

Study of Some Metal Schiff Base Complexes with Biological Action : A Short Review

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Abstract

Schiff bases are compounds obtained from the condensation reaction of a primary amine and aldehyde or ketone. It is ligands may contain a variety of substituents with different electron donating or electron withdrawing groups and they have attracted particular interest due to their biological activities acting as radiopharmaceutical for biological macromolecules. Biological activities that were considered in this review were mainly those of antibacterial and antifungal. The results obtained from the review show that the Schiff base complexes were more effective when screened as anti-microbial compounds than their ligands.

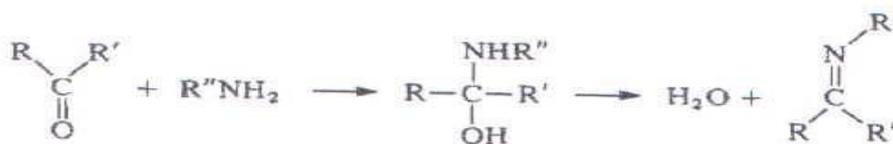
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Introduction

Schiff bases are typically formed by the condensation of primary amine and an aldehyde or ketone. The resultant compound, $R_1R_2C=NR_3$, is called a Schiff base (named after Hugo Schiff), where R_1 is an aryl group, R_2 is a hydrogen atom and R_3 is either an alkyl or aryl group. However, usually compounds where R_3 is an alkyl or aryl group and R_2 is an alkyl or aromatic group are also regarded as Schiff bases. 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 polymerizable¹, while those of aromatic aldehydes having effective conjugation are more stable. In general, aldehydes react faster than ketones in condensation reactions, leading to the formation less hindered than that of ketone. Furthermore, the extra carbon of ketone donates electron density to the azomethine carbon and thus makes the ketone less electrophilic compared to aldehyde². Schiff bases are generally bidentate, tridentate, tetradentate or polydentate ligands capable of forming very stable complexes with transition metals. They can only act as coordinating ligands if they bear a functional group, usually the hydroxyl, sufficiently near the site of condensation in such a way that a five or six membered ring can be formed when reacting with a metal ion. The tetradentate Schiff bases class is of the type reported in this thesis. Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields, e.g., biological, inorganic and analytical chemistry^{3,4}. The applications of many new analytical devices require the presence of organic reagents as essential compounds of the measuring system.

Synthesis

The condensation of primary amines with aldehydes and ketones gives products known as imines which contain a C=N double bond. These compounds rapidly decompose or polymerize unless there is at least an aryl group bonded to the nitrogen or to the carbon atom. The latter imines are called Schiff bases, since



their synthesis was first reported by Schiff.⁵ The most common method of obtaining a Schiff base is straightforward, as indicated in the condensation reaction with the formation of an intermediate hemiaminal. It must be observed that few Schiff bases commonly used as ligands have been prepared and characterized in the uncomplexed state, since the corresponding metal complexes have been directly obtained by other procedures. For example, many metal complexes containing salenH₂ may be obtained directly by reaction between metal ions, salicylaldehydes and ethylenediamine.⁶

Spectroscopic Properties

The C=N stretching frequencies of the ligands occur in the region between 1680 and 1603 cm⁻¹ when H, alkyl or Ar groups are bonded to C and N atoms. The nature of the different substituents on these atoms determines the position of the stretching frequency in the above range, e.g. Ar group on the C and N atoms cause a shift of the frequency towards the lower part of the range. Thus, for compounds such as ArCH=NR a frequency range of 1657-1631 cm⁻¹ has been reported. Typical frequencies are given in Table 1. Compounds of the type ArCH=NAr, with variously substituted aryl groups, exhibit a range of 1631-1613 cm⁻¹ for $\nu(\text{C}=\text{N})$ (Table 1). The presence of an OH group at the 2-position of the phenyl ring of the BA residue effects a bathochromic shift as shown in Table 1. This has been attributed to intramolecular hydrogen bond formation, with the benzenoid form preferred over the quinoid one. In these compounds, the phenolic C-O stretching vibration occurs between 1288 and 1265 cm⁻¹.

Table-1

Typical C=N Stretching Frequencies for some R'C₆H₄CH=NCH₂R'' (a) and R'C₆H₄CH=NC₆H₄R'' (b) Derivatives in CHCl₃ Solutions.⁷

R'	R''	ν (cm ⁻¹)
H	2-OHC ₆ H ₄	1657
2-OH	2-OHC ₆ H ₄	1633
H	CH ₂ N=CHPh	1645
2-OH	CH ₂ N=CHC ₆ H ₄ -2-OH	1635
H	H	1631
4-OH	H	1629
4-MeCONH	H	1630
H	4-OH	1631
H	2-OH	1627
2-OH	4-NH ₂	1625
2-OH	H	1623
2-OH	2-OH	1622

Biological Activities of Schiff Bases

Many biologically important Schiff bases have been reported in the literature possessing, antimicrobial, antibacterial, antifungal, anti-inflammatory, anticonvulsant, antitumor and anti HIV activities⁸⁻⁹. The Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of the amino group of an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate¹⁰. Stereochemical investigations¹¹ carried out with the aid of molecular models showed that Schiff bases formed between methylglyoxal and the amino group of the lysine side chains of proteins can bend back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and the oxygen atoms of the Schiff bases. Schiff bases derived from pyridoxal is the active form of vitamin B₆ and amino acids are considered as very important ligands from biological point of view. Schiff bases are involved as intermediates in the processes of non-enzymatic glycosylations. These processes are normal during aging but they are remarkably accelerated in pathogenesis caused by stress, excess of metal ions or diseases such as diabetes, Alzheimer's disease, and atherosclerosis. The Schiff base and its metal chelates were also screened for their in vitro antibacterial activity against *E. Coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The metal chelates were shown to possess more anti-bacterial activity than the uncomplexed Schiff base.

Crystal packing of Schiff bases

Crystal packing in Schiff bases is determined by interactions between molecules which in turn are determined by functional groups available for forming interactions with neighboring molecules. Although all the Schiff bases with aromatic N-substituent discussed in this review have the ability of forming intermolecular hydrogen bond, the central keto-amino moiety can interact with neighboring molecules only if one of the subunits is not sterically demanding (as is the case in some Schiff bases with aliphatic N-substituent)¹²⁻¹⁴. Unless additional hydrogen bond donors and acceptors are present on the subunits themselves, the packing of the Schiff base will often be governed by weak interactions (dispersion forces, $\text{CH}\cdots\pi$ hydrogen bonding, $\pi\cdots\pi$ stacking etc.¹⁵⁻¹⁶ alone. The presence of strong hydrogen bond donors and acceptors on the molecular periphery leads almost without exception to cross-linking of molecules via strong hydrogen bonds into dimers, oligomers, chains and other supramolecular assemblies. On the other hand if only additional hydrogen acceptors usually O and N atoms, then $\text{C-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{N}$ weak hydrogen bonds are usually the most important interactions between molecules. Crystal structures of Schiff bases derived from aldehydes and amines which have additional groups containing non-bonding electron pairs such as alkoxy, acyl, nitro, cyano, pyridine etc. which may act as hydrogen bond acceptors are often directed by weak hydrogen bonds formed between such groups and aromatic hydrogen donors. An example of such intermolecular bonding can be seen in the crystal structure of N-(2-pyridyl)-3-methoxysalicylideneamine¹⁷ where methoxy oxygen and pyridine nitrogen atoms participate as acceptors of intermolecular hydrogen bonds. The crystal structure comprises of $\text{Car-H}\cdots\text{O}$ hydrogen bonded dimers, which are linked via another set of weak $\text{C-H}\cdots\text{O}$ interactions into a 2D-network. The layers are further interconnected by $\text{C-H}\cdots\text{N}$ interactions between imino methine group and pyridine nitrogen with $\text{C}\cdots\text{N}$ distances of 3.62 Å, which is comparable with $\text{C-H}\cdots\text{N}$ intermolecular bonding in other Schiff bases derived from pyridylamine¹⁸. $\text{C-H}\cdots\text{N}$ intermolecular bonding frequently occurs in crystal structures of Schiff bases derived from aminonitriles. A depicts hydrogen bonding motifs in Schiff bases derived from naphthaldehyde and 2-, 3- and 4- aminobenzonitrile demonstrating the effect of the position of the cyano group on the crystal packing¹⁹⁻²⁰. In the case of the 3-aminobenzonitrile derivative, a combination of $\text{Car-H}\cdots\text{N}$ and $\text{Car-H}\cdots\text{O}$ interactions results in the formation of molecular chains in 2-aminobenzonitrile derivative, due to different directionality of the cyano group, the hydrogen bond involving the same donor or acceptor set results in a different supramolecular topology. The molecules are connected into chains via $\text{Car-H}\cdots\text{N}$ interactions and chains are further connected by $\text{Car-H}\cdots\text{O}$ interactions into layers. A different type of supramolecular topology is observed in the crystal structure of the 4-aminobenzonitrile derivative, where $\text{Car-H}\cdots\text{N}$ and $\text{Car-H}\cdots\text{O}$ interactions leads to a 3D-network. The most important reaction of this type is the formation of imine bonds and Schiff bases. For example, salicylaldehyde and a variety of primary amines undergo reaction to yield the related imines, which can be used as ligands in the formation of metal complexes. Imine formation is a reversible process and isolation of the metal

complex results from its stability, which in turn controls the equilibrium. It is possible, and quite likely, that prior coordination of the salicylaldehyde to the metal ion.

Conclusions

Schiff bases and their complexes have been widely explored for industrial applications. Schiff base compounds and their complexes have been shown to be promising for design of more effective chelates. We have reviewed Schiff bases, which have an unusual capacity for the formation of complexes with metal ions, demonstrating that these Schiff bases and their complexes have biological activity.

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