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Synthesis, Characterization and Antifungal Activity of Some Organotin (IV) Derivatives of Octanedioic Acid

Iornumbe, E. N.[1], Yiase, S. G. [2], Sha'Ato, R.[3],Tor-Anyiin, T. A. [4]

[1, 3, 4] Inorganic Chemistry Research Group, University of Agriculture, P.M.B. 2373, Makurdi, 970001- Nigeria

[2]Department of Chemistry, Benue State University, Makurdi- Nigeria

Abstract: ***Four organotin (IV) derivatives of octanedioic acid: potassium dibutyltin (IV) octanedioate, potassium tributyltin (IV) octanedioate, potassium diphenyltin (IV) octanedioate and potassium triphenyltin (IV) octanedioate were synthesized by reacting octanedioic acid with potassium hydroxide to give the potassium hydrogen salt followed by reaction between the salt and an organotin oxide/hydroxide to give the potassium organotin dicarboxylates. The compounds were characterized by tin content analysis, FTIR, ^{1}H NMR and ^{13}C NMR and tested for antifungal activity against four strains of Microsporum spp and two strains of Trichoephyton spp . Result showed that the compounds synthesized in general exhibited greater fungitoxicity than the Organotin oxides, organotin hydroxide, potassium hydrogen octanedioate and octanedioc acid. Organotin moieties are known to play a vital role in deciding the antifungal activity of an organotin compound, this is true in this work as the order of antifungal activity was potassium triphenyltin (IV) octanedioate > potassium tributyltin (IV) octanedioate > potassium dibutyltin (IV) octanedioate > potassium diphenyltin (IV) octanedioate.***

Keywords: Organotin derivatives, potassium hydrogen octanedioate, Spectroscopic techniques, Antifungal activity

1. Introduction

The chemistry of organotin (IV) compounds continues to be of interest due to their interesting structural features as well as their potential as biocides, homogenous catalysts, antifouling agents, e.t.c [1], [2]. They have found application in agriculture, industries and medicine [3]. The major structural issues in organotin (IV) chemistry are induced by the high coordination ability of tin, especially its ability to be involved in either weak or strong intra or intermolecular coordination due to availability of empty 5d - orbitals of suitable energy in tetravalent tin [4]. Both organotin (IV) carboxylates and dicarboxylates exhibit a wide variety of structural types as the effective nuclear charge on tin increases due to the introduction of electronegative substituents [5]. The coordination characteristics of tin and the structure differ drammatically in solution and in solid state when a nucleophilic group is present in the tin moiety or when an organic group is linked by a Sn─C bond and bears additional functionality with donor properties. This leads to a modification in Sn─C cleavage reactivity with respect to analogous organotin compounds where such functionalities are absent [6].

Organotin carboxylates are widely studied compounds due to their structural diversity and pharmaceutical applications [2] especially with reference to their antitumour [7] and antituberculosis [8] activities. Other applications of organotin carboxylates include their use in the synthesis of polyesters and polyurethanes [9]. Also, due to the tendency of the anionic groups to coordinate inter or intramolecularly, they exhibit a number of interesting structural features [10]. Farooq *et al*.[11] have stated that the wide range of biological applications of organotin (IV) compounds has encouraged scientists to design tin based drugs having good activity and low toxicity for cancer chemotherapy due to their apoprotic inducing character (process of programmed cell death that may occur in multinuclear organisms). Organotin (IV) compounds are known to bind to the phosphate group of DNA in tumor cells and damage them [12], [13]. This antitumor activity of the compounds thus retards the replication and synthesis of new DNA [13]. Based on the above, thus, in an attempt to further explore the interesting features of these organotin compounds, we report here the synthesis, characterization and antifungal properties of four organotin (IV) dicarboxylate compounds prepared from four parent organotin compounds and octanedioic acid as starting materials.

2. Materials and Methods

The organotins: dibutyltin (IV) oxide: $(C_4H_9)_2SnO$, tributyltin (IV) hydroxide: $(C_4H_9)_3SnOH$, diphenyltin (IV) oxide: $(C_6H_5)_2SnO$ and triphenyltin (IV) hydroxide: $(C_6H_5)_3SnOH$ and Solvents: methanol, propanol, DMSO were Sigma- Aldrich products of analytical grade with purity ranging from 98-99.8 %. They were used with out further purification.

2.1 Preparation of potassium hydrogen Salt: $HCOO(CH_2)_6COOK$ (L)

To potassium hydroxide (0.05 mol, 2.8338 g) completely dissolved in 50 mL distilled water in a 250 mL flat bottom flask containing a magnetic stirrer bar, octanedioic acid (0.0241 mol, 4.1920 g) was added and refluxed for 1 hour giving a clear solution. The solution was cooled in an ice-bath during which crystals of potassium hydrogen octanedioate separated out and were filtered using a

Buchner filtering unit and dried in a desiccator to a constant weight.

2.2 Synthesis of potassium dibutyltin (IV) octanedioate $Bu_2SnO[CO(CH_2)_6COOK]_2$ (1)

Dibutyltin (IV) oxide (0.0080 mol, 1.9506 g) was weighed and refluxed in a methanol-n-propanol mixture of ratio 4:1 in a 250 mL flask for five (5) hours using Dean and Stark apparatus to give a clear solution of the intermediate: dibutyltin (IV) dialkoxide. Water in the mixture distilled off as an azeotrope at 96-98 ^{0}C, after methanol, which first distilled over at 67 ^{0}C. The solution was allowed to cool after which 2.1063 g (0.008 mol) of potassium hydrogen octanedioate was added and refluxed for an hour. The resulting mixture was kept in an oven for a period of 72 hrs at 40 ^{0}C to obtain the product. A white crystalline product **(1)** was formed [14]- [16].

2.3 Synthesis of potassium tributyltin (IV) octanedioate:

$Bu_3SnOCO(CH_2)_6COOK$ (2)
Tributyltin (IV) hydroxide (0.0017 mol, 0.6059 g) and potassium hydrogen octanedioate (0.0017 mol, 0.3675 g) were suspended in methanol and the mixture was refluxed using Dean and Stark apparatus for five hours at 60 ^{0}C to 70 ^{0}C. The mixture an initially cloudy white dispersion, largely insoluble in the methanol became soluble with the evidence of a clear solution. The methanol was distilled off at 64.5 ^{0}C giving a white precipitate. This was transferred to an 80 mL beaker and kept in the oven at 40 ^{0}C for 72 hrs to remove the solvent remaining by evaporation. This gave a progressively sticky, glassy mass which finally, dried up to a white crystalline solid.

2.4 Synthesis of potassium diphenyltin (IV) octanedioate: $Ph_2SnO[CO(CH_2)_6COOK]_2$ (3)

Diphenyltin (IV) oxide (0.0014 mol, 0.4055g) was refluxed in a methanol-n-propanol mixture of ratio 4:1 in a 250 mL for five (5) hrs using Dean and Stark apparatus and (0.0014 mol, 0.5955 g) of potassium hydrogen octanedioate in methanol (2 mL) was added. The procedure followed is as reported in the synthesis of Potassium dibutyltin (IV) octanedioate [14]-[17].

2.5 Synthesis of potassium triphenyltin (IV)octanedioate: $Ph_3SnOCO(CH_2)_6COOK$ (4)

Triphenyltin (IV) hydroxide (0.0017 mol, 0.6059 g) and KHSu (0.0017 mol, 0.3675 g) were suspended in methanol and mixture refluxed using Dean and Stark apparatus while being stirred vigorously on a hot plate magnetic stirrer for 4 hrs. The product was obtained after methanol was distilled off at 64.5 ^{0}C giving a white precipitate which was kept in the oven at 40 ^{0}C for 72 hrs [14]-[17].

2.6 Physicochemical Measurements

Melting points were obtained with Fisher-Johns microscope hot stage melting point apparatus and were not corrected. Tin content analysis was carried out using Fansworth and Pekola method [18]. Infrared spectra from 4000 to 400 cm^{-1} were recorded on FTIR-8400S spectrophotometer (SHIMADZU), using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at room temperature using NMR Nujol 400 MHz spectrophotometer.

2.7 Antifungal Activity Test

Clinical isolates of the microbes were obtained from Institute for Agricultural Research (I.A.R) as well as Veterinary Medicine and Medicinal Microbiological Department, Ahmadu Bello University Teaching Hospital, Zaria. Agar well difussion technique and dilution method were used.

2.7.1 Agar Well Difussion Technique
Agar well difussion technique was adopted for determination of antifungal activity of the organotin compounds. Sabouraud dextrose agar (SDA) was used as culture medium and was prepared according to manufacturer's instructions, sterilized at 121 ^{0}C for 15 minutes, poured into sterile petri dishes under an aseptic hood and allowed to cool and solidify. The sterile medium was seeded with 0.1 mL of standard inoculums of the test fungi and spread evenly over the surface of the medium using a sterile swab. A well was cut at the centre of each inoculated medium using a standard cork borer of 6 mm diameter and 200 µg/mL of the test compounds dissoved in DMSO were introduced into their respective wells. Other wells supplemented with standard antifungal drugs; fulcin and fluconazole were used as controls. After allowing for diffusion, the media were incubated immediately at 30 ^{0}C for 7 days and checked daily for inhibition zone (area where the fungi were unable to grow), then it indicated the compounds tested showed antifungal activity. Where inhibition zones were not observed, the organotin used was inactive or concentration used may be less than required [17], [19].

2.7.2 Minimum Inhibition Concentration (MIC)- Broth Dilution Method
The MICs of test compounds were obtained using the broth dilution method. Sabouraud dextrose broth was prepared in a test tube, sterilized at 121 ^{0}C for 15 minutes and allowed to cool [19].Serial dilution of test organotin compounds in sterile broth was made to obtain the concentrations of 200 µg/mL, 100 µg/mL, 50 µg/mL, 25 µ/mL and 12.5 µg/mL. 1.5×10^5 CFU/mL of test fungi in normal saline was made and introduced into each of the concentrations and incubated at 30 ^{0}C for 7 days. The test tubes were observed for turbidity (growth) and the lowest concentration of a compound in the broth which showed no turbidity was recorded as minimum inhibition concentration.

In order to ascertain whether the test fungi were killed completely or their growth only inhibited, minimum fungicidal concentration (MFC) was determined. Content of MIC in the serial dilution was sub cultured onto the prepared medium and incubated at 30 ^{0}C for 7 days and plates were observed for colony growth. MFC was the plate with lowest concentration of compound without colony growth.

3. Results and Discussion

3.1 Synthesis

The synthesis of organotin (IV) dervatives of octanedioic acid (**1**, **2**, **3** and **4**) was successfully achieved from their oxides [$(C_4H_9)_2SnO$, $(C_6H_5)_2SnO$] and hydroxides [$(C_4H_9)_3SnOH$, $(C_6H_5)_3SnOH$], respectively. The reactions occurred in three steps as shown in equations 1-5. The ligand: $HOCO(CH_2)_6COOK$ was first prepared by the reaction between KOH and octanedioic acid: $HOCO(CH_2)_6COOH$ according to equation 1. $(C_4H_9)_2SnO$ and $(C_6H_5)_2SnO$ were refluxed separately in 4:1 CH_3OH and C_3H_7OH (Dean and Stark apparatus) yielding their respective propoxides as intermediates. These were futher reacted with the ligand **L** $HOCO(CH_2)_6COOK$ to produce compounds **1** and **3**. $(C_4H_9)_3SnOH$ and $(C_6H_5)_3SnOH$ were refluxed in CH_3OH which gave their dimethoxides as intermediates (equations 3 and 5, respectively) that were futher reacted with the ligand: $HOCO(CH_2)_6COOK$ to produce compounds **2** and **4**. Water produced in the process was collected in the separator of Dean and Stark apparatus, which was eventually removed by opening the tap and clossing it bact after its removal.

$KOH + HOCO(CH_2)_6COOH \rightarrow HOCO(CH_2)_6COOK + H_2O$ (1)

$R_2SnO \xrightarrow{CH_3OH;C_3H_7OH} R_2Sn(OC_3H_7)_{L} \cdot H_2O$ (2)

$R_3SnOH \xrightarrow{CH_3OH} R_3SnOCH_3 + H_2O$ (3)

$R_2Sn(OC_3H_7)_2 + 2HOCO(CH_2)_6COOK \rightarrow R_2Sn(OCO(CH_2)_6COOK)_2 + C_3H_7OH$ (4)

$R_3SnOCH_3 + HOCO(CH_2)_6COOK \rightarrow R_3SnOCO(CH_2)_6COOK + CH_3OH$ (5)

Where R = C_4H_9 and C_6H_5

The physicochemical data of compounds synthesized are shown in Table 1.

Table 1: Physicochemical Data of compounds synthesized

Compound no.	%Sn		Mpt.	%yield
1	23.03[a]	23.09[b]	88 – 90	94.44
2	23.30	23.70	354 – 356	97.49
3	21.05	21.17	111 – 112	98.00
4	26.82	26.91	118	95.99

a=found, b=theoritical

3.2 Infrared Spectroscopy

Important Infrared absorption bands of synthesized compounds are listed in Table 2.

Table 2: Important IR bands of the compounds synthesized

Compound no.	1	2	3	4	L
$V_{asym}(COO)$	1590	1556	1552	1526	1564
$V_{sym}(COO)$	1463	1422	1425	1424	1444
ΔV	127	133	127	103	118
Sn-O	416	525	425	455	-
Sn-O-C	919	928	928	929	-
Sn-Bu	685	683	-	-	-
Sn-Ph	-	-	1076	1077	-
C-H_{arom}	-	-	3048	3055	-
O-H	-	-	-	-	3424

L = $HOCO(CH_2)_6COOK$

The FTIR spectra of compounds (**1-4**) revealed absence of a strong vibrational frequency due to OH stretching at 3424 cm^{-1} which was present in the ligand and presence of bands in the range 525-416 cm^{-1} and 929-919 cm^{-1} indicated deprotonation of -COOH group and formation of new Sn-O and Sn-O-C bonds, respectively [20], [21]. Thus, appearance of new bands in the region 525 - 416 cm^{-1} for all compounds indicated the formation of new Sn-O bonds. The appearance of medium intensity bands in the range 1077-683 cm^{-1} due to Sn-C-O, Sn-Bu and Sn−Ph further confirmed formation of the compounds.The interesting stretching frequencies of compounds **1**–**4** were those associated with COO, Sn-O, Sn-O-C, Sn-Bu and Sn-Ph groups. The bands at 3424 cm^{-1}which appeared in the free ligand as the V(O-H) stretching vibrations was absent in compounds **1-4**, this indicated metal-ligand bond formation through these sites [22]. The absorption bands in the range 1590 -1526 cm^{-1} and 1463 - 1424 cm^{-1} were assigned to Vasym(COO) and Vsym(COO), respectively. The red shifts of the bands with respect to the free acid also served to confirm the formation of organotin carboxylates [23]. The coordination of carboxylate group was proposed based on the magnitude of separation of the difference ΔV, between Vasym(COO) and Vsym(COO) for the carboxyl group [24]. These values are useful for determining the mode of coordinate bonding between metal and carboxyl group. The value < 200 cm^{-1} indicates that the carboxylate moiety is bidentate, while ≥ 200 cm^{-1} indicates monodentate [20], [22]. The magnitude of ΔV of 133 – 103 cm^{-1} for complexes **1**- **4** indicated that the carboxylate ligands function as bidentate under the conditions employed while that of octanedioic acid with the value 258.5 cm^{-1} indicated its carboxylate group as monodentate. It is, therefore, proposed that the carboxylate group in these compounds was acting as a bidentate ligand. Therefore, we suggest a distorted octahedral geometry for diorganotin derivatives in solid state and trigonal bipyramidal structure for triorganotin compounds [20].

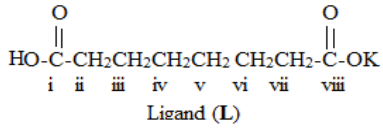
3.3 NMR Spectroscopy

The ^1H NMR data of synthesized compounds are presented in Table 3. In all compounds, signals of the protons were observed within the expected range. They showed the expected aliphatic and aromatic peaks with correct integration and multiplicities. In compounds **2** and **4** a complex pattern is observed in the range 7.43-7.89 ppm due to the aromatic protons of phenyl groups of organotin moiety.

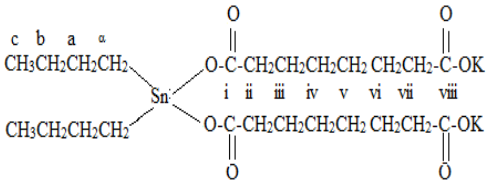
Table 3: ^1H NMR data of compounds (**1-4**) synthesized

	1	2	3	4
ii, vii	2.50	2.39	2.46	2.49
iii – vi	1.48	1.42	1.23	1.14
a	1.25	1.42	-	-
b	1.25m	1.42	-	-
c	0.81t(7.2)	1.39t	-	-
α	1.27m	1.69m(7.3)	7.79	7.89
β	-	-	7.74	7.70
γ	-	-	7.43s	7.69
δ	-	-	7.76	7.86

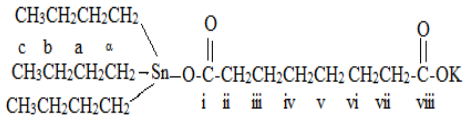
a. Chemical shift(δ) in ppm, J(^{1}H-^{1}H)
b. Multiplicity is given as s = singlet, t = triplet, m = multiplet
c. Fiqure 1 shows the numbers asigned to protons and carbons in the proposed structure of synthesized compounds for ease of reference.



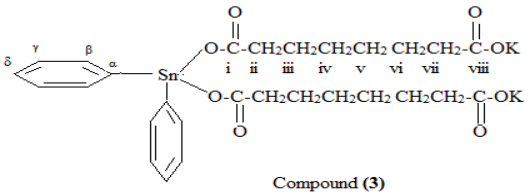
Ligand (**L**)



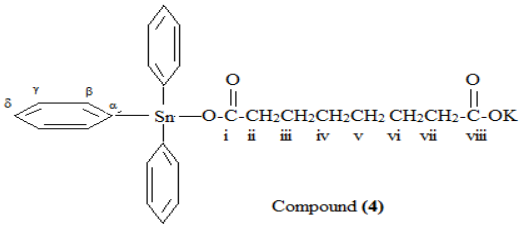
Compound (**1**)



Compound (**2**)



Compound (**3**)



Compound (**4**)

Figure 1: Numbering of protons and carbons in the Structure of synthesized compounds (**1-4**)

Butyl protons found in compounds **1** and **2** (asigned a and b in fig. 1) showed complex peaks due to -CH_2-CH_2-CH_2- in the range1.42-1.48 ppm and a clear triplet due to the terminal methyl group (c) around 0.81-1.39 ppm with (^{1}H-^{1}H) coupling of 7.2 Hz. In all the compounds, methylene protons (ii and vii) bonded to carboxyl group (i and viii) showed peaks in the range 2.39 - 2.50 ppm.

^{13}C NMR spectral data of compounds **1-4** are given in Table 4. All carbon atoms present in the ligand and its derivatives were assigned numbers and alphabets as shown in fiqure 1. The carboxyl carbons (i and viii) of all compounds were assigned signals in the range 175.03-181.43 ppm which are in agreement with literature [16].

Table 4: ^{13}C NMR data of compounds (**1-4**) synthesized

	1	**2**	**3**	**4**
ii, vii	34.20	35.43	33.33	40.67
iii – vi	29.65	28.32	28.80	28.87
i, viii	176.13	181.43	175.03	176.24
a	24.86	24.99	-	-
b	24.84	24.97	-	-
c	14.22	25.03	-	-
α	26.49	28.30	144.54	144.01
β	-	-	134.50	137.01
γ	-	-	128.46	128.31
δ	-	-	133.20	135.00

Signals for butyl carbons (a and b) appeared at 24.86-24.99 ppm while −CH_3 appeared at 14.22 ppm and 25.03 ppm, respectively for compounds **1** and **2**. The −CH_2 group (ii, vii) coordinated to carboxyl groups (i, viii) were assigned signals in the range 33.33-40.67 ppm for both butyl and phenyl organotin compounds. Phenyl carbons were assignned signals in the range 128.31-144.54 ppm with α(Sn-C) at 144.01 ppm and 144.54 ppm for compounds **3** and **4**, respectively. The α signals due to (Sn-C) bond in butyl for compounds **1** and **2** appeared at 26.49 ppm and 28.30 ppm, respectively. These signals are in agreement with earlier report [20].

3.4 Antifungal Activity

The synthesized di and triorganotin (IV) compounds (**1-4**) were tested for their antifungal activity by agar well diffusion/ dillusion method and zones of inhibition were obtained. The data are given in Table 5 and Figure 2. This revealed that all compounds showed high antifungal activity comparable to the standard drugs fulcin and fluconazole. However, there were few cases where the compounds did not show antifungal activity.

Table 5: Zone of Inhibition (mm) of compounds (**1-4**)

Fungus	**1**	**2**	**3**	**4**	A	B
M. gypseum	-	28	29	29	30	-
M. audounii	26	29	28	30	34	-
M. distortum	26	31	29	-	32	30
M. gallinae	-	-	-	31	-	-
T. mentagrophytes	30	-	28	-	32	-
T. equinum	32	26	28	28	-	32

Key: M= Microsporium, T = Tricheophyton, A = Fulcin, B = Fluconazole

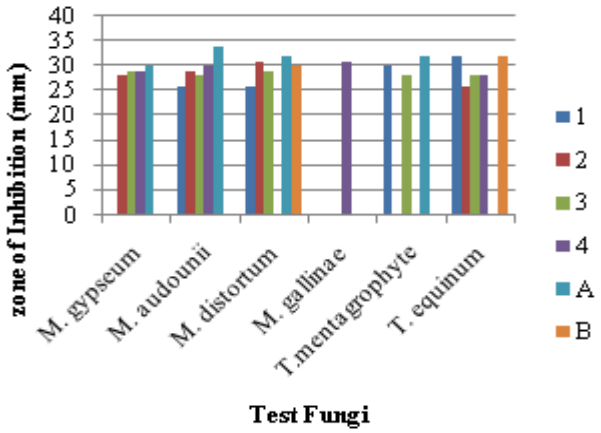


Figure 2: Zone of Inhibition of compounds against test fungi

It was noted that compounds **2**, **3** and **4** were very close in activity against *Microsporium gypseum* to the standard drug, fulcin where as, fluconazole showed no activity at the concentrations used. Only compound **3** showed activity against *Microsporium gallinae* even where the standard drugs failed. Compound **1** showed same activity with fluconazole against *Tricheophyton equinum*. Whilst **2** inhibited the fungus, *Microsporium distortum* slightly higher than fluconazole but slightly lower than fulcin. Overall, compounds **1** – **4** showed good antifungal activity at the concentration used. MIC of the compounds was obtained at the concentrations of 25 µg/mL while their MFC revaeled that all the fungi growths were not just inhibited but were completely killed.

Antifungal activity of carboxylic acids has been reported to be weak [16]. The free acid, $HOCO(CH_2)_6COOH$, used in this work exhibited weaker antifungal activity against test fungi than the ligand, (**L**) $HOCO(CH_2)_6COOK$ and synthesized compounds (**1-4**) as shown in Table 6.

Table 6: Zone of Inhibition (mm) of acid, Ligand and Parent organotin (IV) compounds used.

Fungus	**W**	**X**	**Y**	**Z**	A	L
M. gypseum	-	-	26	24	-	-
M. audounii	-	-	-	-	-	-
M. distortum	-	-	24	-	20	23
M. gallinae	-	-	-	27	-	-
T. mentagrophytes	-	-	25	-	-	-
T. equinum	25	24	-	26	21	22

Key: W= Bu_2SnO, X= Bu_3SnOH, Y= Ph_2SnO, Z= Ph_3SnOH A = $HOCO(CH_2)_6COOH$, L = $HOCO(CH_2)_6COOK$

The fact that the ligand and its derivatives could inhibit growth of test fungi more than octanedioic acid could be due to the presence of metal ions in their sructures which may have increased antifugal activity when the acid was coordinated K^+ and Sn^{4+}. This is in agreement with the known fact that many biologically active compounds become more active upon complexation than in their uncomplexed forms [16]. The findings that potassium organotin (IV) dicarboxylates (**1-4**) are more active than their parent organotin (IV) compounds: Bu_2SnO, Bu_3SnOH, Ph_2SnO, Ph_3SnOH, ligand and dicarboxylic acid was also observed for other studies where organotin (IV) chlorides and salicylic acid were used as parent organotin and ligand, respectively [12] and [16]. The biological activity of organotin compounds especially diorganotin (IV) compounds have been reported to depend solely on the organotin moiety; R_2Sn^{2+} and R_3Sn^+ (where R = Bu or Ph) [5]. The carboxylate groups influence the delivery of organotin (IV) moiety to the point of action. The higher activities of compounds **1- 4** therefore, appear to be a combined effect of the metal ions and carboxylate groups. Since diorganotin (IV) compounds are not known for their high biological activities, the activity of compounds **1** and **3** in this study could propably be due to the potassium and Sn ions present in their structures. However, potassium triphenyltin (IV) octanedioate exhibited antifungal activity more than its diphenyl counterpart while potassium tributyltin (IV) octanedioate exhibited higher activity than its dibutyl counterpart. The obsevation that the triorganotin (IV) compounds (**2** and **4**) are more active agrees with the notion that the number of carbon atoms in an organotin moiety affects its activity [25]. However, in this study, potassium dibutyltin (IV) octanedioate was found to be slightly more active than potassium diphenyltin (IV) octanedioate. This also agrees with the report by [26]. The order for the antifungal activity in this study was potassium triphenyltin (IV) octanedioate > potassium tributyltin (IV) octanedioate > potassium dibutyltin (IV) octanedioate > potassium diphenyltin (IV) octanedioate.

4. Acknowledgement

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Author Profile

Mrs. Esther Nguumbur Iornumbe holds a B.Sc (Hons) Chemistry and M.Sc. Analytical Chemistry from the Benue State University, Makurdi in 2000 and 2008 respectively. She is currently pursuing a course leading to the award of Ph.D in Inorganic Chemistry at the University of Agriculture, Makurdi.

Dr. Stephen Gbaoron Yiase received B.Sc (Hons) in Chemistry from Ahmadu Bello University Zaria – Nigeria, He later proceeded to the University of Sheffield, United Kingdom where he obtained a Diploma and Master of metallurgy, He returned to Ahmadu Bello University Zaria and obtained a Ph.D in Chemistry. He is currently a Senior Lecturer in the Department of Chemistry, Benue State University, Makurdi.

Rufus Sha'Ato is a Professor in the Department of Chemistry at the University of Agriculture, Makurdi, Benue State in Central Nigeria. He is the current Dean of the College of Science in the University. A Fellow of the Institute of Chartered Chemists of Nigeria (FICCON) and that of the

Chemical Society of Nigeria (FCSN) and Member of ANCAP, his research traverses environmental chemistry, analytical chemistry, waste and general environmental management and sustainability. In the main he has focused on processes that determine the fate and transport of chemical pollutants in soil-water systems. In particular, he has worked on ion-exchange and metal adsorption reactions in soil as well as pesticide behaviour (transformation, adsorption, transport, etc.) in soil-water systems. Trained at the Ahmadu Bello University Zaria, in North West Nigeria and the University of Ibadan in South Western Nigeria, Prof. Sha'Ato has also worked as a Research Associate in the Department of Chemistry at Queen's University, Ontario, Canada under the auspices of a CIDA-sponsored project to establish a Center for Agrochemical Technology (CAT) at his University; he collaborates at the Centre in the search for phyto-pesticides and other environmentally friendly agrochemical technologies. In pursuit of the latter, he is currently heading a team (of Faculty and postgraduate students) that is working on novel slow-release combination pesticide/fertilizer formulations (including the use of nano-materials), amongst other pesticide-related investigations.

Dr. Terrumun Amom Tor – Anyiin holds a B.Sc (Hons) Chemistry from the Bayero University Kano, M.Sc (Pharmaceutical Chemistry) at the Ahmadu Bello University Zaria and Ph.D in Organic Chemistry from the Nnamdi Azikiwe University, Awka. He is currently an Associate Professor in the Department of Chemistry and the Deputy Dean of Post graduate School, Federal University of Agriculture, Makurdi.