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Synthesis, spectral characterization of schiff base alkaline earth metal complexes: Antimicrobial activity studies

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ABSTRACT

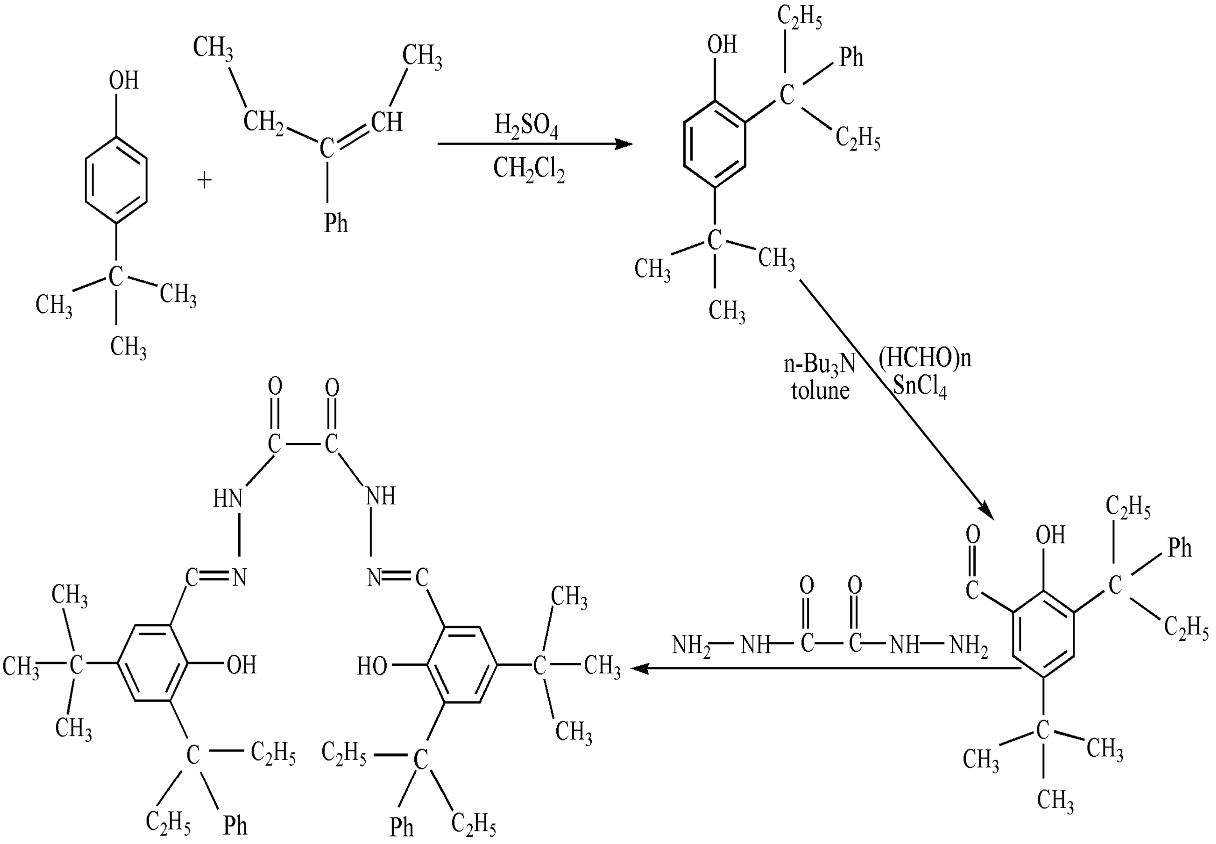
Alkaline earth metal complexes of Ba, Ca and Sr have been synthesized from Schiff base (L) derived from oxayl-dihydrazide and 5-tert-Butyl-2-hydroxy-3-(3-phenylpent -3-yl) benzaldehyde. Structural features were obtained from their elemental analysis magnetic susceptibility, molar conductance, mass, IR, electronic, ^{1}H NMR and ESR spectral studies. The data show that these complexes have composition of ML type. The Electronic, magnetic susceptibility and ESR spectral data of the complexes suggest a octahedral geometry around the central metal ion. Antimicrobial screening tests gave good results in the presence of metal ion in the ligand system.

Key Words: Alkaline earth metals (Ba, Ca and Sr), Schiff base ligand, Metal complexes, Antimicrobial activity.

INTRODUCTION

The group 2 alkaline earth metals calcium (Ca), strontium (Sr), and barium (Ba) are among the most common elements on Earth, abundant in both the sea and the Earth's crust. Although they are familiar in our daily lives, their application to organic synthesis has, so far, been limited. Some particularly useful properties of these elements include (i) low electronegativity, (ii) a stable oxidation state of +2, meaning that they can potentially form two covalent bonds with anions, and (iii) the ability to occupy a variety of coordination sites due to their large ionic radius. Furthermore, the alkaline earth metals, found between the group 1 and group 3 elements, show mild but significant Lewis acidity, which can be harnessed to control coordinative molecules via a Lewis acid-base interaction. Taken together, these characteristics make the metals Ca, Sr, and Ba very promising components of highly functionalized acid-base catalysts. In this Account, we describe the development of chiral alkaline earth metal catalysts for asymmetric carbon-carbon bond-forming reactions. Schiff base complexes have a variety of applications in biological, clinical, analytical and pharmacological area [1-3]. Studies of a new kind of chemotherapeutic Schiff bases are now attracting the attention of biochemists [4, 5].

Earlier work reported that some drugs showed increased activity, when administered as metal complexes rather than as organic compounds [6,7]. 1 : 2 [Ln (III) HBA/ HSBA] complexes were found to be stable when stored under dry condition [8].The bonding between alkaline-earth metals and their ligands depend upon electrostatic or Lewis acid/base interactions. The alkaline-earth metal ions are kinetically labile, so the tendency for ligand rearrangement and decomposition is high. Hanusa et al. employed sterically bulky ligands, which significantly increased the solubility and kinetic stability of many alkaline-earth metal complexes and has made possible the isolation and detailed characterization of new derivative. Schiff base (1, 2) compound is a bulky ligand containing an imino group (−RC = N−) are usually formed by the condensation of a primary amine with an active carbonyl. The chemistry of metal complexes with Schiff base has gained much interest because of their use as models in biological system. There are a number of important molecules shows biological activities including antibacterial, antifungal [9-19], antidiabetic [20], antitumor [21-23], antiproliferative [24,25], anticancer [26,27], herbicidal [28] activities. These Schiff bases have donor sites with the NOON sequence and varied coordination abilities. The ligand and its metal complexes show significant antimicrobial activity. The complexes are found to more effective than the free ligand. The antimicrobial activity of the test compounds are comparable to that of the standard drugs used [29]. This nature of Schiff base has attracted out attention and around our interest in elucidation the structure of Ba, Ca and Sr complexes, which are evaluated for their antimicrobial properties against various pathogenic strains.



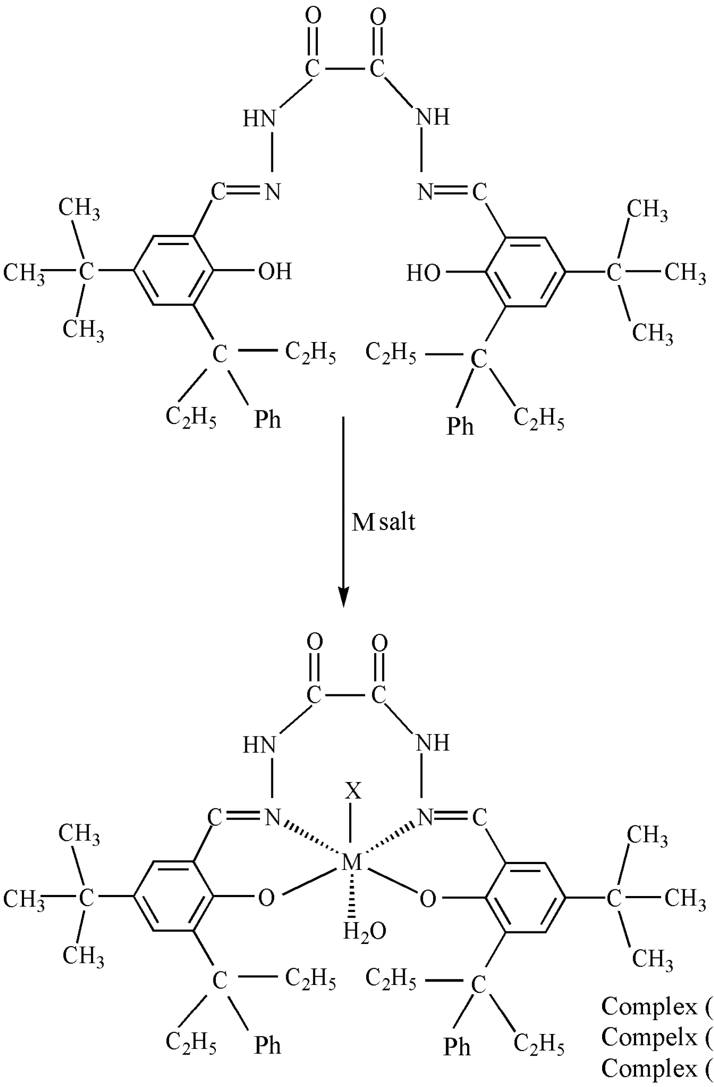
Scheme 1. Formation of Schiff base

MATERIALS AND METHODS

Organic compounds, solvents and metal salts have been used throughout the investigations were of Merck products. The magnetic measurements were made using 'Princeton Applied Research' vibrating sample magnetometer, Model 155 incorporating digital read out at University service. The electronic spectra of the complexes at room temperature were recorded in nujol mull or dimethylformamide on Carl zeiss specord uv-vis-spectrophotometer at IIT , Roorkee and RSIC. Infrared spectra of the complexes in the conventional region (4000-250cm^{-1}) were recorded on a Beckman IR-12 spectrophotometer in potassium bromide pellets. The molecular weight of the complexes were determined by Beckman's cryoscopic method in solvents depending upon the solubility of the compound. The microanalysis of C, H and N were estimated by elemental analyzer Perkin Elmer 2400 and the metal contents of were determined by atomic absorption spectrophotometer (Perkin Elmer 5000).Microanalytical data of the compounds were recorded at Central Drug Research Institute, Lucknow. The antimicrobial activities of the ligands and their complexes were carried out by well diffusion method.

The ligand was prepared by the condensation of 5-tert-Butyl-2-hydroxy-3-(3-phenylpent-3-yl) benzaldehyde with oxalyldihydrazide (2:1). A mixture of ethanol/dichloromethane (1:3) was used as a solvent in the presence of anhydrous magnesium sulphate as a dehydrating agent.

The metal complexes of the ligand were prepared by mixing a hot methanolic solution of the metal salts with required amount of a hot ethanolic solution of the ligand to form metal/ligand complexes.



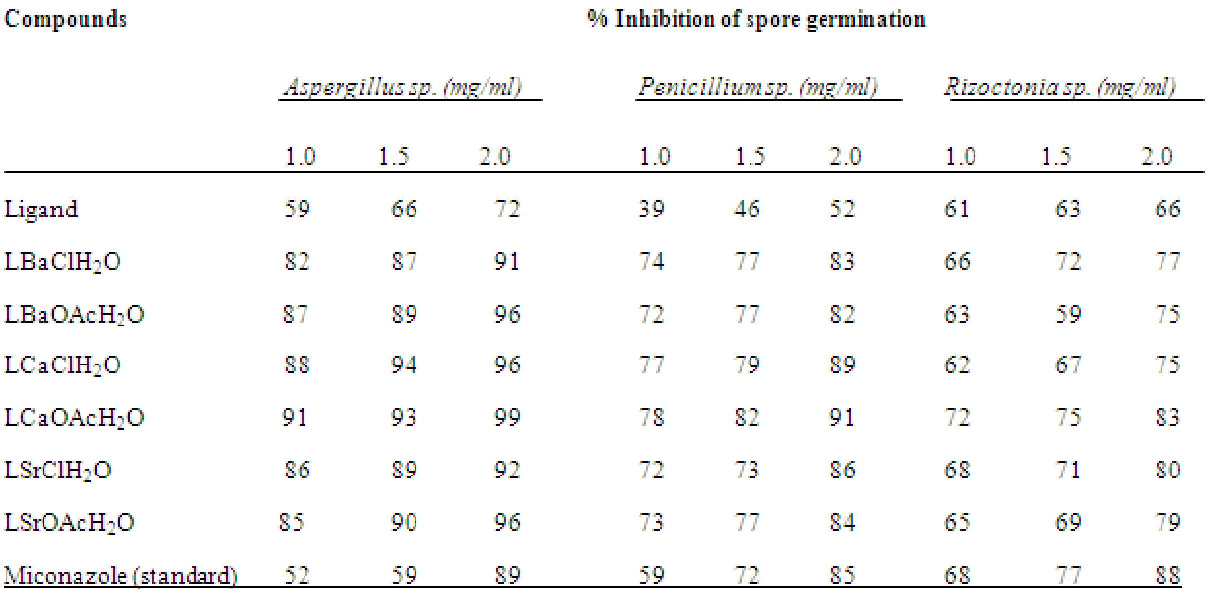
Complex (1): HLMXH$_2$O, M=Ba, X=Cl
Compelx (2): HLMXH$_2$O, M=Ba, X=OC(O)CH$_3$
Complex (3): HLMXH$_2$O, M=Ca, X=Cl
Compelx (4): HLMXH$_2$O, M=Ca, X=OC(O)CH$_3$
Complex (5): HLMXH$_2$O, M=Sr, X=Cl
Compelx (6): HLMXH$_2$O, M=Sr, X=OC(O)CH$_3$

Scheme 2. Formation of Schiff base metal complex

Table 1. Physical characterization, analytical, molar conductance and magnetic susceptibility data of the ligand and the complexes.

Compounds	Molecular Formula	Yield (%)	Found (cacld) (%) M	C	N	H	Molar conductance ∧m (Ω– 1 cm2 mol–1)
L	C_{46} H_{58} $N4O_4$	81%	-	75.5 (75.5)	8.1 (8.0)	7.5 (7.6)	-
$LBaClH_2O$	$C_{46}H_{58}ClBaN_4O_5$	71%	7.4 (7.5)	65.2 (65.3)	6.8 (6.9)	6.5 (6.6)	69
$LBaOAcH_2O$	$C_{48}H_{61}ClBaN_4O_7$	61%	7.2 (7.3)	66.2 (66.3)	7.1 (7.0)	6.4 (6.4)	56
$LCaClH_2O$	$C_{46}H_{58}ClCaN_4O_5$	80%	6.9 (6.9)	65.5 (65.6)	6.9 (6.9)	6.5 (6.6)	12
$LCaOAcH_2O$	$C_{48}H_{61}ClCaN_4O_7$	81%	6.3 (6.7)	65.9 (66.9)	7.0 (7.1)	6.5 (6.4)	9
$LSrClH_2O$	$C_{46}H_{58}ClSrN_4O_5$	77%	6.8 (7.0)	65.5 (65.6)	6.9 (6.9)	6.5 (6.6)	17
$LSrOAcH_2O$	$C_{48}H_{61}ClSrN_4O_7$	75%	6.3 (6.8)	66.6 (66.6)	7.2 (7.1)	6.4 (6.4)	15

Table 2. Fungicidal screening data of the ligand and their corresponding metal complexes.



Compounds	% Inhibition of spore germination *Aspergillus sp. (mg/ml)* 1.0	1.5	2.0	*Penicillium sp. (mg/ml)* 1.0	1.5	2.0	*Rizoctonia sp. (mg/ml)* 1.0	1.5	2.0
Ligand	59	66	72	39	46	52	61	63	66
$LBaClH_2O$	82	87	91	74	77	83	66	72	77
$LBaOAcH_2O$	87	89	96	72	77	82	63	59	75
$LCaClH_2O$	88	94	96	77	79	89	62	67	75
$LCaOAcH_2O$	91	93	99	78	82	91	72	75	83
$LSrClH_2O$	86	89	92	72	73	86	68	71	80
$LSrOAcH_2O$	85	90	96	73	77	84	65	69	79
Miconazole (standard)	52	59	89	59	72	85	68	77	88

Excellent activity (90-100% inhibition), Good activity (60-70% inhibition), Significant activity (30-50% inhibition), negligible activity (10-20% inhibition), na = no activity, Size of well: 6 mm (diameter), Complex 1 = $LBaClH_2O$, 2 = $LBaOAcH_2O$, 3 = $LCaClH_2O$, 4 = $LCaOAcH_2O$, 5 = $LSrClH_2O$, 6 = $LSrOAcH_2O$, Imipenem = Standard drug.

Synthesis of the Schiff base ligand

A round-bottom, 100 mL flask was charged with oxalyldihydrazide (0.295 g, 2.5 mmol, K_2CO_3 (1.2 g, 5 mmol), and water (6 mL). The resulted mixture was stirred for 10 min followed by addition of ethanol (98%, 30 mL) and heated to 60-70 °C for 0.5 h. The temperature was maintained, and 5-tert-Butyl-2-hydroxy-3-(3-phenylpent-3-yl) benzaldehyde (1.62 g, 5 mmol) was added. The mixture was refluxed for 3 h. The mixture was concentrated to 1/4 of its initial volume, dissolved in CH_2Cl_2 (50 mL), and washed with water. The organic phase was dried and concentrated to give a yellow solid which was dissolved in 15 mL of hot ethanol. The resulting solution was cooled to ambient temperature, and 3 mL of 50% aqueous ethanol was added to produce yellow precipitate that was collected with 81% yield: yellow crystals, (scheme – 1).

Synthesis of metal complexes

A solution of metal (Ba, Ca & Sr) compound in methanol was added to a hot solution (75°C) of Schiff base (L) in ethanol and the reaction mixture was refluxed for 2.5 – 5 hours. The solution was concentrated under vacuum. The precipitate was filtered off, washed with methanol and dried under vacuum over anhydrous compound ($BaCl_2$, $CaCl_2$, $SrCl_2$ or $MgSO_4$), (scheme – 2).

Antifungal activity

The free ligand, its metal complexes, fungicide Micronazole and the control DMSO (dimethylsulfoxide) were screened for their antifungal activity against various fungi *viz. Rizoctonia sp., Aspergillus sp., and penicillium sp.* These species were isolated for the infected organs of the host plants on potato dextrose agar (potato 250g+dextrose 20g+agar 20g) medium. The culture of the fungi was purified by single spore isolation technique. The solution of different concentrations 1, 1.5 and 2 mg/ml of each compound (free ligand, its metal complexes and fungicides Miconazole) in DMSO were prepared for testing against spore germination. A drop of the solution of each concentration was kept separately on glass slides. The conidia, fungal reproducing spores (approx. 200) lifted with the help of an inoculating needle, which was mixed in every drop of each compound separately. Each treatment was replicated thrice and a parallel DMSO solvent control set was also run concurrently on separate glass slide. All the slides were incubated in humid chambers at 25°C for 24 h. Each slide was observed under the microscope for spore germination and percent germination was finally calculated. The results were compared with a standard fungicide Micronazole at the same concentrations.

RESULTS AND DISCUSSION

The analytical data for the ligand and complexes together with some physical properties are summarized in table 1. The data from complexes correspond well with the general formula ML, where M = Ba, Ca & Sr; L = $C_{46}H_{58}N_4O_4$. The magnetic susceptibilities of the complexes at room temperature were consistent with octahedral geometry around the central metal ion.

Antifungal activity

For the experimental data table *2*, it has been observed that the ligand as well as its complexes shows a significant degree of antifungal activity against *Aspergillus sp*., *Rizoctonia sp.* and *Penicillium sp.* at 1, 1.5 and 2 mg/ml concentration. The effect is susceptible to the concentration of the compound used for inhibition. The activity is greatly enhanced at the higher concentration. DMSO control has showed a negligible activity as compare to the metal complexes and ligand. However, the metal complexes are show better activity than the ligand [30, 31,32]. The complexes are highly effective against *Aspergillus sp.* and show 91-99% activity at 2 mg/ml concentration. $C_{29}H_{33}N_5Ni_2O_{13}S$ is the only complex to show 100% activity against *Aspergillus sp.* the antifungal activity of the complexes varies in the following order of fungal species: *Aspergillus sp..* > *penicillium sp.* > *Rizoctonia sp*

The antifungal experimental results of the compounds were compared with the standard antifungal drugs Miconazole at the same concentration. All the metal complexes exhibited greater antifungal activity against *Aspergillus sp.* as compare to the standard drug Miconazole. However, they show slightly lesser activity against *Rizoctonia sp.* than standard drug Miconazole. The Sr and Ca complexes are more effective against *Penicillium sp.* than the standard drug.

CONCLUSION

In this report In this report, coordination chemistry of a Schiff base ligand, obtained from the reaction of oxayl-dihydrazide and 5-tert-Butyl-2-hydroxy-3-(3-phenylpent -3-yl) benzaldehyde is described. Ca, Sr and Ba complexes have been synthesized using the Schiff base ligand and characterized by spectral and analytical data. Based on these data, octahedral geometry has been assigned to the complexes. From the activity depends upon the type of metal ion and varies in the following order of the metal ion: Ca > Sr > Ba.

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