



ORIGINAL RESEARCH PAPER

Chemistry

BIOLOGICAL ACTIVITIES OF SHIFF BASE-TRANSITION METAL COMPLEXES: A REVIEW

KEY WORDS: *Imines, Schiff's bases, Metal complexes, Antimicrobial activity, Catalyst, Nonlinear optical properties, Antitumor activity.*

Kishor Hemraj Chaudhari*

Dept. of chemistry SJJT University, Jhunjhunu, Rajasthan, India
*Corresponding Author

ABSTRACT

Schiff's bases are flexible ligands which are synthesized from the condensation of primary amines with carbonyl groups such as aldehydes and ketones. These compounds are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. Most of them exhibit biological activities such as antibacterial, antifungal as well as antitumor activity. Metal complexes of the Schiff's base ligands are generally prepared by treating metal salts with Schiff's base ligands under appropriate experimental circumstances. Transition metal complexes derived from the Schiff's base ligands with biological activity have been widely studied. This review summarizes the synthesis, biological activities and catalytic activities of Schiff base ligands and their transition metal complexes.

1. INTRODUCTION

In coordination chemistry, Schiff's bases are an important class of ligands and come across widespread applications in different fields [1-4]. The interaction of these ligands and metal ions gives complexes of different geometries which are potentially biologically active [5]. The π-system in a Schiff's base often imposes a geometrical constriction and affects the electronic structure as well. Thermochemical properties of Schiff's bases have attracted the attention of many researchers, in view of their ability to bind through NO or N2O2 donor atom sets [6].

These Schiff's base metal derivatives involving bidentate or tetradentate bonding of ligands in biological systems, have considerable interest and also contributing to the knowledge of their structure and behavior in various activities [7].

Schiff's bases have been playing an important part in the development of coordination chemistry. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous scientific areas. These types of complexes have been vigorously explored in recent years and such studies have been the subject of many papers and reviews [8]. Many of them are centered on the catalytic activity of Schiff's base complexes in a large number of homogeneous and heterogeneous reactions. It is difficult to cover in this seminar the literature on Schiff base metal complexes, which embraces very wide and diversified subjects comprising vast areas of organometallic compounds and various aspects of bioinorganic chemistry. Therefore, the introduction part is limited to a brief discussion on the Schiff bases, their metal complexes and general applications of Schiff base complexes with an emphasis on catalytic applications, and their characterization methods [9].

Schiff's bases offer a versatile and flexible series of ligands capable to bind with various metal ions to give complexes with suitable properties for theoretical and/or practical applications. Since the publication of Schiff base complexes, a large number of polydentate Schiff's base compounds have been structurally characterized and extensively investigated [10]. Schiff's base ligands and their metal complexes have been extensively studied over past few decades. Of the various classes of Schiff's base which can be prepared by condensation of different types of amines and carbonyl compounds salicylaldehydes, potential O, N-donors derived from salicylaldehyde and primary amines, are very popular due to diverse chelating ability [7].

Copper (II) - salicylaldehyde complexes play important roles in both synthetic & structural research because of their preparative accessibility and structural diversity [11, 12]. In addition to the varied magnetic property and catalytic

activity, the metal-Schiff base complexes can also serve as efficient models for the metal containing sites in metallo-proteins and -enzymes [13]. Tetradentate Schiff's bases with a N2O2 donor atom set are well known to coordinate with various metal ions, and this has attracted many researchers. Complexes of Schiff's base ligands have been studied for their dioxygen up take and oxidative catalysis. Also complexes of transition metals (II), which involve derivatives of salicylaldehyde and diamine, have gotten considerable attention. This is because of their potential as catalysts for the insertion of oxygen into an organic substrate [14]. Synthesis, X-Ray and magnetic properties of dinuclear Ni(II) and Cu(II) complexes bridged by the Azo-2,2'-bispyridine ligands has been considered, [15]. They studied the magnetic properties of these dinuclear paramagnetic complexes in details and have provided an opportunity for probing the ability of this ligand to mediate exchange interactions between paramagnetic metal centers. Many ketone and β-diketones are condensed with amine and diamines for forming a Schiff's base and their complexes [16]. The present study aimed to investigate the reaction of several tetradentate Schiff bases derived from the condensation of o-phenylenediamine with salicylaldehyde, 2-hydroxy-1-naphthaldehyde, or o-hydroxyacetophenone with nickel, copper and zinc ions.

Schiff's bases have been widely used as ligands because they form highly stable coordination compounds and have good solubility in common solvents [6, 17]. These Schiff's base metal derivatives have considerable interest due to coordinated metal ions acting as bidentate or tetradentate ligands in biological systems, contributing to the knowledge of their structure and behavior in various activities [18].

2. The Chemistry Of Schiff's Base Ligands

Chelating ligands in the field of Coordination Chemistry and their Metal Complexes are of great interest since many years. It is well known that N, S and O atoms play a key role in the coordination of metals at the active sites of numerous metallo-biomolecules. Chelating ligands containing O, N and S donor atoms show broad biological activity and are of special interest because of the variety of ways in which they are bonded to metal ions [19]. The condensation of an aldehyde or ketone with primary amine leads to the formation of an imine called Schiff's base [18, 20].

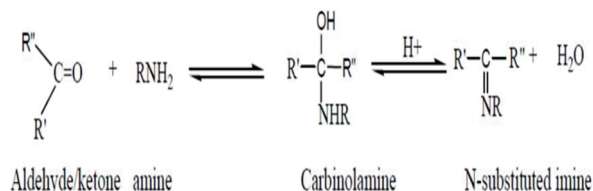


Fig-1. Formation of Schiff's base from carbonyl compounds in

acid catalyzed dehydration

Schiff's base was first reported by Hugo Schiff's in 1864. Schiff bases can be prepared by condensing carbonyl compounds and amines in different conditions and in different solvents with the elimination of water molecules. The presence of a dehydrating agent normally favours the formation of Schiff bases. Though the Schiff's bases are stable solids, care should be taken in the purification steps as it undergoes degradation. Chromatographic purification of Schiff's bases on silica gel is not recommended as they undergo hydrolysis [18].

The common structural feature of these compounds is the azomethine group with a general formula $RHC=N-R'$, where R and R' are alkyl, aryl, cycloalkyl or heterocyclic groups which may be variously substituted. Presence of a lone pair of electrons in a sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical importance and impart excellent chelating ability especially when used in combination with one or more donor atoms close to the azomethine group. This chelating ability of the Schiff bases combined with the ease of preparation and flexibility in varying the chemical environment about the C=N group makes it an interesting ligand in coordination chemistry [21].

2.1. Synthesis of Novel Schiff's Base Ligands

Over the past 25 years, extensive chemistry has surrounded the use of Schiff base ligands in inorganic chemistry. For instance, N,N'-ethylenebis(salicylideneimine) (salen) [22], which is nearly related and similar novel ligand N,N'-bis(benzoylacetone) ethylenediamine, and some related derivatives have been the ligands of choice for several reasons. Firstly, the ease of synthesis of these compounds has meant that bulk amounts can be synthesised both simply and cheaply; properties that become very important when industrial applications are being sought. Secondly, these ligands are multidentate, which means for most metals, several binding sites are occupied, leaving vacant sites for potential catalytic/enzymatic activity [22]. Furthermore, substitution at the aromatic ring can modify the electronic and steric properties of the resulting complexes, which can enable fine-tuning of properties with the ubiquitous nature of the ligands in transition metal chemistry, it comes as a bit of a surprise that main group metals and lanthanoids have only been studied to a limited extent. It is the aim of this project to study some Group 1 and 2 chemistry of these salen ligands and to prepare some "cage complexes" using some lanthanoid metals. Our plan will encompass several fronts [23].

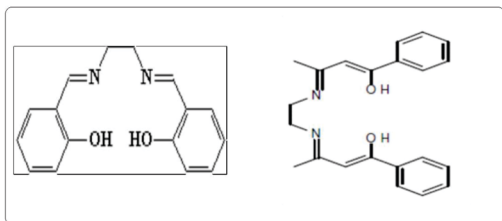


Fig-2. Structure of N,N'-ethylenebis(salicylideneimine) & N,N'-bis(benzoylacetone) ethylenediamine respectively.

Different R groups on the aromatic moieties will be employed to modify the steric and electronic requirements of the ligand; Different bridging groups (eg ethylene and propylene, but also other alcohol containing bridges) between the two nitrogen centers will be incorporated to study the effects of chelate size, rigidity and further coordination sites; Different metals (s block metals) will be used to elucidate the effect of metal size and coordination number requirements, Different coordinating solvents (diethylether, thf, dme, tmeda, pmdeta) will be used to modify the resulting nuclearity of the complexes, To expand some chemistry of lanthanoid "cage complexes" using, in particular, alcohol substituents on the

bridging groups of the Schiff base ligands, for which we have recently isolated some exciting and novel complexes [24,25].

2.2. Metal Complexes with Schiff's Base Ligands

Schiff bases offer a versatile and flexible series of ligands able to bind with various metal ions to give complexes with suitable properties for theoretical and/or practical applications. Since the publication of Schiff base complexes, a large number of poly-dentate Schiff's base compounds have been structurally characterized and extensively investigated, [26]. Schiff's base ligands and their metal complexes have been extensively studied over past few decades. Metal complexes containing synthetic macrocyclic ligands have attracted a great deal of attention because they can be used as models for more intricate biological macrocyclic systems like metalloporphyrins (hemoglobin, myoglobin, cytochromes, chlorophylls), corrins (vitamin B12) and antibiotics (valinomycin, nonactin). So it attracted the attention of both inorganic and bioinorganic chemists [27].

These discoveries have created supramolecular chemistry and its enormous diversity. Metal complexes of the Schiff bases are generally prepared by treating metal salts with Schiff's base ligands under suitable experimental conditions. However, for some catalytic application the Schiff base metal complexes are prepared in situ in the reaction system. For instance five synthetic routes that are commonly employed for the preparation of Schiff's base metal complexes and these are depicted in Figure 3 [28].

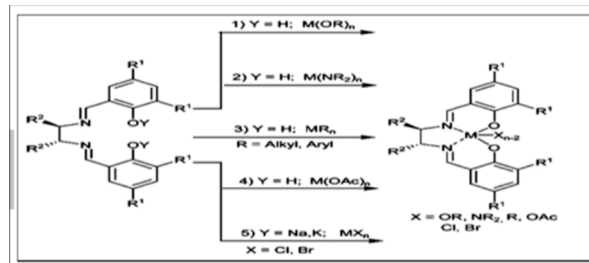


Fig:3 Preparation Of Schiff Base Complexes

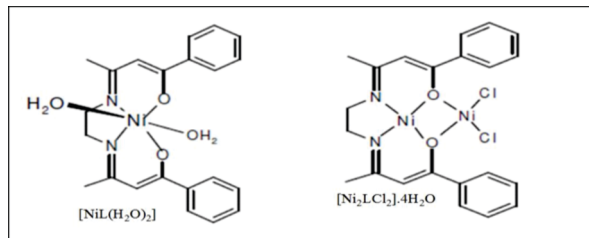


Fig-4. Two Types Of Nickel Complexes With The Noble Ligand (L), N,N'-Bis(Benzoylacetone) ethylenediamine.

2.3. Schiff's Base Transition Metal Complexes in Catalysis

Transition metal catalyzed reactions have had a large impact on the human progress for the last century. Several extremely important areas, such as the agricultural industry and the plastic industry, have benefited from this development. The evolution of different transition metal catalysts has also been very important for the pharmaceutical industry. One vital factor when developing new and more effective catalysts is to obtain mechanistic insights. In this thesis, several different methods to investigate mechanisms for transition metal catalyzed reactions are presented [29].

Schiff's base complexes play a central role in various homogeneous catalytic reactions and the activity of these complexes varies with the type of ligands, coordination sites and metal ions. Literature reports reveal that a large number of Schiff's base metal complexes exhibit catalytic activities. Chiral Schiff's base complexes are more selective in various reactions such as oxidation, hydroxylation, aldol

condensation and epoxidation. In general, aromatic Schiff's base or their metal complexes catalyze reactions on oxygenation, hydrolysis, electro reduction, decomposition, oxygenation of alkenes, etc. [30]

A number of homogenous catalytic reactions involve Schiff base complexes which have a major role in such reactions and variation in the activity of such complexes is observed by alteration of metal ion, coordination site and the type of ligands. Catalytic activities of Schiff base metal complexes are abundantly found in literature. In this regard, more selective behavior of Schiff base complexes has been observed for a number of reactions like hydroxylation, oxidation, and epoxidation and aldol condensation. Oxidation reactions, Ring opening polymerization reaction, Epoxidation reactions, Polymerization reactions, Hydrogenation reactions.

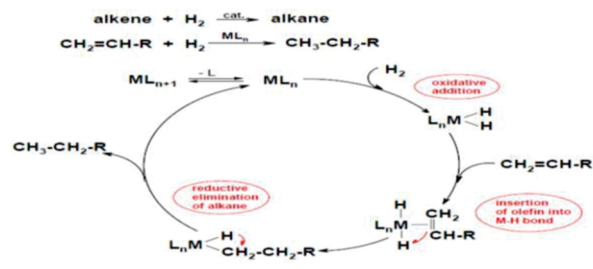


Figure-1. Catalytic applications of transition compounds for organic reactions

3. Characterization Methods

Among various physico-chemical techniques used in complexometric investigations elemental analysis, IR and electronic spectral methods (UV-Vis spectroscopy), Atomic absorption spectroscopy, Molar conductometric and susceptibility measurements being highly sensitive and informative are most popular.

3.1. Elemental Analysis

Novel Schiff's base Ligands and their complexes are analyzed micro analytically for carbon (C), hydrogen (H), Sulfur(S) and nitrogen (N) contents to find out their empirical composition. That means Elemental analysis of a compound enables one to determine the empirical formula of the compound. The empirical formula is the formula for a compound that contains the smallest set of integer ratios for the elements in the compound that gives the correct elemental composition by mass. So physical characteristics and elemental analysis of C, H and N of the compounds are considered to determine the composition of complexes and the novel ligand. The results of C, H and N percentage are in accordance with the composition suggested for the most complexes [28,31].

3.2. Infrared Spectra

IR spectra of the samples are recorded in Nujol or KBr medium in 200-4000cm⁻¹ range to identify coordination sites of ligands, formation and strength of metal-ligand bonds in the complexes, and to study the bonding vibrational modes of ligand in metal complexes. The IR spectra of the complexes and ligands have a diagnostic importance to determine the structure of the compounds. The solid state IR spectra of complexes compared with those of ligands indicated that the (C=N) stretching vibration band at region about 1500-17000cm⁻¹ is shifted to lower frequencies in most complexes as expected. In contrast there are many complexes shifted to higher frequencies, which indicated that the ligands coordinated to the metal ions through nitrogen atom of the azomethine group. In general the observed IR bands of Schiff's bases and their complexes are in conformity with the previously reported results [21,22,32].

The presence of sharp band corresponding to the remaining hydroxyl group at 3400cm⁻¹ but it is obscured by the presence of water molecules bands. This was appeared for the most

complexes and a very broad band at about 3100-3500cm⁻¹ region, which is associated with coordinated or solvent water molecules. The other bands appeared at 1323-1427cm⁻¹ region assigned to the (C—O), which are shifted to a higher frequency after complexation with central metal ions, compared to the free ligands in which was noted at 1261-1315cm⁻¹. In addition the two bands at 729-511 and 531-442cm⁻¹, is attributed to the (M—O) and (M—N) respectively [25,31].

Moreover new bands appeared in some complexes in the 220-290cm⁻¹ regions which is assigned to (M—Cl) vibration, which indicated the formation of (M—Cl) coordinated bond. The IR spectra of [Cu2L1Cl12] 8H2O complex exhibit a strong band at 1568cm⁻¹ which is assigned to the (C=N) stretching, because this band is shifted to lower frequency by 36cm⁻¹ compared to free ligand, indicating that the ligand coordinated to the metal ion through nitrogen atom of the azomethine group and probably dianionic form. The broad band around 3425cm⁻¹ indicating the presence of coordinated or lattice water in the complex. The spectrum reversals a weak band at 1399cm⁻¹ which is attributed to (C—O) vibration, again this band is shifted to higher value compared to the free ligand due to formation (C—O—M) bond. In addition three new bands in the regions 527,466 and 221cm⁻¹ were emerge, which are probably due to the formation of (Cu—O), (Cu—N) and (Cu—Cl) bond respectively [24].

The IR spectra provide valuable information regarding the nature of functional group attached to the metal atom. In order to study the binding modes of the ligand to metal in complexes, the IR spectrum of the free ligand should be compared with the corresponding metal complexes. The electronic absorption spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The electronic spectral measurements have been used by chemists for assisting the stereochemistries of metal ions in the complexes based on the position and number of transition peaks. Ultra violet spectrum recording frequencies of different d-d electronic transitions are called as d-d transition spectrum [22].

3.3. Molar Conductance

The molar conductance for the complexes measured in 10⁻³M solution in DMF and chloroform as solvents at room temperature (29-31°C). The molar conductivity is applied to help in the investigation of the geometrical structures of the complexes. Some complexes showed a lower molar conductivity values in the range 0.03-44.37Scm²mol⁻¹ which indicated their non-electrolytic nature. Other complexes found to be a higher electrolyte with the values more than 50cm²mol⁻¹, these results is demonstrated that the complexes have a binuclear nature [23].

The molar conductance has been demonstrated to be a very useful tool in the investigation of electrolytic nature and geometrical structure of inorganic compounds.

3.4. Magnetic Susceptibility Measurements

Magnetic susceptibility of the complexes will be measured and magnetic moments can be calculated. From the magnetic moment values in conjugation with molecular formulae, geometry (hybridization) of complexes will be determined. The gram magnetic susceptibility values, the magnetic moment in BM are calculated and presented as data. From the obtained result, M-L is concluded to be a high spin complex or M-L as a low spin complex [22]. Magnetic susceptibility measurements are used to determine the extent of electron pairing, the stereochemistry and metal-metal interactions in the complexes.

3.5. Electronic Spectra

Electronic spectra (UV-Vis region-spectroscopy) of the

complexes are recorded in 250-1000cm⁻¹ range to identify ligand field (d-d transitions) and charge transfer and to calculate ligand field parameters, viz. 10Dq (ligand field splitting energy), B and C (Racah inter electronic repulsion parameters), and β (Nephelauxetic ratio) [33].

The electronic absorption spectra and magnetic moment values are often very helpful in the evaluation of results provided by other methods of structural investigation. Information about geometry of the complexes around the Cu(II), Co(II) and Ni(II) ions was obtained from electronic spectra and from values of the magnetic moments. The electronic absorption spectra of the Schiff base ligands and its complexes were recorded at room temperature using (DMF) and (CHCl₃) as solvents [12].

3.6. Antimicrobial Activity

The free Schiff's base ligands and their metal complexes are screened *in-vitro* for their antimicrobial activities against bacterial strains and fungal strains using agar well diffusion method. The samples may dissolve in DMSO or in appropriate solvent to make a concentration of 100 g/ml Schiff's base ligands and their complexes and 2 mg/ml for standards [28]. The inoculums (1 x 10⁸ Cfu/mL) are added to molten agar and the media were shaken to disperse the microorganisms. Four millimeters diameter wells were punched in the agar with a sterile cork borer. 10⁻¹ of the sample was introduced in the well. Imipenem was used as positive reference for bacterial strains while miconazole was used for fungal strains. Antimicrobial activity was evaluated by measuring the diameter of inhibition zone in mm. [34]. Most of the results of the researchers indicated that the Schiff's base ligands do have undersized activity, where as their complexes showed more activity against the same organisms under identical experimental conditions.

4. CONCLUSION

Schiff's bases are generally bi- or tri- dentate ligands capable of forming very stable complexes with transition metals. Some are used as liquid crystals. In organic synthesis, Schiff's base reactions are useful in making carbon-nitrogen bonds. Schiff's bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate one of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff's base.

The interesting advantage of preparation of Schiff's base ligands and their complexes is the activity of antimicrobial. This investigation indicates whether the final product is active microbially or not. So that antimicrobial activities of the ligands as well as the complexes is necessary. These compounds and their metal complexes had a variety of applications including clinical, analytical, industrial they also play important roles in catalysts. Compounds containing an azomethine group (-CH=N-), known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective

conjugation system, are more stable. Schiff bases have number of applications viz., reparative use, identification, detection and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions. They also form basic units in certain dyes.

In this review, the novel Schiff's base ligands and their complexes are examined in terms of elemental analysis, molar conductivity, thermal analysis, infrared spectra, and

ultraviolet-visible and magnetic susceptibility measurements. The analysis may be confirmed the formation of mono-, bi-, tri-nuclear and so on metal complexes. That means from the calculated values of the parameter measurements we get the final coordination compound, which has divalent metal and the multidentate Schiff's noble ligand. For instance we can take as a sample the two nickel complexes in the body of the appraisal.

A variety of Schiff's base complexes derived from salicylaldehyde were found to have immense application in various fields. In the present investigation, we have used N,N'-Bis (Benzoylacetone) ethylenediamine in the place of salicylaldehyde and so whatever studies have been done in the case of Schiff's base derivatives of salicylaldehyde, can be explored in the case of the Schiff base derivatives of N,N'-Bis (Benzoylacetone) ethylenediamine. Starting from this benzoylacetone one can prepare a large number of Schiff bases and their metal complexes and these compounds may find interesting applications in medicine, material science and catalysis.

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