Journal of Science Vocational and Technical Education (JOSVTE). Vol.12 No.2 January 2025

IMPORTANCE OF SCHIFF BASES AND THE METAL COMPLEXES

AMOKO, J.S.
Department of Chemistry, Adeyemi Federal University of Education, Ondo, Ondo State, Nigeria

Abstract

Numerous organisms have been reported to have resistance to some antibacterial drugs currently in use. As a result, attempts are being made to replace these antibiotics. Consequently, considerable attention is being paid to the synthesis of new, more effective, and target-specific metal-based drugs. Thus, Schiff bases and their metal complexes have gained considerable attention because they are nitrogen-containing compounds that serve as a privileged heterocyclic scaffold due to their biological and pharmaceutical properties.

Keywords: Schiff bases, complexes, biological, pharmaceutical properties

Introduction

In coordination chemistry, Schiff bases are significant chelating ligands because they produce stable complexes when reacted with nearly all the transition metals (Bitu et al., 2019; Mapari, 2017; Omidi & Kakanejadifard, 2020). They were discovered by a German chemist, Hugo Schiff, in 1864. They can also be called imines or azomethines. Schiff bases are compounds like ketones or aldehydes except that the carbonyl groups (C=O) are being replaced by imines or azomethines (HC=N) groups (Kalaivani, Priya, & Arumachalam, 2012; Ommenya et al., 2020; Zayed & Zayed, 2015). They are the products of a condensation reaction between primary amines and carbonyl compounds. They have the general formula $RR_1C=N-R_2$ (Fig. 1) where R can be a hydrogen, alkyl or aryl group. When R is a hydrogen and R_1 is an alkyl or aryl group, the compounds are referred to as aldimines ($R_1-CH=NR_2$), while compounds where both R and R_1 are alkyl or aryl groups are called ketimines. R_2 can either be an alkyl or aryl group (More et al., 2017; Omidi & Kakanejadifard, 2020).

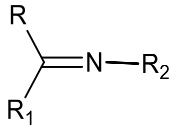
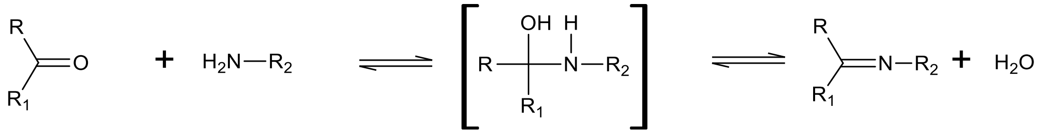


Fig. Error! No text of specified style in document.**:** *General structure of Schiff bases (da Silva et al., 2011)*

Schiff bases can bind to the central metal ions as monodentates and polydentates. Polydentates can be bidentates, tridentates, tetradentates, or pentadentates, which can be used to form several metal complexes. Schiff bases lead to the synthesis of various mononuclear and binuclear complexes, which can be homometallic or heterometallic with different coordination modes and stereochemistry (Aziz et al., 2015; Ortiz et al., 2023). They function as excellent chelating ligands with a wide range of properties tunable by the introduction of various substituents on either the carbonyl or amine ring. They have played important roles in understanding the coordination chemistry of transition metal ions. The resulting imines participate in bonding with metal ions through nitrogen lone pair electrons. The azomethine moiety is essential for biological activities. It is a very useful active centre of many biological systems (Iglesias et al., 2019; Yousif et al., 2017). It helps to clarify the mechanism of transamination and racemization reactions in biological systems. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centres of cell constituents and interferes with normal cell processes (Izuagba et al., 2021; Khan et al., 2013). Imine or azomethine groups are present in various natural, non-natural and natural-derived compounds.

Synthesis of Schiff Bases

Schiff bases are usually formed by the condensation of primary amines and aldehydes or ketones. Primary amines are the best for this reaction since they contain two easily detachable (active) hydrogen atoms. Omidi and Kakanejadifard (2020) proposed that the imine formation occurs via protonation of the carbonyl group by an acid to give a carbonium ion, which reacts with the amine in a very fast reaction. The deprotonation of this carbonium ion gives a carbinolamine (**I**) (Figure **Error! No text of specified style in document.**), which is an unstable intermediate. It eliminates water rapidly to give the imine.



I

Figure 2: *Schiff base condensation reaction*

The imine functional group is readily formed with aliphatic/aromatic aldehydes rather than ketones. Normally, aldehydes react faster than ketones in condensation reactions, leading to the formation of Schiff bases as the reaction centre of aldehydes is sterically less hindered than that of ketones. Moreover, the extra carbon of ketones donates electron densities to the azomethine carbon and thus, makes the ketones less electrophilic compared to aldehydes. This necessitates the use of higher reaction temperatures and longer reaction times than required for aldehydes. The use of acidic catalysts such as methanoic acid, p- p-toluenesulfonic acid, ethanoic acid, and tetraoxosulphate(VI) acid is helpful, and removal of water from the reaction mixture is required, or else the reverse reaction could occur (Lai et al., 2005; Omidi & Kakanejadifard, 2020). There can be product (Schiff base) decomposition through hydrolysis in the presence of water produced during the condensation reaction. Care should be taken in the purification steps, as it undergoes degradation. Chromatographic purification of Schiff bases on silica gel is not recommended, as they undergo hydrolysis (Omidi & Kakanejadifard, 2020). This happens as a result of the instability of the imine-containing compound. Purification is thus better achieved by crystallization with polar solvents if the Schiff bases are insoluble in these solvents. The addition of small portions of polar solvents such as diethyl ether and dichloromethane eliminates impurities (Omidi & Kakanejadifard, 2020).

Schiff bases that contain aryl substituents are substantially more stable and readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable, while those of aromatic aldehydes having effective conjugation are more stable (Omidi & Kakanejadifard, 2020). Several Schiff bases have been synthesized by incorporating substituents with specific electronic effects or with various steric hindrances on both phenoxy and imino groups with the aim of providing stability to their corresponding metal complexes, thereby enhancing activities. The donor atoms in the Schiff bases can also be varied to enhance their donor abilities. Soft pendant donors such as sulphur [S] and phosphorus [P] atoms or hard donors such as nitrogen and oxygen atoms can be incorporated into the ligand through the phenoxy group or the starting amine. Mixed donor Schiff bases - nitrogen, oxygen and phosphorous [N, O, P] and nitrogen, oxygen and sulphur [N, O, S] containing both soft and hard donor atoms have been synthesized (Alka et al., 2023). These are potential bidentate and tridentate compounds in which oxygen, a hard donor atom, is introduced into the Schiff base through the phenoxy group, while phosphorus and sulphur, which are soft donor atoms, are introduced into the compound through the starting amine. Various sources of amine have been used in the synthesis of Schiff bases depending on the target ligand. The amine sources can be alkylamines, arylamines and five-membered ring heterocyclic compounds such as imidazolyl-amines found in the imidazonium salt (Bitu et al., 2019).

Diverse studies showed that the presence of a lone pair of electrons in a sp^2 hybridized orbital of the nitrogen atom of the azomethine group is of considerable chemical and biological importance. It imparts excellent chelating ability, especially when used in combination with one or more donor atoms close to the azomethine group. Some Schiff bases have nonlinear optical (NLO) behaviour. The nonlinear optical effect is based on molecular units containing highly delocalized $\pi - \pi$-electron moieties, extra electron donor and electron acceptor groups on opposite sides of the molecule at the appropriate positions on the ring to enhance the conjugation. Schiff bases are generally accessible due to the relative ease of preparation, synthetic flexibility and the special property of the HC=N group. They are the most widely used organic compounds. Their coordinating properties are designed according to the bonding environments of the metal ions used (Bitu et al., 2019; Zhang et al., 2018).

Metal Complexes of Schiff Bases

A complex is a coordination compound formed when a metal ion (or atom) combines with negative ions or neutral molecules that possess a lone pair of electrons in such a manner that the number of electrons directly attached to the metal ion exceeds its normal oxidation state (Nwabueze & Patel, 2001). A complex can be neutral, cationic or anionic. However, a mixed-ligand complex can be described as a coordination compound or complex containing a central metal ion with two or more different ligands attached to the metal ion. Mixed-ligand complexes are usually prepared to study the synergistic effects of the different ligands. Synergism can be defined as the combined action of two or more agents that is greater than the action of either agent used alone. Mixed-ligand complexes are usually formed via a substitution reaction, which involves a reaction between a metal ion and a ligand followed by partial displacement by an incoming ligand, which is a stronger field ligand (i.e. which has a higher field strength) (Demehin et al., 2024). An alkaline medium is required in the synthetic reaction of most complexes. Hence, a suitable base must be used to increase the pH of the reaction medium, which invariably helps the Schiff base coordinate to the metal. Bases like sodium hydroxide, potassium hydroxide, ammonium hydroxide and ethylenediamine are being used. The right pH must be maintained in order to get the desired complexes (Demehin, Oladipo, & Semire, 2019, 2020).

It is known that the existence of metal ions bonded to biologically active compounds like Schiff bases may enhance their activities because certain metal ions are active in many biological processes. Metals like sodium, potassium, copper, magnesium, calcium, iron, zinc, cobalt, chromium, vanadium and manganese are essential elements and exhibit great biological activities when associated with certain metal-protein complexes. These elements, which are present in trace and ultra-trace quantities, play vital roles at the molecular level in a biological system. The transition metal ions are responsible for the proper functioning of different enzymes. If their concentration exceeds a certain level, then their toxic effects are evident. These metals are involved in the transportation of oxygen, electronic transfer reactions and storage of ions. The ability of metal ions to control the oxidation potentials of organic molecules by complexation has a significant role in biological electron transfer processes and molecular electronics. It has been found that the activities of the biometals are attained through the formation of complexes, and the thermodynamic and kinetic properties of the complexes govern the mode of biological action (Sayed et al., 2020; Zhang et al., 2018).

Complexes of transition metals with Schiff bases have been reported to show better biological activities than the free ligands. Although the activities of some ligands are more than their respective metal chelates. In the area of bioinorganic chemistry, interest in Schiff bases with transition and inner-transition metals has been centred on the role of such complexes in providing interesting models for the metal-containing sites in metallo-proteins and metallo-enzymes. The medicinal uses and applications of metal complexes are of increasing clinical and commercial importance (Zhang et al., 2018).

Schiff base complexes of transition metal ions have become a very important part of supramolecular chemistry due to the formation of stable supramolecular architectures, by employing coordination bonding and/or hydrogen bonding and other intermolecular interactions (Omidi & Kakanejadifard, 2020). The main reason for the preference of transition metal ions over other metal ions is ultimately due to their unique features, such as the flexibility to adopt more than one coordination geometry and the ability to exist in multiple oxidation states. Natural systems utilize one or both of these features for their feasible biological transformations. Complexes play an important role in developing the coordination chemistry related to catalysis, enzymatic reactions, magnetism and bioinorganic modelling studies. Numerous metal ions are recognized to play specific and important roles in biological processes in the human body. They play important roles in living systems, both in growth and in metabolism. The active sites of the biomolecules are coordination compounds comprising one or more metal ions (Izuagba et al., 2021).

Synthetic coordination compounds have contributed significantly to the emergence of the interdisciplinary field of bioinorganic chemistry. The bioinorganic chemistry forms the molecular basis of all possible interactions between the biological molecules and metal ions, which in turn is applied in the field of medicine, biology, environmental sciences, catalysis and technology. In all these fields, both the metal and the ligands are of importance for the structure, stability and processes that are regulated and catalyzed by the metal species (Ndosiri et al., 2020; Ortiz et al., 2023).

Importance of Mixed-Ligand Complexes

The importance of mixed-ligand complexes in various fields of chemical and biological sciences is manifold. Mixed-ligand complex formation is of fundamental importance in many enzyme-catalyzed reactions. Most enzymes contain coordinately bonded metal ions. During the enzymatic process, coordination of the substrate also takes place, and thus, a mixed-ligand complex is formed (Ndosiri *et al.*, 2020). Mixed-ligand complexes act as active catalysts in reactions of industrial importance such as hydrogenation, hydroformation, oxidative hydrolysis of olefins and carboxylation of methanol. They have also shown catalytic activities in various oxidation reactions of environmental and biological importance. The stabilities of mixed complexes are of great importance in biological systems, as many metabolic and toxicological functions are dependent on them (Ortiz *et al.*, 2023).

The coordination chemistry of transition metals with mixed ligands is of current interest because it can provide new materials with useful properties such as magnetic exchange and electrical conductivity. The naturally occurring mixed-ligand complexes of Cu, Co, Fe and Mg have at least two different ligand moieties or a single macromolecule ligand, which consists of two or more different kinds of donor sets of atoms. Several synthetic mixed-ligand complexes have been widely studied. Such complexes have traditionally bioactive compounds, e.g. Schiff base, bipyridine, phenanthroline or imidazole as ligands, and some of them have very promising antimicrobial activities. Mixed-ligand complexes are biologically more active than their constituting ligands or the corresponding homoligated bis complexes (Ibrahim & Saad, 2023).

Applications of Schiff bases and their Metal Complexes

Schiff bases and their metal complexes have large potential applications in various areas such as catalysis, agriculture, analytical, coordination and bioinorganic chemistry, dye and polymer industry, food industry, magneto-structural chemistry, and agrochemical. They are widely used for organic synthesis and drug design (Ibrahim & Saad, 2023). They have gained importance in medicinal and pharmaceutical fields due to their broad spectrum of biological activities: like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidants, anthelmintic, antimalarial, antifungal and antitumour (Alka et al., 2023; Bitu et al., 2019; Iglesias et al., 2019; Sayed et al., 2020; Suleiman et al., 2023).

Schiff base metal complexes have been proven to be effective DNA-binding agents with potential cytotoxic activity. Various transition metal complexes of Schiff bases derived from heterocyclic compounds containing N, O and/or S as donor atoms are used as simple structural models of biological systems. They are found to be potential inhibitors of the enzyme alkaline phosphatase (ALP). They interact with the negatively charged functional groups of ALP that are necessary for regulating the structural and catalytic activities of enzymes. They play a vital role in controlling gene expression, inhibiting cell replication (Alka et al., 2023; Ibrahim & Saad, 2023).

References

Alka, Seema, G., Rajesh, K., Prashant, S., Namita, G., & Pallavi, J. (2023). Pharmacological aspects of Co(II), Ni(II) and Cu(II) Schiff base complexes: An insight. *Results in Chemistry, 5*, 100849.

Aziz, A. A. A., Salaem, A. N. M., Sayed, M. A., & Abo-Aly, M. M. (2015). Synthesis, structural characterization, thermal studies, catalytic efficiency and antimicrobial activity of some M(II) complexes with ONO tridentate Schiff base N-salicylidene-o-aminophenol (saphH_2). *Journal of Molecular Structure, 1010*, 130-138.

Bitu, M. N. A., Hossain, M. S., Zahid, A. A. S. M., Zakaria, C. M., & Kudrat-E-Zahan, M. (2019). Anti-pathogenic Activity of Cu (II) Complexes Incorporating Schiff Bases : A Short Review. *American Journal of Heterocyclic Chemistry, 5*(1), 11– 23.

da Silva, C. M., Modolo, L. V., Alves, R. B., de Resende, M. A., Martins, C. V. B., & de Fa´tima, A. (2011). Schiff bases: A short review of their antimicrobial activities. *Journal of Advanced Research, 2*, 1–8.

Demehin, A. I., Fehintola, E. O., Akinlami, O. O., Babajide, J. O., & Famobuwa, O. E. (2024). Synthesis, Spectroscopic Characterization and Computational Modelling of Ni(II) Complex of (E) -2- (((2-Hydroyphenyl) imino)methyl)-6-methoxyphenol. *Journal of Science, Technology, Mathematics and Education (JOSTMED), 19* (1), 57-69.

Demehin, A. I., Oladipo, M. A., & Semire, B. (2019). Synthesis, Spectroscopic, Antibacterial and Antioxidant Activities of Pd(II) Mixed-Ligand Complexes Containing Tridentate Schiff Bases. *Egyptian Journal of Chemistry, 62*, 423-426.

Demehin, A. I., Oladipo, M. A., & Semire, B. (2020). Synthesis, spectroscopic, biological activities and DFT calculations of nickel (II) mixed-ligand complexes of tridentate Schiff bases. *Eclética Química Journal, 45*(1), 18-46.

Ibrahim, R. B., & Saad, S. T. (2023). Cobalt (II) and Nickel (II) complexes with Schiff base derived from 9,10- 9,10-phenanthrenquinone and 2-mercaptoaniline, synthesis and characterization *Journal of Medical and Pharmaceutical Chemistry Research, 5*, 739-747.

Iglesias, L., Miranda-Soto, V., A., P.-M. D., Martínez-Ortiz, J. G., Díaz-Trujillo, G. C., & Villarreal-Gómez, l. (2019). Biological Activity of New Schiff Base Compounds Derived from Substituted 3-Aminopyrazoles, the Role of Pyrazole on Bioactivity. *Indian Journal of Pharmarceutical Sciences, 81*(2), 333-343.

Izuagba, G. O., Muluh, E. K., Amowie, P. O., & Glen, E. (2021). Antimicrobial Activity of 2-((2-Hydroxybenzylidene) Amino) Nicotinic Acid and Its Cobalt (II) Complexes Synthesized from O- Phenylenediamine and 5 Nitrosalicylaldehyde. *Caliphate Journal of Science & Technology, 2*, 139-151.

Kalaivani, S., Priya, N. P., & Arumachalam, S. (2012). Schiff bases : facile synthesis, spectral characterization and biocidal studies. *International Journal of Applied Biology and Pharmaceutical Technology, 3*, 219-223.

Khan, M. I., Khan, A., Hussain, I., Khan, M. A., Gul, S., Iqbal, M., & Inayat-Ur-Rahman. (2013). Spectral, XRD, SEM and biological properties of new mononuclear Schiff base transition metal complexes. *Inorganic Chemistry Communications, 35*, 104-109.

Lai, Y. C., Chen, H. Y., Hung, W. C., Lin, C. C., & Hong, F. E. (2005). Palladium catalyzed Suzuki cross-coupling reactions using N, O- bidentate ligands. *Tetrahedron, 61*, 9484–9489.

Mapari, A. K. (2017). Synthesis, Characterization and Antimicrobial Activity of Mixed Ligand Complexes of 1-{(E)-[(3-chloro-2,6-diethylphenyl)imino]methyl}naphthalen-2-ol and 2-{(E)-[(2-methyl-5-nitrophenyl)imino]methyl}phenol with Co(II), Ni(II), Cu(II) and Zn(II) ions. *International Journal of ChemTech Research CODEN (USA): IJCRGG, 10* (5), 604-609.

More, G., Raut, D., Aruna, K., & Bootwala, S. (2017). Synthesis, spectroscopic characterization and antimicrobial activity evaluation of new tridentate Schiff bases and their Co(II) complexes. *Journal of Saudi Chemical Society, 21*, 954–964.

Ndosiri, B. N., Nfor, E. N., Marrot, J., Mohamadou, A., & Nenwa, J. (2020). Ni(ii) N-(2-Pyridylmethyl)-L-Alanine) Complex: Structural Diversity and Photoluminiscent Studies. *Crystal Structure T heory and Application, 19*, 430-441.

Nwabueze, J. N., & Patel, K. S. (2001). *Essentials of Coordination Chemistry*. Abuja: Suneg Press.

Omidi, S., & Kakanejadifard, A. (2020). A review on biological activities of Schiff base, hydrazone, and oxime derivatives of curcumin. *Royal Society of Chemistry, 10*, 30186-30202.

Ommenya, F. K., Nyawade, E. A., Andala, D. M., & Kinyua, J. (2020). Synthesis, Characterization and Antibacterial Activity of Schiff Base, 4-Chloro-2-{(E)-[(4-Fluorophenyl)imino]methyl}phenol Metal (II) Complexes. *Journal of Chemistry, 2*, 1-8.

Ortiz, R. J., Shepit, M., Lierop, J. V., Krzystek, J., Telser, J., & Herbert, D. E. (2023). Characterization of the Ligand Field in Pseudo-Octahedral Ni(II) Complexes of Pince-Type Amido Ligands: Magnetism, Redox Behaviour, Electronic Absorption and High-Frequency and -Field EPR Spectroscopy. *European Journal of Inorganic Chemisrty, 25*(28), e202300446.

Sayed, S. S., Shah, D., Ibrahim, K., Sajjad, A., Umar, A., & Atiq ur, R. (2020). Synthesis and Antioxidant Activities of Schiff Bases and Their Complexes: An Updated Review. *Biointerface Research in Applied Chemistry, 10*(6), 6936-6963.

Suleiman, A. K., Sadi, A. H., Badamasi, H., & Ahmadu, M. (2023). Synthesis, Characterization and Antimicrobial Studies of Schiff Base Derived from 2-Amino Phenol and O-Anisaldehyde and Its Co (II), Cu (II) and Zn (II) Complexes *Dutse Journal of Pure and Applied Sciences, 9*(2), 301-310.

Yousif, E., Majeed, A., Al-Sammarrae, K., Salih, N., Salimon, J., & Abdullah, B. (2017). Metal complexes of Schiff base: Preparation, characterization and antibacterial activity. *Arabian Journal of Chemistry, 10*, S1639–S1644.

Zayed, E. M., & Zayed, M. A. (2015). Synthesis of novel Schiff's bases of highly potential biological activities and their structure investigation. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 143*, 81-90.

Zhang, L. W., Liu, L. Z., Wang, F., & Dong, W. K. (2018). Unprecedented fluorescent dinuclear Co(II) and Zn(II) coordination compounds with a symmetric bis(salamo)-like tetraoxime. *Molecules, 23*(5), 1141.