5.1 Introduction

Complex forming (Chelating) agents are becoming of increasing importance in analytical chemistry such as in gravimetric, titrimetric and colorimetric measurements. New types of complexes and complex forming agents are constantly under investigation, for possible analytical and industrial applications. The growing importance of the use of metal chelates in analytical chemistry may be realized by the ever-increasing number of publications on this subject. In the past few years, inorganic chemistry has been greatly enriched by the continuing development of coordination chemistry. There are many new directions in coordination chemistry such as molecular magnetism, supramolecular chemistry, bioinorganic chemistry, medicinal chemistry and biosensors.

It was G.T. Morgan and Drew [1] who first coined the name CHELATE from the Greek word CHELE used for crabs claw to designate to cyclic structures which arise from the union of metallic ions with organic or inorganic molecules, with two or more points of attachments to produce a closed ring.

Coordination compounds were known when Alfred Werner proposed, that Co(III) bears six ligands in an octahedral geometry. The theory allows to understand the difference between coordinated and ionic chloride in the coordination compound. Ligand may be attached to the metal through a single atom (monodentate) or bound to the metal through two or more atoms (bidentate or polydentate etc.). When a bi- or polydentate ligand uses two or more donor atoms bonded to a single metal ion, it is said to form a chelate complex. Such complexes tend to be more stable than similar complexes containing unidentate ligands.
Prior to the 1980’s, research in the field of complex forming reagents (CFRs) was one of the most active research area in inorganic and analytical chemistry. The development of CFRs was stimulated by research and progress in coordination chemistry and by studies of complex equilibrium in solution. CFR are essential in the application of highly efficient separation procedures such as high performance liquid chromatography. From the reagent/reaction chemistry viewpoint it is more logical to classify CFRs based on the characteristic functional group of donor atoms in the various reagents. The list of some important CFR is presented below.

- Acetyl acetone

  \[
  \text{CH}_3\text{-CO-CH}_2\text{-CO-CH}_3
  \]

- Dibenzolymethane

- Phenol Class compounds
- Pyrocatechol

- Pyrogallol
- Gallic acid

- Salicylic acid

- flavones

- Hydroxyanthraquinones
  - Alizarin

- Quinizarin

- O-N-Donating Reagents
  - 0-substituted monoazo Dyes
Nitroso Compounds

Schiff's Bases

8-Quinolinol and Derivatives

N-N-Donating Reagents

Dimethylglyoxime

Benzil dioxime

Aryl-1, 2-diamines

1,2-Phenylenediamine

2,3-Diaminonaphthalene
5.1.1 Formation of Complexes

The formation of complex and its stability depends upon the following three aspects.

(A) The central metal atom
(B) The complex forming groups of molecules
(C) The nature of the metal-ligand bond

(A) The Central Metal Atom

The nature and the oxidation state of the central metal atom influences to a considerable extent the properties of a metal complex. The influence of the central metal atom can be studied by comparing the compounds formed by a series of different metal atoms in a given oxidation state with a particular chelating agent [2].

(B) The Complex Forming Group(s) of Molecules

The organic molecules possessing the ability to form complex rings are very large. When a molecule functions as a complex forming agent it must fulfill two of the most important conditions given below.
(I) The organic molecule must have at least one or more appropriate functional groups, the donor atoms of which are capable of combining with the metal atom by donating a pair of electrons. The functional group may be
(II) An acidic group which may combine with the metal atom by replacement of hydrogen or a coordinating group.
(III) Permit the ring formation with a metal atom as the closing member. However, these two conditions are necessary but are not sufficient always for the formation of a complex ring. Steric factors occasionally The functional group must be appropriately situated in the molecule to influence complexation as in the case of the complexes of Cu$^{2+}$ and Fe$^{2+}$ with 2,9-dimethyl-1,10 phenanthroline [3].

The perusal of the literature reveals that an organic reagent, which forms a chelate or an inner complex with a metal ion, is superior to the rest in analytical work. When an organic molecule containing both an acidic and basic functional groups operate, an
inner complex or a chelate result. The formation [4, 5] of this ring may involve either a primary (ionic) or a secondary (coordinating) valence and may be formed by two primary or two secondary or one primary and one secondary valence. Vallarino and Quagliano [6] believed that the inner complex is a completely chelated nonionic structure formed usually by the union of a metal ion with a bidentate ligand of a uninegative charge.

An organic compound having a suitable number of reactive groups can act as a chelate forming ligand depending upon the coordination number of the metal ion. The ligand may be bidentate, tridentate or quadridentate and may develop a complex ring of varied sizes.

A variety of chelates of metal ions with organic reagents having bidentate groups have been studied [7-11]. When group like-COOH, -CONH$_2$, -SO$_3$H or –OH is suitably placed with a group like –S-, -NH$_2$, -OH or = N-OH, the latter groups are found to be coordinating with a metal ion which is linked through primary valence (ionic) to the former.

Copper and boron were found to form complexes [12,13] with organic reagents having a –COOH and –OH both acidic groups.

The oxygen of the carboxyl group in vicinity to a phenolic –OH group is found to be coordinating. Aromatic o-hydroxy compounds like salicylaldehyde or o-hydroxy acetophenone are reported to form inner complexes [14,15] with Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$ and Fe$^{2+}$ such compounds develop a six membered heterocyclic ring.

Morgan and coworkers [16,17] have investigated complex of β-diketones with Be$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$ and also with Zr$^{4+}$, Hf$^{4+}$, Al$^{3+}$, Fe$^{3+}$, Cr$^{3+}$, Co$^{3+}$ etc. and found them to be stable and soluble in organic solvents.

Wolf and coworkers [18] have reported the exchange of reaction of diketone ligands with acetyl acetonato complexes of Fe$^{3+}$, Rh$^{3+}$ and Ru$^{3+}$. Hazell and coworkers [19] have reported a unidentate beta diketo ligand through its respective methylene group.
Alpha and beta amino carboxylic acids and ortho and meta aminophenols are capable of forming complexes [20-22] with many metal ions. The ability to coordinate metal ions in the body renders o-aminophenol carcinogenic [23]. Charles and Freiser [24] reported greater stability of metal complexes of o-aminophenol than that of the diketones and substituted salicylaldehyde derivatives.

(C) The Nature of the Metal Ligand Bond

It is necessary to understand the nature of the bond between metal and ligand, for the proper interpretation of the structure of metal complexes. The complex ions such as [PtCl$_6$]$^{2-}$, [Co(NH$_3$)$_6$]$^{3+}$ etc. were subject of intensive investigations to find out the factors responsible for their stability the explain the existence of these compounds. Various theoretical approaches to this problem were developed but it was Jorgensen [25] who proved that the earlier theories proposed by the various authors [26-30] were fallacious.

Werner proposed his coordination theory for the recognition of the existence of the species such as [PtCl$_6$]$^{2-}$, [Co(NH$_3$)$_6$]$^{3+}$ etc. He explained the formation and existence of these species by suggesting that the valency of the atom and the number of bonds it can form may not be identical. He postulated that the combining power of an atom is divided into two spheres of attraction the inner co-ordinate sphere and the outer ionization sphere. Neutral molecules or negative ions are coordinated around the central metal ion in the inner sphere. Number of such groups is the coordination number of the metal ion. Negative ions are loosely attached to outer-sphere and can be ionizable. So inner-sphere satisfies the secondary valency (non ionizable valency) and outer-sphere satisfies the primary valency (ionizable valency).

Lewis [31] and Langmuir [32] were the first to interpret the nature of the covalent bond as “Sharing of electrons between two bonding atoms in which each atom contributes one electron”. Later on Sidgwick [33] developed an electronic interpretation to explain the
bonding in metal complexes and he had introduced the idea of coordinate bond by accepting the Lewis concept of covalent bond.

5.2 8-Hydroxyquinoline and Its Derivatives

8-Hydroxyquinoline (8-quinolinol, oxine) might be thought to function as a phenol, but out of the 7 isomeric hydroxyquinolines only oxine exhibits significant antimicrobial activity, and is the only one to have the capacity to chelate metals. If the hydroxyl group is blocked so that the compound is unable to chelate, as in the methyl ether, the antimicrobial activity is destroyed. The relationship between chelation and activity of oxine has been investigated [34-36]. Oxine itself is inactive, and exerts activity by virtue of the metal chelates produced in its reaction with metal ions in the medium. Used by itself or as the sulfate (Chinosol) or benzoate in antiseptics, the effect is bacteriostatic and fungistatic rather than microbiocidal. Inhibitory action is more pronounced upon gram-positive than gram-negative bacteria; the growth-preventing concentrations for staphylococci being 10 ppm; for *streptococci* 20 ppm; for *Salmonella typhosa* and for *E. coli* 100 ppm. [37-38]. However, a 1% solution requires at least 10 hours to kill *staphylococci* and 30 hours for *E. coli bacilli*. The oxine benzoate was the most active antifungal agent in a series of 24 derivatives of quinoline tested. A 2.5% solution of this compound was successful in treating dermatophytosis [39-40]. Iron and cupric salts were found to prolong the antibacterial effect of oxine on teeth [41]. Certain halogen derivatives of 8-Hydroxyquinoline have a record of therapeutic efficacy in the treatment of cutaneous fungus infections and also of amebic dysentery. Among these are 5-Chloro-7-iodo-8-quinolinol (iodochlorhydroxyquin, Vioform), 5,7-Diiodo-8-hydroxyquinoline (diiodohydroxyquinoline), and sodium 7-Iodo-8-hydroxyquinoline-5-sulfonate (chiniofon)[42-44]. Copper 8-Quinolinolate (copper oxinate), the copper compound of 8-Hydroxyquinoline, is employed as an industrial preservative for a variety of purposes, including the protection of wood and textiles against fungus-caused rotting, and
interior paints for food plants. It has 25 times greater antifungal activity than oxine [45].

8-Hydroxyquinoline 5-Chloro-8-hydroxy-7-iodoquinoline

5,7-Dichloro-8-hydroxyquinoline Copper Oxinate

One of the derivative of 8-hydroxyquinoline is 5-Chloromethyl-8-hydroxyquinoline. The literature survey reveals that 5-Chloromethyl-8-hydroxyquinoline (CMQ) is a versatile derivative of 8-hydroxyquinoline. It can be easily prepared by the room temperature reaction of 8-hydroxyquinoline, formaldehyde, conc. HCl and dry HCl gas [46,47]. It is stable in form of hydrochloride other wise it hydrolyzes to methyl group [48]. The reports [46,47] included the number of derivative of CMQ by the reaction of CMQ with alcohols and secondary amines. Aristov. et. al. [49-52] have documented several reports about number of 5-substituted derivatives from CMQ having the structures as follows.
The tetrakis 8-hydroxyquinoline methyl ethylene alkyl diamine shown below has been prepared for their complexation [53,54].

\[ \text{QH}_2\text{C}(\text{CH}_2)_{10}\text{N} - \text{CH}_2\text{QH}_2\text{C} \]

Some reports about the metal analysis complexation and electroanalysis of these derivatives are also found [55-57].

The cellulose is a high molecular weight natural polymer and its reaction with CMQ afford the 8-Hydroxyquinoline-cellulose product which is applied as good ion-exchanger [58,59].

The well-known polymer say polystyrene and or styrene divinyl benzene copolymer were aminated and these on treatment with CMQ afford good ion-exchangers [60-61].

8-hydroxyquinoline terminated polyether was prepared by the reaction between amino terminated polyether and CMQ [62-63].

The various scientists have reported the Bis-8-hydroxy quinolines prepared from CMQ and their co-ordination polymers [64-69].
Sebastian Madonna et al., reported Structure–activity relationships and mechanism of action of antitumor bis 8-Hydroxyquinoline substituted benzylamines. They reported that, a series of twenty six 8-hydroxyquinoline substituted amines, structurally related to compounds were synthesized to evaluate the effects of structural changes on antitumor activity and understand their mechanism of action. The studies were performed on a wide variety of cancer cell lines within glioma and carcinoma models. The results obtained from chemical models and biological techniques such as microarrays suggest the following hypothesis that a quinone methide intermediate which does not react with DNA but which gives covalent protein thiol adducts. Micro-array analysis showed that the drugs induce the expression of a variety of stress related genes responsible for the cytotoxic and cytostatic effects in carcinoma and glioblastoma cells respectively. The described analogues could represent new promising anti-cancer candidates with specific action mechanisms, targeting accessible thiols from specific proteins and inducing potent anti-cancer effects [70].

Balaram Ghosh et al., recently synthesized 8-quinolinol and N-substituted piperazine in one combined molecule and studied in vivo activity indicates potential application in symptomatic and neuroprotective therapy for parkinson’s disease [71].

Ruogu Peng et al., synthesized Fluorescent Sensors for Fe$^{3+}$ containing 8-Hydroxyquinoline. They reported that a series of 5-dialkyl(aryl)aminomethyl-8-hydroxyquinoline dansylates were synthesized and their fluoroionophoric properties toward representative alkali ions, alkaline earth ions and transition metal ions were investigated. Among the selected ions, Fe$^{3+}$ caused considerable quenching of the fluorescence, while Cr$^{3+}$ caused quenching to some extent. The absence of any significant fluorescence quenching effects of the other ions examined, especially Fe$^{2+}$, renders these compounds highly useful Fe$^{3+}$ selective fluorescent sensors [72].
Feng Wang et al., reported they reported that a series of dendritic 8-Hydroxyquinoline (8-HQ) and 5-Dialkyl(aryl)aminomethyl-8-HQ derivatives were synthesized and their fluoroionophoric properties toward representative alkali, alkaline earth, group IIIA and transition metal ions were investigated. Among the selected ions, Zn(II) enhanced the fluorescence of N-Di-(methoxycarbonyylethyl)aminoethyl-3-[4-(8-hydroxyquinolin-5-ylmethyl)piperazin-1-yl]-propanoic amide by 31-fold, while Al(III) caused enhancement to some extent. The absence of any significant fluorescence enhancement by the other ions examined renders a highly useful Zn(II)-selective fluorescent sensor [73].

L. Feng reported synthesis and photophysics of novel 8-hydroxyquinoline aluminum metal complex with fluorine units [74].

Discovery of a new family of Bis-8-hydroxyquinoline substituted benzylamines with pro-apoptotic activity in cancer cells and their synthesis, structure-activity relationship and action mechanism studies reported by V. moret et al., [75].
S. C. Panchani et al., recently reported Coordination Polymeric chain assemblies of some metal ions containing 8-Hydroxyquinoline moieties. They also studied thermal behavior of this polychelates [76].

![Coordination Polymeric Chain Assembly](image1)

G. J. Kharadi et al., also reported some coordination polymeric chains of metal ions containing 8-Hydroxyquinoline moiety [77].

![Coordination Polymeric Chain Assembly](image2)

They also reported In-vitro antimicrobial, thermal and spectral studies of mixed ligand Cu(II) heterochelates of clioquinol and coumarin derivatives [78].

5.3 Synthesis and Characterization of Ligands

5.3.1 Synthesis of 5-Chloromethyl-8-quinolinol (CMQ)

5-Chloromethyl-8-quinolinol (CMQ) was prepared by chloromethylation of 8-Hydroxyquinoline (Oxine) according to the method reported in literature [72,79]. The detail of the procedure is given below.

A stream of hydrogen chloride gas was blown through a solution of 8-hydroxyquinoline (0.1 mol) and formaldehyde (20 mL, 37%) in 37% hydrochloric acid (50 mL) for 8 hours at 50°C. After filtration, the product was washed with 37% hydrochloric acid and dried to afford CMQ in 85% yield.
5.3.2 Synthesis of Ligand 5-((5-(Pyridine-4-yl)-1,3,4-oxadiazole-2-thio)methyl)quinolin-8-ol (L-1) (10)

To the mixture of 5-(Pyridine-4-yl)-1,3,4-oxadiazole-2-thiol (26.0 mmol) and triethylamine (80.8 mmol) in dry pyridine (40 ml), CMQ (26.9 mmol) was added with continuous stirring. The contents were refluxed for 150 min. The completion of the reaction was confirmed by TLC. The excess of pyridine was distilled off and the residue was poured into the ice-cold water to yield a light green product which was filtered and washed with hot water and ethyl acetate and then dried over a vacuum desiccator. Yield, 75%; m.p., 253–255°C. Found (%): C, 60.70, H, 3.59, N, 16.69. C_{17}H_{12}N_{4}O_{2}S (336.00) Calculated (%): C, 60.71, H, 3.57, N, 16.66. IR: 3294 (O–H), 1640 (C=N), 1500 (Ar C=C), 730 (C–S ); \(^1\)H NMR: 9.87 (1H, s, protons -OH), 8.91 (2H, d, pyridine ring), 7.82 (2H, d, pyridine ring), 7.01-8.01 (5H, m, oxine), 4.49 (2H, s, protons S–CH\(_2\)); \(^{13}\)C NMR: 164.9, 151.4, 149.10, 148.89, 143.7, 137.2, 131.9, 128.3, 127.1, 126.3, 121.9, 121.1, 112.8, 36.0.

5.3.3 Synthesis of Ligand 5-((3-(Methylthio)-5-(pyridine-4-yl)-4H-1,2,4-triazole-4-ylamino)methyl)quinoline-8-ol (L-2) (11)

To the mixture of 3-(Methylthio)-5-(pyridine-4-yl)-4H-1,2,4-triazole-4-amine (26.0 mmol) and triethylamine (80.8 mmol) in dry
pyridine (40 ml), CMQ (26.9 mmol) was added with continuous stirring. The contents were refluxed for 150 min. The completion of the reaction was confirmed by TLC. The excess of pyridine was distilled off and the residue was poured into the ice-cold water to yield a green product which was filtered and washed with hot water and ethyl acetate and then dried over a vacuum desiccator. Yield, 70%; m.p., >300°C. Found (%): C, 59.30, H, 4.47, N, 23.09. C_{18}H_{16}N_{6}O_{5}S (364.42) Calculated (%): C, 59.32, H, 4.43, N, 23.06. IR: 3312 (O–H), 3410 (-NH), 1601 (C=N), 735 (C–S); ¹H NMR: 9.88 (1H, s, protons -OH), 8.79-7.85 (4H, 2d, pyridine ring), 7.00-8.49 (5H, m, oxine), 4.30 (2H, s, -CH₂), 2.64 (3H, s, S-CH₃), 8.80 (1H, s, -NH); ¹³C NMR: 160.01, 152.10, 151.40, 148.75, 147.20, 137.15, 134.10, 132.00, 131.90, 128.28, 126.30, 126.90, 121.30, 112.20, 56.80, 14.90.

5.3.4 Synthesis of Ligand 1-((4-Ethylpiperazine-1-yl)methyl)-4-((8-hydroxyquinolin-5-yl)methylamino)-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione (L-3) (12)

To the mixture of equimolar 3-((4-Ethylpiperazin-1-yl)methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H)-thione and hydrazine hydrate in n-butanol refluxed for 3 hrs and then acidified it with dil HCl yielded 4-Amino-1-((4-ethylpiperazine-1-yl)methyl)-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione.

To the mixture of 4-Amino-1-((4-ethylpiperazine-1-yl)methyl)-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione (26.0 mmol) and triethylamine (80.8 mmol) in dry pyridine (40 ml), CMQ (26.9 mmol) was added with continuous stirring. The contents were refluxed for 150 min. The completion of the reaction was confirmed by TLC. The
excess of pyridine was distilled off and the residue was poured into the ice-cold water to yield a light green product which was filtered and washed with hot water and ethyl acetate and then dried over a vacuum desiccator. Yield, 65%; m.p., >300°C. Found (%): C, 60.51, H, 5.97, N, 23.49. C_{24}H_{28}N_{8}OS (476.60) Calculated (%): C, 60.48, H, 5.92, N, 23.51. IR: 3200 (O–H), 3360 (-NH), 1640 (C=N), 1517 (Ar C=C), 743 (C–S ); \textsuperscript{1}H NMR: 9.81 (1H, s, protons -OH), 8.73-8.01( 4H, 2d, pyridine ring), 6.99-8.00 (5H, m, oxine), 3.90 (2H, s, –CH\textsubscript{2}), 2.30 (8H, two t, pip.), 4.51 (2H, s, -CH\textsubscript{2}, exocyclic), 1.1 (3H, t, -CH\textsubscript{3}), 2.12 (2H, q, -CH\textsubscript{2}), 8.85 (1H, s, -NH); \textsuperscript{13}C NMR: 151.30, 148.12, 122.70, 140.00, 179.10, 161.00, 131.11, 121.70, 149.20, 128.50, 137.20, 126.30, 126.97, 112.81, 52.90, 58.17, 70.11, 50.10, 14.12, 51.10.

The techniques used for the characterization of ligands 10,11,12 are discussed in Chapter-2.
Fig. 5.1 IR Spectrum of Compound 10
Fig. 5.2 IR Spectrum of Compound 11
Fig. 5.3 IR Spectrum of Compound 12
Fig. 5.4 $^1$H NMR Spectrum of Compound 10

Fig. 5.5 $^1$H NMR Spectrum of Compound 11
Fig. 5.6 $^1$H NMR Spectrum of Compound 12

Fig. 5.7 $^{13}$C NMR Spectrum of Compound 10
Fig. 5.8 $^{13}$C NMR Spectrum of Compound 11

Fig. 5.9 $^{13}$C NMR Spectrum of Compound 12
5.4 Results and Discussion

All the ligands (10, 11, 12) are soluble in polar organic solvents. The C, H and N contents of all the ligands consistent with their predicted structure. The Infrared spectral data, $^1$H NMR spectral data and $^{13}$C NMR spectral data are given individually and IR, PMR and CMR spectrum for ligands are scanned in fig. 5.1-5.9. IR and PMR spectrum of ligands shows –OH band and peak respectively.
References