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Molecular Structure and Fungicidal Activity against *Ceratocystis ulmi* of the 1:1 Adducts of Triphenyltin Chloride and 2,3-Disubstituted Thiazolidin-4-ones

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Several 1:1 addition compounds between triphenyltin chloride and 2,3-disubstituted thiazolidin-4-one ligands have been synthesized. Their molecular structure has been deduced using far IR and Mössbauer spectroscopies. In addition, molecular modeling of several of the complexes was used to explain the variation of the quadrupole splitting values in the Mössbauer spectra. The structures of the complexes were determined to be trigonal-bipyramidal with the three phenyl groups in the equatorial plane. However, the phenyl groups are not co-planar, on the basis of the observation of both the Sn–C (phenyl) symmetric and asymmetric stretching vibrations. The adducts were screened against the fungus *Ceratocystis ulmi*, the agent responsible for Dutch elm disease, and found to be effective in the inhibition of this fungus. The toxicity of the adducts varied with the hydrophobicity of the molecule. A direct correlation between substitution on the phenyl group on the thiazolidine ring and the toxicity of the compound was not observed.

Keywords: Adducts; *C. ulmi*; thiazolidin-4-ones; Dutch elm disease; IR spectroscopy; Mössbauer spectroscopy; toxicity; triphenyltin chloride

INTRODUCTION

The biological applications of organotin compounds are dependent on the number and type of organic groups attached to the tin atom. For example, cyclohexyl organotins are good miticides[1,2] while organotin compounds containing alkyl groups are good pesticides.[1,2] The biological activities of organotins increase with the number of substituents bound to the tin atom, reaching a maximum activity with three organic substituents.[1,2] The triphenyl organotins have been found to have a broad range of fungicidal properties.[1–3] Another class of compounds having a wide range of biological activity is the 2,3-disubstituted thiazolidin-4-ones.[4,5] When considering a compound as a candidate for an agricultural fungicide, its phytotoxicity must also be considered. One series of organotin compounds that has a high fungicidal/phytocidal ratio is the triphenyltin chloride adducts.[6] Previous *in vitro*[7–10] results have indicated that the triphenyltin moiety is highly effective in the inhibition of *Ceratocystis ulmi*, the fungal agent responsible for Dutch elm disease, which has caused the destruction of millions of elm trees. Thus, organotin adducts formed between triphenyltin chloride and a biologically active ligand, such as the 2,3-disubstituted thiazolidin-4-ones, may be ideal fungicidal candidates. These would possess a high fungicidal-phytocidal ratio and, in addition, they may have a higher toxicity than either parent compound due to synergistic effects. Thus, in our continuing efforts to develop a more effective fungicide against *C. ulmi*, we have synthesized a series of triphenyltin chloride adducts using the disubstituted thiazolidin-4-ones as ligands. These adducts were then screened against the fungus *in vitro* using a shake culture method.

These compounds also present an interesting

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structural problem independently of their fungicidal activity against *C. ulmi*. The ligands possess several possible donor sites. The structures of the adducts have been deduced using IR and Mössbauer spectroscopies.

EXPERIMENTAL

Chemicals

Triphenyltin chloride was obtained from Aldrich Chemical Co., Milwaukee, WI 53233, USA, and used without further purification. The 2,3-disubstituted thiazolidin-4-one ligands were synthesized according to the literature.[4]

Synthesis of the adducts

A typical synthesis of the adducts is as follows. A solution of 2,3-diphenylthiazolidin-4-one (2.55 g, 10 mmol) was dissolved in 30 cm^3 of acetone. This solution was then added dropwise with stirring to a solution of triphenyltin chloride (4.06 g, 10 mmol) dissolved in 80 cm^3 of acetone. The mixture was stirred for an additional 30 min. After standing for another 3 h, it was then filtered. The filtrate was concentrated on a rotary evaporator, then dried *in vacuo* to give an oily residue. Scratching the sides of the flask resulted in solidification of the residue. The products were recrystallized from ligroin.

Elemental analyses

The elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377, USA.

Mössbauer spectra

The Mössbauer spectra were measured at 80 K on a Mössbauer spectrometer, Model MS-900 (Ranger Scientific Co., 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 Teflon holders. The source was 15 mCi $Ca^{119m}SnO_3$, and the velocity was calibrated at ambient temperature using a composition of $BaSnO_3$ and tinfoil (splitting = 2.52 mm s^{-1}). The resultant spectra were analyzed by least-squares fit to Lorenzian-shaped lines.

Far-infrared spectra

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

Molecular modeling

The program MacroModel (V4.0)[11] was used to model the structure of several of the adducts. The structure was minimized using MM2 employing conventional bond distances, bond angles and van der Waals radii obtained from the literature.

Preparation of stock organotin solutions and measurement of fungicidal activity

The preparation of the (1000 mg dm^{-3}) organotin solutions and the fungus for the toxicity studies has been previously described.[7] A stock suspension (1.0 cm^3) of cells (concentration = 10^6 cells cm^{-3}) of *C. ulmi*, strain 32437, obtained from the American Type Culture Collection, Rockville, MD 20852, USA, was added to tin-compound-amended potato dextrose broth, and the resulting suspension was then shaken in an incubator–shaker (7 d; 22 °C). The contents of the flasks were filtered and rinsed with distilled water. The fungal growth was then dried and weighed until a constant weight was obtained. 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 added. The concentration at which 50% of the fungus is inhibited is taken as the IC_{50} value.

RESULTS AND DISCUSSION

The elemental analyses and the melting points for the adducts are given in Table 1. The elemental analyses are consistent with the adducts forming 1:1 addition compounds. This is not surprising, since triphenyltin chloride has a strong tendency to form 1:1 five-coordinated complexes with a variety of Lewis bases.[1,6,12,13]

Isomer shift (IS) and quadrupole splitting (QS) values are listed in Table 2. The IS values are the same within experimental error, based upon the

Table 1 Elemental analyses and melting points of the triphenyltin chloride adducts

Adduct		M.p. (°C)	Analysis (%): Found (Calcd.) C	H	Sn
$Ph_3SnCl \cdot XCHN(Ph)C(O)CH_2S$					
$X=C_6H_5$	**1**	88–89	61.88 (61.85)	4.22 (4.40)	18.30 (18.52)
$X=m\text{-}FC_6H_4$	**2**	74–76	60.32 (60.17)	4.01 (4.13)	18.17 (18.03)
$X=p\text{-}FC_6H_4$	**3**	89–91	60.50 (60.17)	3.99 (4.13)	17.86 (18.03)
$X=p\text{-}BrC_6H_4$	**4**	92–94	54.47 (55.07)	3.61 (3.78)	16.67 (16.49)
$X=m\text{-}ClC_6H_4$	**5**	84–86	58.66 (58.70)	3.58 (4.03)	17.56 (17.58)
$X=CCl_3$	**6**	140–143	49.75 (49.31)	3.01 (3.40)	17.43 (17.40)
$Ph_3SnCl \cdot OCHN(Ph)C(O)(CH_2)_nS$					
$n=1$	**7**	175–178	55.99 (56.04)	3.98 (3.83)	21.00 (20.51)
$n=2$	**8**	155–158	56.74 (56.74)	3.67 (4.08)	19.75 (20.03)

Q-test, indicating that the electronic state of the tin atoms in all the compounds is similar. The observed QS values of 2.49–3.17 mm s^{-1} and IS values of 1.23–1.34 mm s^{-1} are within the ranges found for trigonal-bipyramidal organotin complexes with axial ligands.[14] It is further noted that the observed QS values fall into two groups. The first group, containing adducts **1** and **2**, have QS values of approximately 3.1 mm s^{-1}. The second group, containing adducts **3**–**8**, have QS values of approximately 2.6 mm s^{-1}. One would expect similar QS values for all of these similarly structured complexes, and the observed difference is unexpected. Because the observed QS values are smaller for the second group, it can be concluded that the tin atom in these compounds is in a more symmetrical environment than those of the first group. Refined structures of adducts **1** and **4** using the MacroModel program show that when a substituent is present on the phenyl ring, the molecules are close to one another. For example, in adduct **4** the distance between the Sn atom and the Br atom in an adjacent molecule is 4.448 Å, whereas in adduct **1** the equivalent distance between the Sn atom and the corresponding H atom is 4.549 Å. Hence, there is more interaction between the molecules in adduct **4**. This increase in interaction causes the phenyl rings to rotate and occupy a more symmetrical distribution around the tin atom (as compared with the position of the unsubstituted phenyl rings of the molecule), leading to smaller QS value (Figs 1 and 2).

Table 2 Mössbauer spectral data of the triphenyltin chloride adducts

Adduct	QS (mm s^{-1})[a]	IS (mm s^{-1})[b]
1	3.08	1.28
2	3.17	1.34
3	2.60	1.34
4	2.66	1.33
5	2.57	1.32
6	2.53	1.33
7	2.52	1.23
8	2.49	1.27

[a] All quadrupole splitting (QS) values are reported within ±0.07.

[b] All isomer shift (IS) values are reported within ±0.02.

The relevant far-IR vibrations for the adducts are listed in Table 3. In all adducts, the asymmetric Sn–C (phenyl) vibration appears in the range 270–277 cm^{-1}, and the Sn–C (phenyl) symmetric vibration appears in the range

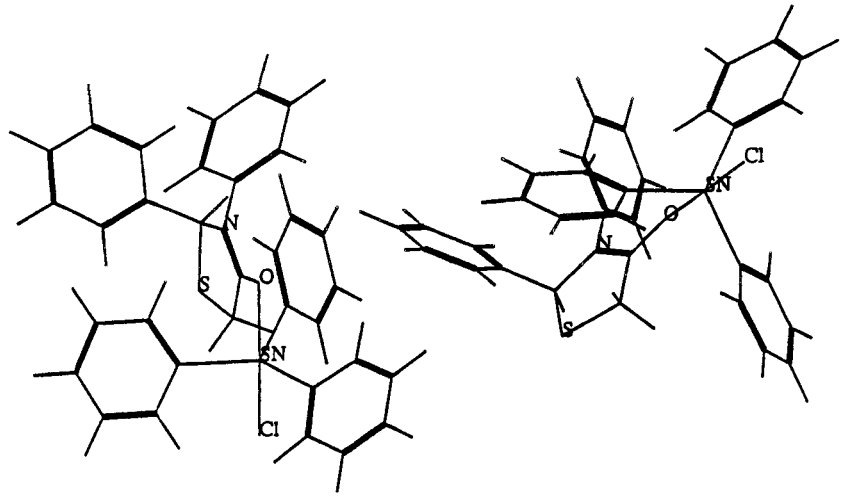

Figure 1 Refined structure of adduct **1**: $Ph_3SnCl \cdot C_6H_5\underline{CHN(Ph)C(O)CH_2}S$.

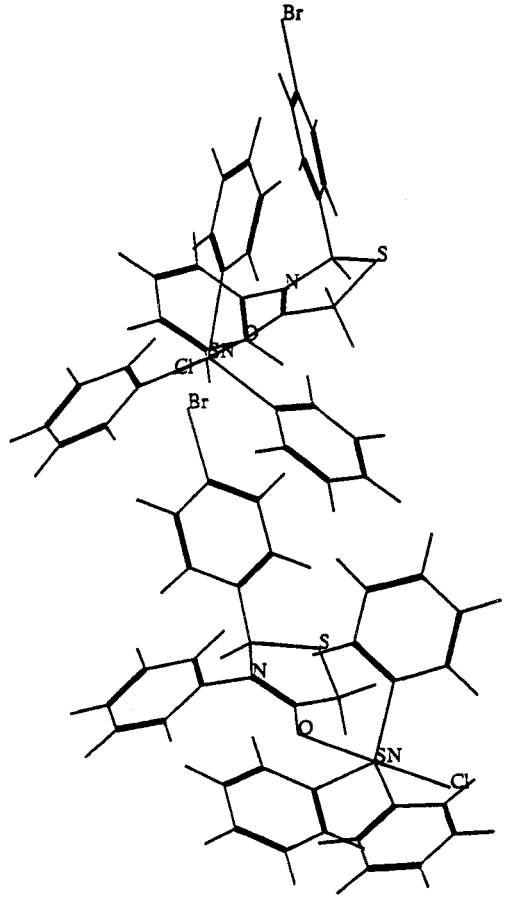

Figure 2 Refined structure of adduct **4**: $Ph_3SnCl \cdot p\text{-}BrC_6H_4\underline{CHN(Ph)C(O)CH_2}S$.

227–239 cm^{-1}. These values are in agreement with stretching values reported for other triphenyltin chloride adducts in which the phenyl groups are in the equatorial plane.[15] This observation gives support to the proposed structure suggested by the Mössbauer data. However, the observations of both the Sn–C symmetric and asymmetric vibrations indicate that the three phenyl groups in the equatorial plane are not coplanar.

A full X-ray structural analysis of the 1:1 adduct of triphenyltin chloride with 2,3-diphenylthiazolidin-4-one[16] confirms the proposed structure suggested by the Mössbauer and far IR data for this adduct. The X-ray analysis reveals that the complex has a trigonal-bipyramidal (TBP) structure with three phenyl groups in the equatorial plane. The chlorine and the ligand oxygen atoms are shown to occupy the axial positions. Furthermore, the mean Cl–Sn–C

Table 3 Selected far-infrared spectral data of the triphenyltin chloride adducts (cm^{-1})[a]

Adduct	ν_{as}(Sn–C)	ν_s(Sn–C)
1	277s	239m
2	273s	239m
3	276s	227m
4	271s	231m
5	277s	227s
6	271s	232m
7	273s	232w
8	270s	231s

[a] s, strong; m, medium; w, weak.

Table 4 Inhibitory concentrations of the triphenyltin chloride adducts against *C. ulmi* in potato dextrose broth at 22 °C

Adduct	log IC_{50} (mmol dm^{-3})
1	−2.73
2	−2.64
3	−2.56
4	−2.95
5	−2.70
6	−2.45
7	−2.38
8	−2.45

(phenyl) angle has been determined to be 97.0°, indicating that the three phenyl groups are not co-planar.

The inhibitory concentrations (log IC_{50}) of the adducts are given in Table 4. The data indicate that these complexes are as effective as Ph_3SnCl (log $IC_{50} = -2.57$ mmol dm^{-3}) in the inhibition of *C. ulmi*. The toxicity of the adducts varies with the hydrophobicity of the molecule. The more hydrophobic the molecule, the greater the toxicity [**1** (Ph)>**6** (Cl_3C)>**7** (O=C)] (Table 4). This observed trend may be due to an increase in the ability of a more hydrophobic molecule to interact with the cell wall component(s). It has been suggested previously that the inhibition of *C. ulmi* by organotin compounds is due to the interaction of the organotin species with the cell wall of the fungus.[10] The addition of a carbon atom to the thiazolidine ring, changing it to a six-membered ring (1,3-thiazin-4-one) increases the hydrophobicity of the compound. The observed increase in toxicity for compounds **7** and **8** (Table 4) may be attributed to the corresponding increase in hydrophobicity.

CONCLUSIONS

The ligand itself, 2,3-disubstituted thiazolidin-4-one, is not a good inhibitor of *C. ulmi*: it was not possible to obtain an IC_{50} value even with a ligand concentration as high as 10 mg dm^{-3}. Thus, the inhibition activities of these adducts at the observed concentration must be due to the triphenyltin moiety. The toxic effect of the TPT moiety is related to the hydrophobicity of the adducts. This is in agreement with our earlier work involving other triphenyltin chloride adducts in which the inhibition was found to be independent of the Lewis base used.[8] Furthermore, the results obtained from the number of compounds tested indicates that there appears to be no direct correlation between substitution on the phenyl group on the thiazolidine ring and the toxicity of the compound. This is most likely due to the point of substitution being far removed from the tin atom, and any inductive effect due to the various substituents would be small.

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