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## A STUDY ON THE SYNTHESIS OF LIGANDS

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### ABSTRACT

With the increasing knowledge about the ability of coordinated metal ions to influence many of the vital processes of living organisms, there has been a revival of interest in the studies of transition metal complexes.

Consequently, remarkable progress has been made in the field of metal complexes derived from simple monoatomic and polyatomic ligands. The development of ligand field theory and bonding concepts made it possible to correlate the electronic and magnetic properties and the constitution of coordination compounds. The X-Ray crystallographic techniques have further added to the knowledge about the structural aspects of these compounds.

The transition metal chemistry has largely dominated inorganic chemistry because of its new emerging facets like the use of polynuclear metal clusters as catalysts. Further, the photosensitive coordination compounds have a potential role to play in converting solar energy into more usable forms.

Metal ions play an important role in a vast number of widely differing biological processes. Some of these processes are highly specific in their metal ion requirements while in others it is possible to replace one metal ion by another, although the activity may be affected.

### KEYWORDS:

Ligand, Metal, Ion

## INTRODUCTION

Iron is the most important transition metal present in the living systems. It is an essential structural. It also plays an important role in the body as an integral part of many enzymes catalyzing oxidation-reduction reactions via electron transfer.

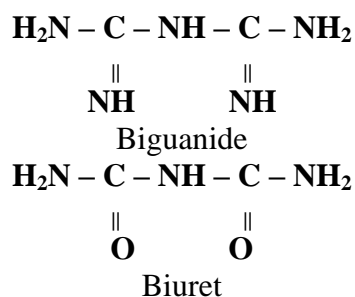
Chromium (III) is essential for mammalian metabolism and together with insulin is responsible for maintaining blood sugar level. Lectins, a group of manganese containing proteins, inhibit the growth of various tumors by inter-acting with tumor cell membranes.

Cobalt is an essential constituent of cyanocobalamin which is a Coenzyme for vitamin. Copper is present in haemocyanin, an oxygen carrying protein and melanin pigment of skin. Vanadium is involved in lipid metabolism and regulation of cholesterol biosynthesis. Zinc is essential for the normal growth and development of the body.

The widespread occurrence of heterocyclic compounds in nature and their use as agrochemicals and pharmaceuticals are the factors which have directed the attention of bioinorganic chemists towards their coordination with metal ions. Such coordination compounds are utilized not only in chemistry and industry but also find applications as agrochemicals e.g. insecticides, bactericides and fungicides.

The antimicrobial activity of heterocyclic compounds such as pyrazoles, hydrazides, biguanides etc. showed a marked increase as a consequence of coordination with some transition metal ions. The herbicidal activity of some hydrazides increased by 100 per cent on coordination with iron(II), copper(II) and manganese(II) where as the fungicidal activity improved by 80 per cent as a result of coordination.

Biguanide and biuret are closely related compounds and the former may be derived from latter by the substitution of both oxygen atoms of latter by the corresponding number of imino (=NH) groups.



These chelating ligands combine with transition metals to yield a large number of coordination compounds.

Ray (1961) reviewed the synthesis, properties and structure of biguanide, substituted biguanides and their metal complexes. Since then many studies have been reported on the synthesis, magnetism, spectroscopy and structure of the coordination compounds of biguanides.

Biguanides have been used for a variety of purposes in medical practice but their clinical importance has been dominated by antimalarial and oral hypoglycemic propents.

Murthy et al., (1986) synthesized N 1-(5- ayayil oil sain 4-oxadiazol-1-yl-N°-(arylsulphonyl)-biguanides and found them to exhibit hypoglycemic activity in rats. The antimalarial activity of 1-p-chlorophenyl-5-isopropylbiguanide was evaluated by Curd et al. (1945)

Merianos et al. (1990) reported that biguanides possess antimicrobial activity. The minimum inhibitory concentration of bis(pyrrolidonylalkylene) biguanide against Escherichia coli and Pseudomonas aeruginosa was 250 ppm whereas against Streptococcus pyrogenes and Staphylococcus aureus it was < 50 and < 100 ppm respectively.

## REVIEW OF RELATED LITERATURE

Gunn et al. (1984) synthesised some bis-biguanide derivatives and found these compounds to be active at 1-12 µg/ml against eight gram positive bacteria and one fungus namely, *Candida albicans*.

Oeckl et al. (1984) evaluated the antimicrobial activity of two different polymeric biguanides which inhibited the growth of *Aspergillus niger* at concentrations of 100 ppm and 50 ppm, respectively. Several compounds with biguanide moiety are also known to possess antihypertensive, anti AIDS, antidiabetic, anticancer, antitubercular, analgesic, antifungal and antidandruff activities.

The change in substituents and/or the side chain length markedly affects the biological activity of ligands. The relative effectiveness of various biguanide compounds against penicillinase increased in the order:

biguanide hydrochloride < propyl biguanide

hydrochloride < hexyl biguanide

hydrochloride << n-decylbiguanide hydrochloride

Substitution on the phenyl ring with methyl or methoxy group on 5-(S-aryl-1,3,4-oxadiazol-2-yl-aminocarboxy)-4-methyl-1-piperazine biguanide afforded more potent compounds.

Brown et al., (1979) synthesized 1-(alkoxyphenyl)-5-(substituted phenyl) biguanides which showed enhanced fungicidal activity as compared to free biguanide.

The activity of a ligand is often altered on coordination with metal ions. Singh et al. (1995) synthesized some novel coordination compounds of cyclo(1,2)-dibiguanidinyl diacetylacetone and screened the ligand and its metal complexes for fungicidal activity against

*Alternaria brassicae*, *Colletotrichum falcatum* *Fusarium lycopersici* and *Rhizoctonia bataticola* and bactericidal activity against *Escherichia coli* and *Xanthomonas compestris* Py. *compestris*.

The activity against *Colletotrichum falcatum* was found to be enhanced significantly on coordination of the ligand with oxovanadium(IV), cobalt(II), nickel(II) and copper(II). Similarly, the hypoglycemic activity of Cu(II) complexes of aromatic biguanides was higher than that of free ligands.

Weinberg et al. (1960) evaluated copper(II) complexes of phenethylbiguanides as well as the free ligands for antimicrobial activity and reported that coordination of metal ion had no effect on the activity pattern of the ligand.

In the light of these reports it was speculated that structural modifications of biguanide and the coordination of resulting ligands with transition metal ions may lead to the development of superior biodynamic agents.

Cohn (1911) carried out the preparation of hydrochlorides of phenyl-, m-nitrophenyl-, p-hydroxyphenyl-, p-phenethyl-, p-ethylcarboxylate-, ni-methyl-, nt-phenyl- and i-naphthyl-biguanides by heating dicyandiamide with corresponding hydrochloride of aromatic amine.

The biguanide derivatives were synthesized by Staniak et al. (1989) from dicyandiamide and aromatic amines especially toluidine or 2,5-xylidine in an aqueous medium in the presence of HCl catalyst and a pH of 2-2.5.

Biguanides and their derivatives have been often used as chelating agents in the field of coordination chemistry and the structural aspects of the chelates have been elucidated by several workers.

Ray and Saha (1937) were the first to elucidate the structure of metal biguanide complexes. These structures explained some of their chemical properties but had several limitations like presence of quaternary nitrogen atoms ( $-NH_3^+$ ) in the charged metal biguanide complexes, localization of charge on a particular nitrogen etc.

Sen (1969) suggested structure (I) and (II) for uncharged and charged metal biguanide complexes respectively on the basis of spectral studies.

Syamal (1978) in a review categorized all the Cu(II) biguanide complexes into three groups viz., bis (biguanide) and dibiguanide complexes; copper(II) hetero-chelates; and mono (biguanide) complexes. In uncharged metal complexes the biguanide behaves as a monobasic bidentate ligand and in charged metal biguanide complexes the ligand acts as neutral bidentate. Like Cu(II), Ni(II) also forms bis(biguanide) and dibiguanide complexes but no monobiguanide Ni(II) complexes have been reported in literature. The properties of Ni(II) biguanide complexes resembled closely those of Cu(II) bis(biguanide). A number of nickel(II) bis(biguanide) complexes are known to occur in two or more modifications differing mainly in color which may be due to differences in their molecular configurations (Ghosh and Banerjee, 1964).

Poddar (1963) reported the synthesis of glucosyl biguanide complexes of Ni(II) having the formula  $[Ni(OH)QL]_2$  (where L=bases derived from glucose and biguanide, methylbiguanide, ethylbiguanide, dimethyl biguanide, diethylbi-guanide and phenylbiguanide) which were diamagnetic and square planar.

Babykutty et al. (1974) studied the thermal decomposition of bis(biguanide) nickel (II) chloride dihydrate. The decomposition of the complexes started at 100°C and it exhibited an endothermic peak at 120° corresponding to the loss of water of crystallization.

Guran et al. (1987) synthesized the chromium complexes of type (HL<sub>3</sub>) [Cr (NCS) 6] (L=ortho-Chlorophenyl-N-isopropyl biguanide, meta-phenyl, n-chlorophenyl-, para-tosylbiguanide) from L. HCl and K [Cr(NCS) 6]. The complexes were characterized by electronic and IR spectra, molar conductance and thermal analysis.

## RESULTS AND DISCUSSION

Methods for the Preparation of ligands, complexes and their base adducts

Synthesis of ligands (L<sub>I</sub>-L<sub>IV</sub>)

The ligands L<sub>I</sub>-L<sub>IV</sub> were prepared by following a four step procedure detailed hereafter.

Preparation of cyclo(1,2)dibigunidinyl bis{ 2-hydroxy-1-phenyl acetophenone} (L<sub>I</sub>)

(a) Synthesis of biguanide sulphate (Ia)

A finely powdered mixture of dicyandiamide (0.3 mol) and ammonium chloride (0.75 mol) was heated with constant stirring until a liquid melt was obtained. The temperature of this melt was maintained for minutes with continuous stirring. After cooling, the melt was crushed into small lumps, dissolved in 150 ml of hot water (90 to 100°C), filtered and the precipitate washed with 25 ml of hot water twice.

The filtrate was treated with a slight excess of ammoniacal copper(II) Sulphate solution. The precipitated (red rose) copper biguanide sulphate was filtered, washed with water and dissolved in 35 ml of hot 10 per cent sulphuric acid (80-90°C). The resulting solution was then cooled by immersion in an ice bath, the crude crystals separated were dissolved in 25 mL of boiling water and the solution was cooled in ice.

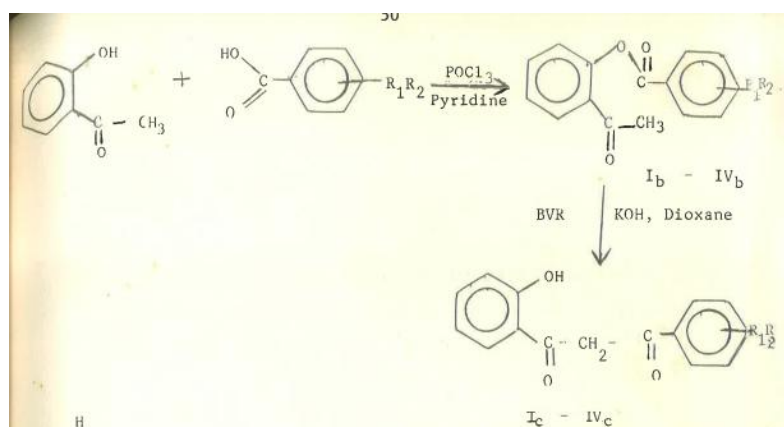
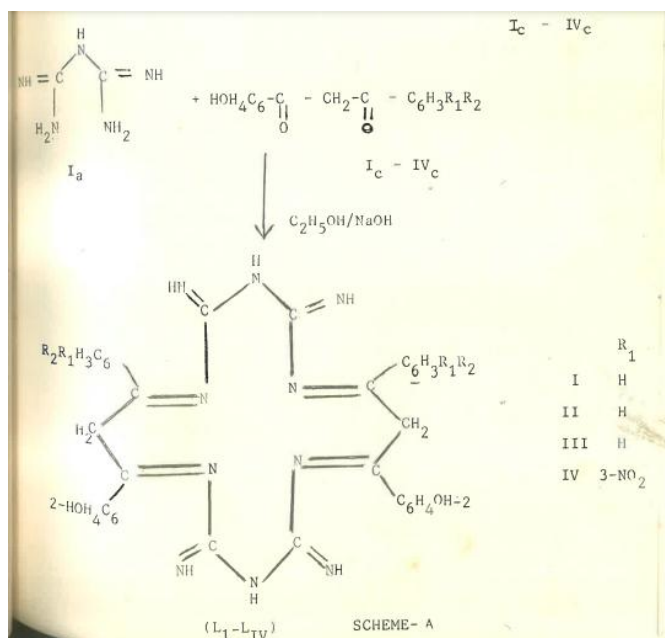
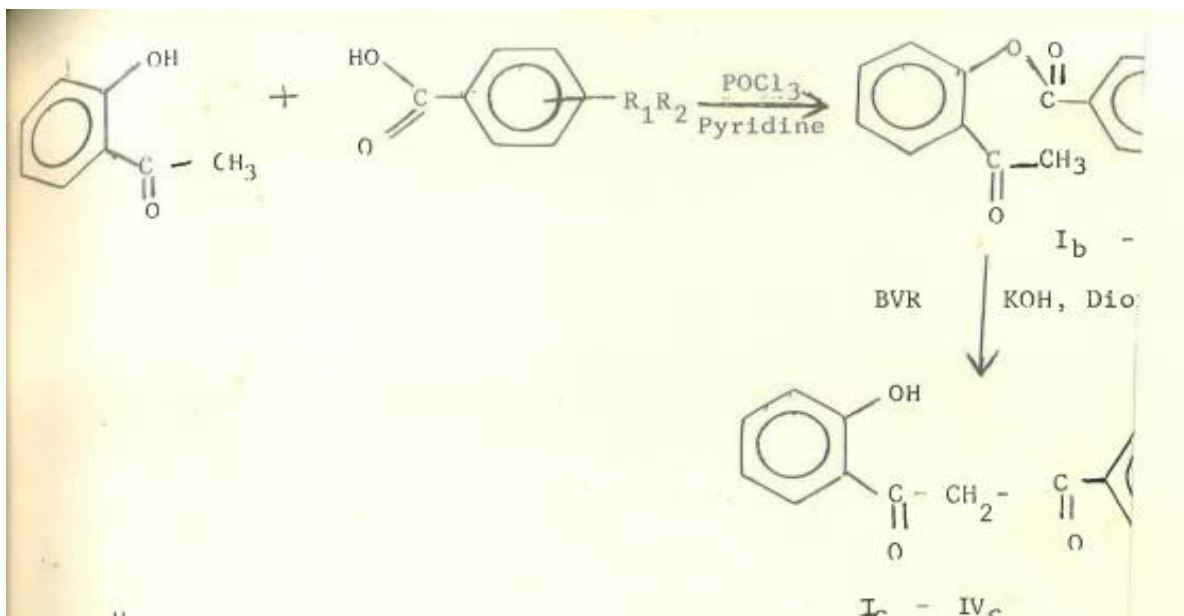
The resulting colorless crystals of biguanide sulphate dihydrate were filtered, washed with cold water and finally with ethanol, dried at 110°C for about 15 h. Yield = 10%.

(b) Synthesis of benzoyloxy/4-chlorobenzoyloxy/3-nitrobenzoyloxy/3,5-dinitrobenzoyloxy acetophenone (I-IV,)

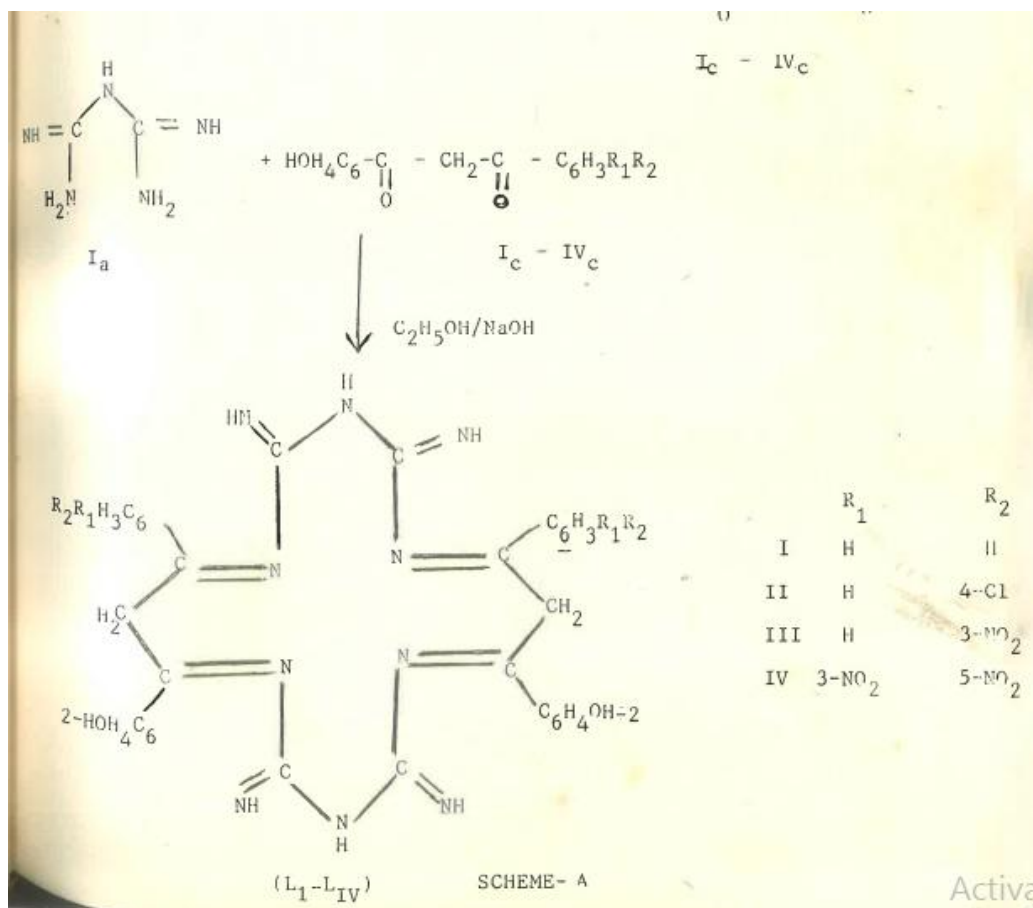
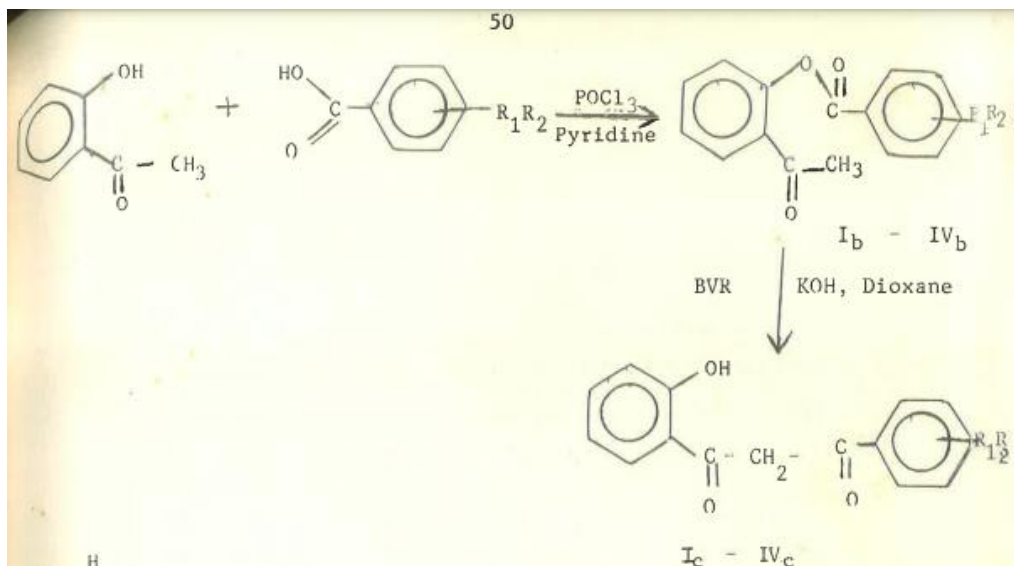
The compounds benzoyloxy/4-chlorobenzoyloxy/3-nitrobenzoyloxy/3,5-dinitrobenzoyloxy acetophenone, were obtained in good yield by stirring the reaction mixture of o-hydroxyacetophenone (6.5 mmol) and benzoic acid/3-nitrobenzoic acid/3,5-dinitrobenzoic acid (7.0 mmol) for 2 h at 70-80°C in presence of phosphorus oxychloride (0.24 ml) in dry pyridine (6 ml)

(c) Synthesis of 2-hydroxy-w=(benzoyl/4-chlorobenzoyl/3-nitrobenzoyl/3,5-dinitrobenzoyl)acetophenone(Ic-IV<sub>C</sub>)

A solution of 2-hydroxy-w=(benzoyl/4-chlorobenzoyl/3-nitrobenzoyl/3,5-dinitrobenzoyl)acetophenone, (10 mmol) in dry dioxane (40 ml) on refluxing for 30 min. in presence of powdered KOH (30 mmol) underwent 'Baker-Venkataraman,' rearrangement (BVR) resulting in formation of Ic-IV<sub>C</sub>







## CONCLUSION

Biguanides, an important class of heterocyclic Compounds are known to exhibit a wide spectrum of biological activity in addition to their applications in industry and analytical chemistry. Various substituent's at different positions and varying side chain lengths have a profound effect on the activity pattern of these compounds, Further, the coordination of such Compounds with metal ion may alter their activity pattern as a consequence of the physico-chemical manifestations acquired thereby. Tailoring more potent bio molecules and synthesizing their coordination compounds with metal ions is, therefore, of considerable biological relevance in as much as it may lead to the development of compounds with enhanced biological activity.

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