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Synthesis and medicinal use of Metal complexes of Schiff Bases

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Abstract
Different Schemes for the synthesis of Schiff bases have been discussed. Solvent free synthesis by microwave irradiation technique is observed to be rapid, more efficient and more economical and at the same time may play a pivotal role in the progress of Schiff base synthesis. Mechanism for the synthesis of Schiff bases at controlled pH range has been studied. Biological functions of metal complexes of Schiff bases have found to be increased potentiality in presence of transition metal ions.

Keywords: Metal complexes, Schiff base, Microwave irradiation, Metallo-elements, Azeotropic distillation, Molecular Sieve

1. Introduction

The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemical science [1]. Schiff bases are the condensation product of an amine and carbonyl compounds and are an important class of ligands that coordinate to metal ions via azomethine nitrogen. Schiff bases are named in the owner of Hugo Schiff in 1864. Solvent based synthesis of Schiff bases through classical condensation of aldehydes (or ketones) and amines require pH control, however the yield of products is low. pH range for such synthesis should be 5 to 8 i.e. weak acid, neutral or weak alkaline medium depending upon the basicity of amines. Microwave assisted synthesis of Schiff base is rapid and efficient with no use of solvent. The yield of products is also high and purification is done by simple recrystallization technique [2]. Schiff bases have active imine (C=N) linkage which provide binding site for the metal ions through nonbonding electrons of nitrogen. They have also many other hetero-elements like Oxygen and Sulphur which provide binding sites through nonbonding electrons. Specially, d block transition metals having vacant d-orbitals are able to bind with such complexes.

Binding of metal ions with polydentate ligands form ring structure, where the metal ion is a part of the ring, is called chelation. Extensive studies revealed that chelation makes the complex more stable and biologically more active in the presence of bio-metals. Metal ions fix the complexes at the specific site of proteins and enzymes of the host and show their potentiality.

Metal based Schiff bases have important applications in medicinal chemistry. Medical science demands such and such types of drugs which are more potent, biologically active, easily absorbable, no toxicity and show fast action for the treatment of diseases. Human body contains seven major and twenty-two

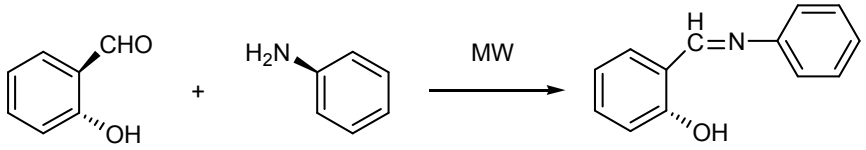
trace elements which are called metallo-elements. They, in trace and ultra-trace amounts, are very essential for the normal functioning of human body and play vital role at the molecular level.

The transition metal ions have binding capacity with the amino acids, proteins and enzymes and catalyze many biological reactions without which the life is impossible. Metal ions provide stability of the complexes by delocalization of electrons of the ligands by chelation and enhance their activity [3]. If their concentration exceeds certain level then their toxic effects are evident. Nitrogen containing bases such as Schiff base, pyridine, pyrimidine, purine and pyrrole, amines such as histamines are well recognized bioligands.

2. Synthesis of Schiff Bases

Scheme 1: Solvent free synthesis by microwave irradiation

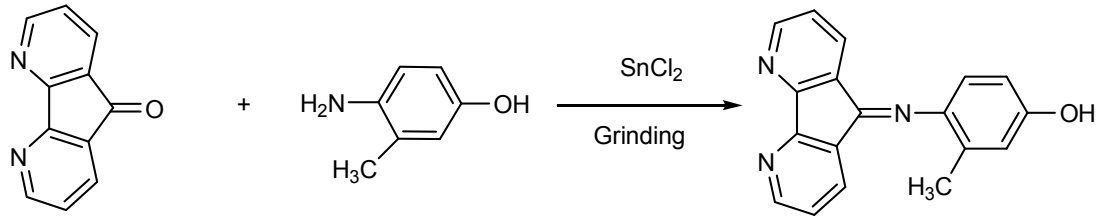
The microwave –assisted synthesis of Schiff base from Salicyldehyde and different aryl amines is performed efficiently and get high yield of products in short time [2]. This is carried in an oven, Midea PJ21B-A 800W and is subjected to microwave for an optimized time on the "M-High" setting.



The solvent free organic synthesis mediated by microwave irradiation performs several economies such as low risk of hazard, time economy and environmental friendship. Purification by simple recrystallization technique offers less contamination.

Scheme 2: Solvent free synthesis by using Catalyst

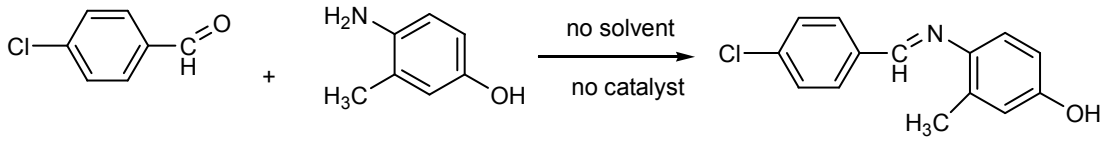
Solvent free synthesis of Schiff bases obtained from 4,5-diazafluuoren-9-one with substituted amines is done efficiently at room temperature by using $SnCl_2$ catalyst [**4].** The reaction mixture is grinded in a mortar with the help of pestle and the progress reaction is monitored by TLC and column chromatography.



Schiff Base

Scheme 3: Solvent and catalyst free synthesis

A mixture of Substituted aromatic amines and substituted aromatic aldehydes is grinded in a mortar with a pestle made of porcelain and the progress of reaction is monitored by TLC. The crude product of Schiff base is purified by column chromatography. The completion of reaction takes place within 2-3 minutes. However the synthesis of Schiff bases from ketone requires acetic acid as a catalyst [5]**.**

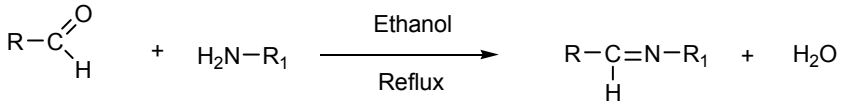


Schiff Base

Scheme 4: Solvent based synthesis

Solvent based Schiff base synthesis generally requires appropriate solvent like ethanol or methanol and mixture is refluxed under pressure by applying acidic, basic or neutral medium.

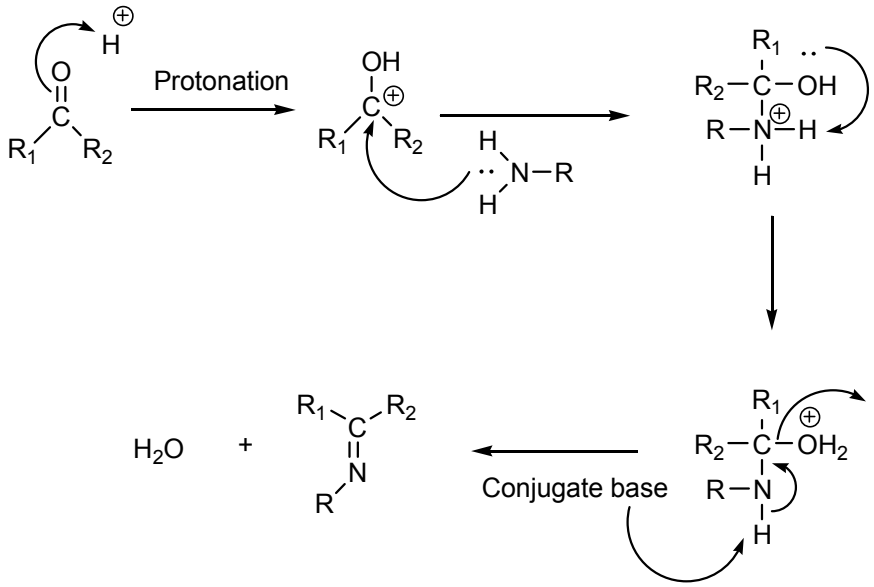
The first preparation of Schiff base was reported in the 19th century by Schiff (1864). Since then a variety of methods for the synthesis of Schiff base have been described. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation [6]. Molecular sieves are then used to completely remove water formed in the system [7]. In the 1990s an in-situ method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate [8,9]. In 2004, Chakraborti et al. **[10]** demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. Presence of water may reverse the reaction by hydrolyzing the Schiff base.



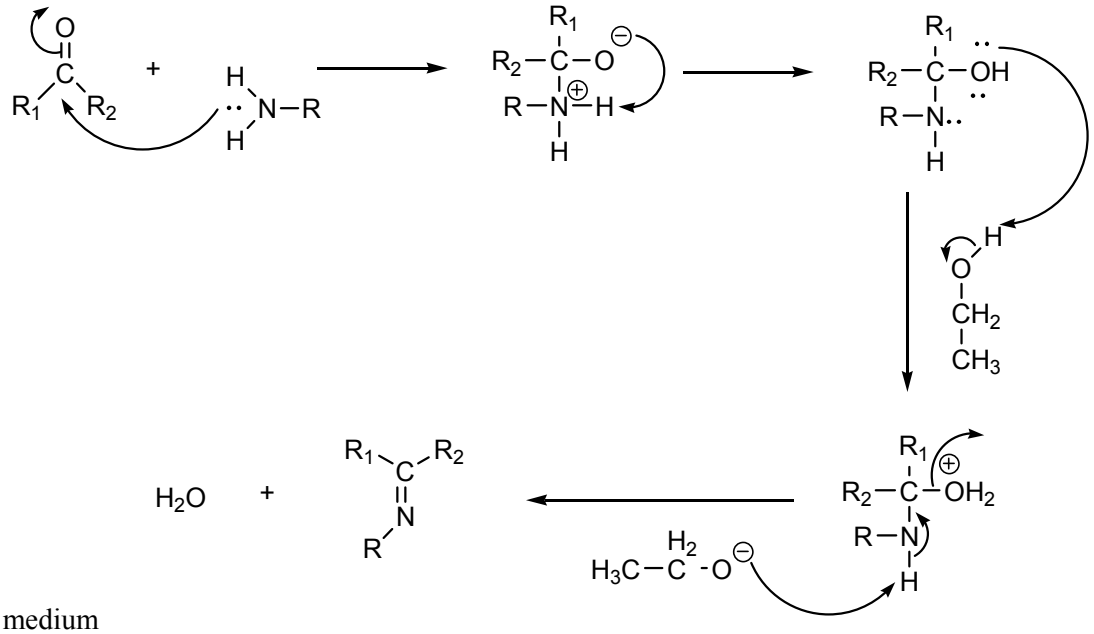
Schiff base

3. Reaction mechanism

3.1 Acidic medium



3.2 Neutral medium

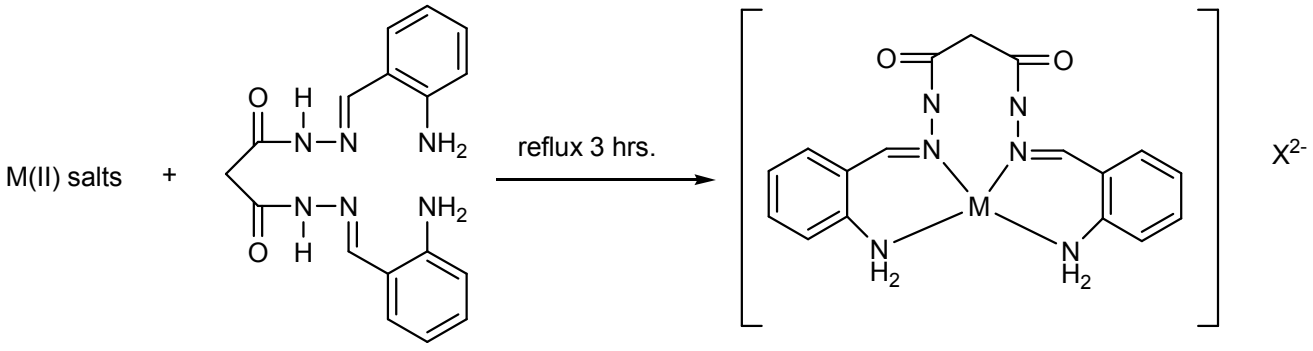


3.3 Basic medium

Mechanism will be similar to that of neutral medium, difference being only in the rate of reaction. The increased basicity of amines in basic medium speed up the nucleophilic attack and thus make rapid formation of Schiff base.

4. Synthesis of Metal complexes of Schiff bases

The metal complex of Schiff bases is prepared by stirring the mixture of metal salts with synthesized Schiff base ligands using suitable solvent generally ethanol and then refluxing the mixture. The complexes obtained is washed with alcohol and dried. In 2008, Rajavel et al. [11] prepared metal complexes of bis(2-aminobenzaldehyde) malonylhydrazone by refluxing the mixture for 3 hrs in alcoholic medium.



bis (2-aminobenzaldehyde) malonylhydrazone

M = Cu, Ni, Zn and $(VO)^{2+}$

metal complex of Schiff base

$X = SO^{4-}$

5. Medicinal use of Metal complexes of Schiff bases

Azomethine nitrogen in Schiff base, not only provides binding site for metal ions but also make attachment with various substrate of bio-molecules like proteins and amino acids in biological systems and that of diseases causing germs. Through the metabolic activities, our body generates Schiff base complexes that show activities against various microbes. Schiff bases in the form of enzymes catalyze many metabolic reactions. Various researches in the field of Schiff bases indicate that metal complexes of Schiff bases have additional and improved bio-functions. They have antibacterial, antifungal, antiviral, antiulcer and anticancer activities depending upon the transition metal ions present in Schiff bases.

Study of Bismuth (V) complex of novel Schiff base mixed ligand obtained from streptomycin and chloramphenicol have found to be better antibiotic activity than parent antibiotics alone [12]. 3d- metal complex of Schiff Base mixed ligands of Streptomycin and oxime have also better antibacterial activity than precursor compounds [13]. Similarly the metallo-elements [Copper(II), Zinc(II) and Oxovanadium (IV)] complexes of Schiff base have more enhanced biological activities than free ligands [14,15].

First row transition metal (II) ion complexes of Chromenyl Schiff base are also associated with lots of biological activities such as antibacterial, antifungal and anticancer. For example, Cu(II), Ni(II) and Co(II) chelates of Schiff base derived from aminoantipyrine and 3-formyl chromone exhibited good in-vitro antibacterial activity against *S.aureus, E.coli and P. aeuriginosa*, [16]. Similarly, the cytotoxic study of Cu(II) Schiff base complex shows that it has best in-vitro anticancer activity against both MCF-7 (human breast adenocarcinoma) and HT-29 (colon carcinoma) [17]. Synthesis of metal [Mn(II), Co(II), Ni(II)and VO(II)] complexes of the Schiff bases 2-[(2,3-dihydro-1H-inden-4-ylimino)methyl]-5-nitrophenol (HL^1) and 3-[2,4-dihydro-1H-inden-4-ylimino) methyl]napthalen-2-ol (HL^2) are found to have better effective antibiotic activity towards *Staphylococcus aureus, Bacillus cereus, Escherichia coli, Proteus mirabilis, Klebsiella oxytoca and Pseudomonas aeruginosa* [18] . Schiff base ligand derived from 5-chlorosalicyldehyde and 2-(2-aminophenyl) 1H-benzamidazole and their derivative have wide biological activities like antitumor, antiamoebic, antihistaminic, anthelmintic and antihypertensive activity [19]. Schiff Base copper(II) complexes of antibiotics: penicillin, streptomycin and tetracycline are reported to have higher antibacterial activity against the bacteria *Staphyloccus aureus, Klebsiella pneumoniae, Salmonella typhi* etc.

6. Conclusion

The simple preparation procedures of Schiff bases and their metal complexes make them versatile ligands in biological systems for the treatment of diseases that will open a new era in medicinal science. Requirement of transition metal ions in trace and ultra trace amounts in the human body are supplemented by the use of metal complex of Schiff bases in addition to their biological activities.

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