CHAPTER 3
Computational Methodology
3.1. Introduction

A number of theoretical methods including molecular mechanics (MM) [1], molecular dynamics [2], quantum mechanics (QM) [3], quantum mechanics/molecular mechanics (QM/MM) have been used to study the CD complexes.

MM methods based on classical empirical potentials have been proven to provide an effective mean for simulating complex molecules. The potential energy of all systems in MM is calculated using force fields. Molecular mechanics can be used to study small molecules as well as large biological systems or material assemblies with many thousands to millions of atoms. MD method is a computer simulation method for studying the physical movements of atoms and molecules, and is thus a type of N-body simulation. The atoms and molecules are allowed to interact for a fixed period of time, giving a view of the dynamical evolution of the system. MD methods involve the application of classical mechanics for simulating the movement of the nucl ei of an assembly of atoms and molecules.

In recent years, theoretical methods primarily consisted of the application of quantum mechanics to solve the problems in chemistry. QM model originates from the Schrödinger equation proposed in 1925. Exact solutions to Schrödinger equation for poly-electronic systems are impossible and approximations are needed to be made. The first approximation was the Hartree-Fock (HF) approximation which laid the foundation for QM methods used for smaller as well as larger molecules. Except for molecules that consist of transition metals, HF model provides good description of molecular geometries; however, the processes where explicit bond making/bond breaking takes place, HF model
gives very poor results. The main drawback of HF model is due to incomplete description of electron correlation or electron-electron repulsion in multi-electron wave function. Neglecting electron correlation can lead to large deviation from experimental results.

A number of approaches to include electron correlation to the multi electron wave function are Density Functional Theory (DFT), Moller-Plesset Perturbation Theory (MP2, MP3 etc.), Configuration Interaction (CI), Coupled Cluster Methods (CC) etc.

DFT has become a promising tool for calculating molecular structures, energies, molecular orbitals, vibrational frequencies, atomization energies, ionization energies, electric and magnetic properties, reaction pathways etc [4-19]. The main objective of density functional theory is to replace the many-body electronic wavefunction with the electronic density as the basic quantity. Whereas the many-body wavefunction is dependent on 3N variables, three spatial variables for each of the N electrons, the density is only a function of three variables and is a simpler quantity to deal with both conceptually and practically.

DFT starts with the seminal theorems by Hohenberg and Kohn showing that the energy of a system in its electronic ground state is a unique functional of the electron density [20]. The Hohenberg-Kohn theorems were not the fruit of immaculate conception, however, but rather built on the ideas and concepts developed by Thomas, Fermi and Dirac some thirty years before [21, 22]. DFT doesn’t attempt to solve the Schrodinger equation for the molecular electronic wave function. DFT would never have been more than a model had Hohenberg and Kohn not shown the existence of a unique and universal energy functional of the electronic density of a system.
This theorem states that the energy and all other properties of a ground state molecule are uniquely determined by the ground state electron probability density. This is expressed by saying that the ground state electronic energy $E_{gs}$ is a functional of density ($\rho$). This is written as,

$$E_{gs} = E_{gs} [\rho(x,y,z)]$$

where, the square brackets denote a functional relation.

More specifically, Hohenberg and Kohn (HK) proved that, for a given electronic density, there can be no more than one Hamiltonian, meaning that the external potential ($r$) of the Hamiltonian can only differ by a constant. In other words, the electronic density of the ground state is exactly determined by the external potential. The theorem can be proved very easily with the help of Variation Principle.

The energy functional mapping a value of the energy from the electron density can be separated in two parts, as in HF theory. One part describes how a system of non-interacting electrons moves in the external potential and the other part describes the electron-electron interactions. This can be expressed as

$$E[\rho(r)] = T_{TF} [\rho(r)] + V_{ne} [\rho(r)] + V_{ee} [\rho(r)] + \Delta T[\rho(r)] + \Delta V_{ee} [\rho(r)]$$

$$= E_{TF} [\rho(r)] + \Delta T[\rho(r)] + \Delta V_{ee} [\rho(r)]$$

All terms of the above expression have the same electronic density as their argument and the first three terms on the right hand side are one-electron functionals and would, for a system of non-interacting electrons, describe this exactly. The first term, $T_{TF} [\rho(r)]$, is the kinetic energy functional as obtained from statistical mechanics for a non-interacting electron gas. The second term, $V_{ne} [\rho(r)]$, expresses the interaction between the nuclei and
electron density and $V_{ee} \left[ \rho(r) \right]$ is the classical electron-electron repulsion for electronic densities.

$$T_{FF} \left[ \rho(r) \right] = C_p \int \rho^{\frac{5}{3}} (r) dr, \quad C_p = \frac{3}{10} (3\pi^2)^{2/3}$$

$$V_{ne} \left[ \rho(r) \right] = \sum_{k=1}^{M} \int \frac{Z_k}{r - R_k} \rho(r) dr$$

$$V_{ee} \left[ \rho(r) \right] = \frac{1}{2} \int \frac{\rho(r_1) \rho(r_2)}{|r_1 - r_2|} dr_1 dr_2$$

The last two terms of equation of equation (3.2) are corrections to the kinetic energy and electron-electron interaction energies needed to account for the errors introduced by assuming a system of non-interacting electrons. These terms are commonly added into a single term, the exchange correlation functional $V_{xc} \left[ \rho(r) \right]$

Within the Kohn-Sham (KS) formalism the assumption is now made that the total density, analogous to the wave function in HF formalism, consists of orbitals, that is

$$\rho = \rho_s = \sum_{i=1}^{N} |\theta_i^{KS}|^2 \quad (3.3)$$

and that the functionals in equation (3.2) are rewritten as a sum of one-electron functionals

$$E[\rho(r)] = \sum_{i} \left[ \left\langle \phi_i \left| -\frac{1}{2} \nabla_i^2 \right| \phi_i \right\rangle - \left\langle \phi_i \left| \sum_{k} \frac{Z_k}{r_i - R_k} \right| \phi_i \right\rangle \right] + \sum_{i} \left( \left\langle \phi_i \left| \frac{1}{2} \int \frac{\rho(r')dr'}{|r_i - r'|} \phi_i \right\rangle \right) + V_{xc} \left[ \rho(r) \right] \quad (3.4)$$

The correction terms in the energy expression in the equation (3.2) are represented here by the exchange–correlation term $V_{xc}[\rho(r)]$. It is important to note that if the exact form of the exchange-correlation term was known, DFT would have been an exact method,
just like full-CI. Also it is not, and even if it was known, it is unlikely that the evaluation of it would prove easier than other methods including electron correlation.

The expression for exchange correlation potential $V_{xc}$ is found to be

$$V_{xc}(x,y,z) = \frac{\partial E_{xc}[\rho]}{\partial \rho}$$ \hspace{1cm} (3.5)

Unfortunately, the functional $V_{xc}[\rho(r)]$ is not known, and hence $E_{gs}[\rho]$ in equation (i) is unknown, so the Hohenberg-Kohn theorem doesn’t tell us how to calculate $E_{gs}$ from or how to find it without first finding the ground state molecular electronic functions.

Kohn and Sham proposed a certain form for $E_{xc}$, called the local (spin) density approximation (LDA or LSDA) that theory shows to be accurate when the electron density varies slowly with position [23]. In a molecule, does not vary very slowly with position. It is found that LSDA KS DFT calculations give satisfactory results for molecular geometries, dipole moments and vibrational frequencies but poor results for atomization energies.

It is convenient to split $E_{xc}$ into an exchange part and a correlation part:

$$E_{xc}[\rho] = E_{x}[\rho] + E_{c}[\rho]$$ \hspace{1cm} (3.6)

This is a good approximation for $E_{xc}[\rho]$ suggested by Kohn and Sham. A better approximation used in the late 1980s was the so called generalized-gradient approximation (GGA), in which $E_{xc}$ is expressed as an integral of a certain function of and the derivatives

$$\frac{\partial \rho}{\partial x}, \frac{\partial \rho}{\partial y}, \frac{\partial \rho}{\partial z} \quad (\text{These derivatives are called gradient of } \rho).$$
The most widely used functional in DFT calculations done in the period 1995-2000 was the hybrid functional called B3LYP where B indicates that it includes a term for devised by Becke, LYP indicates a term for devised by Lee, Yang and Parr and 3 indicates that it contains three empirical parameters whose values were chosen to optimize the performance.

3.2. Basis set

A basis set in quantum chemical calculation is a set of functions used to construct the molecular orbitals, which are expanded as a linear combination of such functions with the co-efficients to be determined [24]. In the early days of quantum chemistry, Slater type orbitals (STOs) were used as basis functions due to their similarity with the eigenfunctions of the hydrogen atom and is defined as,

\[ S_{n,l,m}(r, \theta, \phi) = N_n r^{-\xi} Y_{l,m}(\theta, \phi) \]

where, \( N_n \) is the normalization constant, \( \xi \) is the orbital exponent, \( n \) and \( l \) are the principal and orbital quantum numbers, \( Y_{l,m}(\theta, \phi) \) are the angularly dependant spherical harmonics.

A Gaussian type orbital is a function of the term \( e^{-\alpha r^2} \) and is defined as

\[ G_{n,l,m}(r, \theta, \phi) = N_n r^{-n-1} e^{-\alpha r^2} Y_{l,m}(\theta, \phi) \]

The STOs are not used directly in modern theoretical research because the integrals in the resulting secular determinants are difficult to evaluate. The advantage of GTOs is that the product of two Gaussian functions is itself a Gaussian function that lies between the centres of the two contributing functions.
Gaussian 09 program establish a set of most commonly used basis functions and the minimal basis set is the STO-3G. Computed energy values of a system depend on the number of Gaussian used. Accuracy of STO basis set increase with the number of primitive Gaussian functions (i.e STO-4G, STO-5G, and STO-6G) but the size of the expansion are fairly insensible to energy differences, optimized geometries and atomic charges. On the other hand, split valence basis sets, double, triple, quadruple-zeta basis sets and many more are used to obtain some improvements in the geometry as compared to smaller basis sets.

The hybrid QM/MM approach treats different parts of a system simultaneously with good accuracy and lower computational cost compared to ab-initio and DFT, and it has been proved to be effective and reliable for investigating inclusion interaction of CDs or their derivatives with guest molecules [25-28]

### 3.3. DFT-based reactivity descriptors

The electronic chemical potential of a molecular (including atomic or ionic) species, is defined as the infinitesimal change in energy when electronic charge is added to it. In theoretically chemistry, the chemical potential ($\mu$) is defined as the negative of the electronegativity ($\chi$) by Iczkowski and Margrave [29] and defined as

$$\mu = \left( \frac{\partial E}{\partial N} \right)_{\nu(\vec{r})}$$  \hspace{1cm} (3.7)

Now since the more electronegative a species, the more its energy should drop when it acquires electrons, so there should be a link between the chemical potential and electronegativity. If for convenience electronegativity is chosen as positive, then since
is negative then it may be defined the electronegativity $\chi$ as the negative of the electronic chemical potential:

$$\chi = -\mu = -\left( \frac{\partial E}{\partial N} \right)_{\nu(\vec{r})} \quad (3.8)$$

From this viewpoint, the electronegativity of a species is the drop in energy when an infinitesimal amount (infinitesimal so that it remains the same species) of electronic charge enters in it. It is a measure of how hospitable an atom or ion, or a group or atoms in molecule, is to the ingress of electronic charge which fits in. Hardness ($\eta$) [30] of an electronic system is defined as the second derivative of total energy ($E$) with respect to the number of electrons ($N$) at constant external potential, $\nu(\vec{r})$.

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_{\nu(\vec{r})} = \frac{1}{2} \left( \frac{\partial \mu}{\partial N} \right)_{\nu(\vec{r})} = -\left( \frac{\partial \chi}{\partial N} \right)_{\nu(\vec{r})} \quad (3.9)$$

The hardness of a species is then the amount by which its electronegativity – its ability to accept electrons – decreases when an infinitesimal amount of electronic charge is added to it. Intuitively, a hard molecule is like rigid container that does not yield as electrons are forced in, so the pressure (analogous to the electron density) inside builds up, resisting the ingress of more electrons. A soft molecule may be likened to a balloon that can expand as it acquires electrons, so that the ability to accept still more electrons is not so seriously compromised. Softness is thus the reciprocal of hardness:

$$\sigma = \frac{1}{\eta} \quad (3.10)$$
Using the finite difference approximation, global hardness and chemical potential can be approximated as

\[ \eta = \frac{IP - EA}{2} \]  \hspace{1cm} (3.11)

\[ \mu = -\left( \frac{IP + EA}{2} \right) \]  \hspace{1cm} (3.12)

where, IP and EA are the first vertical ionization potential and electron affinity, respectively, of the chemical system.

Further approximation using Koopmans theorem [31] the above parameter can be expressed by taking IP and EA as negative of the HOMO and LUMO energies,

\[ \mu = \frac{E_{LUMO} + E_{HOMO}}{2} \]  \hspace{1cm} (3.13)

\[ \eta = \frac{E_{LUMO} - E_{HOMO}}{2} \]  \hspace{1cm} (3.14)

where, \( E_{LUMO} \) is the energy of the lowest unoccupied molecular orbital and \( E_{HOMO} \) is the energy of the highest occupied molecular orbital.

Parr et al. [32] introduced the global electrophilicity index (\( \omega \)) in terms of chemical potential and hardness as

\[ \omega = \frac{\mu^2}{2\eta} \]  \hspace{1cm} (3.15)

According to this definition, \( \omega \) describes the electrophilic power of a molecule.
3.4. References


