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Studies in Aryltin Chemistry: Part 7. Spectroscopic and Fungicidal Studies of Some *p*-Substituted Tri-aryltin Acetates, Oxides and Hydroxides

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The fungicidal activity of a series of aryltin compounds, (p-$ZC_6H_4)_3SnX$ (X = OAc, OH, or 1/2O), where Z = F, Cl, CH_3, CH_3O, C_2H_5 or $(CH_3)_3C$, and for which IR and NMR (^{119}Sn) data are reported, has been assessed by radial growth assays on *Aspergillus niger, Botrytis cinera, Mucor hiemalis, Fusarium solani* and *Penicillium chrysogenum*, and the results compared with those for the Ph_3SnOAc and Ph_3SnOH archetypes. In most cases, *para*-substitution only slightly reduces biocidal activity, but with p-CH_3O the aryltin is completely ineffective. This result correlates with the seemingly decreased ability of the '(p-$CH_3OC_6H_4)_3Sn$' moiety to achieve a trigonal-bipyramidal five-coordinate geometry with oxygen atoms in the axial positions, all other Ar_3SnOAc and Ar_3SnOH having this geometry in the solid state. A model for fungicidal action is proposed based on the need for the organotin inhibitor to attain the above geometry in the active site that it occupies in the ATPase enzyme, being the required condition for its biological activity. © **1997 John Wiley & Sons, Ltd.**

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INTRODUCTION

Triphenyltin compounds (Ph_3SnOAc, 'Brestan'; Ph_3SnOH, 'Du-Ter') have enjoyed extensive use as commercial fungicides[1] and a comprehensive review of the earlier research on these compounds is available.[2] In general, although the effect on the activity of Ph_3SnX of varying anion X is still considered secondary,[3] interest in anions which may increase the availability of the fungicide at the active sites in the test organisms, or which are biologically active in their own right, has remained high.[4–6] In contrast, structure–activity studies probing electronic and/or steric effects using substituents on the phenyl rings are relatively few,[5,7–12] and only recently, while this work was reaching completion, was a study of the same type as this one reported.[13] This appeared to confirm that substitution on the phenyl rings at the *para*-position in triaryltins also does not seem to have any major effect on their biological activity.

This work differs in two main aspects from earlier studies.

(a) A wider range of *para*-substituents has been used so as to make possible a more thorough study of both the electronic and steric factors influencing the fungicidal activity of the triaryltin moiety.
(b) The systems chosen for study, Ar_3SnOAc, Ar_3SnOH and $Ar_3Sn)_2O$, are analogues of the commercial fungicides, 'Brestan' and 'Du-Ter', thus allowing a more direct comparison to be made with these compounds as well as avoiding the additional

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phytoxicity of the Ar_3SnCl system[3] used in the earlier work.[13]

EXPERIMENTAL

All experimental details, including materials used, microanalyses and IR and NMR (^{13}C, ^{119}Sn; $CDCl_3$) procedures, have been given elsewhere.[14, 15] All precursors, p-ZC_6H_4SnX (X = Cl, Br, I), are previous preparations,[15, 16] while bioassay techniques followed standard protocols.[17]

Syntheses

Shaking an ethereal solution of the Ar_3SnX (X = Cl or Br) with 10% KOH (aq.) gave the oxide, while the hydroxide was obtained by recrystallizing the oxide from 90% aqueous ethanol. The acetate was produced either by (1) refluxing an acetone solution of the chloride and excess sodium acetate for 2–3 days, evaporating the filtrate and extracting the residue obtained with hexane or benzene, or by (2) reacting the hydroxide with 2–3-fold excess acetic acid in 2,2′-dimethoxypropane.[18] The phenyltin analogues were obtained by standard procedures,[19, 20] and tris (*p*-methoxyphenyltin acetate has already been reported.[21]

Analytical and spectroscopic data are given in Table 1 for all compounds prepared in this work.

Radial growth studies

The test fungi used in this study are listed in Table 2. Each fungus was cultured for 7–10 days on potato dextrose agar (PDA). Using aseptic procedures, ethanol (95%) solutions (6.0 ml) containing the test compound were added to molten PDA (50 °C) to give solutions with concentrations of 8.0, 6.0, 4.0, 2.0 and 1.0 mg l^{-1} of the fungicide as well as a control with zero fungicide, which were then poured into 9-cm Petri dishes — three for each fungus and concentration. A 10-mm disc of the fungus was placed on the centre of each plate, which was then incubated at 25 ± 1 °C for 7–10 days. Colony diameters (along two 90° axes) were measured every 24 h for two days, and then every 48 h. Average growth rates (mm d^{-1}), after the initial slow phase, were then used to provide percentage growth inhibition values. Probit analysis[24] of these data gave the ED_{50} value, i.e. the concentration required for 50% growth rate inhibition compared with the control for each fungus–compound combination.

RESULTS

Synthesis and characterization

Initially, samples of Ar_3SnOAc, $(Ar_3Sn)_2O$ and Ar_3SnOH (Ar = p-ZC_6H_4) were prepared for each substituent (Z = F, Cl, Ch_3 and CH_3O) but as bioassays (*vide infra*) showed the substituent effect on activity to be essentially the same regardless of the organotin system used, only one compound of each type was prepared in later work, i.e. the acetate (Z = C_2H_5) or the oxide [Z = $(CH_3)_3C$]. Infrared data [Table 1(a)] show that all but one of the acetates are polymers in the solid state[24] as confirmed by X-ray analysis for Ph_3SnOAc,[25] except when Z = CH_3O, which acetate has been shown to be monomeric in the solid state.[21]

The oxide/hydroxide pairs are readily interconverted by recrystallizing from absolute or aqueous (10%) ethanol respectively, with the conversion best monitored by their IR spectra[20, 22, 26, 27] [ν_{as}(SnOSn) or ν(OH)]. Only with Z = CH_3O does this not occur, the oxide remaining unchanged even after refluxing with ethanol–water (1:1) for several hours. Since far-IR data for Ar_3SnOH [Table 1(c)] follow those for Ph_3SnOH, which has been shown by X-ray diffraction studies to be polymeric,[28] it is clear that the tin atom in the (p-$CH_3OC_6H_4)_3Sn$ moiety is very reluctant to become five-coordinate with oxygen atoms in the axial positions.

The ^{119}Sn and ^{13}C solution NMR data for the four-coordinate monomers examined here, although limited, allow some comparison with the previous analysis of substituent effects in the NMR spectra of similarly four-coordinate Ar_4Sn and Ar_3SnX (X = Cl, Br, I, NCS).[15] For the acetate system, the best correlation is with σ_p (n = 6, ρ = 0.927) but as with the other Ar_3SnX, it is improved by omitting the Z = H datum point, resulting in the line (n = 5, ρ = 0.961), shown in Fig. 1. Thus the effect of acetate on tin-119 chemical shift data appears to resemble that of iodide or *N*-thiocyanate. In contrast, the oxide system, albeit with very limited data, correlates best with σ_R^0 (n = 5, ρ = 0.897), like the Ar_4Sn series, although in this case the correlation is not improved by omitting the phenyl datum point.

Bio-assays

Typical radical growth data showing the effects of inhibitor concentration on fungal growth rates are shown for Ar_3SnOAc acting on *M. hiemalis*, and for Ar_3SnOH and $(Ar_3Sn)_2O$ acting on *Asp.*

Table 1. Analytical[a] and spectroscopic (IR[b, c] and NMR[b, d]) data
(a) $(p\text{-}ZC_6H_4)_3SnOAc$

	Z					
	CH_3	F	Cl	CH_3O[21]	C_2H_5	
Recrystallization solvent	Hexane	Cyclohexane	—	Cyclohexane	Pentane	
M.p. (°C)	113–114 (113)[e]	135–136	148–149 (148.5–9.5)[f]	108–110	95–96	
C(%)	61.02 (61.23)	52.18 (51.88)	46.93 (46.88)	54.75 (55.35)	62.98 (63.32)	
H(%)	5.52 (5.36)	3.50 (3.27)	3.14 (2.95)	4.86 (4.85)	6.16 (6.13)	
	Z					
	H	CH_3	F	Cl	CH_3O[21]	C_2H_5
IR data						
ν_{as} (CO_2)	1533 (1641)	1535 (1640)	1545 (1641)	1523 (1642)	1646 (1639)	1538 n.a.
ν_s (CO_2)	1423 (1315)	1431 (1319)	1407 (1320)	1418, 1413 (1318)	1305 (1317)	1415 n.a.
$\Delta\nu$ (CO_2)	110 (326)	104 (321)	138 (321)	108 (324)	341 (322)	123 n.a.
NMR data						
$\delta(^{119}Sn)$	−113.63	−102.67	−110.85	−116.00	−94.34	−105.00
$^1J(^{119}Sn–^{13}C)$	648.4	656.7	678.6	669.5	680.1	656.1
$^2J(^{119}Sn–^{13}C)$	48.0	49.8	56.4	55.7	55.3	49.6
$^3J(^{119}Sn–^{13}C)$	62.3	64.4	70.4	67.6	68.7	64.3

(b) $[(p\text{-}ZC_6H_4)_3Sn]_2O$

	Z					
	CH_3	F	Cl	CH_3O	$(CH_3)_3C$	
Recrystallization solvent	Heptane	Ethanol	Hexane	Ethanol	Ethanol	
M.p. (°C)	108 (106–107.5)[g]	125 (dec.)	145 (dec) (121–123)[g]	123–24	>350 (dec)	
C(%)	62.87 (63.04)	52.34 (52.48)	47.03 (46.86)	56.94 (56.29)	68.63 (68.46)	
H(%)	5.58 (5.29)	3.14 (2.94)	2.65 (2.62)	5.00 (4.72)	7.09 (7.48)	
	Z					
	H	CH_3	F	Cl	CH_3O	$(CH_3)_3C$
IR data						
ν_{as} (SnOSn)	776	761	748,754sh	759,761	771	n.a.
δ(SnOSn)	382	386	412	410	395	n.a.
NMR data						
$\delta(^{119}Sn)$	−83.47	−73.74	n.a.	−76.17	−68.65	−79.47
$^3J(^{119}Sn–^{119}Sn)$	410.8	426.7	n.a.	420.6	407.2	428.3
$^1J(^{119}Sn–^{13}C)$	624.9	634.7	n.a.	642.4	652.1	613.3
$^2J(^{119}Sn–^{13}C)$	42.1	46.9	n.a.	46.9	51.0	n.a.
$^3J(^{119}Sn–^{13}C)$	62.1	61.4	n.a.	61.7	65.8	n.a.

Table 1. Continued.

(c) $(p-ZC_6H_4)_3SnOH$				
	Z			
	H	CH_3	F	Cl
M.p. (°C)	—	108 (107–108)[h]	135–136 (135–136)[i]	156–157
C(%)	—	61.88 (61.66)	51.58 (51.36)	45.80 (45.97)
H(%)	—	5.58 (5.42)	3.45 (3.11)	2.79 (2.79)
IR data				
ν(OH)	3617	3611	3617	3601
δ(OH)	911,897	919	907	931
ν(SnOSn)	372	355	384	382

[a] Calculated values or literature data in parentheses. [b] n.a., parameter not measured or not observed.
[c] IR (cm^{-1}); Nujol mull ($CDCl_3$ soln).
[d] $CDCl_3$ solution; $\delta(^{119}Sn)$ ppm (ext. $Sn(CH_3)_4$; nJ (Hz). Complete ^{13}C NMR data are available from the authors.
[e] Ref. 3. [f] Ref. 19. [g] Ref. 22. [h] Ref. 8. [i] Ref. 23.

niger in Figs. 2 and, 3, respectively. [Relative radial growth data for all the inhibitor–fungus combinations used, which also follow the same trends as the two examples given above, are available from the authors.] In the former case replacing *p*-H by F or Cl creates only small changes in inhibitor activity, but with methoxy as the *para*-substituent the Ar_3SnOAc becomes completely ineffective (Fig. 2(a)). In fact it appears to promote the fungal growth rate by about 10%, well within the average experimental error, ±3.0% (s=2.0%), for the data shown in Fig. 1. That this is not a simple steric effect is shown in Fig. 2(a), where the compound with *p*-C_2H_5 is a better inhibitor than is the *p*-tolyl system. Increased fungal growth rates with *p*-methoxy-phenyltin compounds occur with all fungi except *Asp. niger.* In this case, as shown in Fig. 3(a), this type of compound has no effect at all on fungal growth rate, within the average experimental error of ±3.7% (s=2.8%). Pehraps even more surprising was the zero effect on growth, observed for all fungi, of the sterically demanding substituent, the t-butyl group (Fig. 3b), which is inconsistent with the activity of [*p*-$(CH_3)_3CC_6H_4]_3SnCl$ against *C. ulmi* reported earlier.[13] However our bioassay method differs from that used by Eng *et al.* and since all *para*-t-butyl aryltin compounds appear to have very low solubilities in many solvents,[16] our results may simply reflect the fact that the test compound, perhaps having precipitated out of the PDA medium during its preparation, would then not be available to the fungus.

Complete inhibition data, as ED_{50} values, are in Table 3. Not unexpectedly, the effect of different X (OAc, OH, or 1/2O) on fungicidal activity is minimal and, in most cases, the

Table 2. Phytopathogenic and saprophytic fungi used in the bioassays

Fungus	Characteristics
Aspergillus niger	In temperate climates, this fungus generally acts as a secondary invader of plant tissue or as a saprophyte.
Botrytis cinera	Plant pathogenic fungus with a very wide host range; common on senescing or weakened tissue. Temperate crops affected: lettuce, bean, ginseng and strawberry.
Mucor hiemalis	Saprophytic fungus; common soil inhabitant.
Fusarium solani:	Pathogen of pea roots.
Penicillium chrysogenum	Saprophytic fungus; common soil inhabitant.

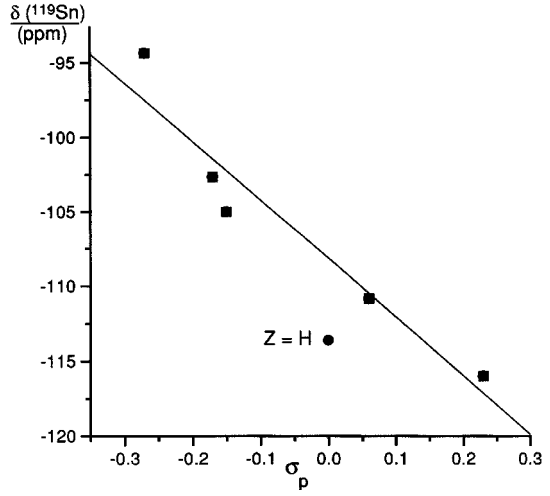

Figure 1 Tin-119 chemical shifts for $(p\text{-}ZC_6H_4)_3SnOAc$ in $CDCl_3$ plotted against σ_p.

phenyltin compounds are still the most active. In general the relative effects due to *para*-substituent changes, including the zero activity noted above, are the same for all fungi.

DISCUSSION

The general mode of biological action of R_3SnX is considered by biochemists to be the same for all eukaryotic cells, with the 'R_3Sn' group the active species at the site of the biochemical activity, i.e. in cell mitochondria. Most early studies involved triethyltin systems but more recently tributyltin species have been examined. Less work has been reported for the triphenyltin fungicides of interest here, but in fact the main features are deemed to be basically the same for all triorganotin systems.[29]

Triorganotin compounds appear to inhibit mitochondrial function in three ways:[30] by (1) causing large-scale swelling at high concentrations, (2) mediating Cl^-/OH^- exchange across membranes, and (3) inhibiting oxidative phosphorylation or ATP hydrolysis, like oligomycin. The last process is usually assumed to be the most significant one although binding of Ph_3Sn^+ to the cell wall was concluded to be responsible for the inhibition of *C. ulmi*;[31] the triorganotin-mediated anion exchange across the mitochondrial membrane, which is electro-silent, i.e. involves neutral R_3SnX species, may also interfere with ATP synthesis or hydrolysis.

More recent studies[32] have compared the effects of venturicidin or R_3SnCl (R = Bu, Ph) with oligomycin and *N,N′*-dicyclohexylcarbodi-

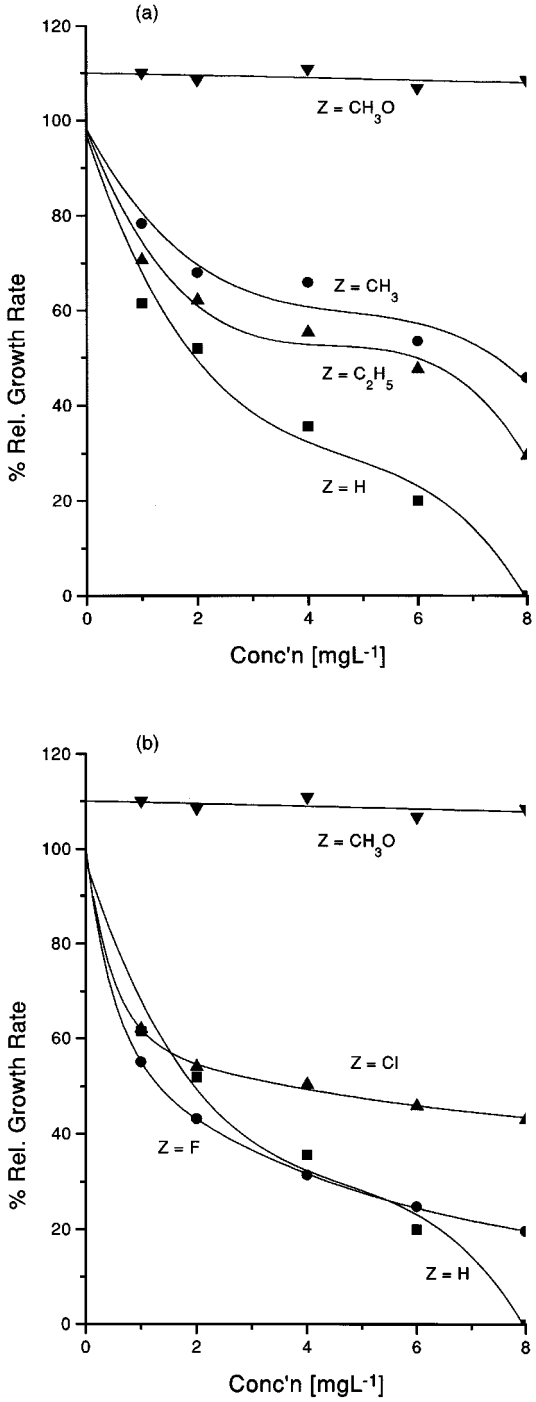

Figure 2 Relative growth rate plots showing the effect of $(p\text{-}ZC_6H_4)_3SnOAc$ on the growth of *Mucor hiemalis*. (a) Z = H, CH_3, C_2H_5, CH_3O; (b) Z = H, F, Cl, CH_3O.

imide (DCDD) on oxidative phosphorylation using bovine submitochondrial particles (SMP).

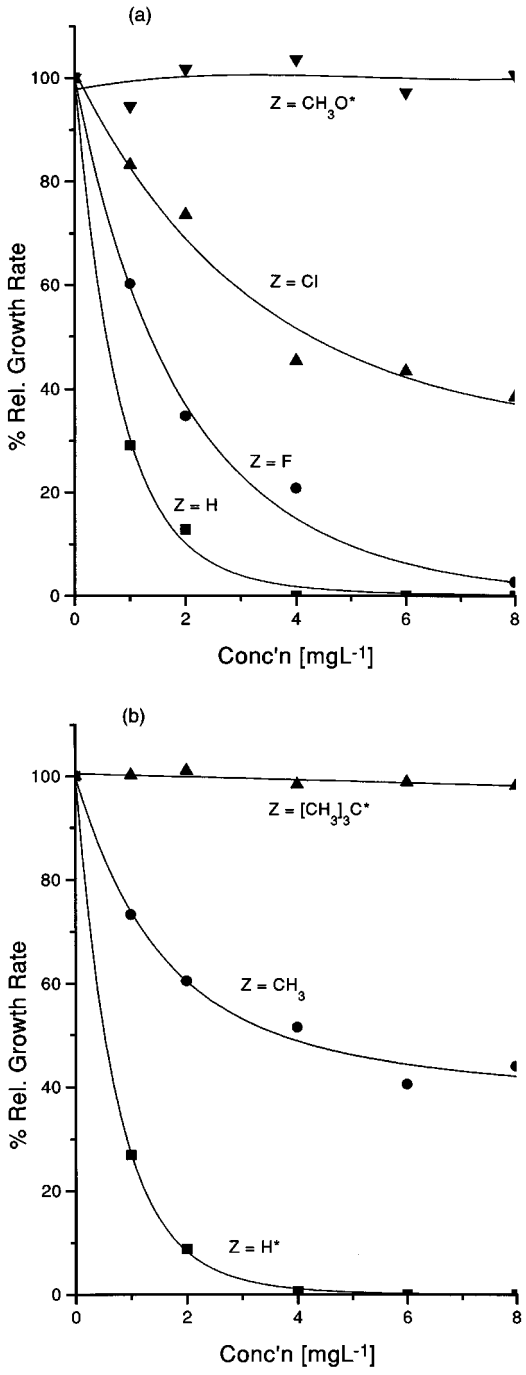

Figure 3 Relative growth rate plots showing the effect of $(p\text{-}ZC_6H_4)_3SnOH$ or $[(p\text{-}ZC_6H_4)_3Sn]_2O$* on the growth of *Aspergillus niger.* (a) Z = H, F, Cl, CH_3O); (b) Z = H*, CH_3, $(CH_3)_3C$*.

The enzyme F-ATPase, the catalyst for ATP synthesis or hydrolysis, consists of two very complex units:[33] F_1, protruding into the mitochondrion and the catalytic sector of the ATP synthase complex; and F_0, consisting of sub-units *a*, *b* and *c*, bridging the membrane and responsible for the proton translocation connected with the above processes. All four inhibitors specified above, including R_3SnCl, act at F_0 with evidence that they all bind to at least one of the *c* subunits. In all ATP synthase complexes there is a free carboxyl group, from Asp or Glu residues, in subunit *c* that appears to be involved in transmembrane proton conduction by hydrogen bonding to amino-acids in subunit *a*. In addition, molecular flexibility of the subunits may be required for the rapid proton transfer needed for multisite ATP hydrolysis or synthesis, the process that is inhibited by R_3SnX. It was therefore suggested that organotins freeze the structure of F_0 so that the rapid proton transmembrane flow is disallowed but the slow proton transfer rate required for unisite processes is still permitted.[32]

Our results indicate that the fungicidal activity of triaryltins correlates with their ability to attain a trans-C_3SnO_2 trigonal-bipyramidal geometry, while the '$(p\text{-}CH_3OC_6H_4)_3Sn$' moiety, which is reluctant to do so, is completely ineffectual as a fungicide. This appears at first to contradict the earlier Mössbauer spectroscopic studies[30] that showed 'R_3Sn' bound at the strong affinity sites in ATPase responsible for catalytic activity, to be four-coordinate or possibly *cis* five-coordinate. However, the Mössbauer studies were carried out on static frozen systems whereas, in contrast, our correlation is found for *in vivo* dynamic systems involving fungal growth.

The scheme we propose for inhibition by triorganotins, and which can account for this apparent contradiction, is shown in Fig. 4. Penetration by the inhibitor as $Ar_3Sn^+(aq)$, or perhaps as Ar_3SnX since the environment is partly hydrophobic, of the neighbouring α-helical peptide chains forming subunit *c*[33] of the F_0 component of the ATP synthase complex occurs until the carboxylic acid residue is reached. Here the 'Ar_3Sn' moiety can now replace the proton, thus occupying a monodentate site with four-coordinate geometry consistent with the Mo̎ssbauer results obtained under static conditions. Moreover, when the enzyme is catalysing synthesis or hydrolysis of ATP under unisite conditions, the higher $[H^+(aq)]$ due to the proton gradient across the

Table 3. Radial growth inhibition data: ED_{50}[a] values[b]

(a) $(p\text{-}ZC_6H_4)_3$ SnoAc

	Z					
	H	F	Cl	CH_3	C_2H_5	CH_3O
A. niger	2.0(0.1)	4.6(1.3)	8.2(2.3)	8(8)	2.4(1.6)	NE[c]
B. cinera	5.2(2.6)	7(6)	6(4)	5.0(1.4)	1.7(1.4)	NE
M. hiemalis	1.9(0.6)	1.4(0.1)	3.8(0.3)	7.6(4.4)	2.6(1.1)	NE
F. solani	0.7(0.2)	2.4(1.0)	3.7(0.7)	3.8(1.5)	4.8(1.2)	NE
P. chrysogenum	5.0(1.0)	14(10)	11(8)	11.7(3.8)	1.3(1.7)	NE

(b) $(pZC_6H_4)_3SnOH$ and $[(p\text{-}ZC_6H_4)_3Sn]_2O$★

	Z						
	H	F	Cl	CH_3	H*	CH_3O*	$(CH_3)_3C$*
A. niger	0.5(0.1)	1.4(0.3)	4.5(1.6)	4.3(1.6)	0.7(0.1)	NE	NE
B. cinera	5(4)	3.2(1.7)	5.0(3.3)	*6*[d]	3(3)	NE	NE
M. hiemalis	1.5(0.4)	2.0(0.8)	2.0(0.7)	7(7)	1.4(0.2)	NE	NE
F. solani	1.1(0.2)	3.1(0.8)	5.3(2.5)	3.4(0.7)	0.9(0.1)	NE	NE
P. chrysogenum	3.7(0.9)	9.1(4.4)	*g*[d]	5.5(2.2)	5(5)	NE	NE

[a] Concentration (mg l^{-1}) to decrease radial growth to 50% of that of the control.
[b] Errors are given in parentheses. [c] NE, no effect. [d]Error greater than ED_{50} value.

membrane can displace part or most of the bound but labile tin, freeing the acidic residue and leaving the low proton flux then required little affected by the inhibitor.

However, the high rate of proton flow resulting from millimolar ATP reactions using the multisite pathway may require more extensive molecular motions in the F_0 unit which can result in a donor atom, e.g. from a carbonyl group in a neighbouring chain, approaching and coordinating with an already-bound Ar_3Sn moiety. In this way the F_0 unit acts as a giant chelate ligand, resulting in a *trans*-C_3SnO_2 trigonal-bipyramidal geometry around the tin, perhaps more like that found in the solid state for both triphenyltin acetate[25] and triphenyltin formate[34] rather than

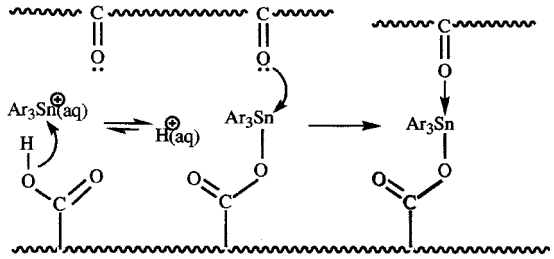

Figure 4 Scheme proposed for organotin inhibition of proton transfer through the E_0 part of the F-ATPase enzyme.

would be the case in solution for the much weaker interaction between an O-donor ligand and an $Ar_3SnOOCR$ unit. The tin would now occupy a strong binding site in the enzyme and this effectively irreversible change would thus enable the triorganotin moiety to freeze the F_0 unit in a state that would disallow rapid proton conduction and therefore indirectly inhibit the multisite mechanism, while leaving the unisite one unaffected as was suggested before.

Two more pieces of evidence further support our proposal that it is the ability of the inhibitor to occupy a site requiring a *trans*-C_3SnO_2 trigonal-bipyramidal geometry around tin rather than the stoichiometry of the 'R_3M (M = Si–Pb) chemical unit itself, that is responsible for the fungicidal action of these compounds.

(a) More than 30 years ago it was found that R_3GeX compounds were ineffective as fungicides when compared with their tin and lead analogues.[35] Four-coordinate R_3GeX compunds are well known but *trans*-bidentate five-coordinate 'R_3Ge' systems are very rare indeed.

(b) More recently $Bu_2Sn(of)Br$ (Hof = 3-hydroxyflavone) has been used as a fluorescent probe of the F_1F_0-ATPase complex in both the membrane-bound and solubilized form.[36, 37] It is an effective

inhibitor of the enzyme activity but it is completely displaced by Bu_3SnCl. This suggests that the Bu_2SnCl (of) Br binding site is in F_0 and is the same as that for Bu_3SnCl. This would then imply that the $[Bu_2Sn(of)]^+$ ion, which can easily survive under the conditions of the study, is able to achieve the same *trans*-bidentate penta coordination as the Bu_3Sn^+ ion itself. This will not be the case for the Bu_2Sn^{2+} moiety derived from Bu_2SnBr_2, and the latter compound indeed does not displace $Bu_2Sn(of)Br$ from its F_0 binding sites.

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