MM methods still somewhat experimental. Furthermore, the inability to perform calibration studies of large systems by pure QM methods makes it difficult to evaluate the severity of the approximations included in QM/MM methods [Jensen, 2007].

2.4 Basis Sets

A basis set is a set of functions used to describe the shape of the orbitals in an atom. Molecular orbitals and entire wave functions are created by taking linear combinations of basis functions and angular functions. Most semiempirical methods use a predefined basis set. When *ab initio* or density functional theory calculations are done, a basis set must be specified. Although it is possible to create a basis set from scratch, most calculations are done using existing basis sets [Young, 2001]. The type of calculation performed and basis set chosen are the two biggest factors in determining the accuracy of results.

The quantum mechanical calculations on ground state energies involve the initial selection of a basis set, which in its simplest, or minimal, form is the electronic configuration of the atom in question. Quantum mechanical calculations are not capable of actually generating their own basis sets that must instead be put in by hand. So whereas the correct ground state electronic configurations can in many cases be selected among a number of plausible options, the options themselves are not provided by the theory [Scerri, 2004].

Basis sets in quantum chemistry are generally built according to the notion that they should reflect both the chemical ideas of orbitals as well as the physical reality of long-range interactions (such as hydrogen bonding) that may be more diffuse than most conventional bonding theories would suggest. Early research showed that Slater functions describe an orbital very well, as they maintain the cusp of the electronic potential near the nucleus; but they are also computationally rather expensive [Barden and Schaefer, 2000]. An alternative that is in general use today is to utilize sets of easier-to-calculate linear combinations of Gaussian functions rather than Slater functions. Generally speaking, a

basis set is a collection of basis functions. For carbon, nitrogen, and oxygen compounds, a minimum basis set is composed of a 1s function for each hydrogen and 1s, 2s, and three 2p functions for each of the second-row atoms. More extensive and flexible sets of basis functions are in wide use [Carey and Sundberg, 2007]. These basis sets may have two or more components in the outer shell, which are called *split-valence* sets. Basis sets may include p functions on hydrogen and/or d and f functions on the other atoms. These are called *polarization functions*. The basis sets may also include *diffuse functions*, which extend farther from the nuclear center. Split-valence bases allow description of tighter or looser electron distributions on atoms in differing environments. Polarization permits changes in orbital shapes and shifts in the center of charge. Diffuse functions allow improved description of the outer reaches of the electron distribution.

Ab initio methods try to derive information by solving the Schrödinger equation without fitting parameters to experimental data. Actually, *ab initio* methods also make use of experimental data, but in a somewhat more subtle fashion. Many different approximate methods exist for solving the Schrödinger equation, and which one to use for a specific problem is usually chosen by comparing the performance against known experimental data. Experimental data thus guides the selection of the computational model, rather than directly entering into the computational procedure [Jensen, 2007]. Specific *ab initio* methods are characterized by the form of the wave function and the nature of the basis set functions that are used. The most common form of the wave function is the single determinant of molecular orbitals expressed as a linear combination of basis functions, as is the case with semiempirical calculations [Carey and Sundberg, 2007].

One of the approximations inherent in essentially all ab initio methods is the introduction of a basis set. Expanding an unknown function, such as a molecular orbital, in a set of known functions is not an approximation if the basis set is *complete*. However, a complete basis set means that an infinite number of functions must be used, which is impossible in actual calculations [Jensen, 2007]. An unknown MO can be thought of as a function in the infinite coordinate system spanned by the complete basis set. When a finite basis set is used, only the components of the MO along those coordinate axes corresponding to the selected basis functions can be represented. The smaller the basis set, the poorer the representation. The type of basis functions used also influence the accuracy. The better a single basis function is able to reproduce the unknown function, the fewer basis functions are necessary for achieving a given level of accuracy. Knowing that the computational effort of ab initio methods scales formally as at least M^4 basis, it is of course of prime importance to make the basis set as small as possible, without compromising the accuracy. The expansion of the molecular orbitals leads to integrals of quantum mechanical operators over basis functions, and the ease with which these integrals can be calculated also depends on the type of basis function. In some cases the accuracy per- function criterion produces a different optimum function type than the efficiency per- function criterion [Jensen, 2007].

In computational quantum chemistry, the period from 1970 onwards has seen numerous studies of organic molecules, with ever increasing sophistication in the treatment of electron correlation, vibronic and environmental effects. It became evident that only the most accurate ab initio methods in conjunction with large and flexible basis sets give quantitative agreement with experiment [Kaupp *et al.*, 2004].

There are two types of basis functions (also called *Atomic Orbitals*, AO) commonly used in electronic structure calculations: *Slater Type Orbitals* (STO) and *Gaussian Type Orbitals* (GTO) [Jensen, 2007]. For diatomic molecules, the basis functions are usually taken as atomic orbitals, some centered on one atom, the remainder centered on the other atom; each AO can be represented as a linear combination of one or more Slater-type orbitals (STO's), called LC-STO. For polyatomic molecules, the LC-STO method uses STO's centered on each of the atoms [Levine, 2000]. To speed up molecular integral evaluation, Boys proposed (in 1950) the use of Gaussian type functions (GTFs) instead of STOs for the atomic orbitals in an LCAO wave function, both STOs and GTOs can be chosen to form a complete basis. The increase in the number of GTO basis functions, however, is more than compensated for by the ease of which the required integrals can be calculated. In terms of computational efficiency, GTOs are therefore preferred and are used almost universally as basis functions in electronic structure calculations. Furthermore, essentially all applications take the GTOs to be centered at the nuclei. For certain types of calculations the centre of a basis function may be taken not to coincide with a nucleus, for example being placed at the centre of a bond or between non-bonded atoms for improving the calculation of van der Waals interactions [Jensen, 2007].

GTO basis sets require more primitives to describe the wave function than are needed for STO calculations. However, the integrals over GTO primitives can be computed analytically, which is so much faster than the numeric integrals over STO functions that any given accuracy can be obtained most quickly using GTO functions. As such, STO basis sets are sometimes used for high-accuracy work, but most calculations are now done with GTO basis sets [Young, 2001]. Early calculations were often done with Slater functions, designated STO for Slater-type orbitals. Currently most computations are done

with Gaussian basis functions, designated by GTOs. A fairly accurate representation of a single STO requires three or more GTOs, which compares the forms for one, two, and three GTOs. At the present time most basis sets use a six-Gaussian representation, usually designated 6G [Carey and Sundberg, 2007]. Choosing a standard GTO basis set means that the wave function is being described by a finite number of functions. This introduces an approximation into the calculation since an infinite number of GTO functions would be needed to describe the wave function exactly. Differences in results due to the quality of one basis set versus another are referred to as basis set effects. In order to avoid the problem of basis set effects, some high-accuracy work is done with numeric basis sets. These basis sets describe the electron distribution without using functions with a predefined shape [Young, 2001].

Having decided on the type of function (STO/GTO) and the location (nuclei), the most important factor is the number of functions to be used. The smallest number of functions possible is a minimum basis set. Only enough functions are employed to contain all the electrons of the neutral atom(s). For hydrogen (and helium) this means a single *s*-function. For the first row in the periodic system it means two *s*-functions (1s and 2s) and one set of *p*-functions (2p_x, 2p_y and 2p_z). Lithium and beryllium formally only require two *s*-functions, but a set of *p*-functions is usually also added. For the second row elements, three *s*-functions (1s, 2s and 3s) and two sets of *p*-functions (2p and 3p) are used. The next improvement of the basis sets is a doubling of all basis functions, producing a Double Zeta (DZ) type basis [Jensen, 2007]. The term zeta stems from the fact that the exponent of STO basis functions is often denoted by the Greek letter ζ . A DZ basis thus employs two *s*-functions for hydrogen (1s and 1s'), four *s*-functions (1s, 1s', 2s

and 2s') and two sets of p -functions (2p and 2p') for first row elements, and six s -functions and four sets of p -functions for second row elements.

Most calculations today are done by choosing an existing segmented GTO basis set. These basis sets are identified by one of a number of notation schemes. These abbreviations are often used as the designator for the basis set in the input to ab initio computational chemistry programs [Young, 2001]. The smallest basis sets are called minimal basis sets. The most popular minimal basis set is the STO-3G set. This notation indicates that the basis set approximates the shape of a STO orbital by using a single contraction of three GTO orbitals. One such contraction would then be used for each orbital, which is the definition of a minimal basis. Minimal basis sets are used for very large molecules, qualitative results, and in certain cases quantitative results. There are STO- n G basis sets for $n=2-6$. Another family of basis sets, commonly referred to as the Pople basis sets, are indicated by the notation 6-31G. This notation means that each core orbital is described by a single contraction of six GTO primitives and each valence shell orbital is described by two contractions, one with three primitives and the other with one primitive. These basis sets are very popular, particularly for organic molecules. Other Pople basis sets in this set are 3-21G, 4-31G, 4-22G, 6-21G, 6-311G, and 7-41G.

Pople developed a system of abbreviations that indicates the composition of the basis sets used in ab initio calculations [Carey and Sundberg, 2007]. The series of digits that follows the designation 3G or 6G indicates the number of Gaussian functions used for each successive shell. The combination of Gaussian functions serves to improve the relationship between electron distribution and distance from the nucleus. Polarization functions incorporate additional orbitals, such as p for hydrogen and d and/or f for second-row atoms. This permits changes in orbital shapes and separation of the centers of

charge. The inclusion of d and f orbitals is indicated by the asterisk (*). One asterisk signifies d orbitals on second-row elements; two asterisks means that p orbitals on hydrogen are also included. If diffuse orbitals are used they are designated by a plus sign (+), and the designation double plus (++) means that diffuse orbitals are present on both hydrogen and the second-row elements. Split-valence sets are indicated by a sequence defining the number of Gaussians in each component. Split-valence orbitals are designated by primes, so that a system of three Gaussian orbitals would be designated by single, double, and triple primes.

Minimal basis sets (STO-3G) is a rarely inexpensive one, which can be used for calculations on quite large molecules. It is minimal in the sense of having the least number of functions per atom required to describe the occupied orbital of that atom, i.e. the smallest number of functions possible is a minimum basis set [Jensen, 2007]. A minimal basis set has rather limited variational flexibility particularly if exponent are optimized [Szabo and Ostlund, 1982]. The first step in improving upon the minimal basis set involves using two functions for each of the minimal basis functions producing a *Double Zeta* (DZ) type basis [Mueller, 2002]. The term zeta stems from the fact that the exponent of STO basis functions is often denoted by the Greek letter ζ . A DZ basis thus employs two s -functions for hydrogen (1s and 1s'), four s -functions (1s, 1s', 2s and 2s') and two sets of p -functions (2p and 2p') for first row elements, and six s -functions and four sets of p -functions for second row elements.

The next step up in basis set size is a *Triple Zeta* (TZ). Such a basis contains three times as many functions as the minimum basis, i.e. six s -functions and three p -functions for the first row elements. Some of the core orbitals may be saved by only splitting the valence, producing a *triple split valence* basis set. The names *Quadruple Zeta* (QZ) and

Quintuple or Pentuple Zeta (PZ or 5Z, but not QZ) for the next levels of basis sets are also used, but large basis sets are often given explicitly in terms of the number of basis functions of each type [Jensen, 2007].

As the Pople basis sets have further expanded to include several sets of polarization functions, *f* functions and so on, there has been a need for a new notation. In recent years, the types of functions being added have been indicated in parentheses [Young, 2001]. Many basis sets are just identified by the author's surname and the number of primitive functions. Some examples of this are the Huzinaga, Dunning, and Duijneveldt basis sets. For example, D95 and D95V are basis sets created by Dunning with nine *s* primitives and five *p* primitives. The V implies one particular contraction scheme for the valence orbitals. The acronyms *SZ* and *DZ* stand for single zeta and double zeta, respectively. A *P* indicates the use of polarization functions. Since this notation has been used for describing a number of basis sets, the name of the set creator is usually included in the basis set name. If the author's name is not included, either the Dunning-Hay set is implied or the set that came with the software package being used is implied. For example, an extension *aug-cc-pVDZ*, the 'aug' denotes that this is an augmented basis (diffuse functions are included). The 'cc' denotes that this is a correlation-consistent basis, meaning that the functions were optimized for best performance with correlated calculations. The 'p' denotes that polarization functions are included on all atoms. The 'VDZ' stands for valence double zeta, meaning that the valence orbitals are described by two contractions. There is a family of correlation consistent basis sets created by Dunning and coworkers and these sets have become popular for high-accuracy correlated calculations [Jensen, 2007 ; Barden and Schaefer, 2000 ; Muller, 2006 ; Muller-Plathe, 1998 ; Carey and Sundberg, 2007 ; Sabin and Brandas, 2005]. There have been many

more basis sets developed, it is also possible to combine basis sets or modify them, which can result in either poor or excellent results, depending on how expertly it is done. The correlation consistent basis sets have been most widely used in recent years for high-accuracy calculations. In this research work, both Pople basis sets and correlation consistent basis sets were incorporated in order to obtain desired.