Abstract

The research described in this dissertation addresses the complexation, evaluation of thermodynamic behaviour and photophysical properties of three new $C_3$-symmetric biomimetic tripodal ligands with trivalent metal ions. The immediate objective of this was to obtain systematic understanding, rational design and new synthetic possibility for the biomimetic chelators with special reference to siderophore analog. To achieve this aim, the synthetic analogues were designed by the biomimetic approach involving hybrid of two natural siderophores: *viz.*, enterobactin and quinolobactin. The feasibility of the proposed metal-ligand systems were tested prior to synthesis using *in-silico* design.

The three novel tripodal multidentate chelators developed are: 5,5'-((((8-hydroxyquinolin-5-yl)methylamino)methyl)-2-methylpropane-3-diyl)bis(azanediyl)bis (methylene)diquinolin-8-ol, (TAME5OX, $L_1$), 5-[[3-[(8-hydroxy-5-quinolyl)methoxy]-2-[(8-hydroxy-5-quinolyl)methoxymethyl]-2-methylpropoxy)methyl]quinolin-8-ol (TMOM5OX, $L_2$), and 5,5',5''-(cyclohexane-1,3,5-triyltris(oxy)) tris (methylene) triquinolin-8-ol (CYTOM5OX, $L_3$). These tripodal multidentate chelators have been synthesized taking the advantage of the chelating effect of three bidentate 8-hydroxyquinoline (8HQ) group, as binding units, appended at C-5 position to central pivotal central units 1,1,1- tris(aminomethyl)ethane, 1,1,1-tris(hydroxymethyl)ethane and 1,3,5 tris(hydroxy)cyclohexane, through functional groups ether (-O-) or secondary amine (-NH-).
The resulting tripods have been characterized by elemental analysis, FT-IR, NMR (\(^1\)H and \(^{13}\)C), electrospray mass spectrometry and theoretical investigations. The solution thermodynamic behaviour of these ligands were determined by potentiometric, absorption and emission spectrophotometric titration methods. In order to evaluate the acid-base properties, protonation constants of these synthesised ligands were calculated. Nine protonation constants for \(L_1\) while six protonation constants for \(L_2\) and \(L_3\) were obtained. The three highest log K values found between \(~7.42\) and \(~10.5\) and three lowest values between \(~2.64\) and \(~4.90\) are assigned of the hydroxyl and pyridinium nitrogen moieties of the three quinolinate groups, respectively, whereas that between \(5.88\) and \(6.71\) are attributed to the secondary amines for TAME5OX. The photophysical studies of these ligands by absorption and emission spectrophotometry reveal that, the special pH dependent behaviours are due to the formation of protonated quinolinium and deprotonated quinolinate forms of the 8-HQ moiety, respectively. This renders these compounds the special OFF-ON-OFF type of pH-dependent fluorescent sensors.

Complexation, thermodynamic and photophysical properties with two trivalent transition metal ions (Fe\(^{3+}\) and Cr\(^{3+}\)), one main group metal ion (Al\(^{3+}\)) and four lanthanide ions (La\(^{3+}\), Eu\(^{3+}\), Tb\(^{3+}\) and Er\(^{3+}\)) have been described. The coordination ability has been confirmed through synthesis, solution as well as theoretical studies. The reaction of TAME5OX, TMOM5OX or CYTOM5OX, \(L\), with the metal ions in ethanolic or aqueous medium led to compound with general formula ML with moderate yields (20-35%). The complexes were characterized by elemental analysis, infra-red and ESI MS mass spectrometry.

The solution thermodynamic behaviour of different metal coordination compounds of these tripodal ligands were determined by above mentioned titration methods. The formation constants of coordination compounds of these ligands formed at
or above physiological pH are found in the range of ~22.02-36.5 in log β unit, with pM values in range of ~16.0 to 31.9, calculated at pH 7.4, indicating TAME5OX (L₁) TMOM5OX (L₂), and CYTOM5OX (L₃) are powerful among synthetic metal chelators. The photophysical properties of novel metallo-quinoline systems were also scrutinized for photonic applications. The absorption and luminescence spectroscopy of these complexes show marked spectral variations due to characteristic ligand metal charge transfer (LMCT) transitions. The intense fluorescence from the 8HQ units of these chelators was intermittently get quenched in presence of Fe³⁺ and Cr³⁺ due to the photoinduced intramolecular electron transfer (PET) from excited N-pyridyl group to hydroxyl moiety. In contrast, for Al³⁺ reverse effect of photoinduced proton transfer (PPT) was observed which greatly enhanced the fluorescence of the ligand. This observed change is likely to be particularly important for the potential application of aluminium chelates of these ligands as luminescent sensors for the detection and remediation of Al³⁺ in surface waters, biological fluids. These complexes may also have potential in organic light emitting devices.

A systematic study has been undertaken on the interactions of the target ligands with La³⁺, Eu³⁺, Tb³⁺ and Er³⁺ ions for determination of their thermodynamic stability and aqueous coordination chemistry. The three chelators lead to the formation of soluble and thermodynamically stable Ln³⁺ complexes in water with high stability constants, featuring resistance toward hydrolysis in physiological pH. Among major species present at physiological pH, the stability constants (Log β) of neutral complexes have been determined to be ~32.84 -35.72 with pLn value of ~14.6-23.8, show interesting photophysical properties in ultraviolet and visible range.

The present work also explores the theoretical investigations carried out to predict the structure, electronic properties and binding efficiency of the ligands and their
corresponding metal complexes using empirical, quantum mechanical and density functional theory (DFT) methods along with the comparative studies with the experimental results. The calculations including geometry optimization, harmonic vibrational frequency analysis, NBO analysis, excitation and emission properties of the protonated, neutral, deprotonated states of the analogs and their Fe$^{+3}$ and Al$^{+3}$ complexes, were performed by employing the B3LYP (Becke three parameter Lee–Yang–Parr) exchange-correlation functional with the all-electron 6–31G* basis set whereas LACVP* basis set was used for and Cr$^{+3}$ complexes. The coordination geometries of the lanthanide complexes of these ligands were optimized by using PM7 as sparkles model. The preferred coordination number nine was predicted for the Ln(III) complexes by coordination scan technique with stepwise addition of three or more water molecules and comparing strain energies of the molecules using SYBYL. The theoretical electronic behaviour of Ln(III) complexes were evaluated by ZINDO/s methodology at configuration interaction with single excitation (CIS) level. These results emphasize the capability of the use of the theoretical models in prediction of geometries and all other calculations of compounds containing lanthanide ions and create new interesting possibilities for the design in–silico of novel and highly efficient lanthanide–organic edifice.

Finally, the interesting and exciting coordination and photophysical properties of these chelators make them excellent candidates with potential applications in chemical and biological fields and the procedures including both experimental and theoretical, may explore further suggestion in improving ligand design pathways.

The work embedded in this thesis is divided into six chapters for convenience. Chapter 1 is an introductory one, which discusses the background of the biomimetics and its relation with coordination chemistry followed by essential role of iron including
other trivalent metal ions in biological systems. The detailed description, classification and significance of natural iron binders called siderophores have been presented. This chapter also includes a brief on the ligand selection, strategies for ligand design and fundamentals of equilibrium thermodynamics with special reference to stability constant and factors affecting stability constant. An overview on different classical and advance methods of molecular modeling has also been discussed. Chapter 2 is concerned with review of literatures. It discusses some common type of siderophores particularly tris-bidentate tripodal ligands with different topologies containing hydroxamates, catecholates, hydroxypyridonates and mixed chelating groups. Some of the representative examples for each category of siderophore are presented. This is followed by a description on importance of bidentate 8-hydroxyquinoline and review on multidentate chelators based on 8-hydroxyquinoline reported so far. The work done by the author is embedded in chapter 3, 4 and 5. Each of these chapters has been further divided into introduction, results and discussion, conclusions and experimental followed by references. Finally, the scope of the present studies for the future work is given in chapter 6.

Some of the work, presented in this thesis have been published in peer reviewed international journals and also presented and discussed in national and international seminar/conferences. The list of such abstracts and papers published/communicated in journals is appended as Appendix I.