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Synthesis and *in vitro* Fungicidal Study of Organotin(IV) Complexes of Monomethyl Glutarate[1]

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Abstract—The synthesis and study of new coordination compounds of some organotin(IV) chlorides with monomethyl glutarate are reported. The ligand molecule appears to be bound to the tin atom through the carboxylic oxygen. The results obtained from ^{1}H, ^{13}C, and ^{119}Sn NMR, FT-IR and ^{119}Sn Mössbauer spectra show that the complexes are pentacoordinated with the trigonal bipyramidal structure. Biological screening of organotin(IV) derivatives shows promising activity, especially for the triphenyltin complex exhibiting higher antifungal activity. In addition, the rest of the compounds also prove to be active against various fungi used.

INTRODUCTION

The chemistry of organotin(IV) complexes has witnessed quantum leap during the past few decades. They have wide applications as catalysts, stabilizers, biocides, antifouling agents, and wood preservers [1–5]. Investigations have also been carried out to find their application as antitumour agents. It has been noted that, indeed, several di- and triorganotin(IV) species, particularly, organotin(IV) carboxylates, are found to be active against various types of cancer [5–7].

In the past few years, a number of biologically important organotin(IV) complexes have been prepared by our research group [8–12]. As a continuation of our interest in organotin(IV) carboxylates we are now reporting the synthesis, spectroscopic characterization, and *in vitro* fungicidal activity of a series of triorganotin(IV) complexes of monomethyl glutarate.

EXPERIMENTAL

All triorganotin(IV) compounds, except tribenzyltin chloride, were purchased from Fluka and used as received. Tribenzyltin chloride was synthesized by a described method [13]. All the reactions were carried out under anhydrous and oxygen-free nitrogen atmosphere. The solvents were dried before use according to the literature method [14]. The melting points were measured on a Reichert thermometer (F.G. Bode Co. Austria). IR spectra were obtained in KBr using a Perkin-Elmer FT IR-1605 spectrophotometer in a range of 400–4000 cm^{-1}. Elemental analyses were carried out on a Yanaco MT-3 high-speed CHN analyzer with an antipyrene as a reference compound. The amount of tin was determined using an inductively coupled plasma atomic emission spectrometry (ICP-AES) method on an ARL 3410 instrument. The ^{1}H, ^{13}C, and ^{119}Sn NMR spectra were recorded on a multinuclear FT NMR (200 MHz) JEOL instrument using TMS as an internal standard. Some of the ^{13}C spectra were measured on a Bruker AM 270 instrument at 50 MHz with a ^{13}C probe. Mössbauer spectra were recorded at 80 K on a Cryophysics instrument equipped with a 15 mCi Ca $^{119}SnO_3$ source.

Synthesis of Monomethyl Glutarate (HL)

Glutaric anhydride (50 mmol) was refluxed in excess dry methanol for 10 h under anhydrous conditions; excess solvent was removed under reduced pressure, resulting a yellow oil. The yield was 85%.

For $C_6H_{10}O_4Sn$ (M = 146)		
anal. calcd (%):	C 49.27,	H 6.80.
Found (%):	C 49.29,	H 6.82.

^{1}H NMR ($CDCl_3$, δ, pmm): 3.5 (s., H-1), 2.5 (t., H-3), 2.3 (q., H-4) 2.0 (t., H-5), 12.6 (s., H-6).

^{13}C NMR ($CDCl_3$, δ, pmm): 52.1 (C-1), 173.8 (C-2), 30.2 (C-3), 29.5 (C-4), 31.5 (C-5), 174.5 (C-6).

IR (KBr, cm^{-1}): 1720 – ν(C=O), 2065 – ν(OH).

Synthesis of Trimethyl, Tributyl, Triphenyl, and Tribenzyltin Complexes of Monomethyl Glutarate (I–IV)

The monomethyl glutarate (5 mmol) was dissolved in a minimum amount of methanol (25 ml). To this triethyl amine (5 mmol) was added, and the reaction mix-

[1] The text was submitted by the authors in English.

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ture was refluxed for 10–30 min, a hot methanolic solution of trimethyl-, tributyl-, triphenyl-, or tribenzyltin chloride (5 mmol) was added to the above reaction mixture, and this mixture was refluxed for 8–9 h under nitrogen. The reaction mixture was centrifuged and filtered to remove triethylaminechloride, and excess solvent was removed under reduced pressure. Liquid complexes were formed for trimethyl- and tributyltin chloride, while solid complexes were obtained for triphenyl- and tribenzyltin, which were recrystallized from a 1 : 2 (vol/vol) mixture of methanol and petroleum ether (b.p. 40–60°C).

I: The yield was 75%, colorless liquid; Λ, Ω^{-1} cm^2 mol^{-1} (10^{-3} M methanol): 2.1.

For $C_9H_{18}O_4Sn$ (M = 310)

anal. calcd (%):	C 34.82,	H 5.80,	Sn 38.69.
Found (%):	C 34.84	H 5.81,	Sn 38.71.

^{1}H NMR ($CDCl_3$, δ, pmm): 3.2 (s., H-1), 2.4 (t., H-3), 2.6 (q., H-4) 2.0 (t., H-5), 0.5 (s., H-α).

^{13}C NMR ($CDCl_3$, δ, pmm): 51.9 (C-1), 173.8 (C-2), 30.3 (C-3), 29.6 (C-4), 29.1 (C-5), 176.8 (C-6); –2.5 (C-α, $^1J(^{119}Sn–^{13}C)$ = 555 Hz).

IR (KBr, cm^{-1}): 1630s—ν_{as}(OCO); 1454br—ν_s(OCO); Δν = 176; 1722s—ν(C=O), 520br—ν(Sn–C), 566sh—ν(Sn–O).

^{119}Sn NMR ($CDCl_3$, δ, pmm): –240.

^{119}Sn Mössbauer ($CDCl_3$, mm/s): quadrupole splitting (**QS**): 3.78 ± 0.05; isomeric shift (**IS**): 1.28 ± 0.01; Γ_1: 1.10; Γ_2: 1.12.

II: The yield was 70%, colorless liquid; Λ, Ω^{-1} cm^2 mol^{-1} (10^{-3} M methanol): 2.3.

For $C_{18}H_{36}O_4Sn$ (M = 436)

anal. calcd (%):	C 49.52,	H 8.25,	Sn 27.50.
Found (%):	C 49.54,	H 8.26,	Sn 27.52.

^{1}H NMR ($CDCl_3$, δ, pmm): 3.3 (s., H-1), 2.5 (t., H-3), 2.5 (q., H-4) 1.9 (t., H-5), 0.5 (s., H-α), 1.32 (m., H-β and H-γ).

^{13}C NMR ($CDCl_3$, δ, pmm): 52.1 (C-1), 174.1 (C-2), 30.7 (C-3), 29.8 (C-4), 31.2 (C-5), 177.2 (C-6); 26.7 (C-α, $^1J(^{119}Sn–^{13}C)$ = 560 Hz), 25.3 (C-β, $^2J(^{119}Sn–^{13}C)$ = 18 Hz), 24.9 (C-γ, $^3J(^{119}Sn–^{13}C)$ = 59.5 Hz), 13.3 (C-δ).

IR (KBr, cm^{-1}): 1642s—ν_{as}(OCO); 1440br—ν_s(OCO); Δν = 194; 1730—ν(C=O), 547w—ν(Sn–C), 572sh—ν(Sn–O).

^{119}Sn NMR ($CDCl_3$, δ, pmm): –171.

^{119}Sn Mössbauer ($CDCl_3$, mm/s): QS: 3.90 ± 0.05; IS: 1.43 ± 0.01; Γ_1: 0.96; Γ_2: 0.98.

III. The yield was 78%, solid, m.p. = 107°C; Λ, Ω^{-1} cm^2 mol^{-1} (10^{-3} M methanol): 2.8.

For $C_{24}H_{24}O_4Sn$ (M = 496)

anal. calcd (%):	C 57.90,	H 4.82,	Sn 24.50.
Found (%):	C 58.06,	H 4.84,	Sn 24.19.

^{1}H NMR ($CDCl_3$, δ, pmm): 3.3 (s., H-1), 2.7 (t., H-3), 2.6 (q., H-4) 2.1 (t., H-5), 7.8 (m., H-α), 7.6 (m., H-β), 7.75 (m., H-γ), 7.80 (m., H-δ).

^{13}C NMR ($CDCl_3$, δ, pmm): 52.3 (C-1), 174.5 (C-2), 31.1 (C-3), 30.2 (C-4), 31.6 (C-5), 178.8 (C-6); 126.3 (C-α, $^1J(^{119}Sn–^{13}C)$ = 690 Hz), 130.7 (C-α, $^2J(^{119}Sn–^{13}C)$ = 22 Hz), 129.2 (C-α, $^3J(^{119}Sn–^{13}C)$ = 62 Hz), 128.5 (C-δ).

IR (KBr, cm^{-1}): 1638s—ν_{as}(OCO), 1454br—ν_s(OCO), Δν = 184, 1720s—ν(C=O), 540w—ν(Sn–C), 563sh—ν(Sn–O).

^{119}Sn NMR ($CDCl_3$, δ, pmm): –98.5.

^{119}Sn Mössbauer ($CDCl_3$, mm/s): QS: 3.15 ± 0.05; IS: 1.22 ± 0.01; Γ_1: 1.36; Γ_2: 1.41.

IV. The yield was 80%, solid, m.p. = 121°C; Λ, Ω^{-1} cm^2 mol^{-1} (10^{-3} M methanol): 2.5.

For $C_{27}H_{30}O_4Sn$ (M = 538)

anal. calcd (%):	C 60.20,	H 5.55,	Sn 22.27.
Found (%):	C 60.22,	H 5.57,	Sn 22.30.

^{1}H NMR ($CDCl_3$, δ, pmm): 3.5 (s., H-1), 2.5 (t., H-3), 2.4 (q., H-4) 2.0 (t., H-5), 2.1 (s., H-α), 7.75 (m., H-β), 7.70 (m., H-γ), 7.72 (m., H-δ), 7.80 (H-ω).

^{13}C NMR ($CDCl_3$, δ, pmm): 51.8 (C-1), 174.7 (C-2); 30.9 (C-3), 30.4 (C-4), 32.2 (C-5), 175.8 (C-6); 29.6 (C-α, $^1J(^{119}Sn–^{13}C)$ = 570 Hz), 134.3 (C-β, $^2J(^{119}Sn–^{13}C)$ = 20 Hz), 128.5 (C–γ, $^3J(^{119}Sn–^{13}C)$ = 57 Hz), 125.5 (C-δ), 123.5 (C-ω).

IR (KBr, cm^{-1}): 1632—ν_{as}(OCO), 1460—ν_s(OCO), Δν = 172, 1722s—ν(C=O), 522br—ν(Sn–C), 560sh—ν(Sn–O).

^{119}Sn NMR ($CDCl_3$, δ, pmm): –150.

^{119}Sn Mössbauer ($CDCl_3$, mm/s): QS: 3.89 ± 0.01; IS: 1.41 ± 0.01; Γ_1: 0.88; Γ_2: 0.86.

Biological Studies

Different concentrations (50, 100, 250, and 500 ppm) of the ligand and test compounds (I–IV) were used to study the effect of germination of *C. glocosporiodes, A. brassicicola, A. brassicae, C. capsici*, and *H. graminium* by the hanging drop method developed by Brian [15].

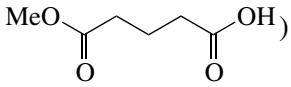
The germination of spores was observed under a microscope after 8 h of incubation. The percentage inhibition of spore germination was calculated as follows.

$$\text{Inhibition of spore germination (\%)} = \frac{\text{Total number of ungerminated spores}}{\text{Total number of spores}} \times 100.$$

RESULTS AND DISCUSSION

Compounds I–IV were prepared by adding trimethyl- (5 mmol), tributyl- (5 mmol), triphenyl- (5 mmol), and tribenzyltin chloride (5 mmol) to monomethyl glutarate (5 mmol) together with Et_3N according to equation:

$$R_3SnCl + HL + Et_3N \longrightarrow R_3SnL + Et_3N \cdot HCl, \quad (1)$$

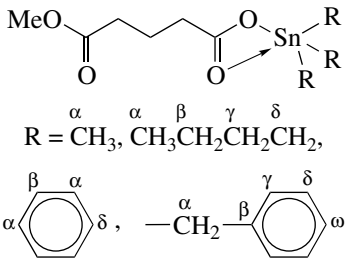
HL = monomethyl glutarate (proposed structure ); R = methyl, butyl, phenyl, and benzyl.

The mixture was refluxed for 8–9 h under nitrogen, which resulted in a good yield of complexes. The complexes of trimethyl- and tributyltin chlorides with monomethyl glutarate were colorless liquids, while those obtained with triphenyl- and tribenzyltin chlorides were colorless solids. The solid complexes were soluble in chloroform, acetone, DMF, and DMSO. The elemental analysis obtained for all the synthesized compounds is in good agreement with the proposed 1 : 1 stoichometry between the organotin moiety and monomethyl glutarate. Structural proposals are based on FT-IR, ^{1}H NMR, ^{13}C NMR, ^{119}Sn and Mössbauer studies.

Spectroscopy

The complexes of tin(IV) with the monomethyl glutarate (HL) are identified by the presence of Sn–O and Sn–C bands in ranges of 560–573 and 520–547 cm^{-1}, respectively [16–18]. Coordination of the complexes was based on the difference ($\Delta\nu$) between ν_s(COO) and ν_{as}(COO). According to [19], the values of $\Delta\nu = (\nu_{as} - \nu_s)$ can be divided into three groups. For $\Delta\nu$(COO) > 350, these compounds contain, with high probability, the monodentate carboxylate group. However, other very weak intra- and intermolecular interactions cannot be excluded. When $\Delta\nu$(COO) < 200, the carboxylate groups of these compounds can be considered to be practically bidentate. Compounds where 200 < $\Delta\nu$(COO) < 350 are considered as an intermediate state between monodentate and bidentate, which is called anisobidentate. On the basis of $\Delta\nu$(COO), the carboxylate group in the synthesized compounds is monodentate, because the $\Delta\nu$(COO) value obtained in all the complexes is greater than 350. The C=O stretching frequencies were also observed at 1720–1735cm^{-1}.

The ^{1}H NMR data of the synthesized compounds are completely resolved. All the protons in the spectra are in good agreement with the expected structure (A)



(A)

The spectra of the ligand contain a peak at 12.6 ppm for the hydroxylic proton. This peak is absent in the spectra of all the complexes, which suggests complexation through the carboxylic oxygen. The proton NMR data for methylic, butylic, phenylic, and benzylic protons are consistent with the earlier reported works [17–19]. All the protons in the spectra were identified, and total number of calculated protons is in good agreement with the proposed structure.

The characteristic resonance peaks in the ^{13}C NMR spectra of the complexes were recorded in $CDCl_3$. The carboxylic carbon in the ligand resonates at 174.5 ppm. This peak shifts to higher range (175.8–178.8 ppm) after complexation. This shift indicates complexation through the carboxylic oxygen [15]. Further the alkyl groups attached to the tin(IV) atom resonate at their

proper positions [15–19], which once again confirms complexation.

The ^{119}Sn chemical shifts of organotin(IV) compounds cover a range of 600 ppm. The data obtained depict the clear picture about the synthesized complexes. The resonance peaks obtained for the synthesized compounds are in a range of –210…–216.5 ppm, which is quite similar with the previously reported works [18–20]. These results are in agreement with the hypothesis that the increase in the coordination number of the tin atom in the complexes is due to tin nuclear shielding screening [21].

The ^{119}Sn Mössbauer method is a powerful tool for the determination of coordination of the synthesized compounds [22]. The results obtained show quadrupole splitting and the isomeric shift in the ranges 3.15–3.90 and 1.28–1.43 mm^{-1}, respectively, suggesting that all the synthesized compounds exhibit coordination number 5 with trigonal bipyramidal geometry (A). The results obtained are in full agreement with the hypothesis of the Sn–O interaction, leading to penta-coordinated complexes as reported for the analogous compounds [22].

Antifungal Activity

The results summarized in Tables 1–5 show that among the synthesized compounds, compound III (triphenyltin complex) was found to be the most efficient against all the species of test fungi at all concentrations used. The inhibition of spore germination was higher at 500 ppm. The complete inhibition was recorded even at 250 ppm in *C. gloeosporioides* and *A. brassicae*. The toxicity of organotin(IV) enhanced up to large extent may be due to the coordination of the tin(IV) atom with oxygen of the ligand. The presence of phenyl groups bonded with the tin(IV) atom is also considered responsible for the rise of toxicity, which may be get free in solution and play a key role to increase the toxic effect of the phenyl complex (III).

All the complexes show promising activity against plant pathogens. In general, the fungicidal activity of the alkyltin complexes were based on the R group attached to the tin atom. On the basis of the R group, the activity of the tin(IV) complexes decreases in the following order: phenyl > benzyl > butyl > methyl > ethyl. The overall results reveal that the triphenyl complex shows more fungicidal activity than others, which is due to the presence of the R group, because phenyl is more active than the other alkyl groups.

Table 1. Antifungal activity of monomethyl glutarate (HL)*

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	na	+	+	+
C. gloeosporioides	+	na	Na	na
A. brassicicola	+	+	+	+
A. brassicae	+	na	Na	na
H. graminium	+	+	Na	na

* (+)—low activity; na—no activity.

Table 2. Antifungal activity of compound I*

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	+	+	+	+
C. gloeosporioides	+	+	na	na
A. brassicicola	+	+	+	+
A. brassicae	++	+	+	na
H. graminium	+	+	na	na

* (+)—low activity; (++)—medium activity; (+++)—high activity; na—no activity.

Table 3. Antifungal activity of compound II*

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	++	+	Na	+
C. gloeosporioides	++	+	+	+
A. brassicicola	+	++	+	na
A. brassicae	+	+	+	+
H. graminium	++	++	+	na

* (+)—low activity; (++)—medium activity; (+++)—high activity; na—no activity.

Table 4. Antifungal activity of compound III*

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	+++	+++	++	+
C. gloeosporioides	+++	+++	+	na
A. brassicicola	++	++	+	+
A. brassicae	+++	+++	+	na
H. graminium	+++	++	+	+

* (+)—low activity; (++)—medium activity; (+++)—high activity; na—no activity.

Table 5. Antifungal activity of compound IV*

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	++	+	na	+
C. gloeosporioides	++	+	na	na
A. brassicicola	+	+	+	+
A. brassicae	++	+	+	na
H. graminium	++	+	na	na

* (+)—low activity; (++)—medium activity; (+++)—high activity; na—no activity.

The fungi toxic activity for other synthesized complexes is significant at maximum concentration.

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