PREFACE

A wide variety of computational methods are available for exploring molecular structures and reactivity in chemistry. These range from molecular mechanics calculations allowing determination of the geometry of a molecule to *ab initio* calculations for the electronic structure of compounds. Electronic structure calculations can be carried out with sufficient rigor so that the results are now comparable with experimental results in many cases. Density Functional Theory (DFT) with hybrid functional like B3LYP, for example, is very popular especially for studies on organometallic molecules and their reactions. Traditional *ab initio* approaches including Hartree-Fock (HF) and post-HF methods that include configuration interaction, such as MP2 and MP4 continue to be used, often for comparison with DFT based methods. Semi-empirical methods now appear to have only limited use except in large systems, in combination with molecular mechanics (MM) calculations. A relatively new use of MM for large systems is in hybrid calculations where the reactive center of the system is treated at a higher level leaving the remainder to be treated at the MM level. These hybrid QM/MM (quantum mechanics/molecular mechanics) calculations, such as ONIOM (our own n-layered integrated molecular orbital and molecular mechanics developed by Morokuma and co-workers) enable one to treat the steric bulk of the big system effectively and computationally efficiently. They appear to be very standard methods particularly in studies relating to reactions of organometallic systems and structures of large biomolecules. A short description of these methods is given below.

- *ab initio:* a wide variety of programs that calculate the electronic structure of molecules using the Schrödinger equation, the values of the fundamental constants and the atomic numbers of the atoms present (Atkins, 1991). Molecular structures, optimized as a function of the electronic structure, are valuable starting points for many studies.

- Density Functional Theory (DFT): a theoretical model in which the energy of an N-electron system is described as a functional of the density.

- Semi-empirical techniques use approximations to evaluate the overlap, repulsion and exchange integrals in solving the Schrodinger equation. Often, these integrals are not evaluated but estimated to reproduce experimental data.

- Molecular mechanics uses classical physics to explain and interpret the behavior of atoms and molecules.

- Molecular dynamics (MD): Newton's laws of motion are used to examine the time-dependent behavior of systems, including vibrations and Brownian motion, using a classical mechanical description. When combined with DFT, it leads to the Car-Parrinello method.

- QM/MM method: It is a molecular simulation method that combines the strength of both QM (accuracy) and MM (speed) calculations, thus resulting in an extremely powerful tool for the study of bigger systems like chemical process in solution, interaction of drugs with biomolecules etc.

Several commercial and educational packages in computational chemistry include a suite of programs that enable study of organic and organometallic molecules in an integrated fashion. While no list can be comprehensive, those that are more popular and useful are listed in several websites URL (http://www.ccl.net/chemistry/links/software/index.shtml).

In the early days of computational chemistry up to 1980's, detailed studies were only carried out on small organic compounds or empirical studies were carried out on transition metal containing organometallics. However, in recent times, significant advancements in theoretical

methods and computer capability (hardware and software), have led to the acceleration of theoretical and computational studies of complex systems including compounds containing transition metal elements. Computational and theoretical studies of organometallic complexes and their reactions have gained immense popularity and the numbers of papers including theoretical studies are dramatically increasing. One reason for this popularity is that organometallic complexes exhibit unusual geometries, bonding, and reactivity which often do not fall into the domain of inorganic or organic chemistry making them difficult to understand.

Catalysis is one of the most extensively studied areas in organometallic chemistry where computational studies already make a real and valuable contribution to the analysis and interpretation of experimental data. However, what might be called 'in silico' catalyst screening and design, has rarely been achieved. One might say that successful prediction of catalyst performance is still a dream. A recent review summarizes the current state of the art in computational chemistry as applied to organometallic catalysis, covering both calculated ligand property descriptors and mechanistic studies of catalytic cycles.[1] Some of the widely studied catalytic reactions of current interest, that provide huge scope for computational and theoretical analysis, are allylic alkylation (Pd),[2] hydrogenation (Rh),[3] hydroformylation (Rh),[4] alkene metathesis (Ru),[5] cross-coupling (Pd),[6] C–H activation (Pd)[7] and amination (Pd).[8] There are many more examples where computational studies appear to be very useful for analysis of crystal structures and NMR structures or prediction of structures where no experimental data are available for complicated organometallic systems. There are a number of studies on drug-DNA/nucleobases interactions using QM/MM-MD simulations where people have investigated the interactions of metal complexes with double stranded (ds) DNA/nucleobases and the effects of their binding on the local and the global structure of DNA. QM/MM methods are also very

helpful for studying catalytic reactions, interpretation of structure of large systems (proteins) and understanding reactions in biological systems.

Scope of the Thesis

In this thesis an attempt is made to use computational chemistry to understand organometallic reactions that are of significance from biological and synthetic view points, such as the action of organometallic complexes on DNA and the mechanism of some catalytic reactions. In many of these cases, the key step involved a nucleophillic attack. Specifically four such problems have been addressed where experimental results are not sufficient to provide a complete mechanistic picture of the reaction. Hence, the thesis contains four chapters with each having an independent brief introduction.

The first chapter deals with the substitution reaction where water replaces chloride ion in the piano stool type ruthenium (II)-arene complexes and subsequently coordination of Ru to guanine/adenine occurs in these complexes. These steps have been studied using density functional theory at the B3LYP level. The complexes have promising anticancer activity. These nucleophilic substitution reactions are very important for activating these complexes so that they can interact with DNA, because DNA is thought to be primary target for their anticancer activity. In this chapter, both associative and dissociative pathways have been explored in the gas phase, as well as in the presence of other solvents for substitution reactions. Among the associative paths, a variety of possibilities can exist for the hydrolysis based on the direction of the nucleophilic attack by a water molecule. The proposed theoretical model for hydrolysis provides new insight into the hydrolysis process in half sandwich ruthenium complexes.

The second chapter deals with the QM/MM calculations to investigate the structural and electronic properties of drug-DNA interactions, where DNA acts as nucleophile towards the metal complex. A series of piano-stool type ruthenium (II)-arene complexes were selected for the present study. These interactions were analyzed using the two layer ONIOM method. The importance of this study lies in the detailed understanding of factors that govern DNA binding and reactivity which is clearly of great pharmacological interest, as it may provide the basis for designing better anticancer agents. Experimental results that explore the structural feature of DNA-metal complexes at a molecular level are very limited. Thus theoretical calculations of molecular and electronic structure represent a valuable complement to experiments. They provide an alternative way to explore structure-activity relationships, and the drug binding mechanism, in detail.

The third chapter reports the use of QM/MM methods in understanding the reaction mechanism and enantioselectivity in an organic transformation. In this section, a computational investigation of the enantioselectivity observed in the allylation of cinnamaldehyde, catalyzed by chiral platinum phosphinite complexes, have been carried out. The catalysts are ascorbic acid based phosphinite complexes where enantioselectivity depends on the substitution of benzyl groups on the chiral phosphinite ligands. From the experiment, it is not clear how the effect of an ancillary ligand can make such a big impact on enantioselectivity. To find out the origin of stereoselectivity, a computational study was taken up. A reaction mechanism was established where the nucleophilic attack determines the rate of the reaction and the corresponding enantioselectivity. A screening process has been utilized to select relevant reactant adducts and corresponding transition states from approximately 200 theoretically possible conformers using MM calculations. Finally with the help of QM/MM calculations, the numbers of contributions of these conformers were estimated. This approach correctly predicts the enantioselectivity in these

reactions catalyzed by these complexes especially when the experimental enantioselectivity is very high.

The fourth chapter of the thesis discusses the use of computational techniques to study the nucleophilic attack of an imine on a Ti-olefin complex. The reaction of Grignard reagents with imines mediated by stoichiometric amounts of titanium isopropoxide has been reported recently. On the basis of deuterium labeling experiments, nucleophilic attack of an imine on a Ti-olefin complex was believed to be a key step. Effect of deuterium labeling on the ratio of products formed is not easy to understand from experiments. Hence a computational study was performed using the DFT method to establish the mechanism of substitution and to understand the role of deuterium labeling.

The thesis also includes a study of Cu-Cu interactions using Atoms in Molecules (AIM) theory in copper complexes with reasonably short Cu-Cu distances. The concept of bond critical points (BCP) from AIM analysis is employed to investigate the Cu^{I}-Cu^{I} bonding interactions in ligand unsupported copper complexes where the Cu^{I}-Cu^{I} contacts are shorter than the sum of their van der Waals radii. There is extensive debate about the nature of interactions between d^{10} "closed shell" systems in copper (Cu^{I}) complexes, which is known as cuprophilicity. In this study, an attempt has been made to compute the electron density between the two Cu^{I} centers and examine the nature of this “interaction”. As this falls outside the main theme of nucleophilic interactions in metal complexes, it has been relegated to an appendix.