Chapter 1

Introduction
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1.1 Biomimetics and Biomimetic Chemistry

The importance of “Learning from Nature” is a prevailing knowledge in each field of science and technology. Since the turn of the century, the research and development on the nature-inspired manufacturing technology which include design, adaptation, or derivation from biology is generally referred to as “biomimetics”. It means mimicking biology or nature. Nature has gone through evolution over the 3.8 billion years since life is estimated to have appeared on the Earth. It mirrors an activity that humans have pursued for a long time: inventing new things inspired by what nature does. For example, when humans were trying to decide how to fly, they examined the flying organisms, birds and insects, and realized that wings were major and fundamental inspiration [1-2]. Nature has evolved objects with high performance using commonly found materials which function on the macroscale to the nanoscale. Development of novel materials, structures and processes with desirable properties is inspired from mimic of biological systems or nature [3].

On the fringe among chemistry and biology, information can flow in both directions. Vital life processes are governed by specific interactions between molecules, such as those occurring between enzymes and substrates, hormones and receptors, antigens and antibodies [4-5]. For example, structures of outer membrane receptors FhuA and FecA are shown in Figure 1.1. Nature device biomolecules
which perform for functions like electron transfer, metal transfer, photosynthesis, binding of exogenous molecules, and catalysis; for example porphyrin group is very effective in chelating and found in number of biological systems: in haemoglobin, cytochromes etc. as iron-porphyrin complex, in vitamin $B_{12}$ as Co(III)-porphyrin complex and in chlorophyll as Mg(II)-porphyrin complex. The structures of the porphyrin, annulene,

![Image](image_url)

**Figure 1.1:** The outer membrane receptors *FhuA* and *FecA*. Structures of ferrichrome receptor *FhuA* in its (a) ligand-free and (b) ligand-loaded conformations. The structures of the ferric citrate receptor *FecA* in the (c) siderophore-free and (d) siderophore-bound conformations. (adapted from [4]).

Fe-heme complex, and Mg-chlorophyll complex are shown in Figure 1.2. Much research effort has therefore been devoted by biologists, chemists and physical chemists to identify the forces that dictate molecular recognition. Powerful physical techniques such as X-ray and NMR, coupled with computational methods, aided in these investigations and provided structural information on the most complex biomolecules. They also stimulated chemists to reproduce some of the structural characteristics of the natural compounds with synthetic molecules and thereby reproduce the capability of molecular recognition [6]. This inspires a new chemistry based on the principles used by nature, a field named “biomimetic chemistry” by
Ronald Breslow [7]. Biomimetic chemistry aims to simulate biological processes with synthetic chemical tools. It relies on identifying the essential structural features of the biological systems and on incorporating these very features into the simplest possible molecules. These molecules not only show similar properties but also able to provide the mechanism of their biological functions. Synthetic biomimetic molecules are implemented as metal ion sequestration due to their very similar selectivity and efficiency for the target metal ions, for which the parent biomolecules performed. Natural metal ion binding molecules, specially iron(III) carriers are used as guiding molecules for the preparation of synthesis binders. This biomimetic approach takes advantage of the evolutionary edge of natural molecules and aims at reproducing the essential characteristics of the most natural compounds with the simplest possible synthetic structures.

Metal ions play major roles in biology and living organisms [8]. The essential biometals (for example, Fe, Zn, Mg, Co) are used by cells in structurally-constrained binding sites in metallo-proteins, where they can carry out structural, regulatory or catalytic roles. As these metallic ions can also promote cytotoxic reactions, their concentrations are tightly regulated to confine them to vital roles.
Indeed, redox-active metals like iron and copper may induce high levels of oxidative stress, due to their ability to promote reactions leading to formation of highly toxic hydroxyl radicals. It has now become obvious that some of these elements like iron, copper, aluminium and zinc are associated with neurodegenerative diseases [9]. The removal or passivation of the metal ions in the biological system is made through design of multifunctional chelating agents. Some of the current challenges are to achieve metal binding selectivity to avoid endogenous metal deficiencies and to target chelators to tissues or even cell compartments to localize their activity. For that purpose thermodynamic and kinetic issues are of paramount importance for the design of the metal chelators and sensors to deal with their bioavailability. Since the 1980s many molecular mechanisms controlling iron homeostasis have been deciphered [5] and now new means are available for chemists to design more specific iron chelators, in particular by taking inspiration from iron cell biology. Microbial iron uptake, and specifically siderophore-mediated iron uptake [10], appears eminently suited to be studied by the tools of biomimetic chemistry. The schematic mechanism of iron uptake and release through membrane receptor is illustrated in Figure 1.3.

![Figure 1.3: Schematic mechanism showing siderophore-mediated iron uptake and release through membrane receptor (adapted from [11]).](image-url)
1.2 Iron in Biological Systems

The biological aspects of iron, particularly its bioavailability, are profound and have affected the evolution of life. It is the fourth most abundant element (after oxygen, silicon, and aluminum, respectively) and the second most abundant metal (after aluminum) in the earth's crust. For all plants and animals, and for virtually all microbes, with the exception of some Lactobacilli and a Borrelia species [12] life without iron would be impossible. Iron holds this central position by virtue of its facile redox chemistry and its high affinity for oxygen. It is critically involved in oxygen metabolism and electron transfer processes in DNA and RNA synthesis. It possesses incompletely filled $d$-orbitals and can exist in various valencies. The most common oxidation states in aqueous media being Fe(II) and Fe(III). The redox potential between these two states has been shown to be very important for its biological functionality [13]. The reduction potential of iron(III) is very sensitive to changes in pH and in the primary condition sphere, permitting iron to either donate or receive electrons depending on its environment. This forms the basis for the functioning of all iron containing proteins, and in humans, the iron redox couple is utilized for such different purposes as oxygen transport, electron transport, and catalysis [13].

Although iron is essential for proper functioning of all living cells, both iron deficiency and iron excess are detrimental. The accessibility of the Fe$^{III}$/Fe$^{II}$ redox couple under many circumstances also means that iron must be carefully monitored at all times while it is in the body. A minor fraction of iron (generally called 'labile iron') is bound loosely to a heterogeneous population of organic anions (phosphates and carboxylates), polyfunctional ligands (i.e. chelates, siderophores, and polypeptides), surface components of membranes (e.g., phospholipid head groups),
or extracellular matrix (e.g., glycans and sulfonates) [14]. In the presence of molecular oxygen, labile iron is able to redox cycle between the two most stable oxidation states $\text{Fe}^{2+}$ and $\text{Fe}^{3+}$, and fosters the generation of highly destructive oxygen species such as hydroxyl radicals via the Fenton reaction [15]. These highly reactive radicals are capable of interacting with most types of biological molecules including sugars, lipids, proteins, and nucleic acids, resulting in peroxidative tissue damage [16]. Since humans lack the effective means to protect human cells against iron overload, serious complications like β-thalassemia or sickle cell disease must be managed using iron chelation therapy [17]. Due to accumulation of iron, hereditary haemochromatosis causes severe tissue damage, fibrosis with irreversible damage to various organs [18] and even death. Furthermore, iron homeostasis is an important factor involved in neuroinflammation and progression of Alzheimer’s disease [19]. This iron overload can be effectively treated by the administration of an organic ligand which is capable of sequestering the excess iron \textit{in vivo} and promoting its excretion as the organic complex. For the past 40 years, a hexadentate hydroxamate siderophore desferrioxamine-B (1) (marketed under the name Desferal and also known as DFO, Figure 1.4), has been used for this purpose [20]. The most desirable characteristics for a therapeutic iron chelator have been extensively discussed [21]. In order to identify an ideal iron chelator for clinical use, careful design consideration is essential; a range of

![Figure 1.4: Structural of Desferal, Desferrioxamine-B.](image-url)
specifications must be considered such as metal selectivity and affinity, kinetic and thermodynamic stability of the complex, bioavailability and toxicity.

Iron deficiency (hypoferremia) is also harmful as, or even more detrimental under certain circumstances than iron overload (hyperferremia). However, adequate iron acquisition is not a trivial task by virtue of its bioavailability. Despite the abundance of iron in the earth’s crust, it is found in nature most prevalently as an iron(III) hydroxide species and is not readily bioavailable. Conventional wisdom asserts that the solubility of Fe\(^{3+}\) at the environmental (physiological) pH of 7.0 is equal to \(10^{-18} \text{M/dm}^3\) [22], this is simply based on the calculation arising from the \(K_{sp}\) of Fe(OH)\(_3\) of \(10^{-38}\). However, it is more correct to base the soluble Fe\(^{3+}\) concentration on the equilibrium shown in equation 1.1, which results in a free Fe\(^{3+}\) concentration of \(10^{-10} \text{M}\) at neutral pH [23].

\[
3\text{Fe(OH)}_3 \rightleftharpoons \text{Fe(OH)}_2^+ + \text{Fe(OH)}^2+ + \text{Fe}^{3+} + 6\text{OH}^-
\]  

(1.1)

Nevertheless, both calculations yield as free Fe\(^{3+}\) concentration that is too low to support microbial growth. In the youth of our planet, it has been speculated that iron existed in the ferrous form, Fe\(^{2+}\). Earth’s maturity effected an oxidizing environment and iron came to exist in its ferric form, Fe\(^{3+}\), which leads to the insoluble hydroxide species. To circumvent this solubility issue, microbes have developed a sophisticated iron acquisition and transport system involving siderophores.

### 1.3 Siderophores

Siderophores (from the Greek for “iron carrier”) are low molecular weight organic compounds synthesized by microbes for the purpose of acquiring iron from the environment and isolated from cultured bacteria. They have remarkable chemical properties with high and specific chelating affinity for Fe\(^{3+}\). In addition,
the importance of selectivity is further compounded when one considers that in the environmental aqueous arena, Fe$^{3+}$ exists with other more highly concentrated metal ions such as Na$^+$, K$^+$, Ca$^{2+}$, Mg$^{2+}$, Cu$^{2+}$, and Ni$^{2+}$ as well as Al$^{3+}$. Their role is to solubilize, bind and assimilate extracellular iron, and to transport it into the cell or to inhibit the iron catalyzed production of hydroxyl (OH$^-$) via Fenton reactions (Fe$^{2+}$/H$_2$O$_2$) [15]. However, with in the last three decades it has been shown in many laboratories that the importance of siderophores is not restricted merely to supply cells with ferric ion. Besides iron transporters, they may also act as growth or germination factors within a selected organism, or virulence factor in the case of pathogenic bacteria [24]. Moreover, pathways for iron uptake in plants are poorly understood, but it is fairly well established that root-colonizing non-pathogenic micro-organisms could prevent invasion of pathogenic strains by excreting siderophores which bind iron strongly and make it unavailable for potentially harmful microorganisms. A siderophore is employed clinically for iron removal from body upon acute iron poisoning and biological hazards posed by other metal ions.

In addition to Fe uptake, siderophores were reported to have additional roles such as the acquisition of other metals [25] antimicrobial activity [26] and quorum sensing [27]. By mimicking the molecular structures of natural siderophores, scientists made attempts to prepare various sequestering agents for different biological important metal ions. Not only the biological aspect of siderophores exciting from a chemical point of view, but they also yield important information on physical mechanisms involving siderophore iron complexes, e.g., the stereochemical recognition of ferric siderophore complexes by membrane receptors. Conclusions can be drawn from the electrochemistry of siderophores about possible
iron release mechanisms in microbial cells. Equilibrium thermodynamics and exchange kinetics studies improve the understanding of iron removal from the mammalian iron transport and storage proteins transferrin, lactoferrin and ferritin. Moreover, sufficient thermodynamic and kinetic data will facilitate estimation of the advantages of certain siderophores over others in their competition for iron and other bio-relevant metal ions.

1.3.1 Natural Siderophores

For nearly fifty years, the structural studies on siderophores have shown a great diversity of structures for these iron chelating molecules synthesized by microorganisms [28]. More than 500 naturally occurring siderophores with variation in structure are known, of which 270 have been structurally characterized till date. As there are enormous different siderophores with varying structures, it is quiet difficult to categorize them. However, structures of some of typical examples of natural siderophores are shown in Figure 1.5. It is evident that the chemical properties of ionic forms of iron and other metal ions have dictated the evolutionary design of siderophores. Thus, high-spin, octahedral ferric ion is most effectively chelated by three bidentate oxygen-containing ligands. In many cases, the required three bidentate ligands are incorporated into the same molecule. The result has been the evolution of compounds such as desferrioxamine-B (1), mycobactin (2), arthrobactin (3), ferrichrome-A (4), enterobactin (5), pyoverdin (6), pseudobactin (7), agrobactin (8), parabactin (9) and others that are capable of binding ferric iron extremely well. For example, the well-characterized enterobactin has a tripodal architecture with three catechol binding groups linked through an amide linkage, one in each arm of cyclic L-Serine unit, shows highest selectivity towards iron (III).
Figure 1.5: Molecular structures of some typical examples of naturally occurring siderophores.

with formation constant (log $K = 49$) [29], among all siderophores. All the siderophores function by the same three elements (i) high iron(III) binding selectivity (ii) high iron(III) binding efficiency and high iron permeability as iron(III) complexes. Despite the considered structural variation found in the siderophores in chemical composition and geometry, they have a common feature to form six-coordinate octahedral complexes with ferric ion of great thermodynamic stability. They are characterized by presence of one, two and in most cases, three
bidentate chelating moieties, generally containing oxygen and nitrogen atoms. On the basis of these groups, the types of siderophores are generally catecholates, phenolates, hydroxamates, hydroxypyridinones, hydroxyquinolines, Hydroxycarboxylates and others (Figure 1.6).

Figure 1.6: The different types of bidentate chelating groups in siderophores

Many volumes and reviews [30-31] have been written on the biological [32], medical [33] and agricultural [34] aspects of siderophores; also the structural features and fundamental coordination chemistry of metal complexes of these biomolecules have been extensively studied and published in several excellent review articles. The details of these reports cannot be discussed here due to limitation, but list of some of them is presented in Table 1.1 in chronological order along with the authors reported.

Table 1.1: Some of the review articles published so far on siderophores

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Brief Description of Review</th>
<th>Author and Year Reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Biological role and structural features of Siderophores</td>
<td>Neilands J. B (1966, 1973)</td>
<td>[35]</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis and therapeutic potential of hydroxamic acid based siderophores and analogues</td>
<td>Marvin J. Miller (1989)</td>
<td>[37]</td>
</tr>
<tr>
<td>4</td>
<td>Bioavailability, coordination chemistry and kinetic studies of hydroxamates</td>
<td>Alvin L. Crumbliss (1990)</td>
<td>[38]</td>
</tr>
<tr>
<td>5</td>
<td>Practical applications of recognition and transport by siderophores</td>
<td>Kenneth. N. Raymond (1994)</td>
<td>[39]</td>
</tr>
<tr>
<td>6</td>
<td>Design features, therapeutic and clinical applications of iron chelators</td>
<td>Gavino Faa (1999) and R. C. Hider (2002)</td>
<td>[40, 41]</td>
</tr>
<tr>
<td>7</td>
<td>Siderophores and iron transport in microorganisms</td>
<td>Mohamed A. Abdallah (2000)</td>
<td>[28]</td>
</tr>
<tr>
<td>9</td>
<td>Relationship between structure and physical-chemical properties of iron chelators</td>
<td>Guido Crisponi (2008)</td>
<td>[42]</td>
</tr>
<tr>
<td>10</td>
<td>Hydroxypyridinones as privileged chelating structures for the design of medicinal drugs</td>
<td>M. Amelia Santos (2012)</td>
<td>[43]</td>
</tr>
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1.3.2 Synthetic Biomimetic Siderophores (Artificial Chelators)

Interest in synthetic biomimetic siderophores includes (i) their potential application as clinical iron removal agents (as iron overload is one of the most common type of poisoning) [40,42] (ii) for iron transport abilities to carry drugs into cells by preparation of conjugates between siderophores and antimicrobial agents (iii) the use of their iron complexes in agriculture for the prevention or treatment of chlorosis [44] (iv) their design as structural probes and diagnostic tools and (v) the mimic of essential structural features that are responsible for different biological functions of natural compounds [45].

During the world wide search for potential siderophore mimic chelators, it has been observed that several research groups have developed different strategies for synthesis of chelating agents. Much effort has been channelled into the synthesis of catechols [46] and hydroxamates [47,48], with typical examples (model chelators) being enterobactin (5) and desferrioxamine (1), respectively. The most important work was carried out by the Raymond group who have reported numerous catecholate ligands [49]. Several series of trishydroxamate ligands have also been reported by Shanzer and Crumbliss group [50,51]. Multidentate siderophore analogues have also been constructed by derivatising prototype bidentate hydroxypyridinones and attaching them to suitable molecular frameworks. Several multidentate ligands based on 1-hydroxypyridine-2-one, 3-hydroxypyridine-2-one and 3-hydroxypyridine-4-one moieties have been investigated in the last decade [52,43].

The various molecular synthetic chelators developed and reported so far have been categorized into four groups (i) catecholate, (ii) hydroxamate, (iii) HOPO
type, and (iv) mixed chelators. Under these categories, a large number of ligands with linear, tripodal, tetrapodal, macrocyclic and macrobicyclic topologies are available. Each category of synthetic chelators are reviewed till March 2015 and presented in the chapter 2. However, some representative chelators are presented in Figure 1.7.

![Figure 1.7: Structures of representative examples of hydroxamate, catecholate, HOPO and mixed type of synthetic chelators (a) Trendrox (R=H, R’=H, R’’=H) (b) Medrox (R=H, R’=H, R’’=H) (c) HOPObactin (d) Tren(Sox)2cams (X=SO3), respectively.]

1.4 Focus on Current Study for Ligand Selection

The efficient synthetic chelators developed so far, involving each of above mentioned chemical functions have certain disadvantages when being considered for both clinical and physico-chemical/photo-physical applications. The pioneering work of K. N. Raymond focused in catechol-based ligands is the most powerful known synthetic siderophores, but catechol subunits are somewhat air-sensitive and are susceptible towards oxidation. Moreover, the hexadentate catechol ligands also must lose upto six protons in sequestering Fe\(^{3+}\) and hence are relatively ineffective...
in complexing Fe\(^{3+}\) below neutral pH. Similarly, the hydroxamate based ligands possess a lower affinity for iron than catechols due to relatively low protonation constant (pK\(_a\)~9), hydrogen ion interface at physiological pH is less pronounced. Many hydroxamates are metabolically labile and are only poorly absorbed via the oral route [53]. In addition another category, hydroxypyridinones, although known as potential iron(III) selective ligands which are stable over a wide range of pH, but the low redox potential of hydroxypyridinones Fe complexes (-620mV) indicates a strong bias toward iron(III) coordination. Moreover, some members of this group are known to toxic and possess undesirable side effects [54].

In view of these limitations, as well as, to retain a high selectivity for iron(III), a search was made for molecules which are related in structure to the catechol, hydroxamate and hydroxypyridinonates, and might lack their relative instability and toxicity under biological conditions. In particular, the ligand should be stable at strongly acidic pH values and resistant to auto-oxidation. In this context, potential synthetic chelators have been developed involving other chelating subunits. Among those ligands of interest, the 8-hydroxyquinoline (8HQ) moiety possesses remarkable abilities to bind a variety of metal ions as it is considered as amalgamation of catechol and bispyridine units. 8HQ binds both Fe\(^{II}\) and Fe\(^{III}\) efficiently as indicated by its higher redox potential (-150mM) than that of HOPO (-620mM). Nevertheless, it is capable of scavenging Fe under biological conditions, forming a 3:1 complex (for bidentate) and 1:1 complex (for hexadentate) at 7.0 pH. In view of tremendous applications of bidentate 8HQ moiety (described in detail in chapter 2), it is expected that hexadentate structures built on three 8HQ units will be more competent. This, as well as the work of Serratrice et al [55] for the last decade stimulated us to investigate synthetic ligands based on 8HQ binding units, as
besides the required thermodynamic features, the properties desired are: good hydrolytic stability, stability towards oxidation, high thermal stability, excellent electron transport properties and unique luminescent properties.

The 8-hydroxyquinolinate ligands therefore seem promising for the development of not only iron and aluminium but other trivalent bio-relevant metal ion sequestering agents, as well as providing synthetic analogs for comparison with native siderophores. The comprehensive review and discussion on mono-, di-, tri-, and tetrapodal ligands based on 8HQ binding sites reported so far are presented in chapter 2 of this thesis.

1.5 Strategies for Ligand Design

For selective complexation of metal ions there is need for a rational approach towards ligand design. At the same time, an understanding of the principles of selectivity would be invaluable in understanding the metal ion selectivity displayed by biological cation transport systems such as in the cell wall, metal ion binding proteins such as metallothionein, or siderophores such as enterobactin and how metal ions act in the environment. Natural ion binding molecules, specifically iron(III) carriers, are used as guiding advantage of the evolutionary edge of natural molecules and aims at reproducing the essential characteristics of the most potent natural compounds with the simplest possible synthetic structures. The major characteristics of a natural iron-carrier (e.g., the most potent iron(III) binder so far known is the siderophore Enterobactin [56]) is its binding site and cavity (Figure 1.8) and the host-guest recognition. The remaining part of the molecule is preorganized to support the binding site, and to be recognized by specific membrane components for transporting the complex into the cell. Natural ion-carriers achieved these
features as a result of selection, and are produced by the biosynthetic machinery of
the living cell.

Figure 1.8: Artificial siderophore analogues designed to encapsulate metal ion in central
cavity.

The triscatecholate based enterobactin is $C_3$-symmetric composed of a trilactone
ring (domain I) as anchor and three pendant side chains with amide linkage,
(domain II) possessing metal binding sites (domain III) that embed the guest ion
in an octahedral cavity (Figure 1.9). This topology has been adopted extensively
used as model compounds for the design of new chelators. In general, the structure
involves at least three distinct moieties: central unit organized

Figure 1.9: Molecular structure of enterobactin showing three distinct units: central unit
(domain I), spacer (domain II) and metal binding unit (domain III).

around a pivotal atom or a pivotal moiety, chelating subunit which can be or not be
identical and connecting group resulting from the reaction of complementary
functional groups. The schematic diagram is presented in Figure 1.10. The central unit plays a paramount role in the complexing abilities. It has to allow the unstressed octahedral coordination sphere involving the three arms of the tripodal ligand. In order to well-accommodate the hard metal ion, bidentate chelating subunits have to possess hard donor atoms like oxygen and nitrogen sets as in catecholate, hydroxamate, hydroxyacid groups or 8-hydroxquinoline occurring in natural siderophores. The central units and binding units are linked through connecting groups like amide as in enterobactin.

![Diagram of tripodal metal chelators](image)

*Figure 1.10: General schematic diagram showing design of tripodal metal chelators.*

### 1.6 Current Study: Ligands Employed in the Dissertation

As part of our approach, the feasibility of the proposed metal-ligand systems is explored prior to ligand synthesis using *in-silico* method, particularly the molecular mechanics. Although these calculations do not guarantee the proposed structure will form, they do help to eliminate the unsuitable structures. If the metal coordination and ligand geometry are correctly chosen, the intended molecular topology should be the only structure that satisfies the binding requirements of the metal, while not creating unfavourable steric interactions in the ligands. Thus molecular mechanics calculations can be used to give an idea of how well a particular ligand coordinated to a metal ion from the steric strain point of view.
With the goal of producing efficient iron chelators, we have undertaken the above approach and develop three new synthetic siderophore analogues (L₁, L₂ and L₃) and are presented in Figure 1.11. The central pivotal units 1,1,1 Tris(aminomethyl)ethane (Tame), 1,1,1 Tris(hydroxymethyl)ethane (Thme) and 1,3,5 Tris(hydroxy)cyclohexane, the connecting functional groups are ether (-O-) or secondary amine (-NH-) whereas the bidentate chelating subunits are hydroxyquinolinate for L₁, L₂ and L₃ respectively. The feasibility of these ligands for coordination with iron and some other trivalent metal ions along with lanthanides have been tested by molecular mechanics method. Since the dissertation intend to describe the synthesis of some biomimetic chelators and their coordination compounds, including experimental and theoretical studies on the thermodynamic stability and photophysical behaviour, a brief description on the metal ions, thermodynamics and computational methods are presented here.

![Figure 1.11: Structures of proposed ligands (a) TAME5OX (b) TMOM5OX and (c) CHTOM5OX.](image)

1.7 Affinity of New Synthetic Chelators for Target Metal Ions Other than Fe(III)

There are many trivalent metals such as Al(III), Cr(III), and Ga(III) which are direct analogs of ferric ion in that their size and charge (and preferred coordination number for nitrogen and oxygen ligands) are very similar. The other elements of interest are the lanthanide ions, which have in many respects similar behaviour with iron. In particular, siderophores and synthetic analogs are excellent complexing
agents for these metals. Besides the complexation studies in solid state, the aqueous chemistry of transition metal ion Cr(III), group 13 element Al(III) and that of the lanthanides, has burgeoned within the last few years in part because of the biological significance of these elements. The interest lies in the coordination behaviour of these metal ions, and in exploiting their physico-chemical and photophysical properties for use in wide pH range of biological systems. In addition to trivalent iron, in the present thesis, the complexation behaviour, photophysical properties and theoretical aspects of Cr(III), Al(III) and La(III), Eu(III), Tb(III) and Er(III) will be described. A very brief description of these metals follows.

1.7.1 Chromium

Chromium is a first row transition element in the periodic table. It may resemble the group 16 elements of the oxygen group but only in the acidity of the trioxide and in its covalent nature. Cr(III) with its d$^3$ configuration forms thousands of inert complexes: an important characteristic of these complexes in aqueous solutions, is their relative kinetic inertness. There is no evidence for any toxic effects of Cr(III), which is an essential trace element in mammals (required daily intake 50-200ug). On the other hand, in surface waters uncomplexed Cr(III) ion partly oxidizes to Cr(VI) ion that is toxic and possesses mutagenic and carcinogenic activity [57]. Most of the soluble chromium in surface waters may be present as Cr(VI) ion and a small amount as organic complexes of Cr(III) ion. It is well known that chromium pollution in surface waters occurs due to waste water from the different sources. The removal of Cr(III) ion form polluted surface water would be possible by complexation either with natural or synthetic ligands.
1.7.2 Aluminum

Aluminum constitutes 7.5% of the earth’s crust by weight and is a non-essential element. Williams [58] has suggested that the reasons for this are 1) the lack of redox chemistry of Al(III); 2) the slow ligand exchange reaction rates of Al(III) which hinders its use as a Lewis acid catalyst; 3) the low concentration of soluble Al(III) at neutral pH ($10^{-11}$ M at pH 7.0); and 4) the strong Lewis acidity which results in high Al(III)-ligand binding constants which in turn blocks binding of essential ions such as Mg(II) to relevant substrates. The free Al(III) concentration in equilibrium with a precipitate causes increase of $[H^+]$. The extensive use of acidifying fossil fuels has decreased soil and water pH levels in many areas and as a consequence dramatically increased aluminum mobility [59]. Abnormally high aluminum levels are linked to dementia dialysis, neurotoxicity and have been shown to accumulate in some of the hallmark lesions of Alzheimer’s disease [60].

The only approved chelator for Al(III) overload is the tris(hydroxamate) siderophore, desferrioxamine B, which shows the same drawbacks as found in case of iron(III). As a result, there is a need to understand the coordination chemistry of Al(III) with biomolecules and their synthetic analogs to ascertain how and why aluminum manifests its toxicity, and to develop selective aluminum chelators for the treatment of Al(III) overload.

1.7.3 Lanthanides

The lanthanides, along with lanthanum, possess an even more diverse biological chemistry than transition and the main group (group 13) metal ions mentioned above. Besides, trivalent lanthanide ions display fascinating optical properties. The discovery of the corresponding elements and their first industrial uses were intimately linked to their optical properties and this relationship has been kept alive
Emphasis was then put on two fast developing aspects of lanthanide luminescence: 1) materials for telecommunications and light emitting diodes, and 2) biomedical imaging and sensing. Linking a luminescent lanthanide such as Eu(III) to a chelator that contains an organic sensitizer yields a strongly luminescent complex. Similarly erbium tris(8HQ) display a bright green emission suitable for OLEDs [61]. For instance Tb(III) have useful luminescent properties which enable the determination of hydration number about the lanthanide, the Ln-Ln distance in a macromolecule binding two or more ions, as well as more established techniques of optical spectroscopy such as determining equilibrium constants. Thermodynamic stability is a necessary requisite in the development of lanthanide complexes to remain bound to the fluorophores or chelators.

Owing to the favourable attributes of multidentate ligands in support of the applications described above, there is always a need of new chelators, which are cost effective, easily available and must fulfil the requirements for encapsulation of the target trivalent metal ions. But for the development of a new metal ion sequestration, the initial requirements are the proper design of chelators and their synthesis, where the donor atoms and the ligand architecture must be well satisfied by the coordination properties of the metal ions. The complex formed must be thermodynamically stable and thus knowledge of equilibrium thermodynamics is essential.

1.8 Equilibrium Thermodynamics

Much of this thesis deals with metal-ligand formation constants, and these can often be misleading since the convention is to define the equilibrium in terms of the deprotonated ligand. However, the actual metal-ligand complex will have a pH dependent speciation, since, thermodynamically there is a second competing
reaction of ligand protonation. Different ligands have differing basicity and it is often difficult to directly compare formation constants. For example, the naturally occurring siderophores enterobactin and ferrioxamine E both bind strongly to Fe(III). For enterobactin, a tris(catecholate) ligand, the log stability constant is 49; for the tris(hydroxamate) ferrioxamine E, log K = 32.5. Thus, equilibrium constants have been used as a measure of the success or failure of ligand design for the purpose of achieving high thermodynamic stability of complexes in solution or for selective complexation of metal ions for the separation or discrimination between the metal ions.

1.8.1 Stability

Stability is something we all seek to achieve molecules included. For molecules, stability is a relative term, since it depends on their environment. Consider an aquated metal ion in aqueous solution; in the absence of any added competing ligands or reaction with water itself, it is perfectly stable. However, when ligands that bind strongly to the metal added, a reaction may occur leading to new complex species. How much of each complex species exists in solution depends on ligand preference, and the stability of the various species. Two key aspects are involved in the above situation. The mixture changes to achieve the energetically most favourable products, and this process does not occur instantaneously. The first aspect is governed by thermodynamics, the second by kinetics. Thermodynamic stability is a view of the process at equilibrium, once the formation chemistry is completed.

1.8.2 Stability Constant

In general, the stability of any metal coordination complex is usually expressed in terms of the overall stability constant $\beta_{xyz}$ as defined in equations 1.2 and 1.3. For
the ordinary cases where \( x \) and \( y = 1 \) and \( z = 0 \), these subscripts are often omitted for convenience sake. In reality, this complexation event does not happen all at once as implied by equations 1.2 and 1.3, but rather in a stepwise fashion. This is illustrated for a bidentate ligand in equations 1.4-1.6 (coordinated waters and ligand/complex charges are omitted).

Note that \( \beta_{xyz} \) is a measure of chelator metal affinity; it is defined as if \( M^{3+}_{(aq)} \) were the only cation available for coordination. In practices aqueous solutions will always contain protons that compete with iron for the coordination site and the complex stability will be pH dependent. This is especially true for “acidic” ligands that must lose a proton before full chelation to metal ion can occur. For these ligands, it is often more convenient to employ the proton dependent thermodynamic constants. These constants are obtained by combining the metal complex formation and the proton dissociation reactions (such equations are not listed here but presented for individual ligand-proton equilibria at appropriate place).

1. General form of overall stability constant

\[
xM(H_2O)_6^{3+} + yL^{n-} + zH^+ \rightleftharpoons M_xL_yH_z^{3-n} + 6H_2O
\]  
(1.2)

\[
\beta_{xyz} = \frac{[MLH^{3-n}]}{[M^{3+}]^n[L]^y[H^+]^z} 
\]  
(1.3)

2. Bidentate stepwise equilibrium and overall stability constants

\[
M^{3+} + L \rightleftharpoons ML; \quad K_1 = \frac{[ML]}{[M^{3+}][L]} \quad \beta_1 = K_1 = \frac{[ML]}{[M^{3+}][L]} 
\]  
(1.4)

\[
ML + L \rightleftharpoons ML_2; \quad K_2 = \frac{[ML_2]}{[ML][L]} \quad \beta_2 = K_1K_2 = \frac{[ML_2]}{[M^{3+}][L]^2} 
\]  
(1.5)

\[
ML_2 + L \rightleftharpoons ML_3; \quad K_3 = \frac{[ML_3]}{[ML_2][L]} \quad \beta_3 = K_1K_2K_3 = \frac{[ML_3]}{[M^{3+}][L]^3} 
\]  
(1.6)
1.8.3 Methods and Factors Determining Stability Constant

Stability constants, or equilibrium constants for metal complex formation, have long been employed as an effective measure of the affinity of a ligand for a metal ion in solution, and have served as a quantitative indication of the success or failure of ligand design. The earliest quantitative determinations were concerned only with the determination of empirical formulas and overall formation constants, and were pioneered by workers such as Von Euler [62] and Bodlander [63]. The stepwise hydrolysis constants of Cr(III) were reported by N. Bjerrum [64]. The measurement of stepwise stability constants for mono-dentate ligands effectively began with classic dissertation of J. Bjerrum [65] on the formation of transition metal-ammonia complexes in aqueous solution. Stability work on chelate compounds began with the seminal paper by Calvin and Wilson [66] wherein the Bjerrum [65] simplification of using a large excess of ligand to prevent hydrolysis and precipitation was avoided. This work was the beginning of a trend involving the use of exact algebraic treatment of equilibrium constants and mass balance equation thus eliminating the approximations of the Bjerrum method. Because of the command of these methods of determining formation constants of complexes, and the relatively inexpensive instrumental requirements, work in this field rapidly proliferated. The results are collected in a series of extensive non-critical compilations [67-68], now sponsored by the sub-commission V₆ on Equilibrium Data of IUPAC. The commission on equilibrium data has also sponsored a series of in depth critical review of stability constants of individual ligands or groups of related ligands, and some of these have appeared [69]. The stability constant data for a large number compounds were summarized in a series of books by A. E. Martel with his co-authors [70] and also various methods available for determining
stability constants as well as interpretations of the results have been described [71].
A number of computer programmes are currently available [72] which employ varying strategies [73] and new programmes are being published with regularity. The classical programmes have been compared [74], but no single program seems to have outstanding advantages over the others.

The formation of metal complex and its stability depends on a number of physical and chemical parameters of the metal ion and the ligand in solution. Thus, the most important one is to find relationship between stability constants and factors determining them. The important factors are intrinsic basicity of donor atom in the ligand, covalent tendency of metal ion, charge neutralization of complex formation, chelate effect, steric effect, macrocyclic effect and preorganization of ligands. The most significant factors which decide the stability of a complex are basicity of the ligands, charge and size of metal ions. The other factors are the electronic configuration of the metal ions, electronegativity of donor atom of the ligands, ionization potential of the metal ions. These factors are described well in several text books [75] and not presented here.

1.9 Molecular Modeling

Advances in computing and in the development of new methods in the area of computational chemistry have greatly increased interest in computer-based molecular modeling. Today, molecular modeling is widely used as an aid in the interpretation of experimental results, and also in the design of new materials with desirable properties. Examples drawn from the area of inorganic chemistry include studies of the interaction of metal ions with proteins and DNA, as well as the design of new metal-based drugs, magnetic materials, metal-ion-selective ligands and stereospecific catalysts.
It deals with the computational prediction of molecular structures and properties. These properties *viz.*, stabilities, reactivates, thermodynamic and kinetic electron transfer parameters and spectroscopy (magnetic resonance, electronic and vibrational spectroscopy) are strongly correlated with molecular structural parameters and environment. Steric strain may lead to decreasing stability, bond stretching to the preference of certain substitution reaction path, and structural vibrations may be accompanied by electron redistribution with possible consequences in various molecular properties. Thus, there are two parts of modeling: (i) the computation of structure of an isolated molecule, a crystal lattice or a solvated species, *i.e.*, the three directional arrangements of atoms in space, and (ii) the computation of relevant molecular properties, based on structural parameters. The result of a modeling study may help to understand observed properties of a molecule when more direct methods are not available, and to design new compound with specified properties.

The different computational approaches are empirical, semiempirical, ab-initio and DFT methods used in molecular modeling calculations. The Schrodinger equation, with many possible approximations, the nuclear positions may be used as structural parameters to compute electronic properties, and an iterative optimization procedure may lead to structural, electronic and other properties of the system in one step. The classical mechanics approaches such as force field calculations assume the arrangement of electrons to be fixed and the nuclear position and, depending on the approach used, steric strain and/or vibrational frequencies are the refined variables. The main result is an optimized structure, from which, then using the separate algorithms the molecular properties are calculated. The major advantage of force field method is that they are computationally less expensive.
But, the accurate prediction of structure and properties of molecules require that all the conformers are to be screened and parameter sets, basis functions and approximations should be reliable. Each method has its own advantages and disadvantages. A brief insight of the classical mechanics and quantum mechanical approaches are described below:

1.9.1 Molecular Mechanics Method

Empirical or molecular calculations provide quantitative information on intramolecular steric effects and it is one such technique used widely to model molecular structure because of computational simplicity, efficiency and allows handling even very large molecules fairly in a relatively less time. Molecular mechanics (MM) is a completely empirical approach, based on Born-Oppenheimer approximation, which assumes that the motion of the nuclei of a molecule is independent of the motions of the electrons. It means the arrangement of the electrons is assumed to be fixed and the position of the nuclei is calculated.

The principle behind MM is to express the energy of a molecule as a function of its resistance towards bond stretching, bond bending, and atom crowding, and to use this energy equation to find the bond lengths, angles and dihedrals corresponding to minimum-energy geometry or more precisely, to the various possible potential energy surface minima. In other words, MM uses a conceptually mechanical model of a molecule to find its minimum energy geometry (for flexible molecules, the geometries of the various conformers). The potential energy of a molecule can be written as in equation 1.7:

\[
E = \sum E_{str} + \sum E_{bend} + \sum E_{oop} + \sum E_{tors} \sum E_{vdw}
\]  

\(E_{str}\) = energy of bond stretched from its natural bond length,

\(E_{bend}\) = energy of bending bond angles from their natural value,
\[ E_{oop} = \text{energy of bending atoms out of plane}, \]

\[ E_{tors} = \text{the torsional energy and} \]

\[ E_{vdw} = \text{the energy due to vander waals interaction}. \]

The form of the mathematical expression for the energy, and the parameters in it, constitute a force field, and molecular mechanics (MM) methods are sometimes called force field methods. A molecular mechanics method may be parameterized against a specific class of molecules, such as proteins and nucleotides. Such a force field would only be expected to have any relevance in describing other proteins or nucleotides. Other force fields are parameterized to give a reasonable description of a wide variety of organic and inorganic compounds.

The following are some commonly used molecular mechanics force fields.

(i) **AMBER**: Assisted mode building with energy refinement (AMBER) is the name of both a force field and a molecular mechanics program.

(ii) **CHARMM**: Chemistry at Harvard macromolecular mechanics.

(iii) **CFF**: The consistent force field (CFF) was developed to yield consistent accuracy of results for conformation, strain energy, vibrational spectra, and vibrational enthalpy of proteins.

(iv) **EFF**: Empirical force field (EFF) is a force field designed just for modeling hydrocarbons. It uses three valence terms, no electrostatic term and five cross terms.

(v) **MM**: MM1, MM2, MM3, and MM4 are general-purpose organic force fields. The MM3 method is probably one of the most accurate ways of modeling hydrocarbons and the results published by MM4 are also encouraging. These are some of the most widely used force fields due to the accuracy of representation of organic molecules. MMY and MM\(^+\) are variations on MM\(^2\).
(vi) **MMFF**: The Merck molecules force field (MMFF) is one of the more recently published force field in the literature. MMFF94 was originally intended for molecular dynamics simulations, but has also seen much use for geometry optimization.

(vii) **UFF**: UFF stands for universal force field. Although there have been a number of universal force fields, meaning that they include all elements. This is the most promising full periodic table force field available at this. UFF is most widely used for systems containing inorganic elements.

(viii) **MOMEC**: MOMEC is a force field for describing transition metal coordination compounds. It was originally parameterized to use four valance terms, but not an electrostatic term. The metal-ligand interaction of a bond-stretch term only. The coordination sphere is maintained by nonbond interactions between ligands. MOMEC generally works reasonably well for octahedrally coordinated compounds.

There are other force fields as well; the detailed description and other important applications of which and all above force fields are given in various books [76-77].

### 1.9.2 Quantum Mechanics Methods

There are three different quantum mechanical approaches: *ab-initio, semi-empirical* and *density functional theory (DFT)* methods can be implemented for the calculation of molecular structure and various electronic properties by solving the Schrodinger’s equation (equation 1.8) for the given molecule.

\[
H \psi = E \psi
\]

where, \( H \psi = \left( -\frac{\hbar^2}{8\pi^2m} \nabla^2 + V \right) \psi \)
1.9.2.1 Ab-initio method

*Ab-initio* calculations are based on solving the Schrodinger equation for a given molecule. In this calculation, it is not possible to obtain exact solutions to the Schrodinger equation for molecules due to the complexity of many-body interactions in electronic systems. As a consequence, approximations are introduced in practical calculations. The simplest approximate method is based on the Hartree Fock (HF) scheme. The *ab-initio* HF method and the related CI treatment have dominated the development of quantum chemistry. However, the demerits of *ab-initio* calculations, like requirement of powerful computational facilities and time, want some alternative methods, which can be implemented for the same with full accuracy. *DFT* and *semi-empirical* methods are two such alternate approaches to quantum mechanical calculations.

1.9.2.2 Semi-empirical methods

Over the past decades the semi-empirical methods have been used widely in computational studies. There are several books [78-79] and reviews [80] which describe the underlying theory, the different variants of semi-empirical methods, and the numerical results. Semi-empirical approaches are normally formulated within the same conceptual framework as ab-initio (Hartree-Fock) methods, but they neglect many smaller integrals and calibrated against reliable experimental or theoretical reference data.

The quantum mechanical approach in *semi-empirical* calculations can be distinguished into methods that are restricted to $\pi$-electrons and to those restricted to all valence electrons. In *semi-empirical* methods, some of the quantities of *ab-initio* calculations are neglected or replaced by parameterized terms, derived from experimentally observed data (structures, ionization energies, heats of formation). A
popular range of approaches is based on the neglect of differential overlap (NDO), ranging from complete neglect of differential overlap (CNDO), intermediate neglect of differential overlap (INDO), modified intermediate neglect of differential overlap (MINDO) and neglect of diatomic differential overlap (NDDO). A number of INDO-based methods have been parameterized and used successfully for transition metal compounds [81]. These included the most frequently used methods like AM1, PM3 or PM5. Parametric method number 7, PM7 [82], is one of the latest in a series of semiempirical methods which succeeded over PM6 [83] that encompass MNDO, AM1, PM3, and RM1. The accuracy of PM6 in predicting enthalpies of formation, yielding an unsigned mean error of 4.4 kcal.mol$^{-1}$ for a representative set of 1373 compounds, exceeds those of Hartree-Fock (7.4 kcal.mol$^{-1}$) or B3LYP DFT (5.2 kcal mol$^{-1}$) methods [84]. The singlet and triplet excited states are the calculated for ground state geometries using the configuration interaction with single excitations (CIS) based on the Zerner's intermediate neglect of differential overlap/spectroscopic (ZINDO/S) methodology [85] for computation of electronic spectra.

1.9.2.2.1 Sparkle Model for Lanthanides

The Sparkle Model is a semiempirical approach to the quantum chemical calculation of lanthanide complexes, originally introduced in 1994 and it allows the treatment of a great number of lanthanide complexes efficiently and in a relatively short time than that of HF and DFT methods [84]. This model replaces the lanthanide ions by a Coulombic charge of +3e, superimposed to a repulsive exponential potential of the form $\exp(-\alpha r)$, which was introduced to mimic the effect of the size of the ion. Thus, the Sparkle model assumes that the angular effects of the $f$-orbitals are negligible and does not take them into account, being
thus, a spherically symmetric model. Semiempirical methods have proven their usefulness for several applications and have evolved in a continuous basis over the last 30 years. This model has been extensively applied to the calculation of ground-state geometry of these molecules, which is necessary to predict spectroscopic properties, singlet and triplet energy positions, and electronic spectra of Ln\textsuperscript{III} complexes [86].

Recently reported [82] that Sparkle/PM7 is an accurate and statistically valid tool for the prediction of the geometrical features of lanthanide coordination polyhedral and, by design, is expected to perform best with ligands with nitrogen or oxygen as coordinating atoms present in the vast majority of all coordination compounds of the trivalent rare earth metals. Semiempirical (sparkle model) methodologies have been applied to study the spectrophotometric properties of the systems reported in 2007 by DFT and TD-DFT methods [83]. The authors have shown that the semiempirical methods can be used to predict the spectroscopic properties of europium cryptates with accuracy comparable to that shown by DFT and TD-DFT results and suggested that experimental spectroscopic data are better reproduced in ZINDO calculations when the lanthanide ion is represented by a point charge, also triplet energies calculated by semiempirical methods have errors similar to those obtained by TD-DFT methodology but are hundreds of times faster [82].

It has also been suggested [81,86,87] that the use of quantum chemical methodology other than semiempirical Sparkle model such as Hartree-Fock (HF) or density functional theory (DFT) using an effective core potential (ECP) to treat the Ln\textsuperscript{3+} ions is unfeasible owing to the high computational effort needed.
1.9.2.3 Density functional theory (DFT)

The premise (idea) behind DFT is that the energy of a molecule can be determined from the electron density instead a wave function. The applications of density functional theory to molecular systems is relatively new compared with ab-initio methods. However, the many recent successful applications of DFT to a variety of molecular properties have prompted a steadily growing interest among theoretical chemists. An excellent review by Ziegler [88] summarized most of the important advances in the applications of DFT.

DFT methods are based on the theorem by Hohenberg and Kohn, which state that the electronic density uniquely determines the ground state energy of a molecule. Further, the electronic energy can be expressed as a sum of the kinetic energy, energy due to external potentials, Coulomb energy, and exchange-correlation energy:

\[ E(\rho) = [T_s] + [V_n] + [V_c] + E_{xc} \] (1.9)

**\( E(\rho) \) = kinetic energy,**

**\([T_s]\) = interaction energy of electronic system with the external potential**

**\([V_n]\) = nuclear attraction potential**

**\([V_c]\) = external magnetic or electric fields**

**\(E_{xc}\) = exchange – correlation energy**

For transition metal systems, DFT methods generally lead to more accurate structures and vibrational energies than single determinant HF methods [89], and often they are similar in quality to high-level post-HF methods. Since, in addition, DFT calculations are less computationally expensive (approximate scaling factor \(N^3\)) they have become the method of choice for routine applications in the area of transitional metal compounds [90].
As mentioned above the basis of DFT is that the ground state energy of a molecular system is a function of electron density. The Kohn-Sham equations provide a rigorous theoretical model for the all-electron correlation effects within one electron orbital based scheme. Therefore, DFT is similar to the one electron HF approach but exchange-correlation term, $V_{\text{ex}}$, is different: in DFT it is created by the functional. $E_{\text{xc}}(\zeta)$ and in real applications we need approximations for this functional. The quality of DFT calculations depends heavily on the functional. The simplest approximate DFT approach is the X$_\alpha$ method which uses only the exchange part in a local density approximation (LDA, local value of the electron integration over space). In recent years, LDA, LSDA, and VWN (The Vosko, Wilks, and Nusair functional) have become synonymous in the literature.

A more complex set of functionals utilizes the electron density and its gradient. These are called gradient corrected methods. There are also hybrid methods that combine functionals from other methods with piece of Hartree-Fock calculations, usually the exchange integrals. In general, gradient-corrected or hybrid calculations give the most accurate results. However, there are a few cases where X$_\alpha$ and LDA do quite well. The current generation of hybrid functionals are a bit more accurate than the present gradient-corrected techniques. Some of the more widely used functionals are HFS (Hartree-Fock Slater), BLYP (Becke correlation functional with Lee, Yang, Parr exchange), PW91 (Perdew and Wang 1991), B3P86 (Becke exchange, Perdew correlation), B3LYP (Becke 3 term with Lee, Yang, Parr exchange) etc. [91].

The currently available functionals for approximate DFT calculations can, in most cases, provide excellent accuracy for problems involving metals, especially
transition metal compounds. Therefore, DFT has replaced *Semi-empirical* MO calculations in most areas of inorganic chemistry.

The most important application of DFT, which will be considered in this dissertation, is in the field of electronic spectroscopy. The primary method for computing transition energies to electronically excited states within the framework of DFT is to employ a time-dependent formalism [92] and the strengths and limitations of that model has been amply reviewed elsewhere [93]. Nevertheless, linear-response TD-DFT with various functionals continues to be an especially useful one-electron model for understanding the optical spectra of metal complexes. Few of them are exemplified here.

Jackson *et al.* [93] have employed TD-DFT to characterize intense near UV absorptions in axially ligated Fe$^{IV}$=O complexes as ligand to Fe=O charge transfer transitions. A recent review provides an overview of DFT and TD-DFT applications to electronic spectroscopy and excited-state properties of d$^6$ metal carbonyls, strongly phosphorescent cyclometallated complexes. Moreover, Fan *et al.*, [94] used spin unrestricted TD-DFT with the BP86 density functional, a continuum salvation model, and empirical corrections to calculate circular dichroism spectra of a number of trigonal dihedral Cr$^{III}$ d$^3$ complexes and compared to earlier related work. It is important to note that medium effects on optical spectra (solvatochromism) can be large for polar transition metal compounds, and the inclusion of such effects in the TD-DFT mode is typically most efficient when the surrounded medium is modelled as a dielectric continuum. This method (TD-DFT) is also known to be sensitive to the functional to gain the correct long-range dependence on the donor-acceptor distance in the π-expanded systems [95]. Configuration Interaction Singles (CIS) is a promising method to compute the
excited states of such systems. This has prompted to use the recently developed coulomb-attenuated long-range corrected version of B3LYP, i.e., CAM-B3LYP, hybrid functional, which has turned out to be very promising as this functional recovers the long-range spectral behaviour for different vertical excited state excitations [96].

The application of DFT to organic and to metal-ligand systems has become well established, even though many studies have been carried out with less than fully reliable density functionals. Given the rapid pace of ongoing functional development and the ever increasing scope of applications, the field must be regarded as still in its infancy. There remains considerable room for improvements, and the future is likely to be exciting.

1.9.2.4 Structure Preference for Coordination Compounds using Coordination Scan

Molecular mechanics is successfully utilized to determine the relationship between ligand selectivity and metal ion size. A highly selective ligand for a particular metal would possess a steep curve with a minima close to the ionic radius, conversely a shallow curve would suggest that the ligand is non selective in its metal binding. A related technique is the “coordination scan”, wherein similar curves are generated by minimizing complexes with various possible geometries with variation of numbers of water molecules coordinated to the metal ion while changing the M-L bond lengths [97]. Detailed procedure of coordination scan is presented in the experimental part (chapter 3) of the thesis.
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