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Research Article

Metal Complexes of First Generation Sulfonylurea Antidiabetic Drug Chlorpropamide: Synthesis, Structural and Biological Evaluation.

Shruti S. Sarwade^{1*}, W.N. Jadhav¹ and B.C. Khade¹

¹Department of Chemistry, Dnyanopasak Science College, Parbhani-431401, Maharashtra, India

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Abstract: Novel complexes of Mn (II), Ni (II) and Cu (II) with chlorpropamide [4-chloro-*N*-(propylcarbamoyl) benzene sulfonamide], have been synthesized and characterized using infrared (IR) spectroscopy, electronic spectroscopy, melting point, elemental analysis and conductivity measurements. From the elemental analyses data, the complexes are proposed to have the general formula $[(C_{10}H_{13}ClN_2O_3S)_2 Cl_2 M]$, $M = Mn(II), Ni(II) \text{ and } Cu(II)$. The molar conductance data reveal that all the metal complexes are non-electrolytes. IR spectra show that chlorpropamide is co-ordinated to the metal ions in neutral bidentate manner with sulfonyl oxygen and enolic oxygen. From the magnetic data and electronic spectra, it is found that the geometrical structures of these complexes are octahedral. Antibacterial screening of the complexes were found to have varied degree of inhibitory effect against the bacteria.

Keywords: chlorpropamide, metal complexes, spectroscopic techniques, antibacterial activity.

INTRODUCTION

The discovery of ability of sulfonylureas to lower plasma glucose resulted from research done in 1942 that noted the hypoglycemic effect of sulfonamides used to treat typhoid fever. Subsequent investigations revealed that modifying the sulfonamide antibacterial agents with urea moiety resulted in sulfonylureas with significant hypoglycemic effects and consequently, the first generation oral hypoglycemic drugs were born, which include tolbutamide, chlorpropamide, tolazamide and acetohexamide.¹⁻⁴

Chlorpropamide is chemically 4-chloro-*N*-(propylcarbamoyl) benzene sulfonamide as shown in Fig. 1. Clinically it is very effective in the treatment of diabetes mellitus. Its mechanism of action involves the stimulation of insulin released from the β -cells of pancreas in response to a glucose load.⁵ It also acts by enhancing the effect of insulin receptors. A perusal of available studies shows that systematic investigations on complexation of metals with sulfonylurea were carried out. The study of chemistry and chemical reactions of coordination compounds helps in establishing structure-activity relationship. It has been reported that in biological activity metal complex is more potent and less toxic as compared to the free ligand or in other words many drugs possessed modified pharmacological and toxicological properties when administered in the form of metallic complexes.⁶

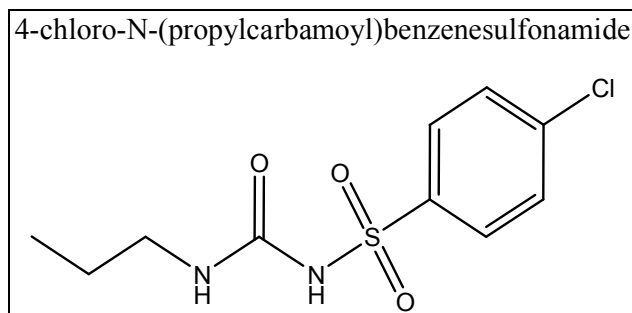


Fig. 1: Structure of Chlorpropamide

EXPERIMENTAL

Physical Measurements: The IR spectra were recorded on Shimadzu FTIR in range 4000-400 cm^{-1} . Carbon, Hydrogen and Nitrogen were determined on thermo Fisher Flash Elemental Analyzer. The Ultraviolet (UV) spectra were recorded in the range 200-800 nm on Perkin Elmer UV spectrometer by making solutions in dimethyl sulfoxide (DMSO). The molar conductance of solid complexes in DMSO was measured using digital conductometer. The magnetic susceptibility was measured by powdered samples on Gouy Balance.

Synthesis of Complexes: The chemicals used in this synthesis were all of analytical grade (AR), and of highest purity available and used without any further purification. A weighed quantity of chlorpropamide (2mM, 1.38 gm) was dissolved in distilled ethanol. The chlorides of Mn (II) (2mM, 0.72gm), Ni (II) (2mM, 0.49gm) and Cu (II) (2mM, 0.34gm) were prepared in the 50 mL of ethanol. Ligand solution was added slowly with constant stirring into the solution of metallic salt at room temperature maintaining the pH between 7 to 8 by adding dilute KOH solution. After refluxing the mixture for 6 hours the complexes were separated out, which was filtered off, washed well three times with ethanol and finally dried in vacuum and weighed.⁷

RESULT AND DISCUSSION

The synthesized complexes are stable solids. They are soluble in dimethylformamide (DMF) and DMSO and insoluble in organic solvents. Analytical data and conductometric studies suggest the Ligand : Metal (L: M) ratio is 2:1. The magnetic studies indicate the Mn (II), Ni (II) and Cu (II) complexes to be paramagnetic as shown in (Table1).

Table-1: Synthesis and physiochemical characteristics of complexes

Ligand / Complex	Ligand Metal ratio	Colour	% yield	M.P. °C	. effec. (B.M.)	Conductivity $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$
$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$	-	White	-	126	-	
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Mn}$	2:1	White	68	135	4.86	3.4
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Ni}$	2:1	Blue	40	138	3.80	5.0
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Cu}$	2:1	Green	54	134	2.25	4.8

Table-2: Analytical data of complexes

Ligand / Complex	% C found (calc.)	% H found (calc.)	% N found (calc.)	% M found (calc.)
$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$	43(43.10)	4.7(4.19)	10(10.04)	-
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Mn}$	35.45(35.65)	3.84(3.96)	8.27(8.35)	8.12(8.41)
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Ni}$	35.25(35.51)	3.81(3.99)	8.22(8.38)	8.62(8.78)
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Cu}$	35(35.22)	3.79(3.92)	8.16(8.22)	9.26(9.32)

Infrared (IR) Spectra Studies: Chlorpropamide showed prominent IR band in the region of 3300-3370 cm^{-1} due N-H stretching in urea. In case of Mn (II), Ni (II) and Cu (II) chlorpropamide complexes, it appeared in the region of 3300-3350 cm^{-1} . The next IR band of structural significance of the ligand appears at 1397 cm^{-1} which may be assigned to S=O group which got shifted to downward at 1365 cm^{-1} in manganese chlorpropamide complex; while in nickel and copper chlorpropamide complexes it appeared at 1381 cm^{-1} and 1372 cm^{-1} respectively.⁸⁻⁹

The shift of C=O and S=O groups by decreased frequencies in the complex indicates that these groups are involved in the complexation. The linkage through amide -O- and sulfone -O- atom was further supported by the appearance of a band in the far IR region at 640 cm^{-1} , 678 cm^{-1} and 624 cm^{-1} in the Mn (II), Ni (II) and Cu (II) complexes of chlorpropamide.¹⁰ (Table.3)

Table-3: IR absorption data of complexes in cm^{-1}

Ligand / Complex	ν NH cm^{-1}	ν C=O cm^{-1}	ν S=O cm^{-1}	ν SO ₂ N cm^{-1}	ν M=O cm^{-1}
$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$	3340	1670	1397	1157	-
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Mn}$	3286	1627	1365	1141	640
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Ni}$	3329	1664	1381	1154	678
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Cu}$	3275	1652	1372	1175	624

Electronic spectra: The electronic spectrum of Mn (II) complex shows three bands at 14715 cm^{-1} , 20830 cm^{-1} and 24735 cm^{-1} which are assigned to $^4\text{A}_1\text{g}(\text{D}) \rightarrow ^6\text{A}_1\text{g}$, $^4\text{T}_1\text{g}(\text{G}) \rightarrow ^6\text{A}_1\text{g}$ and $^4\text{A}_1\text{g}(\text{D}) \rightarrow ^6\text{A}_1\text{g}$ transitions respectively. It has magnetic moment 5.1 B.M., which indicates the octahedral geometry around the Mn (II) ion. The spectrum of Ni (II) complex, shows bands at 14562 cm^{-1} , 17533 cm^{-1} and 22343 cm^{-1} assigned to $^3\text{A}_2\text{g} \rightarrow ^3\text{T}_2\text{g}$, $^3\text{A}_2\text{g} \rightarrow ^3\text{T}_1\text{g}(\text{F})$ and $^3\text{A}_2\text{g} \rightarrow ^3\text{T}_1\text{g}(\text{P})$ transitions. The magnetic moment of 3.30 B.M. falls within the range normally observed for the octahedral Ni (II) complexes. The

Cu (II) complex has a magnetic moment value 1.89 B.M. which indicates an octahedral geometry. The band at 22220 cm^{-1} refers to (L→M) charge transfer.¹¹⁻¹³

Antibacterial Screening: The antibacterial activity studies of the ligand, chlorpropamide and its complexes were performed by agar well diffusion method. The zone of inhibition was measured against *Escherichia coli* (*E.coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Bacillus megaterium* (*B. megaterium*). The complexes were tested at concentration $30\text{ g} / 1\text{ mL}$ in DMSO. A clearing zone around the agar well indicates the inhibitory activity of the compound on the micro-organisms. Results are shown in the **Table 4**. It clearly indicates that the inhibition is much larger by the metal complexes as compared to the metal free ligand. The increased activity of metal chelates can be explained on the basis of chelation theory.¹⁴

Table-4: Antibacterial screening measured in mm

Chlorpropamide / Complexes	<i>E. coli</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>B. megaterium</i>
$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$	+	++	++	+
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Mn}$	++	+++	++	++
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Ni}$	+++	+	++	+
$(\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S})_2\text{Cl}_2\text{Cu}$	+++	++	++	+++

+: 6-10 mm; ++: 10-16 mm; +++: 16-22 mm

CONCLUSION

The ligand molecule, chlorpropamide acts as bidentate ligand. The differences in the melting points (in **Table 1**) of all these complexes as compared to chlorpropamide suggested that a new product has been formed. From the analytical and spectral data, it can be concluded that the synthesized complexes are stable with octahedral environment around them. The proposed general structure of these representative octahedral complexes is as shown in **Fig. 2**.

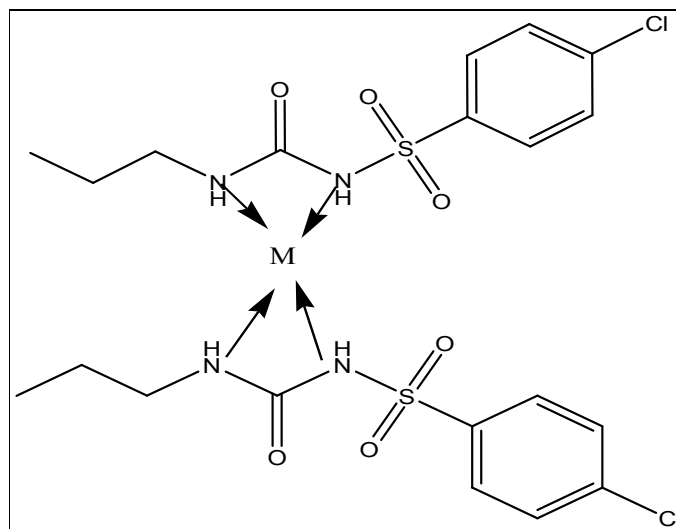


Fig.2: Proposed general structure for metal complexes of chlorpropamide.

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Corresponding author: Shruti S. Sarwade; Department of Chemistry,
Dnyanopasak Science College, Parbhani-431401, Maharashtra, India