Synthesis, Spectroscopic Studies and Antileishmanial, Antibacterial, Antifungal, Cytotoxicity and Insecticidal Activities of Organotin(IV) Derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

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Summary: The di- and triorganotin(IV) derivatives of (E)-4-oxo-(2,4,6-trichloroanilino)-2-butenoic acid have been synthesized by the reaction of organotin (IV) chloride and oxide with corresponding acid in 1: 2 and 1:1 molar ratios. The reported compounds were characterized by vibrational spectroscopy, multinuclear NMR and Electron Impact Mass spectrometry. These complexes were also screened for their antileishmanial, antibacterial, antifungal, cytotoxicity and insecticidal activity.

Introduction

Organotin (IV) compounds R_nSnX_{4-n} exhibit a variety of pharmaceutical applications depending on the number n, on the type of organic groups R bound to tin and ligand X^-. Organotin compounds have been studied as possible candidates for antitumor activity, chemotherapy, leishmaniasis, helminthes and parasitic infection of the skin [1-2]. Recently, considerable attention has been paid to triorganotin(IV) derivatives having high *in vitro* antifungal activities against some medicinally important fungi [3]. The World Health Organization (WHO) has identified leishmaniasis as a major and increasing public problem, particularly in Africa, Asia and Latin America [4]. The total number of infected people in the world is estimated to be 12 million, and 350 million live in areas where the diseases can be transmitted to man. Three million individuals suffer from various forms of leishmaniasis [5]. In view of above mentioned activities of organotin(IV) carboxylates, we have synthesized a series of organotin compounds of corresponding acid, physically and structurally characterized them. Furthermore, these compounds were also screened to check their antileishmanial, antibacterial, antifungal, cytotoxicity and insecticidal activity.

Results and Discussion

All the complexes are solids, generally with sharp melting points, which are stable in light and dry air. The physical data for the synthesized complexes are given in Table-1.

Infrared spectral analysis

The infrared spectra of the synthesized complexes were recorded as KBr discs, in the range 4000-400 cm^{-1}. The most important frequencies of the complexes reported in Table-2 are $\nu_{asym}(COO)$, $\nu_{sym}(COO)$, $\nu(Sn-C)$ and $\nu(Sn-O)$. The IR spectra of the complexes have been compared with the ligand and from the shift in frequency and/or from the intensity change, the coordination sites have been ascertained. The IR spectrum of the ligand shows bands in the region 3429, 3396, 1712 cm^{-1} assignable to $\nu(OH)$, $\nu(NH)$ and $\nu(C=O)$, respectively. The disappearance of OH viberation in complexes and appearance of new bands in the range of 445-410 cm^{-1} and 535-500 cm^{-1} ascrible to Sn-O and Sn-C mode, respectively, confirm the formation of tin complexes. A strong band at 1712 cm^{-1} assignable to ν (C=O) in the ligand, is not shifted to lower frequency site indicating the non-coordination of the C=O group to tin while $\Delta\nu$ i,e; difference of $\nu_{asym}(COO)$ and $\nu_{sym}(COO)$, in compounds (**1**)-(**5**) is less than 200 indicating the bidentate nature of the carboxylate group [6].

Table-1: Physical data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Comp. No.	General Formula	Molecular Formula	M.W.	M.P. (°C)	Yield (%)
(1)Me_2	$SnMe_2L_2$	$C_{22}H_{16}N_2Cl_6O_6Sn$	733	91-92	92
(2)Oct_2	$SnOct_2L_2$	$C_{36}H_{44}N_2Cl_6O_6Sn$	929	153-155	77
(3)Me_3	$SnMe_3L$	$C_{13}H_{14}NCl_3O_3Sn$	457	72-74	80
(4)Bu_3	$SnBu_3L$	$C_{22}H_{33}NCl_3O_3Sn$	583	101-102	67
(5)Ph_3	$SnPh_3L$	$C_{28}H_{21}NCl_3O_3Sn$	645	121-122	70

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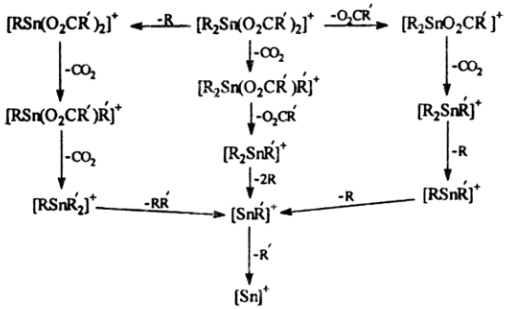
Table-2: IR Spectral data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid (cm^{-1})

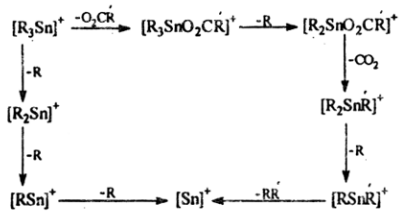
Comp. No.	ν_{NH}	$\nu_{C=O}$	ν_{COO} (Sym)	ν_{COO} (Asym)	$\Delta\nu$	ν_{Sn-C}	ν_{Sn-O}
HL	3396	1712	1540	1320	220	–	–
(1)Me_2	3350	1720	1585	1424	161	500	435
(2)Oct_2	3342	1700	1575	1435	140	535	410
(3)Me_3	3321	1740	1598	1411	187	515	445
(4)Bu_3	3362	1730	1565	1459	106	520	415
(5)Ph_3	3376	1718	1535	1420	115	-	420

Mass spectral analysis

The mass fragmentation patterns of both di- and triorganotin(IV) complexes are given in Scheme-1 and 2. Most common fragments along with their *m/z* values and relative abundance are given in Table-3.



Scheme-1: Fragmentation pattern for diorganotin dicarboxylates.



Scheme 2: Fragmentation pattern for triorganotin carboxylates.

The molecular ion peak is observed in compound (**4**) and (**5**) while it is absent in rest of compounds. Primary fragmentation is due to loss of R group. However, the secondary and tertiary fragmentation occurs by loss of R group in triorganotin (IV) derivatives, while diorganotin(IV) derivatives exhibit slightly different patterns. Secondary fragmentation is achieved due to loss of either R group or CO_2 molecule [7,8].

^1H NMR spectral analysis

^1H NMR spectral data for the reported compounds are given in Table-4. The –NH resonance appears as sharp high field signal in the spectra of all complexes indicating the non-participation of –NH proton in complexation. The OH proton gives broad singlet at 8.56 ppm which disappear in all complexes indicating the deprotonation of the ligand and confirming the complexation. ^3J (^1H, ^1H) values for compounds (**1**)- (**5**) suggests that protons of (HC=HC) are in the cis position. The aromatic protons gives signlet 7.28-7.18 ppm and different R groups attached to tin atom give signals at expected range, thus confirming the complexation.

^{13}C NMR spectral analysis

^{13}C NMR spectral data of $CDCl_3$ solution of ligand acid and its di- and triorganotin(IV) deriva-

Table-3: Mass spectral data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Fragment Ion	**(1)Me_2**	**(2)Oct_2**	**(3)Me_3**	**(4)Bu_3**	**(5)Ph_3**
$R_2Sn(OOCR')_2$	733(n.o)	929(n.o)	-	-	-
$R_3SnOOCR'$	–	–	457(n.o)	583(8)	643(7)
$R_2SnOOCR'$	442(3)	642(5)	442(n.o)	526(100)	566(n.o)
$RSnOOCR'$	427(5)	525(9)	427(n.o)	469(n.o)	489(n.o)
$SnOOCR'$	412(2)	412(5)	412(n.o)	412(4)	412(n.o)
R_3Sn^+	–	–	164(5)	290(30)	350(7)
R_2Sn^+	149(n.o)	345(11)	149(3)	233(34)	273(12)
$C_6H_5^+$	76(8)	76(14)	76(n.o)	76(n.o)	76(4)
Sn^+	120(9)	120(18)	120(4)	120(9)	120(8)
$C_7H_3NCl_3O_2^+$	240(16)	240(100)	240(100)	240(22)	240(14)
$C_6H_3NCl_3^+$	195(100)	195(20)	195(32)	195(18)	195(100)

Table -4: ^{1}H NMR data[a] of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Comp. No.	Cl_3–C_6H_2	–NH	–CH=CH–	R
HL	7.20s	4.57s	6.57-6.66 dd (8.0) 7.45 dd (8.0)	–
(1)Me_2	7.28s	4.46s	7.67-7.70 dd (8.0) 7.45-7.50 dd (8.0)	1.28s
(2)Oct_2	7.21s	4.46s	7.73-7.75 dd (8.0) 7.42-7.49 dd (8.0)	0.85-1.96m
(3)Me_3	7.21s	4.47s	7.44-7.50 dd (8.0) 7.39 d,d (8.0)	0.92s
(4)Bu_3	7.18s	4.47s	7.74-7.78 dd (8.0) 7.39 dd (8.0)	0.93t, 1.35s, 1.65m, 1.27-1.33t
(5)Ph_3	7.28s	4.46s	7.70-7.76 dd (8.0) 7.51 dd (8.0)	7.56-7.69m

[a] s,singlet; dd,doublet of doublet; t,triplet; m,multiplet

Table-5: ^{13}C and ^{119}Sn NMR Data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Carbon No.	HL	(1)Me_2	(2)Oct_2	(3)Me_3	(4)Bu_3	(5)Ph_3
1	137.0	136.6	136.5	136.1	136.1	136.5
2/6	131.0	131.1	131.1	131.1	131.1	131.1
3/5	128.6	128.7	128.7	128.7	128.7	128.7
4	131.1	131.2	131.2	131.2	131.2	131.2
7	165.3	167.2	167.5	167.5	167.5	167.5
8	132.2	132.4	132.3	132.2	132.2	132.2
9	134.2	133.5	133.9	134.7	134.7	134.7
10	174.2	173.7	175.2	175.3	175.2	175.9
11	–	29.67	33.5	-1.2	29.6	143.2
12	–	–	31.8	–	27.8	136.1
13	–	–	29.6	–	17.4	135.7
14	–	–	29.1	–	14.9	129.6
15	–	–	26.2	–	–	–
16	–	–	24.6	–	–	–
17	–	–	22.6	–	–	–
18	–	–	14.05	–	–	–
$\delta(^{119}Sn)$	–	-117.3	-128.71	–	155.05	-48.5

tives are given in Table-5. The position of phenyl carbon signals remains almost unchanged in the complexes as compared with those in ligand acid. The carboxylate carbon gives downfeild signals in the range 173.7-175.6 ppm, indicating participation of the carboxylic group in coordination of tin(IV) [9].The identification of alkyl/phenyl carbons in all the complexes confirms complexation, and the complete assignment of the signals confirms the identity of the compounds.

^{119}Sn NMR spectral analysis

In all complexes, ^{119}Sn spectra show only a sharp singlet indicating the formation of single species. In general ^{119}Sn chemical shifts move to lower frequency with increasing coordination number. The ^{119}Sn NMR chemical shifts of compounds (**1**)-(**5**) are in accordance with the tetrahedral geometry involving the –COO group in coordination to the tin atom and data is given in Table-5.

Biological Activity

Antileishmanial activity

The antiprotozoal activity of the reported compounds against the pathogenic Leishmania was characterized and data is given in Table-6. Compounds (**1**)-(**5**) at concentration µg/ml produced a significant reduction in viable promastigotes. The minimum protozo concentration for promastigotes, defined as that concentration which produced 50% reduction in parasites after 72 h of incubation [10]. Incubation temperature was set at 22 ^{0}C. Compounds (**1**), (**2**), and (**5**) shows the good antileishmanicidal activity while compound (**3**) and (**4**) shows the low activity against the tested leishmania. Amphotericin. B was use as standard drug with the concentration 0.19 µg/ml.

Antibecterial activity

The *in vitro* antibacterial bioassay for the reported compounds was done by agar well diffusion

Table -4: ^{1}H NMR data[a] of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Comp. No.	Cl_3–C_6H_2	–NH	–CH=CH–	R
HL	7.20s	4.57s	6.57-6.66 dd (8.0) 7.45 dd (8.0)	–
(1)Me_2	7.28s	4.46s	7.67-7.70 dd (8.0) 7.45-7.50 dd (8.0)	1.28s
(2)Oct_2	7.21s	4.46s	7.73-7.75 dd (8.0) 7.42-7.49 dd (8.0)	0.85-1.96m
(3)Me_3	7.21s	4.47s	7.44-7.50 dd (8.0) 7.39 d,d (8.0)	0.92s
(4)Bu_3	7.18s	4.47s	7.74-7.78 dd (8.0) 7.39 dd (8.0)	0.93t, 1.35s, 1.65m, 1.27-1.33t
(5)Ph_3	7.28s	4.46s	7.70-7.76 dd (8.0) 7.51 dd (8.0)	7.56-7.69m

[a] s,singlet; dd,doublet of doublet; t,triplet; m,multiplet

Table-5: ^{13}C and ^{119}Sn NMR Data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Carbon No.	HL	(1)Me_2	(2)Oct_2	(3)Me_3	(4)Bu_3	(5)Ph_3
1	137.0	136.6	136.5	136.1	136.1	136.5
2/6	131.0	131.1	131.1	131.1	131.1	131.1
3/5	128.6	128.7	128.7	128.7	128.7	128.7
4	131.1	131.2	131.2	131.2	131.2	131.2
7	165.3	167.2	167.5	167.5	167.5	167.5
8	132.2	132.4	132.3	132.2	132.2	132.2
9	134.2	133.5	133.9	134.7	134.7	134.7
10	174.2	173.7	175.2	175.3	175.2	175.9
11	–	29.67	33.5	-1.2	29.6	143.2
12	–	–	31.8	–	27.8	136.1
13	–	–	29.6	–	17.4	135.7
14	–	–	29.1	–	14.9	129.6
15	–	–	26.2	–	–	–
16	–	–	24.6	–	–	–
17	–	–	22.6	–	–	–
18	–	–	14.05	–	–	–
$\delta(^{119}Sn)$	–	-117.3	-128.71	–	155.05	-48.5

tives are given in Table-5. The position of phenyl carbon signals remains almost unchanged in the complexes as compared with those in ligand acid. The carboxylate carbon gives downfeild signals in the range 173.7-175.6 ppm, indicating participation of the carboxylic group in coordination of tin(IV) [9].The identification of alkyl/phenyl carbons in all the complexes confirms complexation, and the complete assignment of the signals confirms the identity of the compounds.

^{119}Sn NMR spectral analysis

In all complexes, ^{119}Sn spectra show only a sharp singlet indicating the formation of single species. In general ^{119}Sn chemical shifts move to lower frequency with increasing coordination number. The ^{119}Sn NMR chemical shifts of compounds (**1**)-(**5**) are in accordance with the tetrahedral geometry involving the –COO group in coordination to the tin atom and data is given in Table-5.

Biological Activity

Antileishmanial activity

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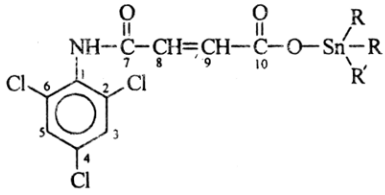
Antibecterial activity

The *in vitro* antibacterial bioassay for the reported compounds was done by agar well diffusion

Table 6: Antileishmanial activity [a]Bioassay of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Compd No.	Standrad Drug	Standrad Drug µg/ml	Inhibition %	IC_{50}
(1) Me_2	Amphotericin B	0.19	100	63.0
(2) Oct_2	Amphotericin B	0.19	100	63.0
(3) Me_3	Amphotericin B	0.19	100	70.0
(4) Bu_3	Amphotericin B	0.19	100	70.1
(5) Ph_3	Amphotericin B	0.19	100	60.2

[a]Test organism; Leishmania (DESTO)



R´ = R for triorganotin

R´ = L for diorganotin

method [11]. Compound (**2**) and (**5**) show the moderate activity while compounds (**1**) and (**4**) show the good activity against the tested bacteria. Compound (**3**) show the low activity. Imipenum was used as standard drug and concentration of sample 3 mg/ml of DMSO is used. The data is given in Table-7.

Antifungal activity

When the reported compounds were screened against different fungi using tube diffusion method

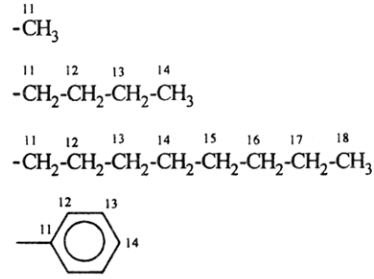


Table-7: Antibacterial activity[a,b] of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Name of Bacteria	Zone of inhibition (mm)						Zone of Inhibition of Std.drug (mm)
	HL	(1) Me_2	(2) Oct_2	(3) Me_3	(4) Bu_3	(5) Ph_3	
Escherichia coli	18	20	14	8	15	10	30
Bacillus subtilis	20	16	–	10	-	5	31
Shigella flexenari	20	10	–	10	-	10	33
Stephlococcus aureus	18	16	12	8	10	10	43
Pseudomonoas aeruginosa	20	10	–	10	-	–	25
Salmonella typhi	18	10	8	5	-	–	41

[a] Standard drug; Imipenum
[b] concentration of sample; 3 mg/ml of DMSO

Table-8. Antifungal activity[a,b] of organotin(IV) derivatives of (*E*)-4-oxo-4- (2,4,6-trichloroanilino)-2-butenoic acid

Name of Fungi	Percent inhibition							
	HL	(1) Me_2	(2) Oct_2	(3) Me_3	(4) Bu_3	(5) Ph_3	Standard Drug	MIC µg/ml
Trichophyton longiusus	40	40	60	60	0	25	Miconazole	70
Candida albicans	60	40	30	0	0	35	Miconazole	110.8
Aspergillus flavis	10	40	40	0	25	40	Amphotericin. B	20
Microsporum canis	10	60	40	70	40	60	Miconazole	98.4
Fusarium solani	10	40	45	0	40	65	Miconazole	73.25
Candida glaberata	30	0	40	0	0	40	Miconazole	110.8

[a] Incubation period; 7 days
[b] Incubation temperature; 27 °C

Table-9: Insecticidal activity[a,b] data of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Name of Insect	% Mortality (-ve Control)					
	HL	(1) Me_2	(2) Oct_2	(3) Me_3	(4) Bu_3	(5) Ph_3
Tribolium castaneum	20	0	0	0	20	25
Sitophilus oryzae	30	0	0	0	0	25
Rhyzopertha dominica	20	0	0	0	25	0
Callosbrchus analis	25	0	0	0	20	25

[a] Standard Drug Premethrin
[b] +ve Control : 100

Table-10: Brine Shrimp (*Artemia salina*) lethality bioassay[a-c] of organotin(IV) derivatives of (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

Comp. No.	Dose (μg/ml)	No. of Shrimps	No. of Survivors	LD_{50} (μg/ml)	Upper toxic limit	Lower toxic limit
	1000	30	10			
HL	100	30	10	149.1010	381.76	139.191
	10	30	10			
	1000	30	0			
(1) Me_2	100	30	0	10.0010	10.8119	0.4001
	10	30	10			
	1000	30	0			
(2) Oct_2	100	30	0	10.1101	10.0010	0.5914
	10	30	10			
	1000	30	0			
(3) Me_3	100	30	0	10.1911	10.8194	0.4110
	10	30	11			
	1000	30	0			
(4) Bu_3	100	30	0	10.9110	10.8149	0.4910
	10	30	14			
	1000	30	0			
(5) Ph_3	100	30	0	10.1914	10.1100	0.5610
	10	30	14			

[a] standard drug (Etoposide); LD_{50} (μg/ml) = 7.4625
[b] no. of replicants; 3
[c] incubation temperature = 28 ± 1 °C

[11], it was observed that all reported compounds show good activity against testes plant pathogens. Miconazole and Amphotericin.B were used as standard drugs and concentration of sample 400 μg/ ml is used. The antifungal data is reported in Table-8.

Insecticidal activity

Insecticidal activity data was collected by Contact toxicity method.[11] and is given in Table-9. Premethrin was used as standard drug with concentration 235.75 μg/cm^2. Compound (**1**) shows moderate activity while compound (**2**) and (**5**) shows 30 and 60 % activity, respectively. Compound (**3**) and (**4**) does not show any insecticidal activity.

Cytotoxicity

Brine Shrimp's method [12] has been used for the determination of toxicity of the organotin carboxylates. The results are reported in Table-10. It has been observed that compounds (**1**)-(**5**) show positive lethality against the tested Brine Shrimp's larvae. Etoposide was used as standard drug with LD_{50} (μg/ml) 7.4625.

Experimental

Dimethyltin dichloride, dibutyltin dichloride and trimethyltin chloride were purchased from Aldrich and were used without any further purification. Dioctyltin oxide was of Alfa Aesar origin. Solvents were purified and dried before use by the literature methods [13]. All melting points are uncorrected. The progress of the reaction was monitored by TLC on silica gel. Infrared spectra were recorded on a Bio-Rad FTIR spectrometer in the range 4000-400 cm^{-1}. ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a Brucker AM-250 spectrometer (Germany) using $CDCl_3$ as an internal reference [δ ^{1}H($CDCl_3$) = 7.25 : δ ^{13}C($CDCl_3$) = 77.0]. ^{119}Sn NMR spectra were obtained with Me_4Sn [(Sn) = 37.296665] as an external reference. Mass spectral data were recorded on a MAT 8500 Finngin (Germany) at 70 eV.

General procedure for synthesis of (E)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

A solution of maleic anhydride (10 g, 0.101 mole) in HOAc (300 ml) was added to a solution of 2,4,6-trichloroaniline (20.08 g, 0.101 mole) in HOAc (150 ml) and the mixture was stirred at room temperature overnight. The light grey precipitates were filtered, washed with cold distilled H_2O (200 ml) and air dried.

General procedure for synthesis of organotin(IV) derivatives of (E)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid

(a) The ligand (E)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic Acid (1 g, 3.41 mmole) was suspended in dry toluene (100 ml) and treated with Et_3N (0.47 ml, 3.41 mmole). The mixture was refluxed for 2-3 hours. To a solution of triethylammonium salt of ligand acid in dry toluene, diorganotin dichloride (1.7 mmole) or triorganotin chloride (3.41 mmole) was added as solid to a reaction flask with constant stirring and reaction mixture was refluxed for 8-10 hours. The reaction mixture contained Et_3NHCl was filtered off such that filtrate had the organotin derivative. The solvent was removed through rotary apparatus. The mass left behind was recrystallized from $CHCl_3$ and *n*-hexane (1:1).

b) The ligand (*E*)-4-oxo-4-(2,4,6-trichloroanilino)-2-butenoic acid (1 g, 3.41 mmole) was suspended in dry toluene, (100 ml). To this solution, Oct_2SnO (1.5 mmole) was added as solid with constant stirring and refluxed for 8-10 hours. Water formed during the reaction was removed *via* Dean and Stark trap. The solvent was evaporated through rotary apparatus and the product obtained was recrystallized in $CHCl_3$: *n*-hexane (1:1) mixture.

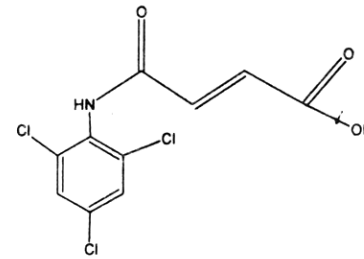
The general chemical reactions for both di- and triorganotin(IV) complexes are given below:

$$R_2SnCl_2 + 2HLNEt_3 \longrightarrow R_2SnL_2 + 2Et_3NHCl$$

$$R_3SnCl + HLNEt_3 \longrightarrow R_3SnL + Et_3NHCl$$

$$Oct_2SnO + 2HL \longrightarrow Oct_2SnL_2 + 2H_2O$$

HL =



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