Synthesis, Spectral Characterization and Antibacterial Studies of Metal Complexes derived from a new mannich base N, N'-(piperazine-1, 4-dibis(4-Nitrobenzyl) diacetamide)

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ABSTRACT : Mannich bases are the end products of Mannich reaction commonly known as beta-amino ketone compounds. Mannich reaction is said to be a condensation reaction because it releases a water molecule during the formation of the mannich base. It is a nucleophilic addition type of reaction. This reaction is important because it produces the nitrogen containing compounds. It posses various pharmacophore activities like antibacterial, antifungal, analgesic, anti-inflammatory and anti-malarial. Mannich reaction can be used in synthesis of wide variety of natural products and pharmaceuticals. Mannich reaction is a carbon-carbon bond forming nucleophilic addition reaction and is a key step in synthesis of a wide variety of natural products and pharmaceuticals. Mannich reaction is important for the construction of nitrogen containing compounds. There is a number of aminoalkyl chain bearing Mannich bases like fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, and so forth with high curative value. Transition metal complexes of piperazine derivatives are of great interest due to their biological activity. The present work deals with the synthesis and characterization of Mannich base complexes with Cu(II), Co(II), Ni(II) and Zn(II) ions. The biological importance of these metals and their role in natural systems are also discussed.

KEY WORDS

Mannich reaction, metal complexes, biological activity.

1.1 Introduction

In recent years the metal complexes of mannich bases have been studied on large scale because of their selectivity and sensitivity towards biologically important metal ions [1-5]. A lot of studies have been done on different mannich base complexes formed by the condensation of secondary amines with different amides and aldehydes [6-10]. Mannich bases are known to have wide range of applications in different industries such as polymer chemistry, surfactants [11], detergent additives [12], anti-oxidants [13]. It is a multi-component reaction in organic synthesis. Along with beta-amino carbonyl compounds it also provides natural products. These possess wide biological applications including diuretic [14], antipsychotic [15], oxytocic [16], anticonvulsant [17], muscle relaxant [18], anti-malarial [19-20], antiviral [21] and anticancer [22]. Many attempts have been made to correlate the relative affinities of metal ions for ligand atom. The stability of coordination compounds is dependent upon the nature of the metal ion and that of the ligand. It is obvious that the heterocyclic bases containing oxygen and nitrogen donors are considered to be potential ligand centers for the coordination to the metal atom [23-24]. The complexes containing nitrogen as donor atom will have more stability if it forms chelate ring. A perusal of the literature clearly reveals that the transition metal ions have been subjected to detailed investigations.

1.2 Chemistry of amides

Amides are known to have derived from carboxylic acids. Carboxylic acid contains –COOH group and in amides the –OH group is replaced by –NH2 group. It is well known from the literature that the compounds containing amide moiety have a strong ability to form metal complexes and exhibit a wide range of biological activities [25-33]. An amide group offers two potential binding sites, *i.e*. through oxygen and nitrogen for complexation with protons and metal ions [34]. It is now generally accepted that for neutral amide groups, both protonation and metal ion binding will be at the amide oxygen [35]. Upon deprotonation, the binding shifts to the amide nitrogen [36]. But for certain reasons, like bite size and steric hindrance, the coordination may also take place at amide nitrogen. Most amides exist as solids at room temperature, the boiling point of amides are found to be much higher than alcohols of similar molar mass.

1.3 Transition metal-amide complexes

Nicotinamide is the basic constituent [37] for the building-up of the nucleotide coenzymes NAD^+ and $NADP^+$. In the red blood corpuscle cells, most of the nicotinamide and nicotinic acid are present as their coenzymes [38]. The coenzymes are playing important roles in lot of transformations in many biological and metabolic processes [39]. Nicotinamide and its derivatives are found to play a major role in the transmethylation reactions [40].Survey of literature reveals some studies on the antimicrobial and pharmacological activities of furfuraldehyde and nicotinamide derived compounds [41-45]. Mishra *et al* [46] reported the complexes of Cu(II), Co(II), Ni(II) with furfurylidene-nicotinamide Schiff base. Bajpai *et al* [47] reported the synthesis and biological studies on Zn (II) complexes of benzamide and nicotinamide. Bhowan *et al* [48] reported the synthesis, biological and catalytic properties of Ru (II) benzamide Schiff base complexes. The coordination is found to be through carbonyl oxygen of amide as evidenced from infrared spectra. They have also showed that the organic ligand 2, 2′-dithiobis[(2-hydroxyphenyl)]benzamide (DNBH) showed interesting biological properties[49].The above literature review clearly indicates the importance of transition metal ions and their metal complexes. Our much interest is on the chemistry of piperazine based derivatives.

1.4 Antimicrobial activity of Metal complexes

The discovery of the disease causing germs induced the man to plan for the destruction of the microorganisms in and around the human environment. With this thrust, the search for substances with high antimicrobial activities acquires an important area of research of this time. The major hindrance associated with the chemical substances as antimicrobials' is their toxicity to the host cells as well as to the microbial cells. Hence, the chemical substances used should have selective toxicity towards the harmful microbes but not to the host tissues. Certain chemicals of synthetic and plant origin are toxic to the bacteria and fungi but not to the host animal. Certain bacteria and fungi develop drug-resistance on prolonged application of the drug, making even a very valuable drug ineffective. So, it has become necessary for the scientists to involve themselves constantly in synthesizing and screening newer compounds for antimicrobial activity. Complexes of transition metal ions with various ligands have been shown to exhibit antimicrobial activity against a spectrum of microbes and also they have been shown to possess toxicity against a number of cell lines of human and rodents in cell culture.Various organic ligands possess strong antibacterial, herbicidal, insecticidal and fungicidal properties [50-54]. A search through the literature reported that the activity of biometals is often altered through the formation of complexes with biologically important compounds [55-60]. Metal chelates play an important role in biological systems, in which enzymes are known to be activated by metal ions. The enzyme containing metal ions acts as a co-factor for enzyme activity.

2. Literature Review

Pitchai et al., [61] reported the synthesis of new mannich base N,N'(Piperazine-1,4-dibis((phenyl)methylene)diacetamide, and their metal complexes along with the antimicrobial activity. The antimicrobial activities of the newly synthesized were studied against the selected bacteria such as P. auriogenosa (gram negative), S. aureus, E. coli, staphylococcus epidermis (gram positive) and the antifungal activities were studied against A. niger and C. albicans by using disc diffusion method. It was observed that all the transition metal complexes showed good antibacterial and antifungal activities as compared to the free ligand.

Sivakumar et al., [62] reported the synthesis of a series of 12 Mannich bases of pyrazol-5(4H)-one moiety containing 3-(hydrazinyl)-2-phenylquinazolin-4(3H)-one and characterized by physicochemical as well as spectral means. These Mannich bases were screened for the antimicrobial activity against Gram-positive and Gram-negative bacteria as well as fungal strains by the determination of zone of inhibition. It was found that all the Mannich bases were more potent antibacterial agents against Gram-positive bacteria.

Frank et al., [63] reported the synthesis of new 5-(2-methyl-4- nitro-1-imidazomethyl)-1,3,4-oxadiazole-2-thione from 2-methyl-4-nitro-imidazole. A new series of 3-substituted aminomethyl-5-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole-2-thiones was yielded by employing the Mannich reaction with appropriate amines. The structure of these compounds was determined by elemental analysis and spectral data. The new Mannich bases were screened for their antifungal, antibacterial activity and many of these compounds have exhibited potent antifungal activity.

Nayeem et al., [64] synthesised and reported Mannich bases of sulphadiazine, sulphamethoxazole, sulphacetamide with 2- amino -3 - methyl benzothiazole, 2 -amino chloro benzothiazole and 2 -amino 5 - chloro 6- fluro benzothiazole. The structures of these derivatives were characterized by various spectral data's and by elemental analysis. The synthesized compounds were screened for their anti microbial activity against bacteria i.e. Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa Klebsiella neumonia, anti fungal activity against Candida albicans and Aspergillus niger.

Chaluvaraju et al., [65] synthesized a series of aminobenzylated Mannich bases of pyrazinamide by Mannich reaction of aromatic aldehydes with pyrazinamide and secondary amines.They elucidated chemical structure of all the synthesized compounds by IR, ^{1}H NMR spectral studies. These compounds have been assayed in vitro for their biological activity against E. coli, B. substilis, S. aureas bacterial species and A. Niger and C. albicans fungal micro organisms.

Chaluvaraju et al., [66] reported newly synthesized aminobenzylated Mannich bases bearing N-methyl piperazine that were studied for their anthelmintic property by using Indian earthworms Pheritima Posthuma against piperazine citrate as standard reference. Studies involved the determination of paralysis and death time of the worms by using three concentrations of each compound (0.1, 0.2, 0.3% w/v). The compound 1g found to exhibit the most significant anthelmintic activity among all the compounds screened against the worms as compared to standard drug.

Sanghani et al., [67] prepared a series of Mannich bases by the reaction of 7-methyl-2-(p-methyl phenyl)imidazo[1,2-a]pyridine with secondary amines and p-formaldehyde in appropriate solvent. Characterization of the newly synthesized compounds was done by IR, ^{1}H NMR, elemental analysis and

mass spectra. All the compounds were tested for their antifungal activities and antibacterial activities against Gram positive and Gram negative bacteria.

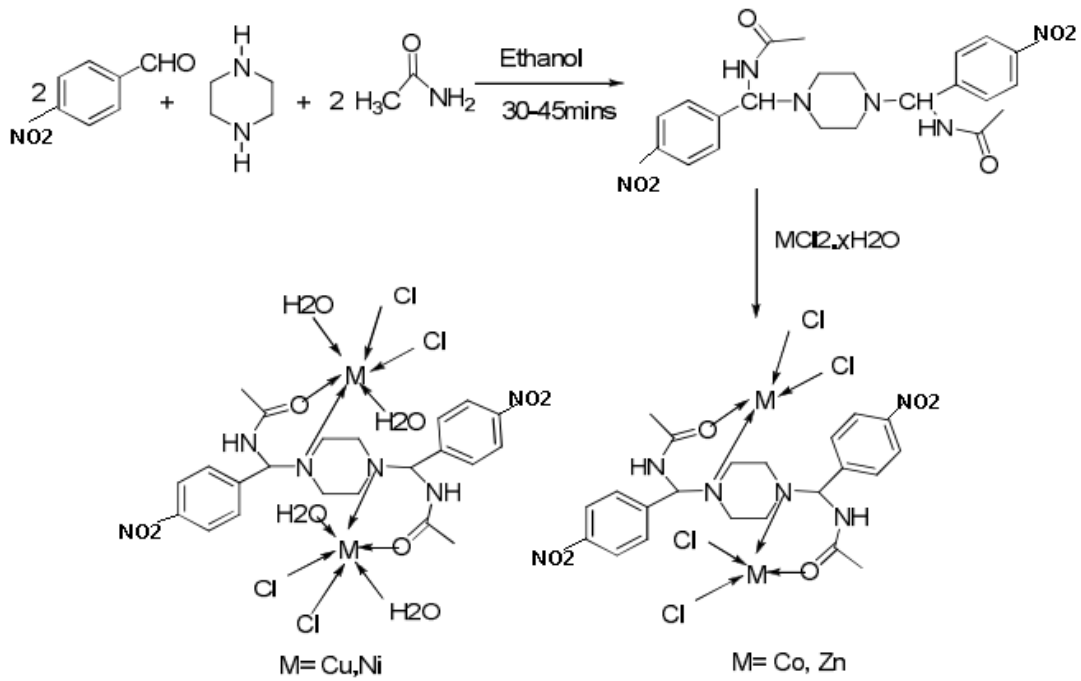
Srinivasan et al., [68] reported (L)-Proline catalyzed Mannich reaction of ketones, aromatic aldehydes and ammonia. This yielded in 3-substituted 2, 6- diarylpiperidin-4-ones enhanced up to five times compared to the reaction involving ketone, aldehyde and ammonium acetate. The catalytic efficiency of proline was ascribable to the involvement of an enamine intermediate that could result from the reaction of ketones with proline and the absence of the formation of bicyclic side product in this reaction.

3.1 Research Methodology

Synthesis of Ligand: An ethanolic mixture of 4-nitro benzaldehye(1 eq) and acetamide(1 eq) will be prepared, kept in ice cold conditions, 1 eq of piperazine will then be added with constant and slow stirring. After continuous stirring of 1 hour, a yellow coloured viscous liquid will be obtained which will be kept in refrigerator for 2 days. The original liquid will gradually filtered and obtained solid will be poured in ice water to eliminate the unreacted piperazine and acetamide. TLC will be used for monitoring the reaction progress where the eluents will be used in the proportion of 7:3, i.e. hexane : ethylacetate.

Synthesis of Complexes:Corresponding metal chloride(2 eq) solutions in hot ethanol, will be mixed slowly with hot ethanolic solution of respective ligand(1 eq) with continuous stirring. This reaction mixture will be refluxed at 60-70^{0}C for 1-2 hours. When cooled down a coloured complex will get separated out in each case, which will then be filtered and washed with 50% ethanol to remove impurities and then dried.

3.2 Structure of the Complex



4. Conclusion

After studying so much about the mannich bases and its properties it can be concluded that it has a wide range of characteristics which can be applied for the welfare of the society. There are numerous diseases without any cure, mannich base holds the power of being explored for its various curing properties. Many heterocyclic Mannich bases were also found which are biologically active and help to the mankind to the great extent. Mannich bases possess very good potential towards the various biological activities and their complexes with different metals show enhanced activities due to increase in their stability. Many heterocyclic Mannich bases were also found which are biologically active and help to the mankind to the great extent.

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