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Synthesis, spectral, catalytic and biochemical activity of Zn (II) and Cd (II) chelates with 5-amino salicylic acid derivative

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ABSTRACT

This work describes synthesis and in vitro studies on methyl 5 –amino 2- hydroxy benzoate and metal chelates of Zn (II) and Cd (II) ions with methyl 5 –amino 2- hydroxy benzoate. The ligand methyl 5 –amino 2- hydroxy benzoate and metal chelates have been prepared by reflux method. These chelates were characterized by elemental analysis, molar conductance, spectral studies, TGA and catalytic studies. The antimicrobial activities of the ligand and their metal chelates have also been screened.

Key words: 5- amino salicylic acid derivatives, chelates, characterization, catalytic and antimicrobial activity.

INTRODUCTION

Looking to the literature survey carried out as well as the significance of the 5 – amino salicylic acid derivatives as well as its coordination compounds, it is quite likely to give modified and improvised biochemical properties. 5 – amino salicylic acid, also known as mesalamine, is an anti inflammatory drug used to treat inflammation of the digestive track, ulcerative colitis and mild – to – moderate Crohn's disease[1-2]. It is also recommended therapy for the induction and maintenance of remission of ulcerative colitis (UC) [3-4].The drug acts topically at the colonic mucosa to reduce mucosal inflammation [5] yet because the active drug is rapidly absorbed in the stomach and small intestine [6] a number of oral formulations have been developed to deliver 5-ASA to the colon [5-7].The drug P-ASA is excellent anti T.B agent [8-9]. Practically only few scientists have made attempts to study with 5 – amino salicylic acid derivatives or biochemical and catalytic behavior of 5 –amino salicylic acid derivatives. Thus this may afford good chelating ligand with better biochemical activity. The present communation comprises the studies on 5 – amino salicylic acid derivatives and its metal chelates.

MATERIALS AND METHODS

Analytical grade chemicals were used through the course of experimental work. Spectroscopic grade solvents were employed for recording the spectra. 5 –amino salicylic acid was obtained from S-d fine. Other chemicals were also of high purity.

Synthesis of ligand

10.0 gm (65.3 mmol) of 5 – amino salicylic acid and 200ml methanol and drop wise adding of 14 ml of concentrated sulfuric acid was carried out .This reaction mixture was heated under reflux for 15 –17 hours in water bath. After addition of $NaHCO_3$ (until the evolution of CO_2 ceased) the reaction mixture was filtered. The filtrate was poured into water and extracted with ether. The combined organic layers were dried over magnesium sulphate and the solvent was removed.A colored solid product obtained [10].

Synthesis of Metal Chelates

The metal chelates were prepared by the mixing of 100 ml (0.372 g) methanol solution of zinc perchlorate / 100 ml (0.311g) cadmium perchlorate with 100 ml methanol solution of ligand in 1:1 molar ratio and refluxed for 3 hours in the water bath. After refluxing, the reaction mixture was cooled and then put on the magnetic stirrer at room temperature. There were no immediate precipitates. The pH of this solutions raise up to ~ 7.0 using dilute alkali solutions which resulted in precipitates. The resulting chelate was filtered, washed with mixture of methanol and water and then dried in oven.

PHYSICO-CHEMICAL MEASUREMENTS

Melting points were determined in open capillary tubes and are uncorrected. The metal content was determined [11] by titration with a standardized solution of disodium salt of EDTA after decomposing the chelates with a mixture of concentrated nitric acid, perchloric acid and sulfuric acid in 1:1:1 ml ratio respectively. The IR - spectra (4000 – 400 cm^{-1}) were recorded on Perkin – Elmer 8201 FT-IR with KBr pellets. Conductance measurements were performed using systronics conductivity meter. The ^{1}H-NMR spectra were recorded on BRUKER AVANCE II 400 MHz Spectrometer. Chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as internal standard in DMSO –d6 and $CDCl_3$ solvents. Elemental analyses were performed on Vario MICRO C, H, N, S Elemental Analyzer system. Thermo gravimetric analysis was carried out under atmospheric condition with heating range 50 – 1000 @10°C min^{-1} on Mettler Toledo.

RESULTS AND DISCUSSION

Conductance Measurement

Metal chelates are found to be only slightly soluble in DMSO and insoluble in water and other solvents. The conductivities of methyl 5 –amino 2- hydroxy benzoate and metal chelates were recorded in DMSO at 10^{-3} M concentration using systronics conductivity meter. The high value of molar conductance (around 100 mho/cm) suggests that both, Zn and Cd chelates are 1:1 electrolytes.

Table – 1 Analytical data and some physical parameters of ligand and metal chelates

[Compounds] Color	Formula weight	Molar conductance (mho $^{-1}cm^{-1}$. mol^{-1})	Elemental Analysis (%) found & (%) calculated						Metal percentage	
			(%) C found	(%) C Cal.	(%) H found	(%) H Cal.	(%) N found	(%) N Cal.	(%)M found	(%)M Cal.
Ligand [$C_8H_9NO_3$] Reddish Brown	167.00	-----	56.64	57.48	5.34	5.38	7.90	8.38	----	----
[$Zn(C_8H_9NO_3)_2.H_2O$] Brown black	232.38	89.3	37.64	38.34	3.80	4.39	4.75	5.59	25.09	26.11
[$Cd(C_8H_9NO_3)_2$] Brown black	279.21	97.7 9797	35.09	34.38	3.14	3.22	4.49	5.01	38.91	40.19

IR – SPECTRA

The ligand methyl 5-amino 2-hydroxy benzoate molecule shows the following characteristic bands, 3280 cm^{-1} and 3360 cm^{-1} (N-H and O-H stretching), 2880-2920 cm^{-1}(aromatic C-H stretching) , 1760 cm^{-1}(C-O stretching of >C=O bond) , 1240 cm^{-1} (C-O stretching of ester group) and 1580, 1600 and 1620 cm^{-1}(aromatic C=C and C-N stretching). In both metal chelates the band at 3360 Cm^{-1} is shifted to 15 – 20 Cm^{-1} lower energy level is indicating coordination by the oxygen of –OH (phenolic) group. 1240 Cm^{-1} peak in ligand is due to C-O group while in Cd - chelate it is shifted to 10 - 15Cm^{-1} lower energy level and this indicating to M-O- C=O and the band about 1740 cm^{-1} indicates that oxygen (>C=O) involved in the formation of M-C=O bond. In both the metal chelates the band at 3300- 3600 cm^{-1} indicating formation of M-N bond due to free $–NH_2$ group of another chelate. 3280 Cm^{-1} (broad) band appeared in ligand and both chelates indicating N-H stretching frequency. The reduction in the intensity of O-H stretching indicates ionization and loss of H^+ due to coordination.

^{1}H-NMR SPECTRA

The ligand methyl 5 –amino 2- hydroxy benzoate and metal chelates show following δ values.

5 –amino 2- hydroxy benzoate: δ = 10.226 (1H, -OH phenolic), δ = 3.075 (2H, $-NH_2$), δ = 6.831- 7.279 (4H, aromatic ring) and δ = 3.937(3H, $-CH_3$).

Zn chelate: δ = 9.846 (1H, -OH phenolic), δ = 3.316 (3H, $-CH_3$), δ = 6.690 - 7.017 (4H, aromatic ring) and δ = 3.807 (2H,$-NH_2$).

Cd chelate: δ = 9.88 (1H,-OH phenolic), δ =3.807 (2H, -NH_2), δ = 6.693- 7.109 (4H, aromatic ring) and δ = 4.203 (3H,-CH_3).

THERMO GRAVIMETRIC ANALYSIS

This analysis shows that there are water molecules present in each metal chelate. The water molecules present in chelates are either water of coordination or water of lattice. Water of coordination is more tightly held by the metal ions where as water of lattice is less tightly held by the molecule. At the low temperature (50 – 150°C) the lattice water molecule will be lost and at high temperature (150 – 250°C) [12] the coordination water molecule is lost. In the Zn chelate at 145°C 8.783 gm weight loss occurred which indicated that no water molecule of lattice and at 225°C temperature 16.777 gm weight loss occurred means one water molecule coordinates with Zn metal ion. In the Cd chelate, at 145°C, 3.629 gm weight loss occurred which indicated that no water molecule of lattice and at 225°C temperature 6.756 gm weight loss indicates practically no water molecule coordinated with Cd metal ion.

Table – 2 Thermo gravimetric analysis of metal chelates

[Compounds]	Weight loss and % found			
	145°C Temp.		225°C Temp.	
	gm	%	gm	%
[Zn.$C_8H_9NO_3.H_2O$]	8.783	3.78	16.77	7.22
[Cd.$C_8H_9NO_3$]	3.629	1.30	6.75	2.42

STRUCTURES PROPOSED

Summarizing the results of Physico- chemical analysis, metal chelates are uni- uni electrolytic nature (conductance measurement), coordinate through –O-H (phenolic) , O = C- O - of ester and > C=O (IR analysis), mono nuclear metal chelates stoichiometry (C, H, N and M analysis), one water molecule of coordination in Zn chelate (Thermal analysis) and presence of –OH (^{1}H-NMR spectra) in chelates etc. In the tetrahedral geometry, their most probable structure can be shown as in figure -1.

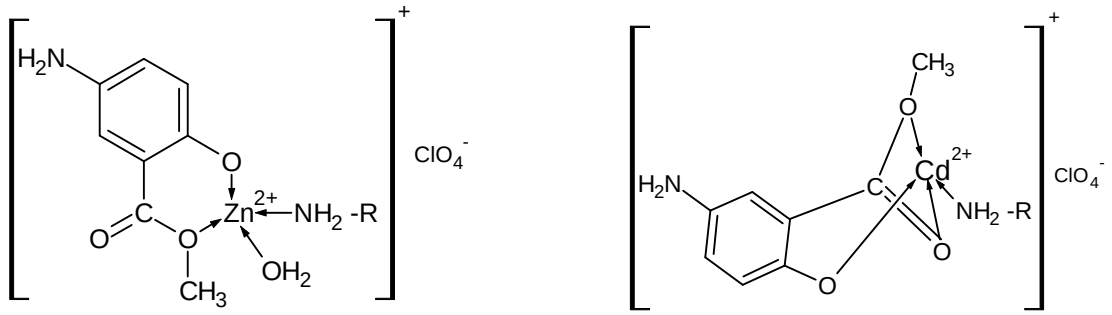
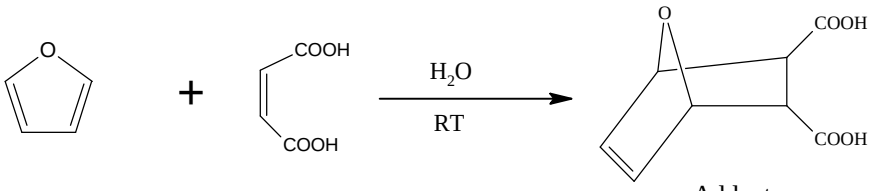


Figure – 1

In the Zn chelate the third and fourth coordination sites of the tetrahedron should be satisfied by one H_2O molecule and the free –NH_2 of the other molecule While in Cd chelate the fourth coordination site of the tetrahedron should be satisfied by only the free –NH_2 group of another molecule and the second oxygen atom of the ester group.

CATALYTIC STUDY

A mixture of furan (1 g) and maleic acid (2 g) in water (10 ml) was stirred for 3 hrs at room temperature. The solid, colorless adduct formed, was filtered, washed with water, dried and recrystallised from aqueous ethanol, m.p. 138 – 140 °C. Yield: 2.1 g (80%).This is a standard organic preparation [13-14] which should be carried out for 3 hrs for getting 80% yield. When this reaction was carried out for 2 hrs, 61% yield was obtained. The same reaction was carried out using 1% catalytic amount of ligand and metal chelates, % yield and % increases in yield of this reaction are indicated in table - 3.This reaction carried out in aqueous medium avoiding benzene.



Furan Maleic acid Adduct

Table – 3 % yield and % yield increases with metal chelates of organic reaction

Temperature Time	% yield Standard reaction	% yield with ligand catalyst	% yield with Zn -chelate catalyst	% yield increase with Zn-chelate catalyst	% yield with Cd -chelate catalyst	% yield increase with Cd -chelate catalyst
Room temp. (25 ± 1°C) 2hrs.	61.0 %	66.0%	63.40%	3.93%	66.56%	9.11%

In comparison with uncatalyzed or with ligand, both the chelates were able to increase the rate of reaction to around 10% higher yield.

Antimicrobial Activity

Antimicrobial activity of methyl 5-amino 2- hydroxy benzoate and their metal chelates were studied against gram positive and gram negative bacteria at a concentration of 50 µg / ml by Agar diffusion method [15]. All the synthesized, new titled compounds were evaluated for antimicrobial activity by using Escherichia coli, Staphylococcus aureus, Bacillus Subtilis and Salmonella Typhi by measuring the zone of inhibition in mm. Streptomycin sulphate was used as a standard drug for antimicrobial activity. $CDCl_3$ and DMSO were used as solvent control for antimicrobial activity. The antimicrobial activity results revealed that the ligand and its metal chelates show moderate to good activity. It is presented in table - 4.

Table – 4 Antimicrobial activity of the ligand and metal chelates

Compounds	Diameter of zone of inhibition in (mm)			
	E. coli	*S. aureus*	*B.subtilis*	*S. typhi*
Ligand $C_8H_9NO_3$	11	11	15	12
$[Zn.C_8H_9NO_3.H_2O]$	21	25	20	19
$[Cd.C_8H_9NO_3]$	20	19	20	15
Streptomycin sulphate	11	11	11	10

CONCLUSION

Ligand, methyl 5 –amino 2- hydroxy benzoate was coordinated with per chlorate salts of Zn and Cd ions. Ligand and metal chelates were characterized by IR-spectra, ^{1}H-NMR, TGA and physical methods. The antimicrobial activity of ligand and its metal chelates shows moderate to better activity against E.coli, S. aureus, B. subtilis and S.typhi. Inspection of the result shown in table – 4 indicates that all compounds exhibit good activity. Out of all compound both metal chelates are highly sensitive against E.coli, S. aureus, B. subtilis and S.typhi. Zn chelate is a good antimicrobial agent against E.coli and S.aureus than the Cd chelate. An overall observation indicates that the ligand and metal chelates possessed much better activity in comparison with the standard antibiotic streptomycin sulphate. The catalytic study result shown in table – 3 indicates that both complexes were very useful in the increased % yield and also time required decreased. Cd chelate is more effective as a catalyst and increased the percentage yield by 10%.

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