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Investigation of Novel Bio-diorganotin (IV) Esters of N-maleoylglycine

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The synthesis and spectroscopic investigations like ^{1}H-, ^{13}C-NMR of novel organotin (IV) esters are described. The FT IR study is successfully applied to verify the bonding mode of endo and exo status of tin (IV) of the dimeric nature of organotin (IV) compound 2. *In vitro* ED_{50}, bactericidal, fungicidal, bioactivities are investigated, which indicate them significantly potential biocides. Based on spectroscopic analysis and literature evidences, the mono-and dimmer organotin (IV) esters are assigned tetrahedral and distorted octahedral cage type geometry.

Key words: Maleic anhydride, N-maleoylglycine, Dibutyltin (IV)-di-N-maleoylglycinato monomer, Tetra-butylbis (N-maleoylglycinato)distannoxane dimer

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INTRODUCTION

Organotin (IV) carboxylates exhibit significant bio activities and promising potential in many other fields of life such as fungicides, bactericides, anitifouling agents, PVC stabilizers, catalysts in the polymer chemistry, precursors for SnO_2 films on glass, wood preservatives, pesticides and anti-leishminiatic agents[1-5]. The structural chemistry of organotin (IV) complexes of amino acids and protected amino acids has also revealed variety of features and rich diversity of structural motifs. As a continuation of investigation in the field of organotin (IV) carboxylates, we here report the biological activities, syntheses and spectroscopic characterization of the title esters.

MATERIALS AND METHODS

Maleic anhydride, glycine, di-n-butyltin (IV) oxide, and triethylamine are AR Grade Fluka Chemicals used without further purification. The ligands were prepared according to the reported procedures[6]. The monomer compound 1 was prepared by dissolving 1 g (4.0 mmol) dibutyltin oxide to 8.0 mmol ligand in 150 cm^3 of toluene and 50 cm^3 ethanol. The mixture was refluxed for 6 h and the ternary azeotrope water/ethanol/toluene was distilled off with Dean-Stark funnel. Half of remaining solution was evaporated under vacuum. The oily compound obtained was crystallized from mixture (4:1) of chloroform and hexane. The synthesis of compound 2 occurs similarly but half the amount of the ligand is used, i.e. 4.0 mmol.

Physical measurements: The melting points were measured on a melting point apparatus Reichert Thermovar of F. G. Bode Co. (Table 1) Austria. FT IR spectra were obtained using KBr disc on a Perkin Elmer FT IR1600 Spectrophotometer. Elemental analyses were carried out on a Yanaco MT 3 high speed CHN analyzer with an antipyrene as a reference compound. The ^1H NMR spectra were recorded on a multinuclear FT NMR 200 MHz of JEOL and ^{13}C spectra were taken at 50 MHz using a ^{13}C probe. ED_{50} of the complexes was determined against a brine shrimp hatching method while bactericidal and fungicidal activities were measured by agar-well diffusion and agar-tube dilution methods[7].

RESULTS AND DISCUSSION

Syntheses: The 2-maleimidoacetic acid was synthesized as described in the literature[6]. The synthesis of di-n-butyltin (IV)di-N-maleoylglycinate, compound 1, Tetra-butylbis (N-maleoylglycinato) distannoxane, compound 2, is described in scheme 1.

$Bu_2SnO+2RCOOH \quad Bu_2Sn(OOCR)_2+2H_2O$

$4Bu_2SnO+4RCOOH \quad [\{Bu_2Sn(OOCR)\}_2O]_2+4H_2O$

Where $R=C_4H_2O_2NCH_2$

Scheme 1

Spectroscopic characterization: The OH absorption of ligand disappeared in the complexes. Both asymmetric and symmetric stretching of the maleimido (C_2O_2N), the carbonyl (CO), for Sn-C and Sn-O groups were exhibited as reported in literature[8]. The asymmetric and symmetric stretching of the CO group in monomer exhibit trend like a: $\nu_{asym\ (compound)} > \nu_{asym\ (ligand)}$, $\nu_{sym\ (compound)} < \nu_{sym\ (ligand)}$, $\Delta\nu_{(compound)} > \Delta\nu_{(ligand)}$. The monomer tin ester shows unidentate or weak bidentate bonding with Sn (IV) atom. The order of asymmetric and symmetric of CO group of compound 2 with respect to ligand is as: $\nu_{asym\ (compound)} < \nu_{asym\ (ligand)}$, $\nu_{sym\ (compound)} < \nu_{sym\ (ligand)}$, $\Delta\nu_{(compound)} > \Delta\nu_{(ligand)}$. In this case, two types of CO absorption bands were observed at 1685 to 1372 cm^{-1} for bonding behavior and 1714 to 1695 cm^{-1} for non-bonding behavior, which indicate two tin sites of compound 2 (Table 3). The butyl protons in mono and dimer were resolved on proper positions as reported[9]. The methyl protons of monomer exhibits a single triplet, which indicate one tin site, and two triplets of methyl protons in compound 2 are due to non-equivalent status of methyl protons bonded to endo and exo tin (IV) atoms (Table 4). The ^{13}C NMR signals are properly resolved (Table 5) showing one signal for each methylene carbon in butyl group monomer and a pair of signals in dimer tin ester around exo and endo cyclic Sn (IV), which are easily identified from their ^nJ (^{119}Sn-^{13}C) coupling constants for both the mono and dimer compounds with well known ranking $[^1J]>>[^3J]>[^2J]$[10]. The ^1H-, ^{13}C-NMR and FT IR data of compounds 1 and 2 are in agreement with the structures proposed in Fig. 1 and 2. The %CHN analysis (Table 2) verifies the mono and dimeric composition of compounds 1 and 2.

Biological activities: The compounds 2 and 3 showed the highest toxicity against brine shrimp larvae (Table 7) as well as exhibited strong bactericidal and fungicidal properties (Table 8). Among such compounds, the carboxylate derivatives are used as anti-cancer, anti-tumour agents, fungicides or bactericides *in vitro* as well as *in vivo*[11]. It is also reported in the literature[12] that the four coordinated motifs has stronger tendency to increase

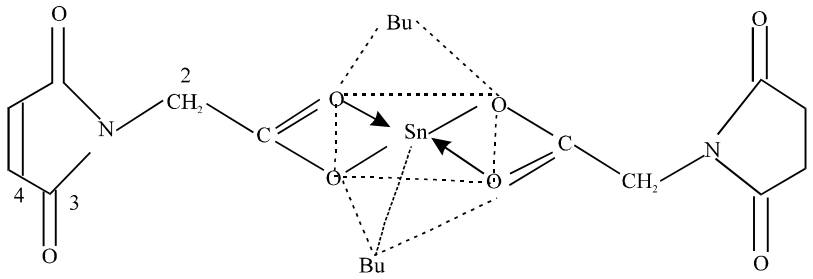

Fig. 1: Structure of compound 1 with ^{1}H-, ^{13}C-NMR and FT IR data

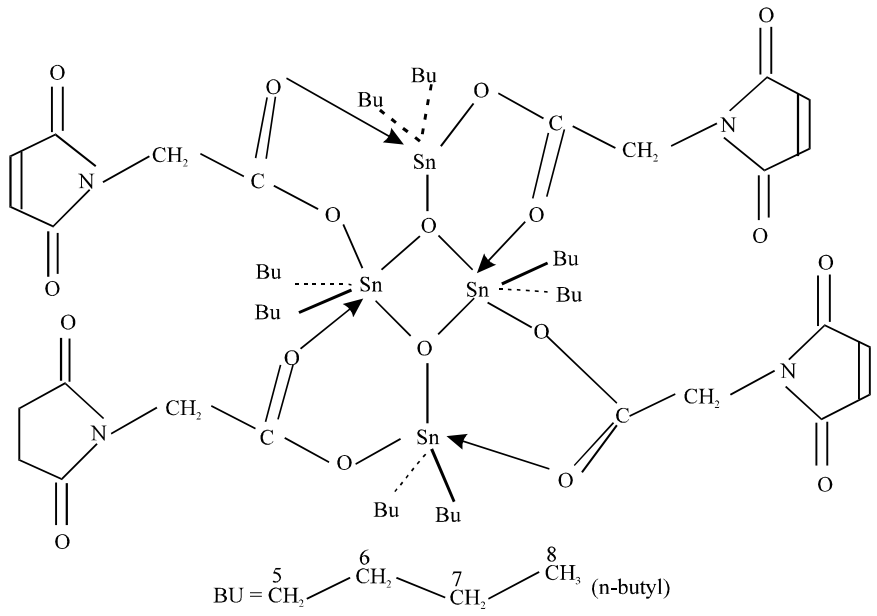

Fig. 2: Structure of compound 2 with ^{1}H-, ^{13}C-NMR and FT IR data

Table 1: Physical properties

Compound Mol. Formula	Physical state	Solubility	M.P (°C)	% Yield	Recrystallization solvent
1-$[C_2H_2(CO)_2NCH_2COO]_2SnBu_2$	Amorphous	$CHCl_3$ and H_3OH	>350	83	$CHCl_3$
2-$[\{C_2H_2(CO)_2NCH_2COOSnBu_2\}_2O]_2$	Crystalline	$CHCl_3$ and C_2H_5OH	158	93	$C_6H_6/CHCl_3$
3-$C_2H_2(CO)_2NCH_2COOH$	Crystalline	C_2H_5OH, H_3OH	114	91	$CHCl_3$

Table 2: CHN analyses

	Analyses*		
Compound	C (%)	H (%)	N (%)
1	44.31 (44.39)	4.81 (4.84)	5.13 (5.17)
2	42.53 (42.56)	5.06 (5.01)	0.36 (0.38)
3	46.39 (46.41)	3.21 (3.24)	9.00 (9.02)

* Calculated values are in parenthesis

Table 3: IR Data (cm^{-1})

	Maleimide (C_2O_2N)		Carbonyl (CO)				
Compound	(asym)	(sym)	(asym)	(sym)	Δν	Sn-C	Sn-O
1	1775sp	1721ssp	1720sp	1380sb	340	525	509
2	1774sp	1720ssp	1685sp	1372sb	313		
			1714ssp	1695sp	19	530	485
3	1781mb	1719sb	1710mb	1710ssp	18	--	--

Abbreviations for IR: asym: asymmetric; b: broad; s: small; sp: sharp; sym: symmetric; w: weak

Table 4: ^{1}HNMR of complexes

	Compound	
Proton	1	2
2	4.23s	4.3s
4	7.43s	7.38s
5	1.2m	1.4-1.3m
6	0.91m	1.6-1.5m
7	4.74m	1.2-1.1m
8	0.89t (6,8)	0.9t (7,9/8,9)

NMR data: All spectra were acquired from $CDCl_3$
Abbreviations for coupling patterns: s: singlet; t: triplet; b: broad resonance; m: complex pattern; nv: non visible

Table 5: ^{13}CNMR data

	Compound	
Carbon	1	2
1	177.5	176.2
2	41.2	40.9
3	168.2	167.2
4	129.0	129.07
5	28.1 (589)	29.8/28.6 (684, nv)
6	31.4 (39)	26.2/26.8 (44, 43)
7	26.8 (109)	27.3/26.1 (131, 129)
8	13.2	13.4/13.1

Coupling constants are given in Hz between parenthesis for ^{n}J (^{119}Sn-^{13}C)

Table 6: Brine shrimp bioassay

	% Deaths at doses				
Compound	1000 μg ml^{-1}	100 μg ml^{-1}	10 μg ml^{-1}	ED_{50} μg ml^{-1}	Results
1	100	90	70	3.370	++++
2	100	90	90	0.008	++++
3	60	20	10	616.770	+

Where ++++ = Significant and + = Moderate Activity

Table 7: Bactericidal bioassay

		Activity of compounds		
Name of bacteria	Clinical implication	1	2	3
(Human pathogens)				
Bacillus cereus	Food poisoning	+++	++++	++++
Cornyebacterium diphtheriae	Dipthera,infection of ear,nose,throat and skin. Toximia: Cardio-respiratory failure.	++++	+++	+++
Escherichia coli ETEC	Infections of wounds and urinary tract. Inflammation of Peritoneum and GIT, dysentry,septicemia, neonatal meningitis.	+	+++	+++
Klebsiella pneumoniae	Infections of respiratory and urinary tract. Supportive infections in sinuses and middle ear etc, septicemia.	++	++	++++
Proteus mirabilis	Infections of urinary tract and wounds, septicemia.	++	+++	++++
Pseudomous aeroginosa	Infections of wounds, urinary tract and eyes. Septicemia.	++	+	++
Salmonella typhi	Typhoid fever, salmonella food poisoning. Localized infection: pyelonephatis, endocarditis,salpingitis,chronic osteomyelitis.	+++	+++	++++
Shigella boydii	Inflammation of GIT, bacterial dysentery.	++	+++	++++
Staphylococcus aureus	Food poisoning,scalded skin syndrome, toxic shock syndrme. Infections of upper respiratory tract and wounds Abacesses, endocarditis.	+++	+++	++++
Streptococcus pyrogenes	Acute rheumatic fever, scarlet fever, sore throat, orysipelas,aeptic wounds, impetigo,inflammations of post glomerulonephrone (kidney),tonsils and middle ear pueperal sepsis, erythema nodosum.	+++	+	+++

a) ++++ = highest, +++ = high, ++ = optimum, + , = no activity. Incubation period: 8 h., 37°C,
Colony forming unit = $10^{4}$$10^{6}$ Size of well = 5 mm radius. Reference Drug: Amoxicillin (H_2O), Ampicillin (H_2O), Cephlaxin Na

Table 8: Fungicidal bioassay

Name of fungi	Clinical implication	Activities of compounds 1	2	3
Human Pathogens	Cutaneous Mycoses			
Epidermophyton Floccosum	Ring worm of groins, arms and torso.	++	++	++
Trichophyton Schoenleinii	Scaring of the scalp, permanent alopecia.	++	++++	++++
Pseudallescheria boydii	Subcutaneous Mycoses Infection of skin sbcutaneous tissue, nasalsinuses, mycetoma and brain abscess.	++++	+++	++++
Candida albicans	Opportunistic Mycoses Candidosis, infection of lungs,vagina, ear, bones, heart and thrush.	+++	+	+++
Aspergillus niger	Infection of lungs, eyes and CNS. Hypersensitivity and fungal ball.	++++	++	+
Animal Pathogens				
Microsporum canis	Cutaneous Mycoses Ringworm infection of hair and skin in dogs and cats.	+++	++++	++++
Trichophyton Mentagrophytes	Ringworm of feet, nails, fore arms and groins in rodents.	+++	++	++++
Trichophyton sirnii	Sever combined inflammatory and hypersensitivity reaction "kerion" in monkeys, rare (India).	++	+++	++
Plant Pathogens	Seed Borue Pathogens			
Fusariumum solani var. *Lycopersici* (tomato)	Root Rot, stemcankers associated with wounds, damping off seedling, destruction of spawn inbeds of cultivated mushrooms and pea crop.	+++	++++	++++
Macrophomina phaseolina	Seed Rot, Wilt, Root rot (Charcoal rot).	++++	++	+
Rhizoctonia solani	Root Rot (necrosis), wilt.	++	++++	++

[a] ++++ = highest, +++ = high, ++ = optimum, +, – = no activity. Incubation time = 7h., 27°C. Reference Drug : [b] Miconazole, Ketoconazole, [c] Amphotenicin-B, Flycytosine, [d] Benlate, Nabam

the coordination numbers through O, S, or N donor groups while the five coordinated species do not undergo further coordination, which play no long term role *in vivo* chemistry of organotin (IV) esters.

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