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Studies on Variable Biological Applications of Schiff Base Complexes

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ABSTRACT

Schiff bases have attracted the attention of chemists due to the case of preparation and complexation. Schiff bases play an important role in Inorganic chemistry due to formation of very stable complexes with various transition and inner transition metals.In this review we have focused on the Schiff base coordination complexes and their biological application such as antibacterial, antifungal, anticancer, DNA interaction, cytotoxicity, Analgesic and anti-inflammatory, Antianxiety activities, ribonucleotide reductase, Anti-HIV activity.

Keywords: Schiff base, coordination complex, antimicrobial, anticancer, DNA-interaction, cytotoxicity, Anti-HIV activity

I. INTRODUCTION

Schiff bases with azomethine are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Schiff base ligands are easily synthesized and potentially capable of forming stable complexes with almost all metal ions.

In recent years, numerous reports are available for its activity in homogenous and heterogeneous catalysis. Because of their excellent sensitivity, selectivity and stability of Schiff bases for specific metal ions such as Ag(I), Al(III), Co(II), Cu(II), Gd(III), Hg(II), Ni(II), Pb(II), Y(III) and Zn(II), and a different number of Schiff base ligands are used as cation carriers in potentiometric sensors. Among the different applications, one of the most interesting applications is the possibility to use as effective corrosion inhibitors. These ligands are used in organic synthesis and chemical catalysis, medicine, pharmacy and chemical analysis, as well as new technologies. Due to broad spectrum of biological activities like anti-inflammatory, analgesic, anti-microbial, anticonvulsant, antitubercular, anticancer, antioxidant and anthelmintic, Schiff bases have importance in medicinal and pharmaceutical fields.

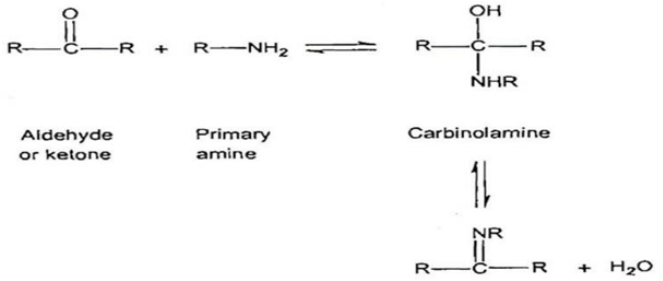
The chemistry of the transition metal complexes of thiosemicarbazones became largely appealing because of their broad profile of pharmacological activity that provides a diverse variety of compounds with different activities. Bis-Schiff base ligands and their coordination compounds having multifunctional groups play an important role in the areas of

stereochemistry, structure of science, spectroscopy, magnetic fields. The sulfur containing ligands such as Di thiocarbamates and thiosemicarbazones and their transition metal complexes have received more attention in the area of medicinal chemistry, due to their pharmacological properties, such as antiviral, antibacterial, antifungal, antiparasitic and antitumor activities. Isatin Schiff and Mannich bases were reported to demonstrate a wide range of biological activities such as antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal and antihelminthic activities.

II. CHEMISTRY OF SCHIFF BASES

The aryl substituted Schiff bases are substantially more stable and more readily synthesized. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable.

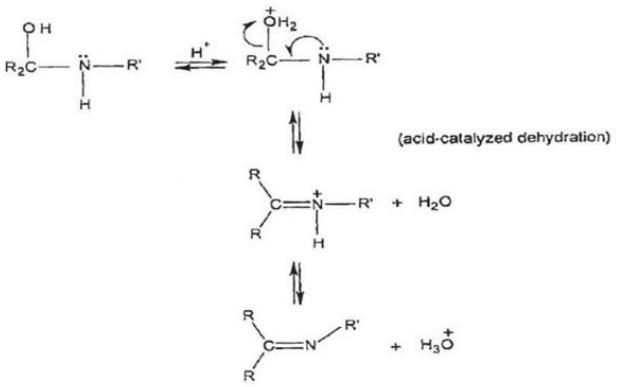
The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating.



Reversible reaction of a Schiff base formed from an aldehydes or ketones

The completion of the reaction is the 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 Schiff base formation is based on the nucleophilic addition to the carbonyl group. In first step, the nucleophile, amine reacts with aldehyde or ketone to give an unstable addition compound called carbinolamine. Since carbinolamine is an alcohol which undergoes acid catalyzed dehydration.



Mechanism of formation of Schiff base

The rate determining step of Schiff base formation is the dehydration of the carbinolamine. If the amine is protonated and becomes non nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. So the synthesis of Schiff base is carried out at mildly acidic pH. The base catalyzed dehydration of carbinolamine is also possible. 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.

III. APPLICATION OF SCHIFF BASE AND THEIR METAL COMPLEXES

ANTIMICROBIAL ACTIVITY

The Schiff base and metal complexes displayed good activity against the Gram-positive bacteria Staphylococcus aureus, the Gram-negative bacteria Escherichia coli and the fungi Aspergillus niger& Candida albicans. The metal complexes show better antimicrobial activity than the Schiff base ligands. The Metal (III) complexes of Cr, Mn and Fe are synthesized from 2-amino-4-ethyl-5-hydroxybenzaldehyde and thiocarbohydrazide. The Schiff base ligand and the complexes were also tested for their antimicrobial activity (against the bacteria Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Bacillus megaterium and the fungi Kluyyeromyces fragilis, Rhodotorularubra, Candida

albicans and Tichodermareesei) to assess their inhibiting potential.

The condensation of 1- napthylamin and 2 – Hydroxynapthalene-1-carbaldehyde (HL) and 1,2-bis-(p-aminophenoxy) ethane with 2-hydroxynaphthalene-1-carbaldehyde (H_2L') form two schiff base ligands are used over the growth of Gram-positive bacteria (staphylococcus aureus) and Gram-Negative bacteria (pseudomonas aeruginosa) added in base media at different concentration to observe the bacterial growth. The effects of ligand H2L' and its complexes with the metals Co, Zn, Cu and Ni on Gram-positive (Staphylococcus aureus) and Gram-negative (pseudomonas aeruginosa) show decrease in the colony when the concentration of Schiff base complex was 4.8µg/100 ml and same effect was noticed with ligand HL and its complex with Ni and Cu on Gram-positive (Staphylococcus aureus) and Gram-negative (pseudomonas aeruginosa) when the concentration was 4.8µg/100 ml. The Schiff base copper complexes with this ligand show more inhibiting effect on Escheriacoli, pseudomonas acurtuginan, Aspergillus niger, aspergillus ferreus, Bariliumsp and Penisilium rubrum.

The condensation of 3-hydroxy-4-methoxybenzaldehyde with furan-2-carboxylic acid hydrazide and thiophene-2-carboxylic acid hydrazide gave L1 and L2 with Co(II) and Cd(II) metals. The free Schiff base ligands and their metal complexes were tested against Bacillus(Gram-positive) and E.coli(Gram-negative) to check their potential as an antibacterial agent by disc diffusion method. L1 and L2 have higher antibacterial activity than its metal complexes. The strong interaction between the imine moieties and the metal ions lowers the antibacterial activity of metal complexes. This type of interaction reduces the activity of imine moieties toward inhibition of bacterial activities where as the ligand has higher antibacterial activity than its metal Complexes.

It was found that Cu(II) complex with Schiff bases derived from aryl-S-benzyildithiocarbazate shows good antibacterial activity.

Antifungal Activities:

The Schiff base is effective in prevention of fungal infection given by many studies. Production of most of the cruciferous crops like cauliflower, cabbage, mustard, radish, etc., is effective by fungi like Alterneriabrassicae and Alterneriabrassicicola. The inhibition of the Schiff base N-(salicylidene)-2-hydroxyaniline for the growth of both fungi by 67-68% at the concentration of 500ppm.Chitison-derived Schiff base inhibited the growth of Botrytis cinerea fungi by 26-33% at concentration of 1000ppm and inhibited the growth of colletotrichumlagenarium fungi by 35-38% at same concentration i.e 1000 ppm.

The Schiff base 2-amino-benzthiazole and 4-amio-salicylic acid have good antifungal activities against Asperigillusniger and Chalara Corda evaluated by using agar disc diffusion method pouring about 50µL Schiff base dissolved in DMSO(25 mg/ml), incubated at 27^{O}c for 3-7 days. The result shows that benzthiazole Schiff base are more effective against fungi than salicylic Schiff base, due to the presence of benzthiazole moiety.

The other Schiff bases of 4(2-aminopheyl)morphine like 4(2-(Benzylideneimino)phenyl) morphines, 4(2-(3-nitrobenzylidine imino phenyl) morphine, 4(2-(2-chloro Benzylidene imino)phenyl) morphines and 4(2-(phenyl propylideneimino) phenyl) morphines compounds evaluated for their in vitro antifungal activity against Asperfillus Niger and Candida albicans using the agar dilution method with sabouraud's dextrose agar. Suspension of these micro-organism (10^5cfu/ml) incubated with diluted Schiff base compounds prepared of concentration of 10µg/ml for 48-72 hrs at 26^{O}c and minimum inhibitory concentration (MIC) were determined. The Schiff bases 4(2-(phenyl propylideneimino)phenyl)

morphines against Aspergillus Niger and 4(2-(Benzylideneimino)phenyl) morphines show maximum inhibition zone toward Candida albicans. Ketoconazole (10µg/ml) used as reference.

IV. ENZYMATIC ACTIVITIES

Vitamin B6 is the Schiff base linkage with pyridoxal 5' Phosphate (PLP), a derivative of pyridoxime abolished the enzyme activities of proteins. The proper binding between PLP with number of specific enzymes and play a critical role in helping these enzymes to catalyze their reaction. The metabolism of amino acids by the PLP catalyze reactions are interact with most enzymes. PLP forms a Schiff base link with Lysine residue on the enzyme, in many PLP dependent enzymatic reactions. Another Schiff base complex of 2-pyridine carbozyaldehyde and its derivative show high super oxide dismutase activities. The DNA cleavage activities are seen in the ternary complex of Cu (II) containing NSO donar Schiff base.

DNA Metal complexes Interactions

DNA acts as storage site of cellular information that is accessed continuously for storing and dispensing information required for existence. So it acts as the main intracellular target for those who arrive to develop a new drug for innumerable diseases, especially cancer. Added to the fact, small molecules that can bind and react with specific DNA sites provide a means to a access and manipulate this cellular information creating the desired results. There are many binding modes by which the small molecules bind to the DNA which are covalent and non-covalent binding. Cisplatin binds covalently with the DNA thereby restricting its replication. Among the non-covalent binding modes, interacalation, groove binding and external electrostatic binding, intercalation is the most important one because it invariably leads to cellular degradation. Copper Schiff base complexes have good interaction with DNA. For, Copper is found in all living organisms and is a vital trace element in redox chemistry, growth and development. It is significant for the function of several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, particularly cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase. Copper is found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation.

Few examples, Acquaye et al. Two new copper Schiff base complexes are synthesized and carried out DNA interactions with CT-DNA. The resultant Kb values are 1.52x105M-1 and 5.00 x a05M-1 respectively for the complexes[102].

Two novel Schiff base copper(II) complexes derived from Kaempferol and polyamine such as ethylenediamine and diethylenetriamine was synthesized and characterized by Yang and his colleagues. DNA interaction was evaluated with CT DNA and predicted the mode of interactions to be intercalation. [103].

The partial intercalation towards DNA study was identified between the two new benzimidazole based copper complexes.[104]

The other set of novel copper complexes are bind significantly to calf thymus DNA by both groove binding and intercalation modes and effectively cleave pBR322 DNA.[105]

Three novel structurally associated copper(II) complexes shows enhanced intercalation into CT DNA.[106].

Anti-Cancer Activity

The Cancer treatment was carried over by the addition of chemical agents known as chemotherapy. With the increasing number of compounds synthesized as potential anticancer drugs, effective screening methods are needed for classification of

these compounds according to their anticancer activities.

For preliminary screening, the in vivo methods are usually more accurate but rather expensive and time consuming whereas the in vitro methods are simpler and more rapid but with lower accuracy. In general, for large scale preliminary screening, the in vitro methods are more effectivefor refined screening on a smaller scale, naturally, the in vivo methods with test animals must be used and the clinical experimental tests are also required.

Cytotoxicity

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells [110]. From literature survey, isatinheterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Bisdiisatin derivatives, Bis-isatinThiocarbohydrazone Metal Complexes, 3-o-Nitrophenylhydrazone of isatin possess cytotoxicity activity. Co(II), Ni(II), Cu(II) and Zn(II) complexes of thiocarbohydrazone ligand were formed by reacting with ethanolic solution of metal chloride or aquepus ethanolic solution of metal acetates with specific amount of the ligand. Compound shows antitumour activity [111]

The synthesized Bis-diisatin [3,3]furan on treatment with furanin presence of diethyl amine under intensive stirring. The compounds were evaluated for cytotoxicity study on the brine shrimp as a test organism.

V. ANTIBACTERIAL ACTIVITIES

Two Schiff base ligand derived from condensation of 1-naphtylamin and 2-hydroxy naphthalene-1-carbaldehyde (HL) and 1,2-bis-(p-aminophenoxy) ethane with 2-hydroxynaphthalene-1-carbaldehyde(H2L'. The ligand H2L' and its complexes with metals Co, Zn, Cu and Ni have shown decrease in activity on Grampositive (staphylococcus) and Gramnegative (pseudomonas aeruginosa), when the concentration of Schiff base complex was 4.8µg/100ml and the same effect was noticed with ligand HL and its complex with Ni and Cu. The more inhibiting effect of Escherichia coli, pseudomonas acurtuginan, Aspergillus niger, aspergillus ferreus, Bariliumsp and Penisilium rubrum with the Schiff base complexes of ligand with copper metal was found.

The Schiff base derived from 2-furancarboxaldehyde and 2-aminobenzoic acid and its metal complexes with Cu (II), Ni(II), Co (II), and Fe (III) has biological activities against *bacteria staphylococcus pyogenes, E. coli*and *pseudomonasaeruginosa* [7]-[8], taking streptomycin as a standard, usingMueller- Hinton agar as a medium with 2% glucose. Thediameter of inhibition was visualized after 24 hr at 37oc andfound to be effective against them.

Anti-bacterial activity of Schiff base complexes Metal complexes of Schiff base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid (HL) and Fe(III) or Co(II) or Ni(II) or UO2(II) showed a good antibacterial activity against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus pyogenes. Fe(III), Cu(II), Zn(II) and UO2(II) complexes caused inhibition for E. coli. The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by E. coli. However, Fe(III), Co(II), Cu(II), Zn(II) and UO2(II) complexes were specialized in inhibiting Gram-positive bacterial strains (Staphylococcus pyogenes and P. aeruginosa). The importance of this unique property of the investigated Schiff base complexes lies in the fact that, it could be applied safely in the treatment of infections caused by any of these particular strains (Mohamed et al., 2005).Four Platinum(II) Schiff bases complexes containing of salicylaldehyde and 2-

furaldehyde with o- and p-phenylenediamine were reported as antibacterial against E. coli, Bacillus subtilis, P. aeruginosa, Staphylococcus aureus.

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