CATION COMPLEXATION AND EFFECT OF SOLVATION IN MOLECULES OF BIOLOGICAL INTEREST: A QUANTUM CHEMICAL STUDY

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The thesis entitled “Cation Complexation and Effect of Solvation in Molecules of Biological Interest: A Quantum Chemical Study” contains six chapters. Chapter I gives an introduction solvation of metal ions and cation-π interactions. Chapter II provides an overview of various computational techniques used for the current work. Chapter III presents the benchmark analysis on the proton and metal ion affinities of hetero cyclic amines. Chapter IV explores the solvation of mono- and di-valent metal ions at high level G3, CCSD(T), DFT, and MP2 methods with a range of basis sets. Sequential binding energies are estimated at all these levels and compared with experimental data available in the literature. Chapter V depicts the complexation of metal ion and proton with α,ω-diamines and aromatic amines. Contrasting binding affinities of proton and metal ion in their mono and bi-dentate forms were observed and addressed the reasons for the disparity in their binding affinities. Finally, Chapter VI explains how the solvent can influence the cation–π interactions. Interaction of Li⁺ and Mg²⁺ with π system in the presence, and absence of aqueous solvent was estimated using quantum chemical calculations. This study revealed that the cation–π interactions are highly sensitive to the site of solvation of cation–π system.
1. Introduction

The importance of metal ions and their diverse applications in chemistry and biochemistry are indubitable. In many biochemical systems, metal ions are of paramount importance. Alkali metal ions are very important in living systems as demonstrated by the fact that, in the last few years, the most extensively studied species in the gas phase biomolecular chemistry field are the alkali metal ion complexes. Alkali metal (Li\(^+\), Na\(^+\) and K\(^+\)) ions can be considered as Lewis acids such as H\(^+\), but they present a different behavior in interaction studies. Therefore, understanding the details of local interactions between alkali metal ions and biological molecules are matter of much interest.

Both mono- and di-valent metal ions are well known to be essential for the folding and stability of large RNA molecules that form complex and compact structures. Understanding of the structures and functions of many biomolecules where metal ions play important role warrants a detailed understanding on solvation and desolvation of metal ions. Thus, there is a high interest in the individual hydration characteristics of metal ions. The study of hydrated metal ions in gas phase provides a connection between the essential chemistry of the isolated ion and that in the solvent. Solvated ions also appear in high concentrations in living organisms, where their presence or absence can fundamentally alter the functions of life. In fact, the structure and dynamics of solvation shells have a large impact on any chemical reaction of metal ions in solution.

Once the solvation of metal ions is studied, by explicit treatment of sequential addition of water molecules, we ventured to further understand the effect of micro solvation on
complexes involves metal ions. Thus, the effect of solvent on structure and energetics cation–π complexes was studied. Cation–π interaction has been recognized as one of the important non-covalent interaction. Arguably cation–π interaction is the strongest of non-covalent interactions but the strength and efficacy of interaction appear to be grossly different in isolated and condensed forms. Metal cations have two major modes of bonding with small organic molecules, namely the σ type interaction in wherein the metal ion coordinated to the lone pair bearing group and cation–π type of interaction.

Studies of cation–π interactions in the solution phase are considerably more complicated. Primarily this is caused by chaotic molecular motions in solutions, with constantly changing solvent-solute interactions, which in turn are non-covalent in nature. Besides, insightful techniques such as X-ray or neutron diffraction are of no or very limited use for solution studies. Thus, there is a considerable potential for the interplay of experimental and computational techniques to gain fundamental insights in this field.

The cation–π interaction is very sensitive to the coordinative saturation of the metal ions involved in the interaction. In the present thesis a systematic study was undertaken to gauge the effect of metal ion in warping the macromolecular structures, so as to attain multi-dentate coordination with the metal ions. These studies provide valuable insights in on how the structures and function of bio-macromolecules. In this study state of the art quantum chemical studies were performed at the popular density functional theory and ab initio post-SCF (MP2) levels of theory. Thus, quantitatively reliable computational methods have been applied to discern the subtle variations of
metal ion interactions due to solvation and chelation. The computed molecular
geometries, interaction energies, charges and the topological bond indices were
analyzed and interpreted.

2. Methodology

This chapter provides an overview of various computational approaches that were
adopted for the current work. Attempts were made to give some brief history about
Hartree-Fock theory, post Hartree-Fock methods, and density functional theory. We
have given simple explanation for each above mentioned theories with required
mathematical equations. The later parts of this chapter focus on various types basis
sets, and the types of basis sets. We also discussed about the energy decomposition
schemes, which is important in understanding the non covalent interactions. The
description for many fragment reduced variational analysis (RVS), and symmetry-
adapted perturbation theory (SAPT) methods are given in detailed manner with require
equations. Finally we have given a brief overview on the atoms in molecules theory.
In this section, the types of critical points were discussed in detail.

3. Proton, Methyl Cation and Metal Ion Affinities of Heterocyclic Amines

This chapter discusses the performance of various computational techniques to assess
the proton, methyl cation, and metal ion (Li\(^+\) and Mg\(^{2+}\)) affinities of 24 heterocyclic
amines, whose proton affinity values are, know experimentally. The experimental
values are taken from Hunter and Lias. Therefore, the objective of this chapter is to
assess the performance of hybrid density functional method B3LYP, in comparison to
the ab initio methods. Although, the site of attack is not controversial in most cases, a
systematic study was undertaken to assess the relative proton affinities of various positions in each of the isomers.

Scheme 1: Heterocyclic bases that are considered for the current study.

The regioselectivity for the protonation has been unambiguously established by performing B3LYP/6-31G(d) calculations on the possible putative sites of attack. For the given series of compounds the performance of B3LYP/6-31++G(d, p) and G3B3
levels of theory have been in excellent agreement with the experimental results with the deviations are of the order comparable with the experimental error.

4. Solvation of Metal Ions

In this chapter, a comprehensive study was done on the water solvation of mono- and di-valent metal ions (Li\(^+\), Na\(^+\), K\(^+\), Be\(^{2+}\), Mg\(^{2+}\), and Ca\(^{2+}\)) using various quantum chemical procedures (B3LYP, second-order Möller–Plesset (MP2) perturbation theory, CCSD(T), and G3). Binding energies and sequential binding energies were predicted for the addition of each water molecule. The sequential binding energies predicted at different levels of theory are compared with the experimental values available in the literature or high level G3 results. An increase in the quality of the basis set from double-\(\zeta\) to triple-\(\zeta\) has a significant effect in the sequential binding energies of hydration, irrespective of the geometries used. Within the same group (I or II), the sequential binding energy predictions at the MP2 and B3LYP are varying appreciably. It was noticed that, for each addition of water molecule, the change of M–O distance in metal-water clusters at the B3LYP is higher than MP2 method.

![Scheme 2: Metal-water complexes that are considered for the benchmark analysis; (M = Li\(^+\), Na\(^+\), K\(^+\), Be\(^{2+}\), Mg\(^{2+}\) and Ca\(^{2+}\)).](image)
5. Ion Binding to $\alpha,\omega$-diamines and Aromatic Amines

The first part of this chapter presents the proton and metal ion complexation to $\alpha,\omega$-diamines having the spacer chain length from 2-8 carbon atoms. Variation in the proton and metal ion chelation to these diamines were investigated by means of quantum chemical calculations. It is observed that from mono dentate to bi dentate chelation the increase in the binding energy for metal ions are higher than that of proton. Metal ion chelation to these diamines is highly symmetric, while the protonation is unsymmetrical in nature.

![Scheme 2: Model systems considered for the current study.](image)

In the second part of this chapter, MP2/cc-pVTZ calculations have been carried out to systematically explore three distinct binding preferences, namely mono-dentate binding in $\pi$ and $\sigma$ fashions to aromatic and amine group respectively and the bi-dentate mode, of Li$^+$ and Mg$^{2+}$ ions with aromatic amines(Ph−(CH$_2$)$_n$−NH$_2$, n = 2–5). Several model systems were devised to examine the binding strength of the interactions where the aromatic and amine motifs are not interconnected. The sensitivity of structures and energetics to the BSSE was examined by doing the geometry optimization with counterpoise option at MP2/6-31G(d) and MP2/cc-pVDZ levels. Contrasting binding affinities of Li$^+$ and Mg$^{2+}$ metals to $\pi$ systems and −NH$_2$ groups were observed. Effect of spacer chain orientation and its length on the binding
of metal ions and proton to aromatic amines were analyzed and observed that Mg$^{2+}$ binding is sensitive to the spacer chain orientation and its length. Reorganization energies were estimated for the complexation of metal ions to aromatic amines. It is observed that the reorganization energy for the complexation of Mg$^{2+}$ is higher than Li$^+$ and H$^+$. 

Scheme 3: Schematic representation of how the metal ions complexes to the aromatic amines at various positions.

6. Explicit Solvation of Cation–π Interactions

This chapter focuses on the effect of aqueous media on the cation–π interactions by taking the model systems Benzene-Li$^+$ and Benzene-Mg$^{2+}$. Sequential attachment of water molecules to cation–π systems reveal that the cation–π interaction strength varies in opposite direction depending on the site of solvation of cation–π system. The solvation of metal ion decreases its interaction energy with π system, while the solvation of π system increases its interaction energy with metal ion. The cation
binding to the benzene clearly enhances the ability of aromatic protons to participate in hydrogen bonding with water molecules. The distance between metal ions and centroid of the benzene inherently varies with the position of water molecules in the vicinity of cation–π complex. Reduced variational space (RVS) analysis on bare and solvated cation–π complexes indicates that the major contributions to the total interaction energy are coming from the polarization and charge transfer energy terms of π system. Topological atoms in molecules (AIM) analysis was done to evaluate the nature of cation–π interaction. Good correlations were found between interaction energies and charge density at the cage critical point of the cation–π complexes.

**Scheme 4**: Some of the solvated cation–π (M = Li⁺ and Mg²⁺) complexes considered for the current work.
7. Publications


The publications marked with # are the part of the thesis.