Larvicidal and structural studies of some triphenyl- and tricyclohexyltin *para*-substituted benzoates

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Abstract

Several new triphenyl- and tricyclohexyltin *para*-substituted benzoates were synthesized. Their structures were characterized by IR and Mössbauer spectroscopies. The structures were determined to be four-coordinated monomers. Larvicidal activities of the new compounds as well as other benzoates were evaluated against the 2nd larval instar of the *Anopheles stephensi* and *Aedes aegypti* mosquitoes. Results from the screening studies indicated that the triphenyltin benzoates were more toxic towards the *Ae. aegypti* larvae. A quantitative-structure activity relationship was also developed for the *An. stephensi* larvae.
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1. Introduction

The biological properties of organotin compounds are well documented. Their applications have ranged from being used as agrochemical miticides to wood preservative fungicides [1,2]. The first recognized entomological use of organotin compounds was as a mothproofing agent in 1928 [3]. It was not until later that the efficacy of organotin compounds against various species of mosquitoes was investigated [4,5]. Recently, in the interest of developing a more effective insecticide against the *Anopheles stephensi* (*An. stephensi*) and *Aedes aegypti* (*Ae. aegypti*) mosquitoes, several classes of organotins have been synthesized and screened against their larvae and the adult mosquitoes [6–12]. The classes of organotin compounds screened included dithiocarbamates [8], *tris*-(*para*-substituted phenyl)tins [9] and carboxylates [10–12]. The toxicity studies indicated that the organotins were effective against these two species of mosquito larvae.

In addition to their toxicity activities, the triorganotin carboxylates also present an interesting structural problem. Depending on the mode of attachment of the carboxylate group, the resultant triorganotin complex can either be four- or five-coordinated. A tetrahedral complex results when the carboxylate group acts as a monodentate ligand [13]. For a bridged carboxylate group, a pentacoordinated polymer usually results [13] while a chelated monomeric compound is formed when the carboxylate ligand acts as a non-bridging bidentate ligand [13]. Generally, triorganotin carboxylates with bulky R groups attached to the tin atom will favor tetrahedral monomeric structures, while sterically less demanding R groups would favor bridged polymeric structures [14]. Since triorganotin carboxylates have been shown to be effective insecticides against various mosquitoes, a series of triorganotin *para*-substituted benzoates were evaluated for their efficacy against the *Ae. aegypti* and *An. stephensi* larvae and is reported herein. In addition, the structural analysis of the previously unreported triorganotin carboxylates is included.

2. Experimental

2.1. Materials

All the organic solvents were reagent grade and used without further purification. In addition, all the chemicals for the syntheses were used as received.

2.2. Synthesis of the benzoates

The preparations of the triphenyl-or tricyclohexyltin *para*-substituted benzoates were synthesized according to conventional methods [13]. Typically, 5 mmol of the triorganotin hydroxide was dissolved in 50–100 mL of toluene in a 100 mL round-bottom flask fitted with a Dean–Stark trap. To this was added, with stirring, an equal molar amount of the appropriate *para*-substituted benzoic acid and the mixture was then refluxed for 2 h. Upon cooling, the solvent was removed using a rotor evaporator resulting in a crude oil. The oil was then dissolved in a small amount of hot toluene (5 mL) and hexane was added dropwise until the solution became cloudy. Upon refrigeration, a white solid formed. Recrystallization from a suitable solvent gave the product. Below are given the recrystallization details and physical measurements for the four new benzoates synthesized. The other benzoates used in this study were synthesized according to literature procedures [15–21].

2.2.1. Triphenyltin para-bromobenzoate

Recrystallization of the crude product from a mixture of chloroform and pet ether produced long clear needle-like crystals. M.p. 128–130 °C; yield 2.1 g (76%). [Anal. Calc. for $C_{25}H_{19}BrO_2Sn$: C, 54.59; H, 3.48; Sn, 21.58. Found: C, 54.72; H, 3.54; Sn, 21.91%]; ^{1}H NMR: δ 7.79–7.85 (m, 6H), 7.35–7.45 (m, 9H), 7.64 (dd, 2H, $J = 8.6$), 8.02 (dd, 2H, $J = 8.4$ Hz).

2.2.2. Tricyclohexyltin para-hydroxybenzoate

The crude product was recrystallized from cyclohexane to give fine crystals. M.p. 171–173 °C; yield 2.1 g (83%). [Anal. Calc. for $C_{25}H_{38}O_3Sn$: C, 59.43; H, 7.58; Sn, 23.49. Found: C, 59.86; H, 7.71; Sn, 23.42%.]; ^{1}H NMR: δ 1.25–1.95 (m, 33H), 7.60–7.70 (m, 2H), 8.02 (dd, 2H, $J = 8.5$ Hz).

2.2.3. Tricyclohexyltin para-bromobenzoate

Recrystallization of the crude product from ethanol yielded fine crystals. M.p. 58–60 °C; yield 1.7 g (60%). [Anal. Calc for $C_{25}H_{37}BrO_2Sn$: C, 52.85; H, 6.56; Sn, 20.89. Found: C, 53.05; H, 7.02; Sn, 21.02%.] ^{1}H NMR: δ 1.25–1.95 (m, 33H), 7.66 (dd, 2H, $J = 8.5$), 8.04 (dd, 2H, $J = 8.4$ Hz).

2.2.4. Tricyclohexyltin para-tert-butylbenzoate

The crude product was recrystallized in ether/pet ether to afford fine crystals. M.p. 125–126 °C; yield 1.97 g (72%). [Anal. Calc. for $C_{29}H_{46}O_2Sn$: C, 63.87; H, 8.50;

Sn, 21.76. Found: C, 64.05; H, 8.39; Sn, 22.01%]. ^{1}H NMR: δ 1.25–1.95 (m, 33H), 1.34 (s, 9H), 7.50 (dd, 2H, $J = 8.3$ Hz)), 8.05 (dd, 2H, $J = 8.5$ Hz).

2.3. Spectral studies

The IR spectra in the 4000–400 cm^{-1} region were recorded as KBr pellets on a Nicolet Magna-IR 760 spectrometer. The Mössbauer spectra of the solid compounds were measured at 80 K on a Ranger Mössbauer, Model MS-900, spectrometer in the acceleration mode with a moving-source geometry using a liquid nitrogen cryostat. The source was 5 m*Ci* Ca^{119m}SnO$_3$ and the velocity was calibrated at ambient temperatures using a composition of BaSnO$_3$ and tin foil (splitting 2.52 mm s^{-1}).

The ^{1}H NMR spectra were recorded at 300 K on a JEOL GSX270 spectrometer at 270.17 MHz. The samples were recorded in CDCl$_3$ using TMS as the internal standard.

2.4. Mosquito larvae

Ae. aegypti eggs were hatched in a tray of tap water and after 2–3 days the 2nd instar stage was attained. The larvae were maintained in an environmental chamber at 27–28 °C with a humidity of 60–90%. The *An. stephensi* larvae were kept in the same environment chamber under the same conditions. Both species of larvae were fed with ground dog food.

2.5. Preparation of the triorganotin stock solutions

Stock solutions of the triorganotin compounds were prepared by dissolving the triorganotin in either 95% ethanol, dimethyl sulfoxide (DMSO), or acetone depending on the solubility of the compound at concentrations between 200 to 760 parts per million (ppm). The dissolution of the triorganotins in the organic media was to facilitate the dispersion of the compounds in water. The acetone and DMSO were spectrograde quality while the 95% ethanol was reagent grade.

2.6. Toxicity assay

The toxicity studies were performed in 100×15 mm disposable Petri dishes using 10 larvae in the 2nd instar stage. The *An. stephensi* or *Ae. aegypti* larvae were transferred into the Petri dishes using a 100:l micro-pipetter. An additional 15 mL of water was then added. Aliquots of the triorganotin solution were then added to the Petri dish containing the larvae and deionized water to give the desired concentration of triorganotin. The total assay volume in each case was 20 mL. Both positive and negative controls were used in the assay. Each assay was done in triplicate. The larvae were exposed to the triorganotin compounds for 24 h, and the mortality rates for the mosquito larvae were determined by visual counting. Mosquito larvae that

showed a slight reflex to disturbance were considered alive. Probit analyses [22] were used to determine the LC_{50} (concentration at which the test compounds killed 50% of the tested organisms).

3. Results and discussion

3.1. Infrared spectra

The mode of coordination of the carboxylate group to metals including tin has been deduced using the differences between the asymmetric and symmetric stretching vibrations of the OCO group [23,24]. It has been reported that differences of greater than 250 cm^{-1} are indicative of carboxylate groups acting as unidentate ligands [23,24]. Using this criterion, the four new compounds synthesized [Nos. **4**, **15**, **18**, **22**] are assigned as four-coordinated monomers, since the differences are all greater than 250 cm^{-1} as shown in Table 1. This assignment would be in agreement with the other carboxylates in Table 1 whose structures have been previously reported.

3.2. Mössbauer spectra

Mössbauer spectroscopy is another common technique that is used to deduce structures of organotin compounds [25]. The two parameters that are obtainable from the Mössbauer spectra are the quadrupole splitting (Δ) and isomer shifts (δ). The coordination number of the tin atom has been related to the ρ value (ratio of Δ/δ) [25]. ρ Value less than 1.9 are indicative of tin compounds that are four-

coordinated while values larger than 2.1 have been assigned to tin complexes with greater than four-coordination [25]. Listed in Table 2 are the Mössbauer parameters for the carboxylate compounds. For the four new compounds, the ρ values ranged from 1.85 to 1.94. This clearly indicates that the complexes are four-coordinated. Quadrupole splitting values have also been used to distinguish between four- and five-coordinated triorganotin carboxylate structures [26,27]. It has been reported that monomeric triphenyl- and tricyclohexyltin carboxylates have Δ values in the range of 2.16–2.60 mm s^{-1} and 2.66–2.77 mm s^{-1}, respectively. On the other hand, five-coordinated derivatives have Δ values greater than 3.0 mm s^{-1} [24]. The data in Table 2 indicate that the newly prepared triphenyltin carboxylate has a Δ value of 2.33 mm s^{-1}, while the tricyclohexyl derivatives have values of 2.86–2.94 mm s^{-1}, supporting the previous structural assignments based on the infrared data. The tetrahedral assignment is also in agreement with other literature studies [18,24]. In addition, X-ray analyses for two of the new compounds (**6** and **18**) [26,27] further confirm this assignment.

3.3. Larvicidal studies

The individual toxicity in ppm and their standard deviations, as well as the average value for each series of compounds screened against the 2nd larval instar stage of the *An. stephensi* and *Ae. aegypti* mosquito are listed in Table 3. Based on the average values, the *An. stephensi* larvae were substantially more tolerant (3.61 ppm) to the triphenyltin compounds than the *Ae. aegypti* larvae (0.62 ppm).

Table 1
Asymmetric and symmetric stretching vibration of the OCO (cm^{-1}) group in the triorganotin *para*-substituted benzoates, $R_3SnOCOC_6H_4X$

X	R							
	Ph				Cy			
	No.	ν_{asym}oco	ν_{sym}oco	$\Delta\nu$	No.	ν_{asym}oco	ν_{sym}oco	$\Delta\nu$
H	**1**	1626	1342	284	**12**	1638	1337	301
		1622 [18]				1625 [15]	1345 [15]	
F	**2**	1629	1340	289	**13**	1630	1340	290
		1620 [16]				1641 [17]	1338 [17]	
Cl	**3**	1643	1331	312	**14**	1649	1331	318
		1640 [19]	1330 [19]			1650 [17]	1349 [17]	
Br	**4**[a]	1633	1331	302	**15**[a]	1643	1332	311
I	**5**	1630	1327	303	**16**	1640	1340	300
		1632 [19]	1330 [19]					
OCH$_3$	**6**	1605	1321	284	**17**	1609	1320	281
		1621 [20]	1335 [20]					
OH	**7**	1605	1321	284	**18**[a]	1600	1331	279
		1611 [20]	1345 [20]					
NO$_2$	**8**	1642	1336	306	**19**	1655	1321	321
		1640 [20]	1332 [20]			1649 [17]	1325 [17]	
NH$_2$	**9**	1600	1350	250	**20**	1601	1348	253
		1608 [20]	1342 [20]			1600 [15]	1345 [15]	
CH$_3$	**10**	1614	1344	270	**21**	1609	1341	268
		1620 [20]	1342 [20]			1631 [17]	1334 [17]	
(CH$_3$)$_3$C	**11**	1631	1329	302	**22**[a]	1621	1331	290
		1622 [19]	1340 [19]					

[a] New compound.

Table 2
Isomer shifts (δ) and quadrupole (Δ) spitting values in mm s^{-1} for the triorganotin *para*-substituted benzoates, $R_3SnOCOC_6H_4X$

X	R							
	Ph				Cy			
	No.	δ	Δ	ρ	No.	δ	Δ	ρ
H	**1**	1.16	2.40	2.07	**12**	1.49	2.75	1.85
		1.24 [18]	2.55 [18]					
F	**2**	1.24	2.39	1.93	**13**	1.49	2.83	1.90
		1.23 [16]	2.37 [16]					
Cl	**3**	1.23	2.28	1.85	**14**	1.50	2.85	1.90
		1.24 [18]	2.36 [18]					
Br	**4**[a]	1.25	2.33	1.86	**15**[a]	1.51	2.94	1.95
I	**5**	1.23	2.36	1.92	**16**	1.55	2.80	1.81
OCH$_3$	**6**	1.23	2.32	1.89	**17**	1.48	2.67	1.80
OH	**7**	1.25	2.36	1.89	**18**[a]	1.48	2.86	1.93
		1.31 [18]	2.55 [18]					
NO$_2$	**8**	1.27	2.49	1.96	**19**	1.59	2.74	1.72
		1.26 [16]	1.76 [16]					
NH$_2$	**9**	1.24	2.35	1.90	**20**	1.54	2.84	1.84
		1.01 [15]	2.46 [15]			1.53 [15]	2.70 [15]	
CH$_3$	**10**	1.24	2.36	1.90	**21**[a]	1.49	2.88	1.93
(CH$_3$)$_3$C	**11**	1.21	2.22	1.83	**22**	1.49	2.76	1.85

[a] New compound.

Table 3
Toxicity of the triorganotin *para*-substituted benzoates, $R_3SnOCOC_6H_4X$ against the 2nd instar stage of the *An. stephensi* and *Ae. aegypti* mosquito larvae in ppm

X	R					
	Ph			Cy		
	No.	*An. stephensi*	*Ae. aegypti*	No.	*An. stephensi*	*Ae. aegypti*
H	**1**	3.06 ± 0.06	0.83 ± 0.02	**12**	0.64 ± 0.03	0.87 ± 0.01
F	**2**	3.94 ± 0.18	0.89 ± 0.01	**13**	1.39 ± 0.12	1.38 ± 0.04
Cl	**3**	3.09 ± 0.04	0.30 ± 0.00	**14**	0.54 ± 0.01	0.91 ± 0.02
Br	**4**	3.11 ± 0.08	0.74 ± 0.01	**15**	2.79 ± 0.50	0.87 ± 0.03
I	**5**	4.73 ± 0.10	0.83 ± 0.01	**16**	1.26 ± 0.15	0.82 ± 0.07
OCH$_3$	**6**	3.69 ± 0.15	0.40 ± 0.17	**17**	0.19 ± 0.02	0.51 ± 0.04
OH	**7**	1.93 ± 0.03	0.67 ± 0.14	**18**	0.18 ± 0.01	1.39 ± 0.02
NO$_2$	**8**	4.62 ± 0.08	0.39 ± 0.01	**19**	1.16 ± 0.03	2.65 ± 0.33
NH$_2$	**9**	2.66 ± 0.02	0.37 ± 0.02	**20**	1.26 ± 0.15	1.59 ± 0.30
CH$_3$	**10**	4.87 ± 0.41	0.81 ± 0.01	**21**	0.35 ± 0.01	0.97 ± 0.02
(CH$_3$)$_3$C	**11**	3.98 ± 0.51	0.59 ± 0.10	**22**	0.42 ± 0.02	0.79 ± 0.03
Average		3.61	0.62		0.93	1.16

This is also substantiated by the individual results. However, this was not the case for the tricyclohexyl compounds except for two compounds. While the average value for the *Ae. aegypti* larvae (1.16) suggested that they were more tolerant to the tricyclohexyl compounds than the *An. stephensi* larvae (0.93), the *t*-test analysis did not support this conclusion. The *t*-test for this series of compounds indicated that there was not a significant difference in the averages between the *An. stephensi* and *Ae. aegypti* larvae at the 95% confidence level. These results suggest that the toxicity of the compounds towards the mosquito larvae is dependent on both the compound and the species of mosquito larvae. The observation that there is a difference in toxicity for a particular series of compound toward two different species of mosquitoes is

not new. For example, similar results have been reported for a series of triorganotin dithiocarbamates against these same two species of mosquitoes [8]. It has also been reported that the same compound, *tris*-(*p*-totyl)tin chloride, showed different toxicities towards different strains of the *Ae. aegypti* larvae [6].

Further examination of Table 3 reveals that there is no correlation between the toxicities of the compounds and a descriptor of the substituent on the phenyl ring. This would indicate that the toxicity of the compounds is not predominantly due to this group. This is not surprising since the substituent is far removed from the tin moiety and its effects should have minimal effects. Similar conclusions were reported for the toxicity of a series of triorganotin dithiocarbamates against the *An. stephensi* larvae [8] as

well as for the inhibition of *Ceratocystis ulmi* by a series of triphenyltin adducts of *N*-alkylsaicylideneimines [28].

A common method used for relating toxicological activities to structures of molecules is quantitative structure–activity relationship (QSAR). QSAR is a regression equation that relates some measurable biological activity to a physicochemical or biochemical property or properties related to the molecule. It was possible to develop a QSAR for the *An. stephensi* using the QSARIS program [29] for this series of triorganotins. The QSAR was generated using the formula weights (fw) and the valence 3rd path χ index (xvp3) of the molecules as defined by the QSARIS program. The equation generated was $LC_{50} = 0.0120fw - 0.308xvp3 + 2.52$ with a multiple R^2 of 0.78 and a cross-validation of 15.8. The training set is very well described by the regression equation, which is statistically very significant. Cross-validation of the training set shows that the constructed model can be used to predict the value of LC_{50}. However, it was not possible to generate a QSAR for the *Ae. aegypti* larvae. This would suggest that the mechanism of kill is different for the two species of mosquitoes. A similar finding was observed for a series of triorganotin dithiocarbamates [8].

In view of the results from this study, triorganotin benzoates as a class can be considered a potential larvicidal candidate against *An. stephensi* and *Ae. aegypti* larvae. Although their toxic results are higher than other insecticides, such as the deltamethrin [30] their main advantage lies in the fact that triorganotin compounds are biodegradable in the environment. Triorganotins have been reported to biodegrade into non-toxic inorganic tin compounds [31]. An example of organotin degradation has been reported for a harbor in Corsica by Michel and Averty [32]. In addition there are no reported resistances of these two species of mosquitoes towards triorganotins.

Acknowledgement

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