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Microwave-assisted synthesis and antibacterial and pesticidal activity studies of aluminum(III) and gallium(III) complexes with a bioactive Schiff base

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Abstract

Biologically potent complexes of aluminum(III) and gallium(III) derived from semicarbazone of 3-acetylcoumarin have been synthesized under microwave irradiation and investigated using a combination of microanalytical analysis, melting point, ultraviolet spectra, infrared spectra, ^{1}H nuclear magnetic resonance (NMR) spectra, and ^{13}C NMR spectra. Aluminum and gallium isopropoxides interact with the ligand, resulting in the formation of colored products. Based on conductance and spectral evidences, a five-coordinated structure for aluminum(III) and gallium(III) complexes has been assigned for 1:1 ratio and a six-coordinated structure for 1:2 and 1:3 ratios. The ligand is coordinated to the aluminum(III) and gallium(III) via the azomethine nitrogen atom and the enolic oxygen atom. The free ligand and its metal complexes have been tested *in vitro* against a number of pathogenic microorganisms in order to assess their antimicrobial and pesticidal properties. Both the ligand and its complexes were found to possess appreciable bactericidal and pesticidal properties.

Keywords: 3-acetylcoumarin; antibacterial and pesticidal activities; Schiff base; semicarbazone.

Introduction

Microwave dielectric effects are used increasingly in organometallic synthesis (Kidwai, 2001). In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry since the mid-1980s. Heating a chemical reactor by microwave radiation has the advantage that it is rapid and the entire volume of the reactor is heated simultaneously, which can lead to less by-product and/or decomposition products. In this system, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent used (Lindstrom et al., 2001). When we compare this unconventional energy source technology with classical heating, we find that conventional heating process usually starts at the wall of the reactor; because of this, the core takes a much longer time to achieve the target temperature. Rapid and homogeneous heating in an unconventional method has many benefits, such as reaction rate acceleration (Varma, 2001), milder reaction conditions, higher chemical yield (Mahajan et al., 2007); along with these, it is a cost-effective technique and less equipment is required. The shorter reaction time and expanded reaction range offered by microwave-assisted synthesis are suited to increase demand in industry.

Coordination complexes of metals are gaining importance in recent years particularly in the design of repository, slow-release or long-acting drugs in nutrition, and in the study of metabolism (Maurya et al., 2000a). Metal ions are known to accelerate the drug action (Sanchez-Delgado et al., 1993). Metal complexes of the Schiff bases have also been widely studied because of their unusual magnetic properties, novel structural features, and relevance to the biological systems (Maurya et al., 2000b).

Schiff bases and their structural analogs, as ligating compounds containing cyclic and cyclic imine C=N bonds, are of great importance in modern coordination chemistry (Garnovskii et al., 2009). Schiff bases are superior reagents in biological, pharmacological, clinical, and analytical applications (Raman et al., 2009). Schiff base metal complexes are broad-spectrum antimicrobial, antitumor (Gupta et al., 2002), antiviral (Ibrahim et al., 2004), and antifertility (Biyala and Singh, 2006) agents. Ever since the discovery of radiation protection by cysteine, several synthetic compounds have been examined for their protective action on biological systems (Ramakrishnan et al., 1992). The Schiff base complexes of main group elements containing ligands such as semicarbazones have remained a topic of considerable current research interest (Nagpal and Singh, 2005). This is mainly because of the biological applications of not only the ligands, but also the compounds derived from them. They can show tautomerism and can exist in keto/enol form. Usual coordination through oxygen and azomethine nitrogen is observed (West et al., 1999) in the formation of a five-membered chelate ring. Semicarbazones also have attracted special attention because of their biological activities. These compounds present a wide variety of biological activities such as antitumoral (Ackerman et al., 1999; Tarasconi et al., 2000), fungicidal (Bermejo et al., 1999; Teoh et al., 1999), and bactericidal (Abram et al., 1998), and a number of metal chelates inhibit tumor growth (Noblía et al., 2005).

Aluminum is the third abundant element in the earth inferior to oxygen and silicon, and it is widely used as building

materials, flocculant in water purification, food additives, and clinical drug (Wang et al., 2008). In Schiff base complexes of aluminum, the coordination environment at the metal center can be modified by attaching different substituents to the ligand, providing useful steric and electronic properties essential for the fine-tuning of structures and reactivity (Jain et al., 2006). Aluminum, a well-known and commonly exposed neurotoxin, was found to alter glutamate and *c*-aminobutyrate levels, as well as activities of the associated enzymes with regional specificity (Nayak and Chatterjee, 2003; Yang et al., 2007). Aluminum(III) also inhibits glutamate dehydrogenase – a central enzyme in glutamate metabolism (Zatta et al., 2000). Gallium plays an important role in pharmaceuticals and as an antitumor (Foster and Leyland-Jones, 1986), antiviral (Kratz et al., 1992), and anticoagulant agent, and as a probe for K+ in biological systems (Cox et al., 1988). The trivalent gallium cation is capable of inhibiting tumor growth, mainly because of its resemblance to ferric ion (Jakupec and Keppler, 2004). Gallium(III) complexes of an aminophenol ligand are active against chloroquine and *Plasmodium falciparum* strains (Ocheskey et al., 2003). Keeping all the facts into consideration, one semicarbazone of 3-acetylcoumarin and its aluminum(III) and gallium(III) complexes have been synthesized and screened for their biological activity during these investigations.

Results and discussion

The reactions of aluminum and gallium isopropoxides with monobasic bidentate ligand have been carried out in 1:1 (Equation 1), 1:2 (Equation 2), and 1:3 (Equation 3) molar ratios in dry benzene, followed by refluxing for 11–20 h, which resulted in the successive replacement of isopropoxy groups according to the following (Equations 1–3).

$$M(OPr^i)_3 + HO\overset{\frown}{N} \longrightarrow M(OPr^i)_2(O\overset{\frown}{N}) + Pr^iOH \quad (1)$$

$$M(OPr^i)_3 + 2HO\overset{\frown}{N} \longrightarrow M(OPr^i)(O\overset{\frown}{N})_2 + 2Pr^iOH \quad (2)$$

$$M(OPr^i)_3 + 3HO\overset{\frown}{N} \longrightarrow M(O\overset{\frown}{N})_3 + 3Pr^iOH \quad (3)$$

M represents either Al or Ga, and $O\overset{\frown}{N}$ is the donor set of the ligand molecule.

The resulting products are colored solids and soluble in DMF, DMSO, tetrahydrofuran, and methanol. The molecular weight determinations using Rast's camphor method revealed the monomeric and dimeric nature of the metal derivatives.

Spectroscopic studies

The ultraviolet spectra of the ligand L^1H exhibit three bands at 237, 272, and 332 nm. The bands at 235 and 275 nm are assignable to π-π* transitions of the azomethine group. The considerable hypsochromic shifting of the third band in the spectra of the complexes may be attributed to the coordination of the azomethine nitrogen to the metal atom.

IR spectra

The IR spectra of the free ligand and its complexes were scanned in the form of KBr pellets. The band due to υ(C=O) mode in the spectra of the ligand is observed at 1705 cm^{-1}. This band disappeared in the spectra of the metal compounds, suggesting the enolization of the ligand and its chelation through the amido oxygen. In the ligand L^1H, the most significant band at 1620 cm^{-1} assignable to (C=N) (Sharma et al., 2010) group shifts to the higher wave number in the complexes, suggesting the coordination of the azomethine nitrogen to the metal atom. There are no changes in the υ sym and υ asym modes of the NH_2 group appearing at approximately 3360 and 3480 cm^{-1}, respectively, indicating the non-involvement of this amino group in chelation. The complexes exhibit new bands in the regions 760–612 and 590–460 cm^{-1}, which may be attributed to the different vibrational modes of Al–O (Bohra et al., 2001) and Al←N (Atwood et al., 1996), respectively. The gallium complexes exhibit new bands in the regions 660–600 and 480–350 cm^{-1}, which may be attributed to the different vibrational modes of Ga–O and Ga←N (Shen et al., 1999), respectively.

^{1}H NMR spectra

The ^{1}H NMR spectra of the ligand and its complexes have been recorded in DMSO-d_6 using TMS as an internal standard. In the ligand, the signal at δ10.66 ppm is due to -NH, which disappears in the complexes and confirms the deprotonation and complexation. The NH_2 group gives a singlet at δ3.32–3.98 ppm in the ligand (L^1H) and its complexes. This shows that the NH_2 group is not taking part in the complexation. The free ligand and its complexes show multiplets in the region δ6.22–8.66 ppm which is attributable to aromatic protons.

The spectra of $\{Al(OPr^i)_2(L^1)\}_2$, $\{Al(OPr^i)_2(L^1)_2\}_2$, and $Al(L^1)_3$ display doublets which are attributed to gem-dimethyl protons of the bridging isopropoxy groups. One set of signals appeared as a doublet ($OCH(CH_3)_2$) and septet ($OCH(CH_3)_2$) at δ1.16–1.25 and δ4.42–4.38 ppm, respectively, in the spectra of 1:1 and 1:2 complexes, indicating the presence of one isopropoxy group. These signals are absent in the spectra of 1:3 complexes. Chemical shift values of all the complexes are listed in Table 1.

^{13}C NMR spectra

The ^{13}C NMR spectral data also support the authenticity of the proposed structures. The considerable shifts in the positions of carbon atoms adjacent to the azomethine nitrogen (δ167.15–174.36 ppm) and enolic oxygen (δ176.24–184.20 ppm) support the proposed coordination in the complexes. Thus, the shifts in the position of carbon atoms adjacent to the coordinating atoms clearly suggest the bonding of the azomethine nitrogen and amido oxygen to the aluminum and gallium atoms. The signals for ($OCH(CH_3)_2$) carbons of isopropoxy group in the spectra of 1:1 and 1:2 metal complexes have been observed in the regions δ73.16–74.25 and

Table 1 ^{1}H NMR spectral data (δ ppm) of $L^{1}H$ and its aluminum(III) and gallium(III) complexes.

Compound	-CH_3	-NH	-NH_2	Aromatic protons (multiplet)	Isopropoxy groups	
					Gem-dimethyl (doublet)	Methine (septet)
$L^{1}H$	2.08	8.60	3.32	6.22–8.38	–	–
$\{Al(OPr^{i})_2(L^{1})\}_2$	2.21	8.64	3.34	6.48–8.25	1.16 (bridging)	4.38 (bridging)
$\{Al(OPr^{i})(L^{1})_2\}_2$	2.45	8.72	3.55	6.60–8.29	1.18 (bridging)	4.42 (bridging)
$Al(L^{1})_3$	2.63	8.95	3.76	6.64–8.34	–	–
$\{Ga(OPr^{i})_2(L^{1})\}_2$	2.98	9.10	3.82	7.25–8.55	1.22 (bridging)	4.20 (bridging)
$\{Ga(OPr^{i})(L^{1})_2\}_2$	3.12	9.22	3.91	7.42–8.60	1.25 (bridging)	4.32 (bridging)
$Ga(L^{1})_3$	3.31	9.36	3.98	7.62–8.66	–	–

δ23.38–24.42 ppm, respectively, but are not observed in the spectra of 1:3 complexes. Chemical shift values of all the complexes are listed in Table 2.

^{27}Al NMR spectra

^{27}Al NMR spectra of these compounds have been recorded in $CDCl_3$ solution with reference to $Al(NO_3)_3$. The ^{27}Al NMR spectra of the metal complexes have a sharp signal at δ11.97–14.90 ppm assigned to five-coordinated aluminum (Vajpayee and Singh, 2008) complexes.

Conclusions

Based on the analytical data and spectral studies, it has been established that the ligand coordinated to the metal in a monobasic bidentate mode, giving five- and six-coordinated geometries around the metal. The complexes showed better antimicrobial and pesticidal activities than the parent ligand. The compounds also inhibit the growth of bacteria depending on the concentration. In the present case, we have used *E. coli* and *P. cepacicola*(-) for antibacterial activity. The results showed that the compounds are more active than the ligand, but less active than the standard drug.

Experimental

All the chemicals used in the synthesis of the complexes were of analytical reagent grade. All the solvents were dried and distilled before use. Aluminum and gallium isopropoxides were prepared according to literature methods (Belwal and Singh, 1999; Saini et al., 2009).

Synthesis of the ligand $L^{1}H$

The ligand $L^{1}H$ was prepared by the condensation of semicarbazide hydrochloride (1.190 g, 0.01066 mol) with 3-acetylcoumarin (2.00 g, 0.01062 mol) in the presence of sodium acetate in a minimum amount of dry alcohol, in a round bottom 100 ml flask, kept on water bath at 40–50°C. The resulting reaction mixture was stirred and refluxed for 5 h. The solution was then concentrated under reduced pressure, which on cooling gave a white precipitate. This was recrystallized twice in alcohol (Figure 1). The physicochemical properties and analytical data of the ligand are given in Table 3

Preparation of the complexes

To a weighted amount of aluminum(III)isopropoxide (0.5 g, 0.0024 mol) and gallium(III)isopropoxide (0.5 g, 0.0021 mol) and the calculated amount of the ligand $L^{1}H$ in 1:1, 1:2, or 1:3 molar ratios was added in dry benzene (60 ml). The contents were refluxed over a ratio head for 11–20 h in conventional method. The white precipitate of NaCl obtained was removed under suction. The excess of the solvent

Table 2 ^{13}C NMR spectral data (δ ppm) of $L^{1}H$ and its aluminum(III) and gallium(III) complexes.

Compound	Chemical shift values				
	>C=O	>C=N	Aromatic carbons	Isopropoxy groups	
$L^{1}H$	165.15	180.03	160.72, 138.92, 130.15, 129.83, 129.88, 125.42, 122.57, 120.51, 118.77	–	–
$\{Al(OPr^{i})_2(L^{1})\}_2$	168.10	181.22	160.54, 139.62, 131.15, 128.63, 129.28, 125.42, 122.57, 120.51, 118.77	73.16 (bridging)	23.38 (bridging)
$\{Al(OPr^{i})(L^{1})_2\}_2$	168.27	181.58	160.86, 138.99, 130.46, 129.79, 128.95, 123.58, 122.64, 120.68, 118.94	74.18 (bridging)	24.42 (bridging)
$Al(L^{1})_3$	169.02	181.62	160.72, 138.92, 130.15, 129.63, 129.58, 125.42, 121.56, 121.51, 119.77	–	–
$\{Ga(OPr^{i})_2(L^{1})\}_2$	169.22	182.12	160.48, 139.58, 130.24, 129.53, 129.88, 125.42, 120.57, 120.51, 118.76	74.16 (bridging)	24.20 (bridging)
$\{Ga(OPr^{i})(L^{1})_2\}_2$	169.58	182.36	160.54, 138.92, 130.15, 129.83, 129.88, 124.42, 122.57, 120.51, 118.57	74.25 (bridging)	24.32 (bridging)
$Ga(L^{1})_3$	169.82	182.64	160.72, 138.92, 130.15, 129.83, 129.88, 124.42, 122.57, 121.51, 118.77	–	–

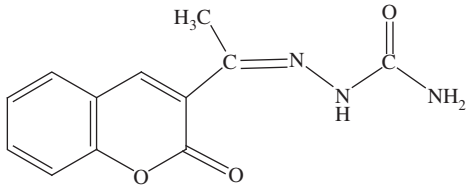

Figure 1 Structural formula of 3-acetylcoumarin semicarbazone.

was then removed and the compounds were dried under reduced pressure for 3–4 h. These were purified by repeated washing with *n*-hexane. All the compounds were isolated as powdered solids.

Eco-friendly method In microwave-assisted synthesis, the reaction mixtures were taken in a 50-ml conical flask, covered with glass wool, and then irradiated for 8–12 min inside the microwave oven. Anhydrous conditions were attained by using a beaker with silica gel or anhydrous $CaCl_2$ which was placed near the reaction vessel during the compound formation inside the microwave oven. The products were recovered from the microwave oven and were dried under reduced pressure. The resulting products were repeatedly washed with *n*-hexane and dried at 40–60°C/0.5 mm Hg for 3–4 h. The purity was further checked by thin layer chromatography (TLC) using silica gel-G.

Conventional method Aluminum(III) and gallium(III) complexes were also synthesized by the thermal method. The contents were boiled under reflux for 11–20 h on the fractionating column. In the thermal method, instead of 8–12 min, reactions were completed in 11–20 h, and the yield of the products was also less than that obtained in the microwave-assisted synthesis. A comparative study has also been done between microwave technique and conventional method and the results have been summarized in Table 3.

Physical measurements and analytical methods

The molecular weights were determined using Rast's camphor method. Infrared (IR) spectra of the ligand and its metal complexes were recorded with the help of a Nicolet Megna FT IR 550 spectrophotometer (USA) using KBr pellets. The purity of the ligand and its metal complexes was checked by TLC on silica gel-G using anhydrous dimethylsulfoxide and benzene (1:1) as solvent. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as standard on a JEOL AL 300 FT NMR spectrometer (Japan). Electronic spectra of the complexes were recorded in dimethylformamide (DMF) on a UV-160 A Shimadzu spectrophotometer (Kyoto, Japan) in the range of 200–600 nm. Nitrogen and sulfur were estimated using Kjeldahl's and Messenger's methods, respectively (Makode and Aswar, 2004).

Antibacterial activity

Various methods are available for the evaluation of the antibacterial activity of different types of compounds. In the present work, activities of synthesized compounds were evaluated by the 'paper-disc agar-plate method' using inhibition zone technique. The complexes were screened against *Escherichia coli* and *Pseudomonas cepacicola*(-) bacteria.

Inhibition zone technique The activity against bacteria was evaluated by 'paper-disc agar-plate method'. For this purpose, pure cultures of the organism were dissolved in peptone-water and then uniformly seeded on the nutrient agar plate having the following composition: peptone 5 g, beef extract 5 g, NaCl 5 g, agar-agar 20 g, and distilled water 1 l. The reference drug used was streptomycin. All the compounds were dissolved in methanol in different concentrations. Paper discs of Whatman No. 1, with a diameter of 5 mm were soaked in these solutions. These discs were placed on the medium previously seeded with organisms in Petri dishes at suitable distances. These discs were stored in an incubator at 35±2°C. The inhibition zone around each disc was measured (in millimeters) (Sharma et al., 2000) after 24–30 h and the activity index was calculated.

Activity index=(Inhibition zone of the compound)/(Inhibition zone of the standard).

The antibacterial activity of the ligand and its metal complexes has been screened against two bacteria, and the results are recorded in Table 4. The results clearly indicate that in the case of bacterial activity, the aluminum and gallium complexes exhibited sufficient potential in inhibiting the growth of pathogens. Thus, it can be postulated that further intensive studies of these complexes in this direction as well as in agriculture could lead to interesting results. Conventional bactericide streptomycin was taken as standard.

Pesticidal activity

Chrotogonous trachypterus (Blanchard) is the most common pest occurring throughout the year. Both nymphs and adults cause cell damage to plants in its seedling stage. Rearing of insects was maintained in the laboratory for bioassay. Insecticidal solutions in acetone were prepared from chemicals which were synthesized in the laboratory for bioassay studies, against nymphs and adults of *C. trachypterus*. A thin layer was prepared inside Petri dishes (10 cm in diameter) using 1 mol of solution in each part of the paired dish, after drying at

Table 3 Comparison between conventional and microwave method of synthesis, and physical properties and analytical data for L^1H and its metal complexes.

Compound	Color	Melting point (°C)	Analysis found/(calcd.) (%)		Molecular weight found/(calcd.)	Time		Yield (%)	
			Metal	Nitrogen		Thermal (h)	Microwave (min)	Thermal (h)	Microwave (min)
L^1H	White	214–216	–	17.04 (17.12)	242.74 (245.13)	5	7	72	80
$\{Ga(OPr^i)_2(L^1)\}_2$	Yellow	288–290	8.44 (8.48)	10.18 (10.22)	858.38 (861.87)	11	8	68	75
$\{Ga(OPr^i)(L^1)_2\}_2$	Yellow, solid	276–278	5.82 (5.85)	14.05 (14.09)	1233.79 (1235.90)	15	12	66	78
$Ga(L^1)_3$	Yellow	280–284	8.61 (8.68)	15.58 (15.69)	801.87 (802.40)	20	12	74	82
$\{Al(OPr^i)_2(L^1)\}_2$	Off-white	240–242	3.39 (3.46)	10.62 (10.70)	775.83 (778.76)	14	12	68	72
$\{Al(OPr^i)_2(L^1)_2\}_2$	Off-white	235–238	2.28 (2.34)	14.56 (14.62)	1144.98 (1148.72)	16	8	62	75
$Al(L^1)_3$	Off-white	246–248	3.49 (3.55)	16.52 (16.58)	752.84 (759.66)	20	8	64	72

Table 4 Antibacterial screening data of L^1H and its aluminum(III) and gallium(III) complexes.

Compound	*E. coli* (conc. in ppm)		*P. cepacicola*(-) (conc. in ppm)	
	500	1000	500	1000
L^1H	4	5	2	3
$\{Ga(OPr^i)_2(L^1)\}_2$	5	7	3	4
$\{Ga(OPr^i)(L^1)_2\}_2$	9	13	8	9
$Ga(L^1)_3$	12	16	10	12
$\{Al(OPr^i)_2(L^1)\}_2$	11	14	9	11
$\{Al(OPr^i)_2(L^1)_2\}_2$	6	9	5	7
$Al(L^1)_3$	7	10	6	10
$\{Ga(OPr^i)_2(L^1)\}_2$	9	12	7	9
Streptomycin	15	18	15	20

Table 5 Toxicity of ligand L^1H and its metal complexes against 20-day-old nymphs of *C. trachypterus* (Blanchard).

Doses in ppm	Mortality (%)		
	L^1H	$\{Al(L^3)\}$	$\{Ga(L^3)\}$
250	42.1	48.02	65.45
500	38.12	52.22	74.55
1000	62.5	80	86.2
LC_{50}	322.5	180	140
LC_{90}	1842	1134	880

Table 6 Toxicity of ligand L^1H and its metal complexes against adult females of *C. trachypterus* (Blanchard).

Doses in ppm	Mortality (%)		
	L^1H	$\{Al(L^3)\}$	$\{Ga(L^3)\}$
250	9.1	12.02	16.4
500	12.2	20.2	22.5
1000	42.5	71	84.2
LC_{50}	822.5	485	250
LC_{90}	1885	1176	990

Table 7 Toxicity of ligand L^1H and its metal complexes against adult males of *C. trachypterus* (Blanchard).

Doses in ppm	Mortality (%)		
	L^1H	$\{Al(L^3)\}$	$\{Ga(L^3)\}$
250	11.1	15.02	32.4
500	13.2	28.2	36.5
1000	32.5	58	62.2
LC_{50}	852.5	425	350
LC_{90}	1485	870	780

room temperature for 1 h to 15 days. Old nymphs of *C. trachypterus* were released in each Petri dish. Mortality counts were made after 24 h. Thus, 10 replications of each concentration including control were run simultaneously. For adults, topical method was used; 0.01 ml of various solutions was introduced to the intersegmental part of the insect using a microsyringe. These data were subjected to probit analysis (Finney, 1971) for calculation of LC_{50} values to determine the relative toxicity (Tables 5–7).

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