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Fungicidal and Spectral Studies of Some Triphenyltin Compounds

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In the interest of developing a more effective fungicide to combat Dutch elm disease, our laboratories have synthesized several triphenyltin carboxylates and some 1:1 addition compounds of triphenyltin chloride using 2,3-disubstituted thiazolidin-4-ones as the ligand and screened them *in vitro* against *Ceratocystis ulmi*, the causative agent of Dutch elm disease, using a shake culture method. Elemental analyses and spectroscopic data indicate that the structures of the carboxylates in the solid state are monomeric with a tetrahedral tin atom with the exception of the furan-2-carboxylic acid derivative, which was found to be polymeric. The triphenyltin chloride adducts are trigonal-bipyramidal with the three phenyl groups in the equatorial plane. Far-infrared data indicate that the three phenyl groups are not co-planar. Screening results for both series of organotins indicate that these two classes of compounds are effective inhibitors of *Ceratocystis ulmi*, with the adducts having a higher activity. The furan-2-carboxylic acid derivative has a markedly decreased activity compared with the other carboxylates and this is attributed to its polymeric structure. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

Dutch elm disease (DED) continues to devastate the diminishing population of American elm trees in the United States today. The pathogenic fungus, responsible for the disease *Ceratocystis ulmi (C. ulmi)* causes a blockage in the vascular tissue that can lead to the eventual death of the elm. The development of a more effective fungicide to combat DED would reduce the loss of these graceful trees and preserve the aesthetics of the environment. It has been well established that organotin compounds possess various biocidal properties depending on the number and specific organic groups attached to the tin atom. A class of organotins that has been found to have a broad range of fungicidal properties are the triphenyltins.[1–3] Previous *in vitro*[4–8] results have indicated that the triphenyltin moiety is highly effective in the inhibition of *Ceratocystis ulmi*. In our continuing efforts to develop more effective fungicides in the inhibition of *C. ulmi*, our laboratory has synthesized a series of triphenyltin carboxylates and several triphenyltin chloride adducts with 2,3-disubstituted thiazolidin-4-ones and screened them against the fungus *in vitro* using a shake culture method. The results of the screening studies and the structures based on the spectroscopic data of these compounds are reported herein.

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EXPERIMENTAL

Synthesis of the compounds

All starting materials were obtained commercially and used without further purification. The organotin carboxylates and adducts were synthesized by previously published methods. The triphenyltin carboxylates were either prepared by the reaction of triphenyltin hydroxide with an equimolar amount of the corresponding acid in benzene[9] or by reacting triphenyltin chloride with the sodium salt of the corresponding acid in methylene chloride.[10] The triphenyltin chloride adducts were synthesized by reacting the triphenyltin chloride and the appropriate ligand in a 1:1 molar ratio in acetone.[11]

Preparation of stock organotin solutions and fungicidal activity

The activity of the organotin compounds was tested by incorporating the appropriate amounts of organotin compound into 100 cm^3 of potato dextrose broth (PDB). The amount of organotin compound added represented a range of concentrations to be studied. Stock solutions of organotins were made up in methanol or acetone (1000 mg dm^{-3}). The appropriate solvent, methanol or acetone, was added to the control and test flasks so that the total volume (methanol or acetone and organotin solution) was 400 μl. A stock suspension (1.0 cm^3) of cells of *C. ulmi* (concentration = 10^6 cells cm^{-3}), strain 32437, obtained from the American Type Culture Collection, Rockville, MD 20852, USA, was added to the amended PDB, and the resulting suspension was then shaken in an incubator–shaker (7 d; 22 °C) in total darkness. The contents of the flasks were filtered and rinsed throroughly with distilled water. The fungal growth was then dried and weighed. Three replicates were used for each concentration tested.

The IC_{50} values were obtained by plotting the percentage growth of the fungus versus the concentration of organotin compound (parts per million) added. The concentration at which 50% of the fungus was inhibited was taken as the IC_{50} value.

Mössbauer spectroscopy

The Mössbauer spectra were measured at 80 K on a Mössbauer spectrometer model MS-900 (Ranger Scientific Corp., Burelson, TX 70682, USA) in the acceleration mode with a moving-source geometry using a liquid-nitrogen cryostat (CYRO Industries of America Inc., Salem, NH 03811, USA). The samples were mounted in Telfon holders. The source was 15 mCi $Ca^{119m}SnO_3$, and the velocity was calibrated at ambient temperatures using a composition of $BaSnO_3$ and tinfoil (splitting 2.52 mm s^{-1}). The resultant spectra were analyzed by least-squares fit to Lorentzian-shaped lines.

Far-infrared spectroscopy

The far-IR spectra were recorded under a nitrogen atmosphere on a Nicolet 20F far-IR vacuum spectrometer (Nicolet Instrument Corp., Madison, WI 53711, USA). Samples were prepared as Nujol mulls and recorded on polyethylene sheets.

RESULTS AND DISCUSSION

All the triphenyltin carboxylates were identified by their elemental analyses and their spectroscopic data. The spectroscopic data were compared with literature values, when available.[9, 10]

The Mössbauer parameters, i.e. isomer shifts (IS) and quadrupole splitting (QS), and the Sn–Ph stretching frequencies along with the *in vitro* screening studies for the triphenyltin carboxylates are given in Table 1. The quadrupole splitting parameter is frequently used to deduce the coordination of the tin atom in organotin compounds.[1, 2, 12, 13] The observed QS values for all the triphenyltin carboxylates are in the range 2.14–2.52 mm s^{-1}, with the exception of the furan-2-carboxylic derivative (3.11 mm s^{-1}). The range of the QS values observed for compounds **2–8** indicate that these compounds are monomeric with tetrahedrally coordinated tin atoms. This is in agreement with earlier results.[9, 10, 14] Triphenyltin carboxylates with a polymeric structure in which the tin atom is five-coordinated have higher QS and IS values[10, 13] than those found for compounds **2–8**. As evident in Table 1, the QS and IS values for compound **1** are the highest of all the carboxylates studied. Using these criteria, compound **1** is assigned a polymeric structure with a trigonal bipyramidal configuration which is in agreement with the

Table 1. Spectroscopic parameters and inhibitory concentrations for the triphenyltin carboxylates $Ph_3SnOCOR$ (**1–8**)

		Mössbauer parameters		$Sn–C_6H_5$ stretching vibrations (cm^{-1})		Inhibitory concentrations
Compd	R	IS (mm s^{-1})	QS (mm s^{-1})	Asym.	Sym.	log IC_{50} (mmol dm^{-3})
1	2-C_4H_3O	1.28 ± 0.01	3.11 ± 0.02	287.9 265[a]	241.8 250[a]	− 2.19
2	2-C_4H_3S	1.22 ± 0.01 1.33 ± 0.03[a]	2.29 ± 0.02 254 ± 0.06[a]	280.2 265[a]	228.6 245[a]	− 2.50
3	4-$CH_3OC_6H_4$	1.13 ± 0.01	2.14 ± 0.02	279.1 278[b]	227.1 225[b]	− 2.66
4	3-$CH_3COOC_6H_4$	1.20 ± 0.01	2.16 ± 0.06	282.5	228.6	− 2.42
5	C_6H_5	1.21 ± 0.01	2.24 ± 0.03	276.4	234.6	− 2.59
6	4-$CH_3C_6H_4$	1.23 ± 0.01	2.34 ± 0.02	271.8 267[b]	218.3 228[b]	− 2.78
7	4-$NH_2C_6H_4$	1.04 ± 0.01	2.27 ± 0.02	268.0 267[267]	231.4 226[b]	− 3.08
8	4-$NO_2C_6H_4$	1.25 ± 0.01	2.52 ± 0.02	272.5 270[b]	237.7 235[b]	− 2.63
						− 2.60 (average)

[a] From Ref. 10. [b] From Ref. 9.

findings of Sandhu and Verma.[10]

The infrared data give further support in the assignment of the structures. As evident from Table 1, both the Sn–Ph asymmetric (268–280 cm^{-1}) and the Sn–Ph symmetric (218–242 cm^{-1}) stretching vibrations were observed for all the carboxylates. This indicates that the three phenyl groups are not co-planar, which would be consistent with a tedrahedal structure for compounds **2–8**. Although compound **1** has a pentacoordinated polymeric structure, the observation of both Sn–Ph stretching frequencies indicates that the Ph_3Sn moiety is non-planar.

The *C. ulmi* inhibitory data listed in Table 1 for the carboxylate compounds indicate that this class of compounds are effective inhibitors of the fungus, since the observed log IC_{50} values are equal or are lower than those observed for Ph_3SnOH (-2.26 mmol dm^{-3})[4] or Ph_3SnCl (-2.28 mmol dm^{-3}),[4] both of which are known commercial fungicides. The higher result for the furan-2-carboxylic acid derivative indicates that it is the weakest inhibitor and this can be attributed to the polymeric nature of the compound.

Previously, a quantitative structure–activity relationship (QSAR) was observed between the biotoxicity of a series of triaryltin chloride derivatives and the substituent parameter σ.[4] The Hammett correlation, obtained by plotting log $1/C(C = IC_{50})$ against the σ constant for the substituent present on the aryl ring of the triaryltin chloride derivatives, was parabolic (convex). It was proposed that the shape of the curve was suggestive of a change in the rate-determining step[15] of the mechanism of biotoxicity, from the formation of the triphenyltin cation to its reaction with the cell wall. These results confirmed the proposal that the triphenyltin cation was the causative agent of the biotoxicity.[16]

The triphenyltin carboxylates **3–8** prepared in this study were used to investigate the mechanism of biotoxicity as a function of the leaving group present on the tin atom. Compounds **3–8** should all give the same triphenyltin cation in solution and therefore any change in the biotoxicity should be a function of how readily the triphenyltin cation is formed, i.e. the leaving ability of the carboxylate ion formed.

Figure 1 illustrates the results when log $1/C$ was plotted against σ for the substituent present on the carboxylate moiety.[17] The results can best be pictured as two intersecting straight lines: one line of slope -0.72 corresponding to the

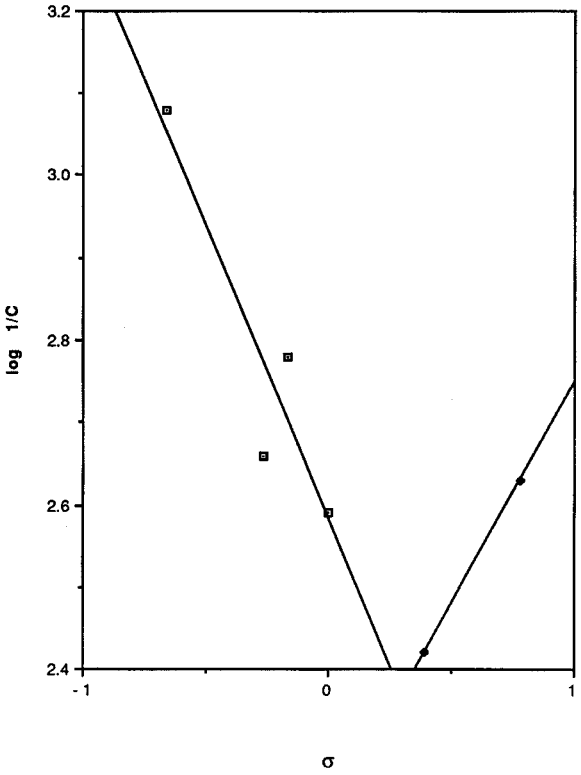

Figure 1 A plot of the logarithm of the reciprocal of the inhibitory concentration (IC_{50}), log 1/*C*, versus Hammett sigma values (σ) for the triphenyl carboxylates **1–8**.

presence of electron-donating substituents on the carboxylate moiety, and the other of slope 0.54 corresponding to the presence of electron-withdrawing substituents. This type of plot is typical of reactions in which there are two competing and different mechanisms operating.[15]

The line with a positive slope corresponds to the ionization of the triphenyltin carboxylate to give the triphenyltin cation and a carboxylate anion. Formation of the carboxylate anion is favored by the presence of electron-withdrawing groups (the carboxylate is a better leaving group) and disfavored when electron-donating substituents are present.

If the competing reaction were a concerted process in which the tin atom became attached to the cell wall at the same time as the carboxylate group left, the slope would still be positive but smaller in magnitude. An analogous situation is encountered in some nucleophilic substitution reactions where S_N1 and S_N2 are in competition.[15] Another possibility is that the organotin compound becomes attached directly to the cell wall and its coordination number changes from four to five. This pocess should also be favored by electron-withdrawing substituents with a positive slope. The observed negative slope indicates that a second mechanism is in effect. A plausible mechanism would involve the transport of the undissociated triphenyltin carboxylate through the cell membrane where it can interact with the mitochondria. This would be in agreement with earlier work which suggested that the acute toxicity of triorganotin derivatives is related to the derangement of mitochondrial function.[18–20]

Interestingly, the polymeric furan-2-carboxylate derivative (compound **1**) also exhibits biotoxicity, but at a lower level compared with compounds **3–8**. This suggests the possibility of a direct interaction between the tin compound and the cell wall, given that ionization of the polymer to the triphenyl tin cation seems unlikely.

The elemental analyses and the melting points for the new triphenyltin chloride–thiazolidin-4-one adducts synthesized are given in Table 2. The analyses indicate that 1:1 addition complexes are formed for the adduct, which is

Table 2. Analytical and melting point data of the triphenyltin chloride–thiazolidin-4-one adducts (**9–11**)

	$Ph_3SnCl{\cdot}XCHN(Y)C(O)CH_2S$			Analysis (%): Found (calcd)		
Compd	X	Y	M.P. (°C)	C	H	Sn
9	σ-$CH_3C_6H_4$	C_6H_5	82–83	62.16 (62.36)	4.75 (4.62)	18.11 (18.13)
10	C_6H_5	*m*-$NO_2C_6H_4$	182–183	57.61 (57.80)	3.64 (3.97)	17.46 (17.31)
11	C_6H_5	*m*-$CH_3C_6H_4$	99–101	62.02 (62.36)	4.37 (4.62)	17.96 (18.13)

Table 3. Spectroscopic parameters and inhibitory concentration data of the triphenyltin chloride–thiazolidin-4-one adducts (**9–16**)

	$Ph_3SnCl{\cdot}XCHN(Y)C(O)CH_2S$		Mössbauer parameters		$Sn–C_6H_5$ stretching vibrations (cm^{-1})		Inhibitory concentrations
Compd	X	Y	IS (mm s^{-1})	QS (mm s^{-1})	Asym.	Sym.	Log IC_{50} (mmol dm^{-3})
9	*o*-$CH_3C_6H_4$	C_6H_5	1.22 ± 0.01	2.97 ± 0.02	275.0	235.0	− 3.34
10	C_6H_5	*m*-$NO_2C_6H_4$	1.37 ± 0.01	3.05 ± 0.02	275.0	227.0	− 3.36
11	C_6H_5	*m*-$CH_3C_6H_4$	1.36 ± 0.01	3.04 ± 0.02	275.0	228.0	− 2.86
12	C_6H_5	C_6H_5	1.28 ± 0.01[a]	3.08 ± 0.01[a]	277.0[a]	239.0[a]	− 2.73[a]
13	*m*-FC_6H_4	C_6H_5	—	—	—	—	− 2.64[a]
14	*p*-FC_6H_4	C_6H_5	—	—	—	—	− 2.56[a]
15	*p*-BrC_6H_4	C_6H_5	—	—	—	—	− 2.95[a]
16	*m*-ClC_6H_4	C_6H_5	—	—	—	—	− 2.70[a]
							− 2.80 (average)

[a] From Ref. 11.

consistent with previous results.[11]

The observed QS values of 2.97–3.05 mm s^{-1} and IS values of 1.22–1.37 mm s^{-1} (Table 3), along with the observation of both the Sn–Ph symmetric and asymmetric stretching vibrations (Table 3), are consistent with the data prevoiusly reported for similar adducts.[11] A full X-ray structural analysis has also been reported for the 1:1 adduct formed between triphenyltin chloride and 2,3-diphenylthiazolidin-4-one.[21] The results of the X-ray study indicated that the structure of this adduct was trigonal bipyrimidal in nature with three non-coplanar phenyl groups in the equatorial plane. A comparison of the spectroscopic data between the adducts reported here and that of the 2,3-diphenylthiazolidin-4-one adduct indicated that the data of the two are identical within the limits of experimental error. Thus, it is reasonable to assume that the present adducts should have a similar structure to the 2,3-diphenylthiazolidin-4-one adduct.

The low IC_{50} values obtained for the adducts indicate that this series of organotins are effective inhibitors of *C. ulmi*. A comparison of the IC_{50} values for the two series of organotins studied indicates that, in general, the triphenyltin chloride–thiazolidin-4-one adducts are slightly more effective in the inhibition of *C. ulmi*. This can be attributed to the ability of the triphenyltin chloride adducts to form the triphenyltin cation upon dissolution; this is the species that has been reported to be responsible for the inhibition of this fungus.[4–6] Attempts to obtain a QSAR correlation between the toxicity data and descriptors for the triphenyltin chloride–thiazolidin-4-one adducts were unfruitful. This is most probably due to the fact that the X and Y groups attached to the thiazolidin ring are too far removed from the tin atom to have any significant influence on the formation of the triphenyltin cation. Thus, any further modifications of organotin molecules in the hopes of increasing their activity against *C. ulmi* should be focused on incorporating substituents into the triorganotin compounds that would enhance the formation and stabilization of the triphenyltin cation.

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