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Chapter

Introduction to Schiff Base

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Abstract

When any primary amine reacts with an aldehyde or a ketone under specific conditions, Schiff bases are formed. The general structure of Schiff base is \( R_2C=NR' \) and is considered as a subclass of imines which is commonly used as a synonym for azomethine. The first imines were prepared in the nineteenth century by a classical method that involves condensation of a carbonyl compound with the help of amine under the distillation of azeotropic and to remove water formed in the system, molecular sieves are used. Later many ways of synthesis of Schiff bases are invented. Schiff bases exhibit a wide range of biological activities and are commonly used for industrial purposes. These are the most widely used as intermediates in organic synthesis, catalysts, pigments and dyes, polymer stabilizers, etc.

Keywords: Schiff bases, biological activity of Schiff bases, azomethine, Schiff base metal complexes, formation mechanism of Schiff base

1. Introduction

In the year 1864, Hugo Schiff was the first to synthesize Schiff’s base under azeotropic distillation by using aldehyde or ketone and primary amine. They can be considered a sub-class of imines with the general structure \( R_1R_2C=NR' (R' \neq H) \) [1–5]. Depending on their structure, they can be considered as either secondary aldimes or secondary ketimines. When these compounds are being used as ligands to form coordination complexes with metal ions, the term Schiff base is applied. Corrin complexes occur naturally, but the majority of artificial Schiff bases are used to form many important catalysts, such as Jacobsen’s catalyst (Figure 1).

Schiff bases are imines in which \( R_3 \) is an alkyl or aryl group (not hydrogen). \( R_1 \) and \( R_2 \) may be hydrogen. Schiff bases have a wide range of biological properties such as antimicrobial, anticancer, and antiviral. Inhibition of amyloid-\( \beta \) aggregation is achieved by Schiff bases [6]. They are common enzymatic intermediates where an aldehyde or ketone of a cofactor or substrate reversibly reacts with the terminal group of a lysine residue. Lysine residue forms a Schiff base with the common enzyme cofactor pyridoxal phosphate (PLP) and is transaldiminated to the substrate(s) [7]. Similarly, the cofactor retinal forms a Schiff base in human rhodopsin (via Lysine 296), which is key in the photoreception mechanism.

In coordination chemistry, Schiff bases are common ligands. The ligands are derived from aromatic aldehydes and alkyl amines [8]. The imine nitrogen is
basic in nature and exhibits pi-acceptor properties. In 1968, Ryōji Noyori was awarded a share of the 2001 Nobel Prize in Chemistry for the development of a copper-Schiff base complex for the metal-carbenoid cyclopropanation of styrene (Figures 2–4) [9].
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2. Schiff base ligands

Researchers’ interest in Schiff bases prepared from ortho-hydroxyl aromatic aldehydes is due to their ability to act as bidentate ligands for transitional metal ions [10–14]. Later, in studies, it has been observed that azomethines from salicylaldehydes gave the best quantitative structure-antitumor activity relationship which has been studied for a series of Schiff bases derived from a variety of substituted aromatic amines and aldehydes [15, 16]. Schiff bases prepared from salicylaldehydes have also been reported as antmycotic or antimicrobial activity and plant growth regulators [17–19]. They also show some analytical applications [20]. The –N=CH– (imine) group is the characteristic of Schiff bases. Imine group imports in elucidating the mechanism of racemization and transamination reaction in biological systems [21, 22]. Schiff bases are active against many organisms such as Erysiphe graminis, Bacillus polymixa, Staphilococcus aureus, Candida albicans, Escherichia coli, Trychophyton gypseum, Plasmopora viticola, and Mycobacteria. They have shown excellent stability, and selectivity for specific metal ions such as Pb (II), Co (II), Al (III), Ag (II), Gd (III), Cu (II), Ni (II), Y(III), Zn (II), and Hg (II) [23–28], so that large number of different Schiff base ligands have been used in potentiometric sensors as cation carriers.

Due to the important properties of Schiff bases in catalysis [29], they have been studied. In the hydrogenation of olefins, Schiff bases show catalytic activity [30] and applications in biomimetic catalytic reactions. An interesting application of Schiff bases based on their ability to spontaneously form a monolayer on the surface to be protected, as an effective corrosion inhibitor Schiff bases function more efficiently than many commercial inhibitors including aldehydes or amines due to the C=N bond [31]. The principal interaction between the metal surface and inhibitor [32] is Chemisorption. The inhibitor molecule should have centers that can form bonds with the metal surface by electron transfer. In such cases, the inhibitor acts...
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as a Lewis base and the metal acts as an electrophile. The protective compound has oxygen and nitrogen atoms with free electron pairs which are readily available for sharing and serves as a nucleophilic center. They create multiple absorption sites for the inhibitor along with the atoms of the benzene rings thus enabling stable monolayer formation [33].

Imines also have biological importance. In the chemistry of vision, an imine linkage between the protein opsin in the retina of the eye and the aldehyde derived from vitamins plays an important role. Vitamins are large proteins that catalyze chemical changes in cells. They are also called coenzymes as vitamins do the functioning of many enzymes. Pyridoxal phosphate is a biologically important aldehyde that is the active form of vitamin B6. It serves as a coenzyme by forming an imine with an amino acid grouping an enzyme. In a transamination reaction, the coenzyme, bound to the enzyme, is involved. The transfer of the amino group from one amino acid to another, is important in biosynthesis of amino acids and the metabolism. In the enzyme-catalyzed hydrolysis, which is the last step, involves the cleavage of the imine to the modified amino acid and pyridoxal. Schiff bases biological properties, such as antifungal, antibacterial activities are reported [34–37]. Because of the anticancer and herbicidal applications [38, 39], their metal complexes have been widely studied. For biologically important species, they serve as models. For Schiff bases, we chose hydrazides, dihydrazides, hydrazones, and mixed derivatives such as hydrazide-hydrazones.

3. Synthesis of Schiff bases

The first imines were synthesized in the nineteenth century by Hugo Schiff in 1864. Since then, a variety of methods have been developed for the synthesis of imines [40]. The classical synthesis involves the condensation of a carbonyl compound with an amine under azeotropic distillation reported by Schiff. Water formed in the system was completely removed by using a molecular sieve [41]. An in-situ method for water elimination was developed using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate in the 1990s [41, 42]. Chakraborti et al. [43] demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. Schiff bases are often polydentate in coordinating ability, because of synthetic flexibility, the special property of C=N group and the relative ease of preparation, especially when –SH or –OH are present close to the azomethine group which can form a five or six membered ring with the metal ion (Figures 5 and 6).

![Figure 5. General formation of Schiff base.](figure-url)
3.1 Denticity and basicity of Schiff base

The Schiff base ligands are classified according to the number of donor atoms and are named as uni-, di-, tri-, and tetra-dentate ligands. Schiff bases possess nitrogen donor atoms, so can act as bi-, tri-, tetra- or polydentate ligand. In general the donor nature of the ligand depends both on the type of aldehyde/ketone used and the nature of primary amine/diamine.

The basicity of the Schiff base also plays a key role in the formation and stabilization of the complexes. The $\cdot\mathrm{OH}$ group present in the Schiff base can induce tautomerism in the compound, which leads to a compound with different structures. A large number of Schiff base compound show keto-enol tautomerism. Also, the deprotonation of alcoholic and phenolic groups is favored due to the stabilization of various oxidation states of different metal ions. Coordination with transition metal Schiff base metal complexes is prepared \textit{in situ} by producing a reaction between the Schiff base and well-defined metal. This approach is clearly simple and suitable for catalytic applications. Different concentrations of different complexes can be present, when an equilibrium constant is expressed as a concentration quotient. However, the identity and homogeneity of the complex can be controlled by the introduction of a bulky group in the Schiff bases due to the shifting of the equilibrium toward the formation of a single species. A disproportionation between Schiff base metal complexes and the metal alkoxides can occur and the stability of the complexes is regulated by the equilibrium constant.

Schiff base ligands are able to coordinate many different metals with various oxidation states, enabling the use of Schiff base metal complexes for a large variety of useful catalytic transformations. Schiff-base ligands containing imidazole groups have potential donor and acceptor character in the formation of a coordination bond and function as a ligand-complex or as a self-complementary building block for the construction of the assembly structure due to the formation of a coordination bond with Cu (II) ions [43, 44]. The versatility of Schiff base ligands and the biological, analytical, and industrial applications of their complexes have promoted further investigations in this area. The importance of Schiff base complexes for bioinorganic chemistry, biomedical applications, supramolecular chemistry, catalysis and material
science, separation and encapsulation processes, and formation of compounds with unusual properties and structures has been well recognized and reviewed. A large number of Schiff bases and their complexes are of significant attention because of their biological activity including antitumor, antibacterial, fungicidal, and anticarcinogenic properties and catalytic activity [45, 46].

4. Application of Schiff base complexes

4.1 Catalysis

The Schiff base transition metal complexes are cheap, easy to synthesize, and their chemical and thermal stability [47] make them a family of attractive oxidation catalysts for a variety of organic substrates. Important oxidation reactions include the oxidation of sulfides to sulfoxides, the activation of hydrocarbons, alkenes to epoxides and diols, and the transformation of alcohols to either the corresponding carbonyl compounds or carboxylic acids. The catalytic activities of the Cu (II), Co (II), Fe (III), and Mn (II) complexes are observed for the phenol hydroxylation reaction. The activities of these cobalt complexes are slightly lower than that of manganese (II), iron (II), and copper (II) analogs of the investigated Schiff bases [48, 49]. Catechol was found as the major product of the reaction [50]. Due to the dimer formation, the cobalt (II) complex is found to be inactive. So, it is unable to form the intermediate by binding with oxygen. The most active catalyst found was the copper complex.

The environment at the coordination center in Schiff base metal complexes can be modified by attaching different substituents to the ligand and a useful range of electronic and steric properties essential for the fine-tuning of reactivity and structure can be achieved [51–53]. Metal complexes of Schiff bases with p-block and d-block metals have been known to act as highly efficient catalysts in various reactions and other useful syntheses [54–60].

In the syntheses of quality polymers, many Schiff base complexes of ruthenium and palladium are used as a catalyst. Katsuki reviewed the unique asymmetric catalysis of metal complexes of Salen and the related Schiff-base ligands [51]. The review summarizes the formation of cis metallo-salen and its related complexes, their structural features, and their application to asymmetric syntheses. In 1999, the effective oxidation of olefins using Mn (II) amino acid Schiff base complexes was reported by Wang et al. [58]. The catalytic activities of transition metal complexes—both simple and polymer anchored were reviewed by Gupta and Sutar. They have highlighted the use of Schiff base complex as a catalyst for ring closures, hydrogenations, various coupling reactions, oxidations, and polymerizations [61, 62]. Due to the better selectivity and recyclability of homogeneous and heterogenous catalysts, they have recently attracted the attention of chemists. In recent years, the number of publications in catalysis supported by Schiff base complexes was exponentially increased. However, homogeneous catalysis is more relevant due to the mechanism of the reaction that can be arrived at. Ligand famous for their stereoselective transformations is BINAP ligands (BINAP is the abbreviation for the organophosphorus compound 2,2′- bis (diphenylphosphino)-1,1′binaphthyl). The catalytic activity of chiral BINAP Schiff base complexes in stereoselective organic transformations has been reviewed by Cheand Huang [63]. Their studies reveal that these types of chiral metal complexes are active catalysts for stereoselective organic transformations including aldol reactions, ring-opening polymerization of lactide, hydroxylation of styrene, Diels-Alder reactions of 1,2-dihydropyridine, trimethylsilyl
cyanation of aldehydes, Baeyer-Villiger oxidation of aryl cyclobutanone, desymmetrization of meso-N-sulfonylaziridine, and alkene epoxidation.

### 4.2 Biological activity

Schiff bases exhibit a broad range of biological activities, including antiviral, antipyretic properties, antimalarial, antibacterial, anti-inflammatory, antifungal, and antiproliferative [64]. In various natural, natural-derived, and non-natural compounds, imine or azomethine groups are present. The imine group present is critical to their biological activities in such compounds [65]. Schiff bases are interesting moieties for the design of antimalarial agents. Schiff base was the most effective antimalarial agent among the synthesized 5-nitroisoquinoline derivatives. Ancistrocladidine is a secondary metabolite produced by plants from the families of Ancistrocladaceae and Dioncophyllaceae that present an imine group in its molecular scaffold. Rathelot et al. [66] described the synthesis of Schiff-base functionalized 5-nitroisoquinolines and investigated the in vitro activity of these compounds. Isatin-derived Schiff bases have also been reported to possess antibacterial activity. Other isatin derivative Schiff bases also have antibacterial activities [67, 68]. The natural or non-natural origins that are platforms for the synthesis of Schiff bases for antibacterial activities include amino acids, coumarins, sulfonamides, or resacetophenone, aminothiazolyl bromocoumarin, crown ethers, o-phthaldehyde, or 2-aminophenol and 1,2,4-triazoles [69]. Kumar et al. [70] reported a series of 3-(benzylidene amino)-2-phenylquinazoline-4(3H)-one and evaluated their cytotoxicity and antiviral activity. Compounds having 2-hydroxy substitution showed better antiviral activity. Some bis-Schiff bases of isatin, benzylisatin, and 5-fluoroisatin, were reported by Jarrahpour et al. [68] as antiviral agents. Sashidhara et al. [71] presented a series of Schiff’s bases of benzo-coumarin and evaluated in vitro for their antioxidant activity and in vivo for their antidyslipidemic activity. During antioxidant screening, the compound exhibited significant activity and significant lipid-lowering activity. Ferrocenyl Schiff bases antioxidant capacities including o-(1 ferrocenyl ethylidene amino) phenol (OFP), m-(1-ferrocenyl ethylidene amino) phenol (MFP), and p-(1-ferrocenyl ethyl idene amino) phenol (PFP) were evaluated OFP. MFP and PFP possessed similar activities to trap DPPH and ABTS+, which was reported by Li et al. [72]. The antioxidant effectiveness of Schiff base increased by the introduction of the ferrocenyl group more remarkably than benzene-related Schiff bases.

#### 4.2.1 Ribonucleotide reductase

While forming chelates with essential metal ions, thiosemicarbazones in their neutral or deprotonated form, act as N, N, S-thiodentate ligands. On different tumor cell lines, they display antiproliferative activity. A strong correlation has been established between the enzyme Ribonucleotide Reductase (RR), a necessary enzyme for DNA synthesis, and tumor growth rate [73]. In the 60s, the first antitumor effect of thiosemicarbazones was obtained and deserves a brief resume. In 1956, Brockman et al. first reported the antileukemic effect of 2-formyl pyridine thiosemicarbazone [61]. The hypotheses about the mode of action of the α-(N)-heterocyclic thiosemicarbazones, the active molecules with tridentate nature, that allows them to be effective chelators, and a better activity was obtained by modifying the aromatic system was formulated in 1965, by French et al. [62]. The activity of 1-formyl isoquinoline thiosemicarbazone and pyrazine carboxaldehyde thiosemicarbazone was predicted
based on this principle. The reduction of ribose to deoxyribose through a free radical mechanism that is triggered by a tyrosyl radical was promoted by Ribonucleotide reductase, which is an iron-dependent enzyme. The synthesis phase of the cell cycle was blocked due to the inhibition of this enzyme and eventually cell death by apoptosis. The active species was the iron (II) complex of 1-formyl isoquinoline thiosemicarbazone, which is also indirectly demonstrated by them. In fact, it was later discovered that iron and copper complexes are more active than the free ligands [63]. Thelander et al. proposed a reasonable mechanism [74] which proved, by exposing ribonucleotide reductase to the aforementioned molecules, that the drug targeted the tyrosyl free radical of the enzyme which was inhibited by the thiosemicarbazone complex by destroying the radical. This mechanism excludes the role of thiosemicarbazones as

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<th>Structure</th>
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<td><img src="image4.png" alt="Structure" /></td>
<td>Antiviral activity, Inhibits the replication of vesicular stomatitis virus and shows cytotoxicity in Vero clone CCL-81 cell lines</td>
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Table 1. Various semi-carbazones, Schiff bases, and their biological applications.
simple iron chelators and requires oxygen. This is in agreement with the experimental observations and the reaction is reversible, as reported by them. In the enzyme, there must be a hydrophobic pocket or patch with which the aromatic system interacts, which indicates that methylation on the aromatic ring of 2-formyl pyridine thiosemicarbazone renders this compound more active. It proves that 1-formyl isoquinoline thiosemicarbazone inhibits more strongly ribonucleotide reductase than 2-formyl pyridine thiosemicarbazone. It was identified by Agrawal et al. [75] while searching for an optimum bulk for the aromatic fragment, the most active compound found in the quinoline series was 2-formyl-4-(3-amino) phenyl pyridine thiosemicarbazone instead 1-formyl-5-aminoisoquinoline thiosemicarbazone (Table 1) [75–77].

5. Conclusion

Schiff bases have been widely used in various organic transformations and for industrial applications. However, further investigation is required about the biological activity of this class of compound. This becomes clear when plant pathogens are considered. Recently, there is an increase in the number of reports including the effects of the Schiff bases on the pathogens of clinical interest. The promising leads for the design of more efficient antimicrobial agents have been shown by Schiff base compounds. Analyses of the mechanism of action of these compounds as well as the structure-activity relationships of the Schiff bases require advanced research in this field.

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