Chapter 1

Introduction
1. Introduction

The term “theoretical chemistry” is defined as the mathematical description of chemistry and the term “computational chemistry” is generally used when a mathematical method is adequately developed and can be programmed to work on a computer. Computational chemistry involves a set of techniques for investigating chemical problems on a computer. It is rapidly emerging as an area of research, where the chief focus is solving chemically related problems using computational methods. Some of the important aspects in chemistry can be tackled with computational methods without involving experimental studies like:

(a) Molecular geometry: The shapes of molecules, and conformational analysis and related properties.
(b) Energies of molecules in the ground and excited states and transition states determination.
(c) Structure and reactivity relationships.
(d) Prediction of IR, UV, and NMR spectra with variety of computational methods.
(e) Designing artificial enzymes and proteins for specific purposes including the ligand-enzyme/protein interactions.

The Computational methods that can deal with such problems can be classified into five broad classes namely: Molecular mechanics (MM), Semi empirical (SE) calculations, Ab initio calculations, Density functional Theory (DFT) and Molecular dynamics simulations. The selection of computational methods is important to examine the problems in hands and the computational resources available within the group.

The study of solvent effects on chemical reactions has a long history, and it has played a central role in solution chemistry and biology. There has been a long-standing interest in understanding the role of solvent molecules, which affects chemical reactions and physical or chemical properties of chemical systems. Recently, increasing attention is being devoted to understand the microsolvation in clusters as a relatively new avenue in this area. However, the molecular level mechanism of solvation is very difficult to establish experimentally, but computational approaches with advances in algorithms and much faster hardware facilities provide unprecedented mechanistic insight.

Solvation, also sometimes called as ‘dissolution’, is the process of attraction and association of solvent molecules with molecules or ions of a solute. As any solute dissolves in a solvent they spread out and become surrounded by solvent molecules. From the IUPAC definition, it can be
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stated that solvation is an interaction of a solute with the solvent, which leads to stabilization of the solute species in the solution. Solvents may be polar, non-polar, protic and aprotic in nature. Polar solvents are those with a molecular structure that contains dipoles and have high dielectric constant. Solvents with low dielectric constant are considered to be non-polar. A protic solvent contains a labile H⁺ ion and can readily donate protons (H⁺) to the reagents whereas aprotic solvents does not contain such hydrogen. Water is the most common and well-studied polar solvent, but others such as acetonitrile, dimethyl-sulfoxide, methanol, propylene-carbonate, ammonia, ethanol, acetone etc. are some of the commonly used solvents. Solvation involves different types of intermolecular interactions: hydrogen bonding, ion-dipole and dipole-dipole attractions, van der Waals forces. The hydrogen bonding, ion-dipole, and dipole-dipole interactions occur only in polar solvents whereas, ion-ion interactions occur only in ionic solvents. The solvation process will be thermodynamically favored only if the overall Gibbs free energy of the solution is decreased, compared to the Gibbs free energy of the separated solvent and solid (or gas or liquid).

Solvation can be broken down into three parts:-

1. the breaking of the solid lattice to give soluble guests

   \[ \Delta H_1 \quad \Delta S_1 \]

2. the reordering of the solvent to make a good host

   \[ \Delta H_2 \quad \Delta S_2 \]

3. the response of the solute (guest) by the solvent (host).

   \[ \Delta H_3 \quad \Delta S_3 \]

From these three steps, we can build an equation for the free energy of solution:
ΔG_solv = (ΔH_1+ΔH_2+ΔH_3) – T(ΔS_1+ΔS_2+ΔS_3)

Solvation plays an important role in different organic and inorganic reactions as well as in crystal growth. Solvation of biomolecules is also an active area of research. In this thesis, we have discussed about the dissolution process of alkali halides i.e., potassium chloride at molecular level and also at the bulk level. Secondly, the role of solvation on the conformational behaviour of some organic molecules loaded with stereoelectronic effects has been discussed. Furthermore, a computational approach has been developed to predict the stereoselectivity in electrophilic attack to sterically unbiased olefins through remote electronic perturbation. The role of solvation on such stereoselectivities has also been discussed. In this thesis, binding affinity of small cyclic diamines on the DNA base pairs and effect of explicit solvent molecules on such interactions have also been explored. Furthermore, interactions of larger polyamine ligands with the DNA in bulk solvent have also been discussed.

Solvations of inorganic salts, especially alkali halide solvation is important in solution chemistry and possesses a problem of fundamental importance in which the electronic and molecular structure of an electrolyte is modified by placing it in contact with a polar solvent like water. According to Arrhenius’ theory of electrolytic dissociation, a strong electrolyte is a compound that will completely ionize or dissociate into ions when dissolved in water. Such examples include the alkali halides which are ionic in nature. Examples of alkali halides include the common salt NaCl, and accordingly it should completely dissociate into Na⁺ and Cl⁻ ions when dissolved in water. However, some experimental findings of salt solutions are in contrast with the solvation process discussed above. Their findings imply that in aqueous solutions simple electrolytes, such as NaCl, aggregate even at moderate concentrations, and make it necessary to understand the dynamical hydration process of salt nano-clusters (Figure 1) in liquid water, which is also important for the dissolution mechanism in aqueous solutions. The dissolution process involves a “tug of war” between the ionic bonds and the hydration of those ions.
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Figure 1: An alkali-halide nanocrystal in bulk water
The bulk solvation of such nanocrystals requires a molecular-level understanding of the alkali-halide solvation. According to the textbook, from the saturation concentration, it can be deduced that on average nine water molecules are necessary to solvate one NaCl molecule, and the studies suggest that nine water molecules initiates the solvation phenomenon of NaCl. Since alkali halides such as Na⁺Cl⁻ ion pair will theoretically interact at any distance so to monitor the solvation of such systems the concept of contact ion pair (CIP) and solvent separated ion pair (SSIP) have emerged. No solvent molecules lie between the atoms (Na⁺, Cl⁻) in the CIP, whereas at least one water molecule separates the two ions in SSIP. Quantum chemical calculations suggest that six water molecules with specific orientation is enough to dissolve a rock salt molecule and confirmed it to be the smallest water cluster which forms a balanced three-dimensional non-cyclic structure (Figure 2). The solvation of another important alkali halide CsF in the molecular level also showed the importance of the orientation of water molecules (Figure 3). The solvation of alkali halides are relevant towards environmental chemistry, atmospheric chemistry and cloud physics. Environmentally important photolytic formation of molecular chlorine in a reaction of ozone with airborne sea-salt microparticles in the marine boundary layer crucially depends on their degree of hydration.

Figure 2. Side and top view of the solvent separated Na+/Cl⁻ ion pair in water hexamer (Na⁺: purple; Cl⁻: green, O: red; H: off-white).

\[
\begin{align*}
\text{Dist}_{\text{Cs…F}} &= 4.278 \text{ Å} \\
\text{b (prismatic)} &= 3.216 \text{ Å} \\
\text{c} &= 2.869 \text{ Å}
\end{align*}
\]
Figure 3. Different orientations of 6 water molecules interacting with the Cs\(^{-\text{+}}\)F showing different intermolecular distance between Cs\(^{-\text{+}}\)F.

In the cluster containing one salt molecule, the ions are always ‘paired’ in the sense that they are confined in the finite cluster environment which could be different from that in the bulk\(^{16}\) where a large number of solvent molecules surround the crystal and may form numerous clusters with ‘paired’ or ‘unpaired’ salt molecules. The dissolution process of the crystals in the bulk can either start from the corner or from the edge of the microcrystal surface (Scheme 1). The dissolution of NaCl crystal having \{100\} and \{111\} planes for a 7ps Molecular dynamics simulation in a periodic box showed that the departure of Cl\(^{-}\) ions is first from the crystal lattice (Figure 4).\(^{24,25}\) It has been concluded that the repulsive forces arising between the chloride ions and the water molecules, strongly attracted to the sodium ions around the chloride ions, push the chloride ion out from the crystal surface. Recently classical and \textit{ab initio} molecular dynamics (metadynamics) studies performed on the solvation of NaCl crystals in the bulk showed that the dissolution of the ions occur in a sequential manner i.e. the ion-sequence in the solvation phenomenon of NaCl is preserved to maintain the electrical neutrality.\(^{26,27}\)

Scheme 1. The separation of ions from the corner or the edge positions of the lattice. Potassium - purple; Chlorine – green; Oxygen – red; Hydrogen – white.
Figure 4. Displacement of the ions from the centre of the box with time

Figure 5. The arrangement of potassium and chloride ions on the \{100\}, \{110\} and \{111\} planes of the KCl crystal (green: chloride; purple: potassium)

Solvation is also important in controlling the morphology of alkali halide salts crystals.\textsuperscript{28} Sodium chloride caking (agglomeration and lump formation) is a very common problem in daily life. To avoid such agglomeration, the habit of NaCl to be tuned to enhance the free-flow property of the salt crystals. Habit modification of NaCl occurs due to the presence of impurities, solvation, pH, temperature and super saturation etc.\textsuperscript{29,30}

Conformational analysis has always been an important topic of research in physical organic chemistry\textsuperscript{31} as most of the properties like reactivity,\textsuperscript{32} spectroscopic behaviors etc. depends on the conformation. The stereoelectronic behavior of X-C-Y-containing systems (X = N, O, S and Y = Br, Cl, F, N, O, S), known as the anomer effect, and that of the X-C-C-Y molecular unit, known as the gauche effect (Scheme 3), have been studied extensively\textsuperscript{33-35} The anomer effect in an X-C-Y system is due to an Xnπ-\(\sigma^*\)C-Y two-electron-two-orbital interaction\textsuperscript{330,0} (negative hyperconjugation\textsuperscript{34} in valence bond terms) and is to be manifested\textsuperscript{35} as follows: (1) structural parameters, for example, shorter or longer anomer bonds and larger anomer bond
angles; (2) relative energy, that is, greater stability of gauche (axial) forms over anti (equatorial) forms; and (3) stereoselective reactivity. The anomeric effect is no longer an anomaly and proved to be an important factor toward the stability of substituted conformers of cyclohexanes and other heterocyclic compounds.\(^{35(k,l)}\) The gauche effect was originally defined as the tendency for a molecule to adopt that structure which has the maximum number of synclinal (sc, gauche, 60°) interactions between adjacent electron pairs and/or polar bonds in a molecular fragment X–C–C–Y, where X and Y are two electronegative substituents.\(^{36}\) Both gauche and anomeric effects are absent when X and Y do not contain any interacting lone pair. In recent studies, interpretations of gauche effect are based on hyperconjugation effect.\(^{37}\) The hyperconjugation approach states a two electron/two orbital interaction which depends on the donor–acceptor ability of the orbitals, on the energy difference between them and on overlap symmetry.\(^{38}\)

![Scheme 3. Schematic diagram of anomeric and gauche effect](image)

Conformational analysis of stereoelectronic systems began to evolve mainly in the 1960s and 1970s with the development of spectroscopic techniques.\(^{39} \) Ethylenediamine (EDA) is one of the most studied structures for the conformational analysis for its vast number of structures available. Previous reports suggest that EDA consists of 10 minimum energy structures based on the different position of the lone pairs (g, t, g’ in Scheme 4).\(^{40,41}\) Electron diffraction experiments in the gas phase have shown that non-protonated EDA is predominantly (95%) in a gauche conformation. DFT calculations on the conformational search of EDA also showed that gauche conformers are the most stable conformers in both gas and aqueous phase.\(^{43}\) The structural stabilities of such types of molecules depend upon stereoelectronic effect, steric effect and hydrogen bonding. Politzer et al. calculated the energies of different aza cyclic, acyclic systems and observed that \(\sigma\)-delocalization of nitrogen pair or anomeric effects are responsible for their extra stability than the simple cyclic or acyclic systems.\(^{44}\) Many studies on anomeric RYCH\(_2\)XR compounds involving second-row atoms (X, Y = NH\(_2\), OH, F) have shown that \textit{ab initio} MO calculations adequately reproduce the energetic stabilities and the geometric trends in
bond lengths and bond angles associated with the anomeric effect. Among these studies, natural bond orbital (NBO) analysis have been used to support the model of charge delocalization. The NBO method allows separation of the energy contributions due to hyperconjugation from those caused by electrostatic and steric interactions, so that hyperconjugative interactions can be studied separately. Salzner and Schleyer investigated the origin of the generalized anomeric effects in CH₂(XH)₂ compounds (X = O, S, Se, Te) by means of MP2 calculations and NBO analyses of the Hartree-Fock wave functions. Smaller anomeric effects were found for compounds containing S, Se, or Te than for X = O, which were due to non-hyperconjugative (e.g., steric and electrostatic) contributions increasingly favoring the anti conformations in going down the group.

\[ \text{Scheme 4. A schematic diagram showing the different conformers of EDA.} \]

The cyclic systems with similar kind of stereoelectronic effects are also studied. The conformations of both symmetrical and unsymmetrical heterocyclic systems with the X-C-Y or the X-C-C-Y moiety are interesting and have been studied with experimental and computational techniques. The conformational behavior of such compounds that contain polar bonds and atoms with unshared pairs of electrons can be affected by solvent effects. Lemieu et al. observed that the polar solvent CD₃CN favors the more polar equatorial conformer of 2-Methoxy-tetrahydro-pyran 6e (Figure 6) to a greater extent than does the nonpolar CCl₄. In D₂O the two conformers have a near equal population. These results conclude that the anomeric effect operating in compound 6 is diminished in water.
Figure 6. A schematic diagram to show the axial and equitorial conformers of 2-Methoxy-tetrahydro-pyran.

The 1,3-diazacyclohexane derivative are used for the preparation of neuroblocking-active drugs such as clothianidin and high energy materials. The conformational analysis of such systems in both gas and solvent phase with implicit and explicit solvent phase have been performed by Ganguly et al. There calculations showed that gas and implicit solvent phase have similar conformations suggesting that the stereoelectronic effects such as anomeric effects are unperturbed even in solvent medium, however, in the presence of explicit solvent molecules the hydrogen bonding interactions of the water molecules with the nitrogen lone pairs of the 1,3-diazacyclohexane reversed the stability of conformers.

The importance of stereoelectronic effects has also been examined in organic reactions such as π-facial selectivity. π-facial stereoselectivity is a phenomenon associated particularly with additions to trigonal carbon centers. It arises when the structural environment of the center renders the π-faces in-equivalent. Consequently, preferential attack by various reagents in nucleophilic, electrophilic, radical, and pericyclic reactions preferentially occurs on one face. An understanding of the origins of this phenomenon is of vital importance in the quest to perform stereochemical syntheses. Several control elements have been identified (steric, conformational, chelation, and electronic effects), and some of them are now reasonably well understood. Several studies have clearly demonstrated that remote substituents can influence the facial selectivity of addition reactions (particularly nucleophilic and electrophilic processes) to trigonal carbon centers through electronic effects. The nature and role of the electronic interaction remains a subject of continuing debate. The electrostatic and orbital effects determining the difference in energy between the respective diastereomeric transition states are important. Electrostatic interactions clearly need to be considered when polar substituents are present. Several models embracing orbital effects in both the initial state and transition state have been invoked over the years to explain π-facial stereoselection, in particular, nucleophilic reagents in their additions to ketones. The various important orbital interactions in the transition state advanced by Felkin-Anh and Cieplak are shown.
pictorially in scheme 2 for a generalized addition process. The Felkin model concerns repulsive interactions (torsional effects) which are maximized when the incipient bond (σ‡) in the transition state eclipses a vicinal σ-bond (syn periplanar relationship). The other model (Cieplak) focus on attractive hyperconjugative interactions between an electron-donor σ-bond antiperiplanar to an electron-acceptor antibonding orbital (σ*). The Cieplak model was employed in several studies to predict the face selectivity for the nucleophilic additions to ketones.

Scheme 5. Schematic diagram of Felkin-Anh and Cieplak model

Modeling face-selectivity has been a challenging task for theoretical and computational chemists.\textsuperscript{60} The quest for devising chemically intuitive models to predict π-face selectivity and to discern the factors responsible for such selectivities continues to engage attention. The semi-empirical MNDO model and the transition state model to predict the π-face selectivity for the nucleophilic addition to sterically unbiased ketones helped to segregate the importance of orbital and electrostatic effects.\textsuperscript{60(d),61} However, segregation of the various electronic factors responsible for the π-face selectivity in electrophilic additions to sterically unbiased alkenes have received only limited attention.\textsuperscript{62}

The role of medium (i.e. solvent) has been found to be crucial in predicting the right selectivity to π-faces and several examples of solvent-dependent face selectivity have appeared in the literature.\textsuperscript{63} Solvent effects are closely related to the nature and the extent of solute-solvent interactions developed locally in the microenvironments of the solute molecules.\textsuperscript{64} Solvents can change both the equilibrium constants and reaction rates.\textsuperscript{64}

In addition to the importance of solvation on the inorganic and organic systems and reactions, the solvation effects on the biological systems especially Deoxyribonucleic acid (DNA), one of the fundamental units of the living organisms is also of current interest. Along with RNA and proteins, DNA is one of the three major macromolecules essential for all known forms of life. To prevent different malignant diseases, DNA is a pharmacological target molecule to various antitumor drugs already in use and also an attractive object to design newer drugs for over than 3-4 decades.\textsuperscript{68} Binding of low molecular weight ligands to DNA causes a variety of significant
The selective binding of drugs with the DNA duplex has been of great interest in the recent years and is specifically of three types (Scheme 8):

a) Covalent binding \(^{(69)}\), eg: cisplatin.

b) Intercalation \(^{(70)}\); eg: Nogalamycin; Menogari etc.

c) Minor and Major Groove binding \(^{(71)}\); eg: Netropsin  Distamycin  Pentamidine; Spermine etc.

Scheme 8. A schematic diagram to show the different modes of ligand binding to DNA

The interaction through the covalent binding is much higher and cisplatin acts as a strong anticancer agent but its high toxicity\(^{(72)}\) promoted the researchers to search other anticancer agents with less toxicity. Low molecular weight aromatic molecules carrying positive charges are more common in designing the different drugs that bind to the DNA through intercalation and groove binding.\(^{(73)}\) Major toxicity for the intercalation type of binding include nausea, vomiting, and alopecia and also cardiotoxicity, myelosuppression and severe local tissue necrosis.\(^{(74)}\) The presence of metal ions in different intercalators is also responsible for the toxicity of such ligands. Groove binders are mostly non-metal and are less toxic. As the minor groove is much narrower than the major groove, different ligands interact through the major groove.\(^{(75)}\)

Simple organic compounds like polyamines are polycationic species, and are known to play a vital role for many biological processes like stabilisation of membrane and mitochondria functions to facilitate DNA transfection by phase.\(^{(76,77)}\) Natural polyamines such as putrescine, spermidine, and spermine have important role in cell replication, modulating gene expression and enzyme activities, activation of DNA synthesis, facilitating protein-DNA interactions\(^{(77)}\), in neurological diseases,\(^{(76)}\) anti cancer drugs,\(^{(79)}\) anti AIDS drugs.\(^{(80)}\) Previous reports suggest that spermine interacts through the major groove though with some exceptions.\(^{(81-84)}\) Synthetic polyamines acts as good anticancer agents or prevents neurological diseases,\(^{(85,86)}\) but couldn’t mimic the cell replication or enzymatic activity like the biogenic polyamines, primarily due to the
less binding affinity of the synthetic polyamines with the DNA.\textsuperscript{80,87} Recently, synthesized branched polyamines show good binding results with the DNA.\textsuperscript{88,89}

Hydration of DNA (Figure 6) plays an important role in its structure, conformation, and function.\textsuperscript{91} X-ray crystallography, NMR, dielectric relaxation, and molecular dynamics simulation studies have shown that a significant amount of water molecules are bound to DNA.\textsuperscript{92} Recent papers also show that the water is dynamically ordered at the surface of DNA and is crucial for interfacial recognition, not only of drugs but also between macromolecules.\textsuperscript{94} Polar solvents like water also play an important role in the hydrogen bonding and electrostatic interactions of the DNA base pairs among themselves\textsuperscript{95} and with different ligands.\textsuperscript{96} When drugs bind to DNA, it results in a displacement of solvent from the binding site on both the DNA and drug. Since the DNA and drug are oppositely charged, some counter ions present near the DNA would be released into the bulk solvent and are solvated fully to maintain the charge neutrality. The binding process is associated with some structural deformation/adaptation of the DNA as well as the drug molecule in order to accommodate each other (Figure 7).\textsuperscript{97}

Figure 6. A schematic diagram showing the major and minor grooves and orientations of the water molecules around the DNA.\textsuperscript{91a}
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Chapter 1

1.1 Thesis Objectives

The objective of the present thesis is to undertake the theoretical investigations to examine the effects of solvation on some inorganic, organic and biological systems and their applications in the area of chemistry and biology.

Chapter 2 describes a fundamental problem of the dissolution phenomenon of Potassium Chloride in molecular and microcrystal levels. Potassium chloride occurs naturally as sylvite, and it can be extracted from sylvinite and very useful as fertilizers. It is also used as medicines, food processing and also as a lethal weapon in judicial execution. Potassium chloride can act as a source of chloride ion. KCl is sometimes used in water as a completion fluid in petroleum and natural gas operations, as well as being an alternative to sodium chloride in household water softener units. KCl is also used as salt substitute but it is mainly mixed with common salt NaCl to improve the taste (Morton Salt). This chapter has been divided into two sections. The first section reveals the dissociation of a single Potassium Chloride molecule and the second section describes the solvation of Potassium Chloride microcrystal in water cluster as well as in the bulk water. We have examined various equilibrium geometries of the dissociated and undissociated clusters-KCl(H₂O)₁₋₆, with different n (n = number of water molecules) and observed that half- dissociated or paired structures were generated from the 2 water molecule cluster and the formation of prismatic structure of Potassium Chloride with 4 water molecules is sufficient to separate the cation and the anion. This result reveals the smallest water cluster used to dissociate an alkali halide. The larger separation of K⁺ ion and Cl⁻ ion was achieved with 6 water cluster in a cubic structure which has been proved to be a magic number for other alkali halides as well.
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The second section deals with the solvation of Potassium Chloride crystal in water cluster as well as bulk water. DFT calculations performed on a microcrystal \((\text{KCl})_6\) with different number of water molecules \((n = 1-15)\) showed that 4 water molecules initiated the dissolution of the crystal, and a \(\text{Cl}^-\) ion from the edge is pulled out of the crystal structure as an initial stage of the dissolution instead of rupture of the total crystal. Classical molecular dynamics calculations with a larger Potassium Chloride crystal \({\{100}\} \text{ surface}\) in bulk water revealed that both ions seem to separate from corner sites of the crystal lattice in the initial stages of the simulation process and solvation of ions occurred from a single layer, while other layers remain intact. MD studies are performed with other unstable planes of the Potassium Chloride crystal lattice like \{110\} and \{111\} were observed to be solvated much faster than the stable \{100\} plane, which is also corroborated with MSD analysis.

Chapter 3 involves the solvation effect on the various properties of different simple organic systems. It consists of two sections. The first section describes the solvation effect on the conformational behaviour on the stereoelectronic effect like (gauche and anomeric effect) of two very important heterocyclic systems of which one is the symmetrical 1,4-diaza-cyclohexane and the other is unsymmetrical i.e., 1-oxa-3-aza-cyclohexane.

1,4-diaza-cyclohexane also known as piperazine is important in medicinal/biological fields. The stability order of 1,4-diazacyclohexane conformers was found to be an interplay of steric, dipolar repulsions and hyperconjugative \(n_n-\sigma^*_{C-C}\) interactions and was similar in the gas phase and solvent continuum model: \(1\text{ee} > 1\text{aa} > 1\text{ea}\). The interactions of explicit water molecules with 1,4-diazacyclohexane conformers, however, predicted a different order of stability compared to the gas phase and continuum phase results due to presence of hydrogen bonding interactions. \textit{Ab initio} molecular dynamics (AIMD) study showed the minor perturbation in the orientation of explicit water molecules compared to the DFT results and no dramatic change was observed during the simulation with 1,4-diazacyclohexane conformers.

1-oxa-3-aza-cyclohexane is important in pharmacological industries and also acts as reagents in fine organic synthesis.\(^{100}\) The stability of this type of unsymmetrical system is largely determined by conformational behavior of the nitrogen atom. It has been observed that the geometry with the N-H in the axial position is more stable in the gas as well as in implicit solvent (water). The effects of explicit solvation in the conformational analysis of the 1-oxa-3-aza cyclohexane have been also studied. Different orientations are possible for the explicit water molecules. We have taken two different water clusters of 2 and 4 water molecules in this study.
The MD simulations performed with AIMD (ADMP) calculations showed that the water clusters with the chain forms are more stable than with cluster water molecules. A computational approach to segregate the factors responsible to control the \(\pi\)-face selectivity of electrophilic addition to sterically unbiased olefins has been described in the second section. We have examined the origin of \(\Lambda\)-facial diastereoselection in sterically unbiased olefins with different electrophiles. It was also observed that the Cieplak effect fails to rationalize the origin of selectivity in many cases. In this section, we have ventured to delineate the orbital and electrostatic factors responsible for the face selectivity of such sterically unbiased systems and the effect of electrostatic and polarization interactions is exclusively modeled using CHelpG charge of a specific atom taken from the transition state calculations. This derived charge model explained the face selectivity in these cases. Though the stereoselectivity of majority of the sterically unbiased systems were rationalized with this model however, one of the best known examples of \(\Lambda\)-facial selectivity with 5-Fluoro-substituted-2-methyleneadamantane and meta-chloroperbenzoic acid (m-CPBA), was not explained using the computational approach reported recently. It appears that the incorporation of solvent (dichloromethane) in the transition state calculations predicted the \(\text{syn}\)-selectivity as observed in experimental results. The difference in predicting the selectivity in the gas and solvent phase arises due to the distortional effects in the transition states. The distortion/interaction model accounts for the correct selectivity in solvent for 5-Fluoro-2-methyleneadamantane with per acid. The molecular dynamics calculations (AIMD) performed for the substrate molecule with explicit DCM molecules suggest that the distortion is likely to be possible in the ground state of the substrate molecule. Such distortions in the ground-state can induce the difference in transition state barriers that is explained by the reaction theory. The face selectivity of 5-Fluoro-2-methyleneadamantane with per-acid appears to a be a special case, where the role of solvent overrides the electronic effects.

Chapter 4 elucidates the interaction of the linear and cyclic polyamine ligands with the DNA base pairs and the effect of solvation on such interactions in the first section. In the second section, it states the importance of bulk solvation of the DNA and its interaction with different polyamines.

In the first section of this chapter, in search of more efficient polyamine analogues, we have performed \textit{ab initio} and DFT levels of theory on the interactions of some simple cyclic and constrained protonated diamines with the DNA base pairs and compared the results with linear diamines, which mimic biogenic polyamine like spermine. The interactions are mainly governed
by the strong hydrogen bonding between the ligand and DNA base-pairs. The major groove N-7 interaction (GC base-pair) has been found to be the most effective site of interaction for the linear diamine as reported with spermine. The cyclic diamines showed stronger binding with the DNA base-pairs compared to the linear diamine by ~5-9 kcal/mol. The cyclic rings induce the change in the hybridization of carbon centers, which influence the bond polarization and results better binding with the DNA base-pairs. The larger flexibility in the Cyclohexadiamine (CHDA) allows the protonated amines to interact much more strongly compared to the smaller cyclic diamines. These calculated results suggest that the better binding of ligands with the DNA base-pairs can be achieved through the appropriate fit of binding sites of ligands with DNA base-pairs. In general, the cyclic diamines experience the additional –C=O–H-N interaction with GC base pair and hence becomes the energetically preferred than the AT-base pair. The orientation of the diprotonated amino groups in 1,2-ee isomer of CHDA allows the additional interaction with the phosphate group of AT base pair, which leads to a stronger interaction compared to the GC-base-pair. The calculated IR spectral data corroborate well with the binding energies calculated for such cyclic systems. The MD simulations suggest that the strong ionic hydrogen bonding interactions between the ligands and the base of DNA are not influenced by the solvent molecules.

The second section of the chapter deals with the importance of the solvation on the DNA. Gas phase, implicit solvent phase and bulk solvent effect on the DNA and its interaction with biogenic polyamine spermine and other synthetic cyclic polyamines have been reported. In this section, we have examined the interaction of cyclic polyamines with DNA in implicit solvent phase and in bulk explicit solvent molecules. The MD simulations suggest that DNA is unstable in the gas phase suggesting that gas phase calculations are not suitable for the studies performed on DNA. In implicit solvent model, the interactions of the polyamines with DNA were performed through the phosphate group binding at the major groove site. The simulation results corroborate the previous reports towards the interaction of spermine with the phosphate group and the N-7 site of the GC base pair at the major groove site. The cyclic polyamine ligand with small spacer was also observed to have similar interactions like the spermine. The interaction of the 1,2-CHDA moiety of the ligand with the single strand of DNA showed similar interactions as observed for a simple protonated 1,2-CHDA with the DNA base pairs in the previous section. The interaction of the other cyclic polyamines with larger spacers showed no definite pattern of association with the single and dual strands of DNA in implicit solvent model. The MD simulations have been performed for the interaction of cyclic polyamines with both the major
and minor groove of DNA using explicit solvent molecules in periodic boundary conditions. The observed interaction of cyclic polyamines of smaller spacer units prefers to bind the major groove site, whereas, the larger spacer units showed better preference for interaction on the minor groove site. The explicit water molecules does not interfere the ionic hydrogen bonding interaction of ligands with the DNA and hence calculations performed in implicit solvent model can also be considered as a suitable model in examining the interaction of protonated ligands with DNA. The MD simulation results suggest that the sites of interaction can vary with the chain length of cyclic polyamines and hence a generality for the interaction of ligands is not appropriate in such case.

1.2. Theoretical Methodologies Adopted in the Thesis

In this section, we have discussed briefly the computational methods employed in this thesis. Computational chemistry is broadly classified in two different approaches: one is based on classical mechanics, and the other is based on quantum mechanics. Classical mechanics is based on the Newton’s laws of motion and is being extensively used to study molecular structures and their properties. This approach is generally called as “molecular mechanics” (MM) or “force-field” method. All molecular mechanics methods are empirical in nature and hence this method is computationally less expensive. This MM approach is very useful in modeling of bigger molecules such as protein and nucleic acids. Although, molecular mechanics calculations are quite inexpensive in term of computational resources and time, however, this method lacks to determine many electronic properties of general importance.

Unlike molecular mechanics, quantum mechanics describe molecules in terms of interactions among nuclei and electrons. Quantum mechanics based methods are generally more accurate than MM methods, however, the calculations are computationally more intensive than MM calculations. Three major categories of quantum mechanics are: semi-empirical, \textit{ab initio} and density functional theory (DFT) methods.

1.2.1. Quantum mechanics

1.2.1.1 \textit{Ab Initio} method

The term \textit{ab initio} is Latin for “from the beginning”. In this method computations are derived directly from theoretical principles with no inclusion of experimental data. This method provides an approximate solution of the Schrödinger equation.

\[ \hat{H} \Psi = E \Psi \]  \hspace{1cm} (1)

Where, \( E \) is the energy, \( \Psi \) is a many-electron wavefunction and \( \hat{H} \) is the Hamiltonian operator, representing all the forces on the system. \( \hat{H} \) is expressed as:
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\hat{H} = -\frac{\hbar^2}{8\pi^2} \sum_A \frac{1}{M_A} \nabla_A^2 - \frac{\hbar^2}{8\pi^2 m} \sum_a \nabla_a^2 - e^2 \sum_A \sum_a \frac{Z_A}{r_{aA}}
\]

\[
+ e^2 \sum_A \sum_a \frac{Z_A Z_a}{R_{AB}} + e^2 \sum_a \sum_b \frac{1}{r_{ab}} \ldots \ldots \ldots (2)
\]

Where \( h \) = plank’s constant; \( M_A \) = mass of nucleus; \( m \) = mass of electrons; \( r_{aA} \) = distance between nuclei and electrons; \( R_{AB} \) = distance between two nuclei; \( r_{ab} \) = distance between two electrons.

The first two terms describe the kinetic energy of the nuclei ‘A’ and electrons ‘a’, respectively, and last three terms describe the Coulombic interactions between the particles. The exact solutions of the Schrödinger equation for multi-electron system are too complicated, as it requires solving many integration terms. To simplify the Schrödinger equation a series of well-defined approximations have been applied.

One way to simplify the Schrödinger equation for multi-electron system is to assume that the nuclei do not move, as electrons move much faster than nuclei and can rapidly adjust the changes in nuclear position. This is termed as Born-Oppenheimer approximation and leads to an ‘electronic Schrödinger equation’.

\[
\hat{H}^{el} \psi_{el} = E^{el} \psi_{el}
\]

The electronic Hamiltonian \( H^{el} \) is represented as follows:

\[
\hat{H}^{el} = -\frac{\hbar^2}{8\pi^2 m} \sum_a \nabla_a^2 - e^2 \sum_A \frac{Z_A}{r_{aA}} + e^2 \sum_a \sum_b \frac{1}{r_{ab}} \ldots \ldots (3)
\]

Even with the Born-Oppenheimer approximation, the Schrödinger equation is not solvable for more than a single electron, so additional approximation required. The most obvious simplification to the Schrödinger equation involves the separation of variables, i.e., replacement of the many-electron wavefunctions by a product of one-electron wavefunctions. This approximation is termed as Hartree-Fock approximation or Central field approximation and gives the Hartree-Fock equation.

\[
f_{\psi} \chi_{Xi} = E \chi_{Xi} \ldots \ldots (4)
\]

Where, \( \chi_{Xi} \) represent the ‘spin orbital’ and \( f_{\psi} \) is the Fock operator. ‘Spin orbital’ is defined as the wavefunction for an electron that describes both its spatial distribution and its spin. The Fock operator \( f_{\psi} \)

\[
f_{\psi} = -\frac{1}{2} \nabla_i^2 - \sum_{A=1}^{M} \frac{Z_A}{r_{iA}} + \psi^{HF} \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots (5)
\]
Where, $v_{i}^{HF}$ is the average potential experienced by the $i^{th}$ electron due to the presence of other electrons.

The Hartree-Fock potential $v_{i}^{HF}$ feel by the $i^{th}$ electron is depends on the spin orbitals of other electrons (i.e. Fock operator depends on its eigen functions). Thus the Hartree-Fock equation is non-linear and must be solved iteratively. The procedure for solving the Hartree-Fock equation is called the Self Consistent Field (SCF) method.

Further, application of the variational SCF method to the Hartree–Fock equations with a linear combination of atomic orbitals (LCAO) leads to the Roothaan–Hall equation. In the linear combination of atomic orbitals (LCAO) N atomic orbitals overlap and generate same number of molecular orbitals. Variational principle states that for the ground state of any antisymmetric normalized function of the electronic coordinates the expected value for the energy will always be greater than the energy for the exact wavefunction.

1.2.1.2 Møller-Plesset perturbation theory

HF model considers the motion of the individual electrons independent to one another. However, in reality the motion of the electrons are pair-wise correlated to keep the electron apart. This correlation of electron motions is a stabilizing effect, and thus SCF energy is too high, even at the Hartree-Fock limit. The difference between actual energy and SCF energy at Hartree-Fock limit is called the correlation energy.

Consideration of the correlation energy for the coupling of electron motion results in a decrease of the total energy. Møller-Plesset perturbation theory is an alternative approach to electron correlation. Qualitatively, Møller-Plesset perturbation theory adds higher excitations to Hartree-Fock theory as a non-iterative correction using ‘many body perturbation theory’. It is commonly represented as MPn, where, n represent the order of perturbations considered. MP2 is the most economical method for including electron correlation. Higher order models such as the MP3 and MP4 models have been formulated, however, their application is limited to very small systems due to the extreme computational cost.

1.2.1.3 CCSD(T)

Coupled cluster (CC) is a numerical technique used for describing many-body systems. Its most common use is as one of several post-Hartree–Fock ab initio quantum chemistry methods in the field of computational chemistry. It essentially takes the basic Hartree–Fock molecular orbital method and constructs multi-electron wavefunctions using the exponential cluster operator to account for electron correlation. Some of the most accurate calculations for small to medium sized molecules use this method.
Coupled-cluster theory provides the exact solution to the time-independent Schrödinger equation

\[ \hat{H}\Psi = E\Psi \]

where \( \hat{H} \) is the Hamiltonian of the system. The wavefunction and the energy of the lowest-energy state are denoted by \( |\Psi\rangle \) and \( E \), respectively. Other variants of the coupled-cluster theory, such as equation-of-motion coupled cluster and multi-reference coupled cluster may also produce approximate solutions for the excited states (and sometimes ground states) of the system.\(^\text{111}\)

Coupled-cluster equations are equations whose solution is the set of coefficients \( t \). There are several ways of writing such equations but the standard formalism results in a terminating set of equations which may be solved iteratively. The naive variational approach does not take advantage of the connected nature of the cluster amplitudes and results in a non-terminating set of equations. The coupled cluster Schrödinger equation is formally:

\[ \hat{H} T |\Psi_0\rangle = E T |\Psi_0\rangle \]

Suppose there are \( q \) coefficients to solve for. Therefore, we need \( q \) equations. It is easy to notice that each \( t \)-coefficient may be put in correspondence with a certain excited determinant: \( t_{ijkl} \) corresponds to the determinant obtained from \( |\Phi_0\rangle \) by substituting the occupied orbitals \( i, j, k, ... \) with the virtual orbitals \( a, b, c \). Projecting the Schrödinger equation above by \( q \) such different determinants from the left, we obtain the sought-for \( q \) equations:

\[ \langle \Psi^* | \hat{H} T |\Psi_0\rangle = E \langle \Psi^* | T |\Psi_0\rangle \]

where by \( |\Psi^*\rangle \) we understand the whole set of the appropriate excited determinants. To manifest the connectivity of these equations, we can reformulate the above equation in a more convenient form. We apply \( e^{-T} \) to both sides of the coupled-cluster Schrödinger equations.

After this we project the Schrödinger equation to \( |\Psi_0\rangle \) and \( \Psi^* \), and obtain:

\[ \langle \Psi_0 | e^{-T} \hat{H} e^T |\Psi_0\rangle = E \]
\[ \langle \Psi^* | e^{-T} \hat{H} e^T |\Psi_0\rangle = E \langle \Psi^* | e^{-T} e^T |\Psi_0\rangle = 0, \]

the latter being the equations to be solved and the former the equation for the evaluation of the energy. Consider the standard CCSD method:

\[ \langle \Psi_0 | e^{-(\hat{T}_1+\hat{T}_2)} \hat{H} e^{(\hat{T}_1+\hat{T}_2)} |\Psi_0\rangle = E, \]
in which the similarity transformed Hamiltonian (defined as $\tilde{H}$) can be explicitly written down with the BCH formula:

$$\tilde{H} = e^{-\tilde{T}} \hat{H} e^{\tilde{T}} = H + [H,T] + (1/2)[[H,T],T] + \ldots$$

The resulting similarity transformed Hamiltonian is not hermitian. Standard quantum chemistry packages (ACES II, NWChem, etc.) solve the coupled-equations iteratively using the Jacobi updates and the DIIS extrapolations of the amplitudes.

The classification of traditional coupled-cluster methods rests on the highest number of excitations allowed in the definition of $\tilde{T}$. The abbreviations for coupled-cluster methods usually begin with the letters "CC" (for coupled cluster) followed by

1. S - for single excitations (shortened to singles in coupled-cluster terminology)
2. D - for double excitations (doubles)
3. T - for triple excitations (triples)
4. Q - for quadruple excitations (quadruples)

Thus, the $\tilde{T}$ operator in CCSDT has the form

$$\tilde{T} = \tilde{T}_1 + \tilde{T}_2 + \tilde{T}_3.$$ 

Terms in round brackets indicate that these terms are calculated based on perturbation theory.

For example, a CCSD(T) approach simply means:

1. A coupled-cluster method
2. It includes singles and doubles fully
3. Triples are calculated non-iteratively.

**1.2.1.4 Density Functional Theory (DFT)**

An alternative approach to implementing the Schrödinger equation for quantitative electronic structure calculations has appeared as density functional theory. In 1965, Kohn and Sham made a significant breakthrough when they showed that the problem of many interacting electrons in an external potential can be mapped exactly to a set of non-interacting electrons in an effective external potential. This led to a set of self-consistent, single particle equations known as the Kohn-Sham (KS) equations:
\begin{equation}
\left\{ -\frac{\nabla^2}{2} + \nu_{\text{eff}}(r) \right\} \varphi_{i,s}(r) = \varepsilon_{i,s} \varphi_{i,s}(r) \tag{6}
\end{equation}

with

\begin{equation}
\nu_{\text{eff}}(r) = \nu(r) + \int \frac{\rho(r')}{|r-r'|} dr' + \mu_{\text{xc}}[\rho](r) \tag{7}
\end{equation}

where $\nu_{\text{eff}}(r)$ is the external potential and $\mu_{\text{xc}}$ is the exchange-correlation potential, which depends on the entire density function and the exchange-correlation potential $\mu_{\text{xc}}[\rho](r)$ is the functional derivative of the exchange correlation energy. Thus, the density needs to be known in order to define the effective potential so that Eq. (6) can be solved. The ground state density is given by:

\begin{equation}
\rho(r) = \sum_{i=1}^{N_i} \sum_{s=1}^{2} \left| \varphi_{i,s}(r) \right|^2 \tag{8}
\end{equation}

To solve Eq. (2) then, an initial guess is used for $\varphi_{i,s}$ which is used to generate Eq. (8), which is subsequently used in Eq. (7). This equation is then solved for $\varphi_{i,s}$ iteratively until the $\varphi_{i,s}$ that result from the solution are the same as the $\varphi_{i,s}$ that are used to define the equations, that is, the solutions are self-consistent. Finally, the ground state energy is given by:

\begin{equation}
E_{\text{KS}}[\rho] = \sum_{i=1}^{N_i} \sum_{s=1}^{2} \varepsilon_{i,s} - \frac{1}{2} \int \int \frac{\rho(r)\rho(r')}{|r-r'|} dr dr' + \left\{ E_{\text{XC}}[\rho] - \int \rho(r) \mu_{\text{xc}}[\rho](r) dr \right\} \tag{9}
\end{equation}

Walter Kohn shared the Nobel Prize in chemistry in 1998 for this work.\textsuperscript{112a} The other half of the prize went to John Pople for his efforts in wave function based quantum mechanical methods.\textsuperscript{113}

### 1.2.1.5. Dispersion Correction

The dispersion corrected total energy\textsuperscript{114} is given by

\begin{equation}
E_{\text{DFT-D}} = E_{\text{KS-DFT}} + E_{\text{disp}} \tag{2}
\end{equation}

Where, $E_{\text{KS-DFT}}$ is the normal self-consistent Kohn–Sham energy, and $E_{\text{disp}}$ is an empirical term involving pair-wise dispersive interactions.

\begin{equation}
E_{\text{disp}} = -s_{ij} > i > j > i (C_{ij}^6 R_{ij}^6) f_{\text{damp}}(R_{ij}) \tag{3}
\end{equation}
Here, the summation is over all atom pairs, $C_{ij}$ is the dispersion coefficient for the pair of atoms $i$ and $j$ (calculated from the atomic $C_6$ coefficients), $S_6$ is a scaling factor that depends on the density functional used and $R_{ij}$ is the interatomic distance between atoms $i$ and $j$. A damping function is used in order to avoid near singularities for small distances. This function is given by

$$f_{dmp}(R_{ij}) = \frac{1}{1 + \exp \left(-\alpha (R_{ij}/R_0 - 1)\right)} \quad \text{(3)}$$

where $R_0$ is the sum of atomic van der Waals radii and $\alpha$ is a parameter determining the steepness of the damping function. In order to obtain the composite dispersion coefficients $C_{ij}$, a simple average of the form is used.

$$C_{ij} = \frac{2C_iC_j}{(C_i||C_j)} \quad \text{(5)}$$

### 1.2.1.6. Exchange and Correlation Functional

The two main types of exchange/correlation approximation are used in DFT, the local density approximation (LDA) and the generalized gradient approximation (GGA). The exchange-correlation energy $E_{xc}[\rho]$ is a function of $\rho$. The various approximation of $E_{xc}[\rho]$ separate the different DFT methods from each other. The simplest approximation to $E_{xc}[\rho]$ is the local density approximation, which assumes the system is homogeneous electron gas and $E_{xc}[\rho]$ depends only on the local value of the electron density. $E_{xc}[\rho]$ can be written in a simple form:

$$E_{xc}[\rho] = \int \rho(r) e^{\text{LDA}}_{xc}[\rho] dr \quad \text{(4)}$$

where $E_{xc}[\rho]$ is the exchange-correlation energy per particle of a uniform electron gas of density. $E_{xc}[\rho]$ is composed of two parts:

$$E_{xc}[\rho] = E_x[\rho] + E_c[\rho] \quad \text{(5)}$$

The correlation part was studied by various authors based on sophisticated interpolation schemes. For instance, the most popular $E_{xc}[\rho]$ functional was developed by Vosko, Wilk and Nusair\textsuperscript{115} and the more recent and probably the more accurate expression of $E_{xc}[\rho]$ was the one given by Perdew and Wang.\textsuperscript{116} The inclusion of the exchange-correlation term in LDA approximations makes it more accurate than HF approximations with similar computational costs.\textsuperscript{117} Experience has shown the LDA can successfully determine the optimized geometries and harmonic frequencies for investigated systems.\textsuperscript{118-120}

The electron density in a real molecule varies greatly from place to place. To get a more accurate approximation of the exchange-correlation energy, functional which include not only
the electron density but also the gradient of the electron density were developed. The basic idea of GGAs is to express the exchange-correlation energy in the following form:

$$E_{XC}[\rho] = \int \rho(r) \varepsilon_{XC}[\rho(r)] dr + \int F_{XC}[\rho(r), \nabla \rho(r)] dr \quad \text{............... (6)}$$

Where, $F_{xc}$ is a function which satisfies different conditions like sum rules, long-range decay and so on for the exchange-correlation hole. The most widely used exchange functional was developed by Becke, and was designed to recover the exchange energy density asymptotically far from a finite system. Other exchange energy functional is PW91 (Wang & Perdew, 1991). One of the most popular correlation functional is the LYP (Lee, Yang, & Parr) functional.

### 1.2.1.7. Numerical Basis Sets

A large variety of methods via basis sets have been available for the Kohn–Sham equations, on which many practical implementations are based. In particular, a successful basis set choice employed in a variety of all-electron implementations is numeric atom-centered orbitals (NAOs). These offer an efficient prescription that can be used for accurate full-potential, all-electron calculations of periodic and non-periodic systems on equal footing. Numerical atomic orbitals are defined by their numerical values on a grid. They are in general compactly supported in spheres centered at the nuclei and whose radii do not exceed a few atomic units. The use of the exact DFT spherical atomic orbitals has several advantages. For one, the molecule can be dissociated exactly to its constituent atoms (within the DFT context). Because of the quality of these orbitals, basis set superposition effects are minimized, and an excellent description, for even weak bonds is possible. The basis sets which is used in DMol3 are minimal basis (MIN), double numerical plus d-functions (DND) and double numerical plus polarization (DNP). These basis sets quality have been analyzed in detail by Delley (1990).

### 1.2.2. Continuum solvation model

Solvation is one of the major factors that perturb the properties of the chemical systems. One of the important solvation models, generally used in the quantum mechanics, is the continuum solvation model, which focused on the use of the self-consistent reaction-field (SCRF). In the continuum solvation model, a continuum of uniform dielectric constant, $\varepsilon$ (the reaction field) represents the solvent, and the solute is placed into a cavity within the solvent. The cavity is defined as the union of a series of interlocking atomic spheres. SCRF approaches differ in how they define the cavity and the reaction field. The simplest SCRF model is Onsager reaction field model in which the solute occupies a fixed spherical cavity of radius $a_0$ within the
solvent field. Tomasi’s polarizable continuum solvation model (PCM) has significant improvement over the Onsager model as it incorporates improved description of solute-solvent interaction and one can employ a non-spherical complicated charge density for calculation. In the PCM calculations, the shared polarization of the solute and the dielectric is calculated by numerical integration rather than by an approximation to the analytical form used in the Onsager model.

The PCM has undergone a number of modifications and improvements.

1. An integral equation formalism (IEF) is introduced into the PCM-method to solve the electrostatic solvation problem with the help of apparent surface charges.

2. C-PCM polarizable conductor calculation model deals the continuum as a conductor-like picture similar to COSMO Solvation Model.

COSMO abbreviation for "conductor-like screening model", is a calculation method for determining the electrostatic interaction of a molecule with a solvent. The details of the cavity construction differ in different COSMO implementations. In most cases it is constructed as an assembly of atom-centered spheres with radii approximately 20% larger than the Van der Waals radius.

1.2.3. Molecular Mechanics

Molecular mechanics uses classical mechanics to model molecular systems. The potential energy of all systems in molecular mechanics is calculated using force fields.

The following functional abstraction, known as a potential function or force field in Chemistry, calculates the molecular system’s potential energy ($E$) in a given conformation as a sum of individual energy terms.

$$E = E_{\text{covalent}} + E_{\text{noncovalent}}$$

where the components of the covalent and noncovalent contributions are given by the following summations:

$$
E_{\text{covalent}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}}
$$

$$
E_{\text{noncovalent}} = E_{\text{electrostatic}} + E_{\text{van der Waals}}
$$

The exact functional form of the potential function, or force field, depends on the particular simulation program being used. Generally the bond and angle terms are modeled as harmonic potentials centered around equilibrium bond-length values derived from experiment or theoretical calculations of electronic structure performed with software which does ab-initio type calculations such as Gaussian. For accurate reproduction of vibrational spectra, the Morse potential can be used instead, at computational cost. The dihedral or torsional terms typically
have multiple minima and thus cannot be modeled as harmonic oscillators, though their specific functional form varies with the implementation. This class of terms may include "improper" dihedral terms, which function as correction factors for out-of-plane deviations.

1.2.3.1. Force Fields

The GROMOS 43a1 forcefield\(^\text{129}\) have been used for the alkali halide solvation and the AMBER 03 forcefield\(^\text{130}\) have been used for the DNA solvation. TIP4P solvation model have been used for both the cases.\(^\text{131}\)

1.2.4. Molecular Dynamics (MD) Simulations

In molecular dynamics, successive configurations of the system are generated by integrating Newton’s law of motion. The result is a trajectory that specifies how the positions and velocities of the particles in the system vary with time. There are two main type simulation techniques available. These are molecular dynamics (MD) and Monte Carlo (MC) simulation. Apart from this, there is a whole range of hybrid simulation technique present which combines features from both, such as metadynamics (MTD), quantum mechanical molecular mechanical (QM/MM) dynamics.\(^\text{132}\)

MD simulations provide atomic details of the structures and motions of classical many-body particles and hence allows for computing its dynamic and thermodynamic properties. Instead of its great success, the drawback of the MD arises when interatomic interactions are described through empirical potentials. MD also have inherent problem when applying for breaking and formation of chemical bonds and the transferability of the force field parameters can often be questioned. Moreover, induced polarization and charge transfer effects are difficult to implement and are currently neglected in most MD studies.

Ab initio molecular dynamics (AIMD) overcome the above mentioned limitations of classical force field simulations. Molecular dynamics in total energy DFT schemes is implemented in essentially the same way as in conventional force field-based methods. The main difference is that the atomic forces are derived by solving DFT equations rather than from empirical potentials of interatomic interactions. The advantage of DFT is that its computational cost, at least within local or semi-local approximations like LDA and GGA, is significantly lower than Hartree-Fock based wave function methods. MD in DMol3 is based on the velocity Verlet algorithm for integration of the equation of motion. The implemented algorithm performs the Yoshida-Suzuki multiple-step numerical integration of varying quality, depending on the choice of interpolation parameters.\(^\text{133}\) Ab initio molecular dynamics (AIMD) were also performed at the B3LYP/6-31G(d) level of theory.\(^\text{134}\)
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