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A short review on chemistry of schiff base metal complexes and their catalytic application

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Abstract

Schiff bases and their complexes are flexible compounds synthesized from the condensation of an amino compound with carbonyl compounds and extensively used for industrial purposes and also show a broad range of biological activities including antibacterial, antifungal, antiviral, antimalarial, antiproliferative, anti-inflammatory, anticancer, anti-HIV, anthelmintic and antipyretic properties. Many Schiff base complexes show excellent catalytic activity in various reactions and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis. The high thermal and moisture stabilities of many Schiff base complexes were useful attributes for their application as catalysts in reactions involving at high temperatures. The activity is usually increased by complexation therefore to understand the properties of both ligands and metal can lead to the synthesis of highly active compounds. The influence of certain metals on the biological activity of these compounds and their intrinsic chemical interest as multidentate ligands has prompted a considerable increase in the study of their coordination behavior. Development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. This review compiles the various synthesis procedures and application of Schiff bases and their metal complexes.

Keywords: Schiff bases, Metal complexes, catalytic application, Fluorescent, ribonucleotide reductase

1. Introduction

Schiff bases played an important role as ligands even a century after their discovery in coordination chemistry [1, 2]. Schiff bases are an important class of ligands in co-ordination chemistry [3-5]. Schiff bases are derived from the condensation reaction of aromatic/aliphatic aldehydes and amines and form stable complexes with different transition metal ions are still relevant to be of great interest in inorganic chemistry, although this topic has been extensively studied [6-8]. Schiff bases and their metal complexes have been shown to be promising leads for both synthetic and structural research due to their relatively simple synthesis and structural diversity and have been widely investigated, due to their incredible chemical properties and applications in various areas [9-14]. The chelating ability and biological applications of metal complexes have attracted remarkable attention and they can work as models for biologically important species [15-18]. A number of Schiff bases containing the imino functionality have been shown to have a wide range of biological activities, including antibacterial, antifungal, antidiabetic, antitumor, antiproliferative, anticancer, anticorrosive and anti-inflammatory activities [19-22]. It is believed that the biological activity is related to the hydrogen bonding through the imino group of Schiff bases with the active centers of the cell constituents [9, 23]. Metal-imine complexes have been widely investigated due to catalytic and herbicidal utilization [15, 3]. Thiosemicarbazones are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones and they are also applicable in fields of inorganic chemistry. They are used as a chelating ligand for the formation of metal complexes because of variety of flexible donor sets of sulfur and nitrogen [24, 25]. People are working from last many years on the synthesis and characterization of transition metal complexes with thiosemicarbazones because of their wide range of medicinal applications and their abilities to coordinate with the transition metal ions which is highly desirable [26-31]. The properties of thiosemicarbazones have received considerable attention because of their variable bonding modes, promising biological implications, structural diversity, and ion-sensing ability [32-35].

They have been used as drugs and are reported to show a wide variety of biological activities against bacteria, fungi, and certain type of tumors, and they are also a useful model for bioinorganic processes [36-38]. A number of thiosemicarbazones are comparatively specific inhibitors of ribonucleotide reductase, which is an important metabolic target for the development of chemotherapeutic agents against tumor cells [39, 40]. Like thiosemicarbazide and its derivatives as ligands with potential sulphur and nitrogen are fascinating and have achieved unique attention due to their importance in therapeutic and pharmaceutical field and also possess biological activities consisting of antibacterial, antifungal, anticancer, herbicidal, anticorrosion and anti-inflammatory activities [41-43]. Thiosemicarbazone derivatives have found application in drug improvement for the treatment of central nervous system disorders, of bacterial infection, as well as analgesic and antiallergic agent [25]. Over the years, thiosemicarbazone derivatives have exhibited a broad biological activity *viz.* antimicrobial [44-51], antitumor, sodium channel blocker, anticancer, antitubercular, antiviral [52-58].

2. Chemistry of schiff bases

Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by a German chemist, Nobel Prize winner, Hugo Schiff [59]. Structurally, Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group (Figure-1) [60-63]. A Schiff base or Schiff's base is a type of chemical compounds containing a carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group (R) but not hydrogen. The Schiff base is synonymous with an azomethine. These compounds were named after Hugo Schiff on honor and have the following general structure:

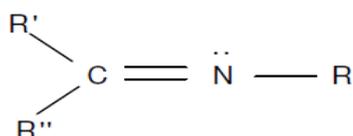


Fig 1: Schiff base

Where R stands for a phenyl or alkyl group which makes the Schiff base a stable imine. This kind of ligands is able to coordinate metal ions through the imine nitrogen and another group, usually linked to the aldehyde. The chemists still prepare Schiff bases and nowadays active and well-designed Schiff base ligands are considered "privileged ligands"[64]. The bridged Schiff's bases have the following structure which contains many functional groups able to change according to the purpose required.

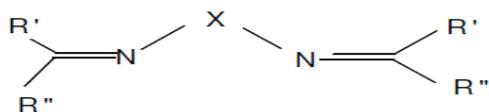


Fig 2: bridged Schiff's base

Where R' = H or alkyl group, R'' = phenyl or substituted phenyl, X = alkyl or aryl group.

In fact, Schiff bases are able to stabilize many different metals in various oxidation states controlling the performance of metals in a large variety of useful catalytic transformations

[65]. Most commonly Schiff bases have NO or N₂O₂-donor groups but the oxygen atoms can be replaced by sulphur, nitrogen, or selenium atoms.

It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:

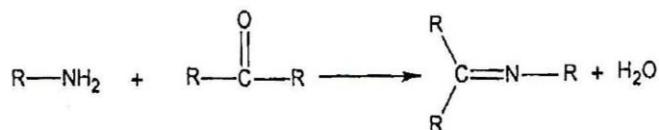


Fig 3: Formation of Schiff base by condensation reaction.

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [66, 67]. While those of aromatic aldehydes having effective conjugation are more stable [68-70].

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating

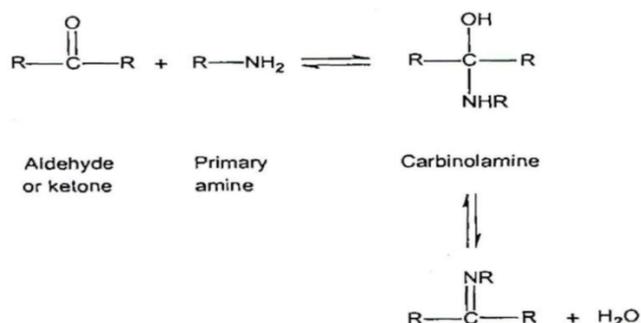


Fig 4: Reversible reaction of a Schiff base formed from an aldehydes or ketones.

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base. The mechanism of Schiff base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.

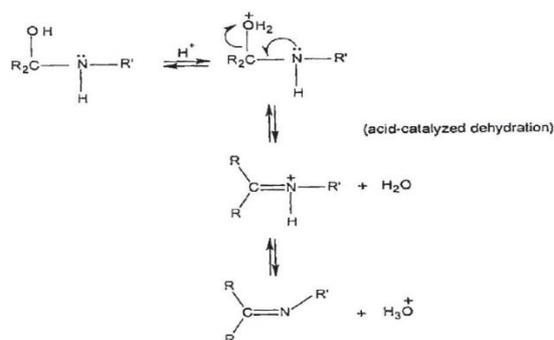


Fig 5: Mechanism of formation Schiff base

Typically the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff bases synthesis are best carried out at mildly acidic pH. The dehydration of carbinolamines is also catalyzed by base. This reaction is somewhat analogous to the E₂ elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate. The Schiff base formation is really a sequence of two types of reactions, i.e. addition followed by elimination [71].

2.1. Formation of Schiff bases

Condensation between aldehydes and amines are carried out in different reaction conditions, and in different solvents. The common solvents used for the preparation of the Schiff Base are methanol or ethanol. Schiff base formation occurs either at room temperature or in refluxing conditions. The presence of dehydrating agents like magnesium sulphate normally favors the formation of Schiff bases. The water produced in the reaction can also be removed from the equilibrium mixture using a Dean Stark apparatus, if the syntheses are carried out in toluene or benzene. Degradation of the Schiff bases may occur during the purification step. Chromatography of Schiff bases on silica gel can cause some degree of decomposition of the Schiff bases through hydrolysis. In such cases, it is better to purify the Schiff bases by crystallization. In general, Schiff bases are stable solids and can be stored without precautions. A large series of Schiff bases could be easily prepared as there is enough scope for varying the amines and the aldehydes. The mono-, di-, tri- and multi- dentate chelating Schiff base ligands are designed according to the binding environments of metal ions. The preparation of Schiff bases and their complexes can be carried out by the following methods:

a. Direct Ligand Synthesis Followed by Complexation

In this method, the isolation and purification of Schiff bases are carried out before complexation. The complexes are then prepared by treating the metal ion and Schiff bases. One of the advantages of this method is that it is possible to perform the spectral characterization of complexes by comparing with the spectral data of the ligands.

b. Template Synthesis

In this method, the syntheses of complexes are carried out without the isolation of Schiff bases by interacting aldehyde, amine and the metal compound in a one-step reaction [72, 73]. The metal ions catalyze the reaction by acting as a reaction template. Busch has defined template as the chemical species, which "organizes an assembly of atoms, with respect to one or more geometry, in order to achieve particular linking of atoms". Template synthesis has been used to prepare assemblies that have unusual topologies, such as rotaxanes, helicates, macro cycles and catenanes [74]. Therefore, a templating agent can be said to contain the required information to organize a collection of building blocks so that they can be linked together in a specific manner. There are two types of template processes: thermodynamic and kinetic. In the former, the template binds to one of the reactant and shifts the equilibrium towards the formation of the product. In the case of kinetic processes the templates operate under

irreversible conditions stabilizing all the transition states leading to the formation of the wanted product. In many of the kinetically controlled reactions, the template is strongly bound to the final species. In these cases it acts not only as a kinetic template, but also as a thermodynamic one. In practice, it is often very difficult to unambiguously determine whether a template reaction is kinetically or thermodynamically controlled. Gimeno *et al.*, in their review considered a template as any species that organizes an assembly of molecular building blocks by non-covalent interactions favoring the formation of a specific product [75].

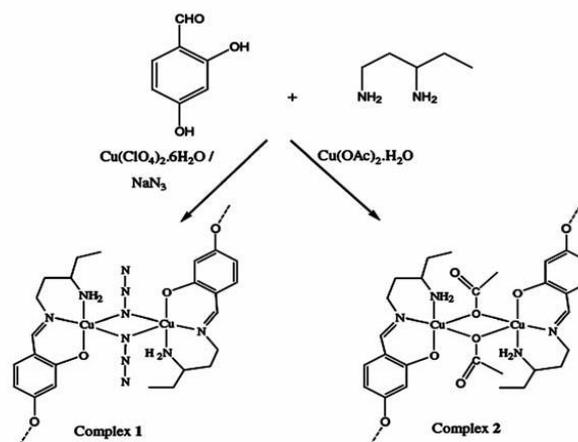


Fig 6: Formation of bridged dinuclear copper (II) Schiff base complexes by template method

c. Rearrangement of Heterocycles (oxazoles, thiazoles etc.)

The direct approach in synthesizing a Schiff base from the condensation of an o-hydroxy-, o-amino- or o-mercaptoamine with a carbonyl compound often results in the undesirable side reaction involving ring closure with the formation of a hetero cyclic compound [76, 77]. The solution to avoid this problem, which was first used by Schiff in 1869, is to prepare the Schiff base in the form of its metal chelate by reacting the metal complex of one of the starting materials (aldehyde or amine) with the other one [78]. Benzothiazoline and benzoxazole ring are reported to open in specific environments in presence of metal ions, and rearrangement of the ring leads to the formation of corresponding metal chelates of the Schiff bases. Figure-7 illustrates such a ring opening complexation reaction reported by Duatti *et al.*

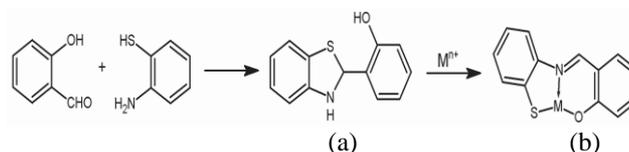


Fig 7: 2-(2-Hydroxyphenyl) benzothiazoline: (a) synthesis; (b) interaction with metal ion

3. Denticity and Basicity of Schiff Bases

Ligands are classified according to the number of donor atoms contained and are known as uni, di, tri, or quadridentate ligands. When donor sites of a ligand occupy two or more coordination positions on the same central metal ion, a complex possessing a closed ring is formed. The phenomenon of ring formation is called chelation and ring formed is called chelate ring. The term 'chelate' was first introduced in 1920 by Morgan and Drew. Schiff bases primarily possess nitrogen donor atoms, though many can act as bi-, tri-, tetra- or

polydentate mixed donor capabilities as shown in Fig. 1.8. In general, the donor nature of the ligands depends both on the type of aldehyde/ketone used and the nature of primary amine/diamine amine/diamine.

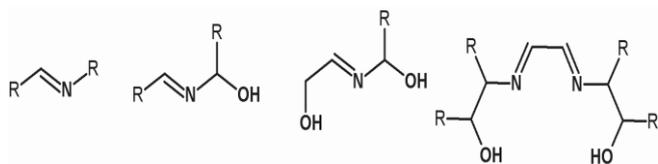


Fig 8: Schiff bases of varying denticity; monodentate to tetradentate, R groups may be variously substituted

A large number of tetradentate Schiff base ligands are reported in literature. Majority of them are derived from salicylaldehyde and 1,2-diamines (Figure-8). The ONNO donor Schiff bases form a family of compounds, salen or salophen, which possess a wide variety of applications. Similarly there are a good number of reports on tridentate Schiff bases [79-82]. They may be of ONN, ONS, ONO, NNS or NNN donors. The tridentate ligands can tune the formation of complexes and these Schiff base complexes have found various applications in medicines such as antibacterial agents, local anaesthetics, antiviral agents and antispasmodics [83, 84].

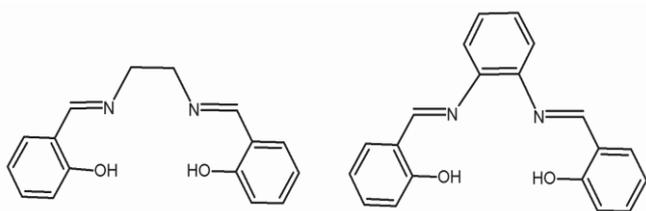


Fig 9: Tetradentate Schiff base family salen and salophen

For several reasons, Schiff bases have been found to be the most convenient and attractive ligands for forming complexes. First, steric and electronic effects around the metal core can be finely tuned by an appropriate selection of bulky and/or electron withdrawing or donating substituents incorporated into the Schiff bases. Secondly, the two donor atoms, N and O, of the chelated Schiff base exert two opposite electronic effects: the phenolate oxygen is a hard donor and stabilizes the higher oxidation state of them *et al* atom; whereas the imine nitrogen is a border line donor and stabilizes the lower oxidation state of the metal ion [85]. Thirdly, Schiff bases are currently prepared in high yield through one-step procedures via condensation of common aldehydes with amines, in practically quantitative yields. While sulphur donor ligands, being soft bases, prefer to combine with late transition elements and with metal ions in lower oxidation state, the ONS donor Schiff bases can show symbiosis [86]. The presence of soft sulphur atom softens the hardness of the oxygen atom, and this enables such ligands to form a large number of complexes with structural diversity. The basicity of the Schiff bases also plays a key role in the formation and stabilization of the complexes. The -OH or -SH groups present in the Schiff bases can induce tautomerism in the compound, which leads to complexes with different structures. A large number of salen complexes shows keto-enol tautomerism. Also the deprotonation of thiolic, alcoholic and phenolic groups are favoured due to the stabilisation of various oxidation states of the central metal ion.

4. Applications of Schiff Bases and Their Metal Complexes

Versatility of Schiff base ligands and the biological, analytical and industrial applications of their complexes make further investigations in this area highly desirable. The applications of the Schiff bases specially thiosemicarbazones and their complexes are discussed here briefly:

4.1. Catalytic Applications

In Schiff base metal complexes, the environment at the coordination center can be modified by attaching different substituents to the ligand and a useful range of steric and electronic properties essential for the fine-tuning of structure and reactivity can thus be provided [87-89]. The Schiff bases form metal complexes with p-block and d-block metals and these complexes have been known to act as highly efficient catalysts in various syntheses and other useful reactions [90-94]. Many Schiff base complexes of ruthenium and palladium are used as catalyst in the syntheses of quality polymers. Unique asymmetric catalysis of metal complexes of salen and the related Schiff-base ligands has been reviewed by Katsuki [95]. The review summarizes the generation of cis metallo-salen and its related complexes, their structural features, and their application to asymmetric syntheses. Wang *et al.* in 1999 reported the effective oxidation of olefins using Mn(II) amino acid Schiff base complexes [96]. Gupta and Sutar reviewed the catalytic activities of transition metal complexes-both simple and polymer anchored. They have highlighted the potential of Schiff base complex as catalyst towards oxidations, hydrogenations, polymerizations, various coupling reactions and ring closures [97,98]. Heterogeneous and homogeneous catalysts have recently attracted the attention of chemists due to better selectivity and recyclability of the catalysts. In recent years there is an exponential increase in the number of publications in catalysis by supported Schiff base complexes. However, homogeneous catalysis is more relevant as the mechanism of the reaction can be arrived. BINAP ligands (BINAP is the abbreviation for the organophosphorus compound 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) are famous for their stereoselective transformations. Che and Huang has reviewed the catalytic activity of chiral BINAP Schiff base complexes in stereoselective organic transformations [99]. Their studies reveal that these types of chiral metal complexes are active catalysts for stereoselective organic transformations including hydroxylation of styrene, aldol reactions, alkene epoxidation, trimethylsilyl cyanation of aldehydes, desymmetrization of meso-N-sulfonylaziridine, Baeyer-Villiger oxidation of aryl cyclobutanone, Diels-Alder reactions of 1,2-dihydropyridine, and ring-opening polymerization of lactide.

4.2. Ribonucleotide Reductase

Thiosemicarbazones in their neutral or deprotonated form, act as a N,N,S-thio-dentate ligands while forming chelates with essential metal ions. They display antiproliferative activity on different tumor cell lines. A strong co-relation has been established between tumor growth rate and the enzyme Ribonucleotide Reductase (RR), a necessary enzyme for DNA synthesis [100]. The first breakthrough in the comprehension of the antitumor effect of thiosemicarbazones was obtained in the Sixties and deserves a brief résumé. The anti-leukemic effect of 2-formylpyridine thiosemicarbazone was first reported by Brockman *et al.* [101] in 1956. Almost ten years later, in 1965, French *et al.* [102] formulated hypotheses about the mode of action of the α -(N)-heterocyclic

thiosemicarbazones, the active molecules shared a tridentate nature, that allows them to be effective chelators, and a better activity was obtained by modifying the aromatic system. Based on this principle they managed to predict the activity of pyrazine carboxaldehydethiosemicarbazone and 1-formylisoquinoline thiosemicarbazone. Ribonucleotide reductase is an iron-dependent enzyme that promotes the reduction of ribose to deoxyribose through a free radical mechanism that is triggered by a tyrosyl radical. Inhibition of this enzyme leads to a block in the synthesis phase of the cell cycle and eventually to cell death by apoptosis. They also indirectly demonstrated that the active species was the iron (II) complex of 1-formylisoquinolinethiosemicarbazone. In fact, it was later discovered that iron and copper complexes are by far more active than the free ligands^[103]. A reasonable mechanism was proposed by Thelander *et al.*^[104] who proved, by exposing ribonucleotide reductase to the aforementioned molecules, that it is the tyrosyl free radical of the enzyme that is targeted by the drug and that the thiosemicarbazone complex inhibits the enzyme by destroying the radical. This mechanism requires oxygen and excludes the role of thiosemicarbazones as simple iron chelators. They also report that the reaction is reversible, and this is in agreement with the experimental observations. The fact that 1-formylisoquinoline thiosemicarbazone inhibits more strongly ribonucleotide reductase than 2-formylpyridine thiosemicarbazone gave an indirect hint about the fact that in the enzyme there must be a hydrophobic pocket or patch with which the aromatic system interacts, which could justify the fact that methylation on the aromatic ring of 2-formylpyridine thiosemicarbazone renders this compound more active. In search of an optimum bulk for the aromatic fragment Agrawal *et al.*^[105] identified it with 2-formyl-4-(3-amino)phenylpyridinethiosemicarbazone that was the most active of the 3-aminophenyl derivatives. The most active compound found in the isoquinoline series was instead 1-formyl-5-aminoisoquinoline thiosemicarbazone^[106, 107].

5. Conclusion

Schiff bases and their metal complexes are one of the most important chemical classes of compounds having a common integral feature of a variety structural diversity and of active medicinal agents. This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades. The present paper is an attempt to review the chemistry of Schiff bases and their metal complexes also their catalytic and Ribonucleotide Reductase activity.

6. Acknowledgement

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Conflict of interest

The authors have no conflict of interest to publish the article.

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