



RESEARCH ARTICLE

**Synthesis, Characterization, Antimicrobial and Catalytic Studies on Novel
Complexes of 5 - Amino Salicylic Acid Derivatives**

Gurjar JG¹, Solanki JN¹, Vora JJ²

¹Chemistry Department, C. U. Shah Science College, Ahmedabad, Gujarat, India.

²Department of Chemistry, Hemchandracharya, North Gujarat University, Patan, Gujarat, India.

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ABSTRACT

In the present investigation methyl 5 –amino 2- hydroxy benzoate and some novel metal complexes of Ca (II) and Mg (II) with methyl 5 –amino 2- hydroxy benzoate derivative have been synthesized. All metal complexes and ligand are characterized by elemental analysis, conductance measurement, ¹H-NMR, IR spectra, and thermo gravimetric analysis. These complexes were used as catalyst for some standard organic reaction. The antimicrobial activity of the ligand and their metal complexes were screened against various bacteria.

KEYWORDS

Complexes, Catalytic Study, Antimicrobial Activity, 5 – Amino Salicylic Acid Derivative

INTRODUCTION

The derivatives of 5 -amino salicylic acid are used of medicinal purpose. Practically only few scientists have made attempts to study with 5 – amino salicylic acid derivatives or catalytic behavior of 5 –amino salicylic acid derivatives. Looking to the literature survey carried out as well as the significance of the 5 – amino salicylic acid derivatives and its coordination compounds, it is quite likely to give modified and improvised biochemical. Prompted by the above biological properties of 5 – amino salicylic acid, it was contemplated to synthesize novel complexes of 5 – amino salicylic acid derivatives. Catalytic behavior, antibacterial and antifungal activities of the newly synthesized compounds are discussed in this paper. The ligand methyl 5 – amino 2-hydroxy benzoate synthesized from 5 – amino salicylic acid also known as mesalamine or

mesalamine, is an anti-inflammatory drug used to treat inflammation of the digestive tract Ulcerative colitis¹ and mild – to – moderate Crohn's disease². 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 inflammation⁵ yet because the active drug is rapidly absorbed in the stomach and small intestine⁶ a number of oral formulations have been developed to deliver 5-ASA to the colon^{5,7}. The most common side effects of 5-ASA are headache and flatulence. Hair loss and itching also may occur. Infrequent side effects include increased heart rate, pancreatitis, back pain, fatigue, tremor, ear pain and blood disorders. Therefore, search of its derivative became imperative.

MATERIAL 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

*Address for Correspondence:

Jagdish G. Gurjar

Chemistry Department,
C. U. Shah Science College,
Ahmedabad, Gujarat, India.

E-Mail Id: jagdishgurjar72@yahoo.com

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 gas) 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 removed⁸.

Synthesis of Metal Complexes

The metal complexes were prepared by the mixing of 100 ml (0.236 gm) methanolic solution of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ /100 ml (0.256 gm) $\text{Mg}(\text{NO}_3)_2$ with 100 ml methanolic 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 ~ 6.8 using alkaline solution which resulted in precipitates. The resulting complexes were 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 determined⁹ by titration with a standardized solution of disodium salt of EDTA after decomposing the complexes with a mixture of concentrated. Nitric acid, Perchloric acid and Sulfuric acid in 1:1:1 ml ratio respectively. The IR - spectra ($4000 - 400 \text{ cm}^{-1}$) were recorded on Shimadzu Perkin – Elmer 8201 FT-IR with KBr pellets. Conductance measurements were performed using systronics conductivity meter. The $^1\text{H-NMR}$ 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 $\text{DMSO}-d_6$ and CDCl_3 solvent. 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 $50 - 1000 @10^\circ\text{C min}^{-1}$ on Mettler Toledo.

RESULTS AND DISCUSSION

Conductance Measurement

Metal complexes are found to be only slightly soluble in DMSO and insoluble in water and other solvents. The conductivities of metal complexes are recorded in DMSO at 10^{-3} M concentration using conductivity meter. The molar conductance data of the complexes indicating their electrolytic nature of 1:1 type.

IR Spectra Study

In the IR spectra of $\text{Ca}(\text{II})$ and $\text{Mg}(\text{II})$ complexes the bands in the region of $1680 - 1700 \text{ cm}^{-1}$ and at $2920, 1320 \text{ cm}^{-1}$ were obtained due to stretching vibrations of $>\text{C}=\text{O}$ and $\text{C} - \text{H}$ ($-\text{CH}_3$) respectively. The band at 3360 cm^{-1} of the ligand due to the $-\text{OH}$ (phenol) stretching while in both the complexes it is shifted to $20 - 25 \text{ cm}^{-1}$ lower energy level indicating coordination by the oxygen. At 1240 cm^{-1} peak shows in ligand due to $-\text{C}-\text{O}$ group while in both complexes it is shifted to 20 cm^{-1} lower energy level indicates that oxygen from $-\text{C}-\text{O}$ group is coordinated with metal ions. In the metal complexes the band around 540 cm^{-1} indicates $\text{M} - \text{O}$ suggesting that phenolic $-\text{OH}$ are involved in bond formation with metal ions. The $\text{M}-\text{N}$ frequency in the metal complexes is obtained at higher wave number because of the double bond character of $\text{M}-\text{N}$ bond due to MN- interaction. At 3280 cm^{-1} band appeared in ligand and both complexes due to present of $-\text{N}-\text{H}$ stretching frequency. The bands at 3400 cm^{-1} present in both complexes indicated the water of coordination.

$^1\text{H-NMR}$ Study

The $^1\text{H-NMR}$ spectra of ligand recorded in CDCl_3 solvent and complexes in $\text{DMSO} - d_6$ spectroscopic solvent. $^1\text{H-NMR}$ spectra exhibited multiple singlets at $\delta 6.90 - 7.59$ ppm indicated aromatic protons. The methyl proton of the $-\text{CH}_3$ were observed at $\delta 3.937$ ppm. A singlet is observed at $\delta 3.075$ ppm due to $-\text{NH}_2$ proton.

Table 1: Analytical Data and Some physical parameters of ligand and metal complexes

(Compounds) Color	Formula weight	Molar Conductance $\text{mho}^{-1} \text{cm}^{-1} \cdot \text{mole}^{-1}$	Elemental Analysis (%) found / (%) calculated			Metal percentage found (calculated)
			(%) C found (calculated)	(%) H found (calculated)	(%) N found (calculated)	
Ligand [C ₈ H ₉ NO ₃] Reddish Brown	167.00	62.3	56.64 (57.48)	5.34 (5.38)	7.90 (8.38)	-----
[Ca(C ₈ H ₉ NO ₃) ₂ .H ₂ O] Brown black	392.08	121.1	46.88 (48.96)	4.80 (5.10)	6.50 (7.14)	11.10 (10.22)
[Mg(C ₈ H ₉ NO ₃) ₂ .2H ₂ O] Brown black	394.30	126.4	47.27 (48.69)	4.97 (5.57)	4.62 (3.55)	6.90 (6.16)

Note: Metal complexes are soluble in DMSO solvent.

Table 2: Thermo gravimetric analysis of ligand and metal complexes

Compounds	Weight Loss and Percentage Found			
	147°C Temp.		247°C Temp.	
	gm	%	gm	%
[Ca(C ₈ H ₉ NO ₃) ₂ .H ₂ O]	9.239	2.47	21.58	5.769
[Mg(C ₈ H ₉ NO ₃) ₂ .2H ₂ O]	30.92	8.63	46.0	12.86

A singlet at δ 10.226 ppm due to -OH phenolic proton present in ligand while in both complexes this peak is obtained at δ 10.401 ppm indicates that oxygen coordinates with metal ions.

Thermo Gravimetric Analysis

This analysis shows that there are water molecules present in each metal complex. The water molecules present in complexes is either water of coordination or water of crystallization. Water of coordination is more tightly held by the metal ions whereas water of crystallization is less tightly held by the molecule. At the low temperature (50 – 150°C) the crystallization

water will be lost and at high temperature (150 – 250°C)¹⁰ the coordination water molecule is lost. In Ca metal complex at 147°C 9.239 gm weight loss occurred which indicated that no water of crystallization molecule and at 247°C temperature 21.58 gm weight loss occurred. This means one water molecule coordinate with metal ions.

In Mg complex at 147°C 30.92 gm weight loss occurred which indicated that two water molecules of crystallization and at 247°C temperature 46.0 gm weight indicates loss two water molecules co-ordinated with metal ion.

Structures Proposed

Summarizing the results of Physico chemical analysis complexes are uni- uni type of ion (conductance), coordinate through $-O-H$ (IR), 1:2 metal: ligand stoichiometry (C,H,N & Metal), one and two water molecules of coordination (Thermal) and presence of $-OH$ (^1H-NMR) in complexes etc. In the most probable octahedral geometry, their most probable structure can be shown as figure -1.

In case of Ca^{2+} complex the sixth coordination site of the octahedron should be satisfied by the free $-NH_2$ group of another complex.

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 recrystallized from aqueous ethanol, m.p. 138 – 140 °C. Yield: 2.1 g (80%). This is a standard organic preparation¹¹⁻¹² which should be carried out for 3 hrs for getting 80% yield. When this reaction was carried out for 2 hrs, 61% yield obtained. The same reaction was carried out using 1% catalytic amount of ligand and metal complexes, % yield and % increases in yield of this reaction are indicated in table - 3.

Green Context: Reaction carried out in aqueous medium avoiding benzene. Efficient at room temperature itself 100% atom efficient.

In comparison with uncatalyzed or with ligand, both the complexes were able to increase the rate of reaction to around 24% higher yield.

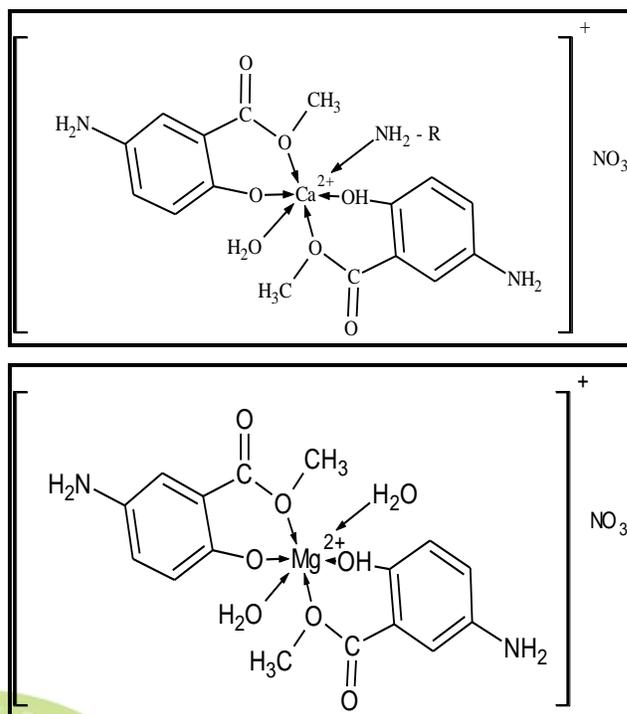


Figure 1

Antimicrobial Activity

The ligand and its metal complexes of Ca (II) and Mg (II) have been screened for their antimicrobial activity by Agar diffusion method¹³. All the synthesized new titled compounds were evaluated for antimicrobial activity against Escherichia coli, Staphylococcus aureus, Bacillus Subtilis and Salmonella typhi by measuring the zone of inhibition in mm. The activities were performed at a concentration of 50 μg / ml. Streptomycin sulphate was used as a standard drug for antimicrobial activity. DMSO was used as solvent control for antimicrobial activity. The result is reported in table - 4.

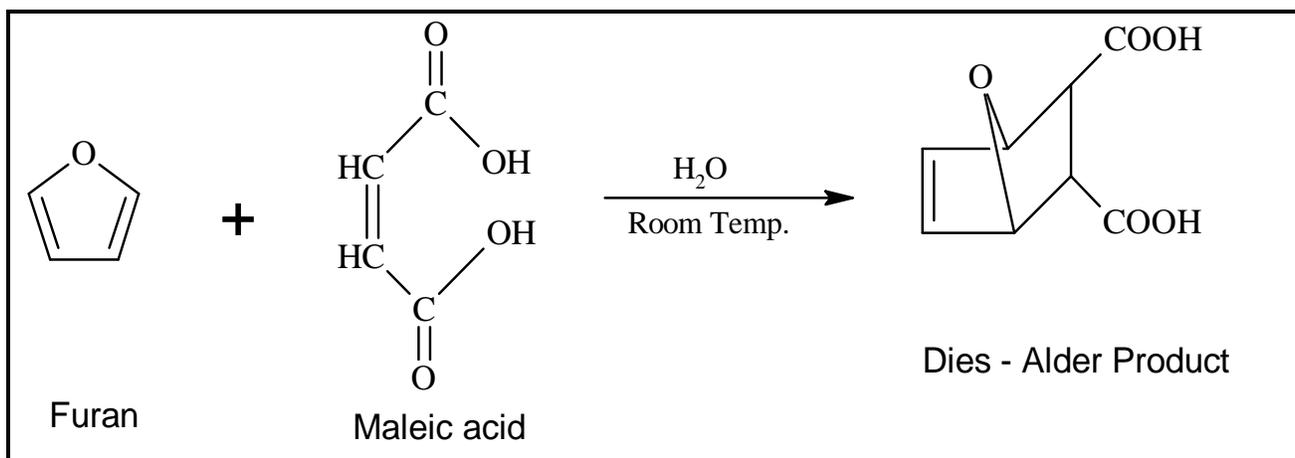


Table 3: Percentage Yield of Organic Reaction

Temperature Time	% yield Standard reaction	% yield with ligand catalyst	% yield with Ca - complex catalyst	% yield increase with Ca - complex catalyst	% yield with Mg - complex catalyst	% yield increase with Mg - complex catalyst
Room temp. (25 ± 1°C) 2 hrs.	61.0 %	66.0%	72.55%	18.93%	75.50%	23.77%

Table 4: Antimicrobial activity of the ligand and metal complexes

Compounds	Diameter of zone of inhibition in (mm)			
	Escherichia coli	Staphylococcus aureus	Bacillus subtilis	Salmonella Typhi
Ligand C ₈ H ₉ NO ₃	11	11	15	12
[Ca(C ₈ H ₉ NO ₃) ₂ .H ₂ O]	19	21	14	09
[Mg(C ₈ H ₉ NO ₃) ₂ .2H ₂ O]	15	18	12	11
Streptomycin sulphate (std. drug)	11	11	11	10

CONCLUSION

Ligand, methyl 5 -amino 2- hydroxy benzoate was coordinated with nitrate salts of Ca and Mg ions. Ligand and metal complexes were characterized by IR-spectra, ¹H-NMR, UV, TGA and physical parameters.

The antimicrobial activity of ligand and its metal complexes 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 Ca- complex and Mg-complex are highly sensitive against E.coli, and S. aureus better than the B. subtilis and S.typhi. Ligand was also good active against B. subtilis better than the other pathogens.

An overall observation indicates that the complexes 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. The complexes were able to effectively increase the rate of reaction to 24% higher yield and show their tremendous industrial application potential.

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