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NOTES

Biological Activities of Some New Molecular Adducts of Triphenyltin Pseudohalides

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Some new molecular adducts of triphenyltin pseudohalides of the general formula $Ph_3SnX.L$ (X=NCS, NCO) with several O, N, S-donor bases have been synthesised by the direct interaction of pseudohalides Lewis bases either in a suitable solvent or without it. All these compounds have been evaluated for their antibacterial, fungicidal and insecticidal activity. These compounds have also been tested for their *in vivo* and *in vitro* (monoamine oxidase and acetylcholinesterase) CNS activity.

Compounds containing triorganotin derivatives particularly triphenyltin and tributyltin(IV) have been reported to possess excellent biocidal activity[1–4]. They are highly toxic to mammals and cause neurological damage to rats[5]. Ph_3SnX (X = NCS, NCO) compounds have been reported as effective fungicides, bactericides and insecticides[1,6,7]. Fungicidal and bactericidal activities with low plant toxicity have also been shown by molecular adducts of organotin with certain sulphoxide and phosphin oxide bases[8–11]. Encouraged by these findings a series of $Ph_3SnX.L$ (X = NCS, NCO), (L = DMSO, DMF, $Ph_3P{-}O$, Ph_3P = S,E.V., TMTS, 2 pic N-oxide, pyrrolidine, 1 Me = 2 pyrrolidine) were prepared by the reported method[12] and evaluated for their antibacterial, fungicidal, insecticidal, monoamineoxidase and acetylcholinesterase activity *in vitro*. Few compounds were screened for CNS activity and their ALD_{50} values were calculated.

In a representative experiment, to a solution of Lewis acid (5 mmole) in about 15 ml of the solvent, was added a solution of the excess Lewis base (10 mmole) in about 20 ml of the same solvent and the mixture was refluxed for 2-3 hrs. Excess of the solvent was distilled off and the residual solution was kept overnight in a deep freeze to yield a crystalline adduct. In some cases the adduct was precipitated by addition of excess solvent ether, hexane and petroleum ether mixture. The crude products were recrystallised by the same solvent.

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$$Ph_3SnX + nL \xrightarrow[\text{or heat}]{\text{Solvent}} Ph_3SnX.Ln$$

(n = 1 or 2; L = Ligands)

Antibacterial Activity : All the compounds were screened for their inhibitory effects against *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus pumilus*, *Escheriochia coli* and *Salmonella typhi* by agar plate diffusion technique[13] in nutrient agar media. The zones of inhibition measured in milimetres, are cited in Table 1.

TABLE I

ANTIBACTERIAL ACTIVITY

Sl. No.	Compounds $Ph_3SnX.L$		Antibacterial Activity				
			B. subtilis	B. pumilus	S. aureus	E. coli	S. typhi
	X	L					
1.	NCS	DMSO	+++	+++	++	++	++
2.	NCS	Ph_3PO	++	++	++	++	++
3.	NCS	HMPA	++	++	++	++	++
4.	NCS	DMF	++	+++	++	++	++
5.	NCS	E.U.	++	++	++	++	++
6.	NCS	$Ph_3P=S$	++	++	++	++	++
7.	NCS	Pyrro	++	++	++	++	++
8.	NCO	2 pic N oxide	++	++	++	++	++
9.	NCO	Ph_3PO	++	++	++	++	++
10.	NCO	HMPA	++	++	++	++	+++
11.	NCO	DMF	+++	+++	+++	++	++
12.	NCO	DMA	++	++	++	++	++
13.	NCO	$Ph_3P=S$	++	++	++	++	++
14.	NCO	1, 10 phen	++	++	++	++	++
15.	NCO	1 Me-2 Pyrro	++	++	++	++	++

− = No inhibition; + = zone size 6–8 mm; ++ = zone size 9–15 mm; +++=zone size 16–20 mm; +++ = zone size 20 mm.

The results indicate that all the complexes exhibit considerable activity against all the test organisms. In general the gram negative species *E. coli* and *S. typhi* are less sensitive than gram positive bacteria. Contrarily, the parent compound is completely inactive towards *E. coli* and *S. typhi*

(zone diameter 7 mm) which on complexation with lewis bases show enhanced activity in most cases (zone diameter 11–13 mm). The nature of isocyanato/thiocyanato group attached to the metal atom and the lewis bases present in the molecule does not appear to affect the activity significantly. The adducts of Ph_3SnNCO with DMF and 2 pic. N-oxide possess significant activity amongst all the compounds examined (zone diameter 14–20 mm).

Fungicidal Activity : These compounds were screened for fungicidal action against *Helminthosporium* sp., *Colletotrichum falcatum Went*, *Fusarium moniliforme* and *Aspergillus terreus* using as agar plate technique[14]. The percentage inhibition is given in Table 2. In addition, minimum inhibition concentration was evaluated for *Aspergillus niger*, *Candida albicans and Tryptogames mentagrophytes* (skin pathogens) using two-fold serial dilution method[2].

It appears from the data that all the compounds are significantly active against all the fungi tested. *Helminthosporium* sp. and *C. falcatum* Went fungus species are comparatively more affected than others which is comparable to standard fungicide tributyltin oxide (TBTO). The adduct of 1,10-phen and HMPA with Ph_3SnNCO show significant activity.

The minimum inhibitory concentration (MIC) values collected in Table 2b reveal that Ph_3SnX (X=NCS, NCO) inhibits the growth of *T. mentagrophytes*, *A. niger* and *C. albicans* at 10, 15 and 20 μg/ml respectively. The complex formation with lewis bases results in decreased activity against *C. albicans* (20–30 μg/ml). However, most of the adducts possess same activity as Ph_3SnX (X=NCS, NCO) against *A. niger* and *T. mentagrophytes* excepting $Ph_3SnNCO.Ph_3PO$ which is significantly active against *T. mentagrophytes* only. The biocidal activity is not influenced significantly by varying X or L groups in the adducts, but it is mainly effected by Ph_3Sn^+ moiety as reported earlier by Srivastava *et al.*[2–4].

Insecticidal Activity : Method of topical applications by micrometer syringe was employed to test insecticidal activity on adult female and male cockroaches[15] using parathion, a standard insecticide. It reveals from observation that the introduction of Lewis bases does not impart any enhanced activites except mild insect toxicity exhibited by compound nos. 4, 5, 9, 12. The most active compound is $Ph_3SnNCS.EU$ (Table 3). Like bactericidal activity, variation of X group in the adducts has no marked effect on insecticidal activity.

Monoamineoxidase Activity : Monoamineoxidase activity (MAO) of rat brain homogenate was determined by the method of Krazil[16] using kynuramine as substrate in an Amino Bowman spectrophotofluorometer at activation 315 nm and emission at 380 nm. *In vitro* studies on monoamineoxidase enzyme show that all the molecular adducts instead of inhibiting the growth of the microorganism, actually increases their activity

TABLE 2a

FUNGICIDAL ACTIVITY OF MOLECULAR ADDUCTS OF TRIPHENYLTINPSEUDOHALIDES

	Compounds Ph_3SnX. L X = NCS	Concentration	Colony diameter (cm)				Percentage inhibition			
			A. terreus	C. fal went	Helm sp.	F. moni	A. terreus	C. fal went	Helm sp.	F. moni-
	(L)									
1.	DMSO	1:1,000	0.3	0.0	0.2	0.9	92.50	100.00	100.00	80.00
		1:10,000	0.7	0.0	0.0	1.2	80.00	100.00	100.00	71.76
		1:1,00,000	0.3	0.8	0.0	1.6	75.55	87.00	87.00	62.35
2.	Ph_3PO	1:1,000	—	0.2	0.0	0.4	—	100.00	100.00	91.55
		1:10,000	—	1.2	0.0	0.9	—	80.00	100.00	80.00
		1:1,00,000	—	1.2	0.0	1.3	—	80.00	100.00	70.00
3.	HMPA	1:1,000	—	0.0	0.0	—	—	100.00	100.00	—
		1:10,000	—	0.0	0.0	—	—	100.00	100.00	—
		1:1,00,000	—	1.5	0.0	—	—	75.00	100.00	—
4.	DMF	1:1,000	0.5	0.0	0.0	1.0	85.00	100.00	100.00	76.47
		1:10,000	0.5	0.0	0.0	1.0	86.00	100.00	100.00	76.46
		1:1,00,000	0.3	1.6	0.0	1.0	75.00	73.00	100.00	76.47
5.	Ph_3PS	1:1,000	0.5	0.0	0.0	1.1	85.00	100.00	100.00	75.00
		1:10,000	0.7	0.0	0.0	1.2	80.00	100.00	100.00	72.00
		1:1,00,000	0.7	0.0	0.0	1.2	80.00	100.00	100.00	71.76
6.	Pyrrolidine	1:1,000	0.4	0.4	0.0	0.9	87.50	92.00	100.00	80.00
		1:10,000	0.5	0.4	0.0	0.9	85.00	91.20	100.00	78.82
		1:1,00,000	0.3	0.4	0.0	0.9	75.00	91.20	100.00	78.82
	X = NCO									
7.	Ph_3PO	1:1,000	0.4	0.0	0.9	0.4	87.50	100.00	88.88	91.75
		1:10,000	0.4	0.1	0.9	0.1	87.50	82.40	88.88	85.85
		1:1,00,000	0.8	1.2	1.0	1.1	77.50	80.73	87.50	74.11

8.	HMPA	1:1,000	0.0	0.0	0.0	1.1	100.00	100.00	100.00	76.29
		1:10,000	0.0	0.0	0.0	1.2	100.00	100.00	100.00	70.95
		1:1,00,000	0.8	0.0	0.0	1.2	77.50	100.00	100.00	70.95
9.	DMF	1:1,000	0.4	0.0	0.0	0.9	81.50	100.00	100.00	78.80
		1:10,000	0.5	0.4	0.0	1.2	85.00	91.00	100.00	72.00
		1:1,00,000	0.5	1.1	0.0	1.2	85.00	80.44	100.00	72.00
10.	1,10–Pheny	1:1,000	0.0	0.0	0.0	0.0	100.00	100.00	100.00	100.00
		1:10.000	0.0	0.0	0.0	0.4	100.00	100.00	100.00	81.41
		1:1,00,000	0.7	2.2	0.0	1.2	80.00	63.10	100.00	71.76
	TBTO	1:1,000	0.2	0.0	0.0	0.3	95.00	100.00	100.00	94.11
		1:10,000	0.2	0.0	0.0	0.3	95.00	100.00	100.00	94.11
		1:1,00,000	0.2	0.0	0.0	0.6	95.00	100.00	100.00	88.23
	Control		3.5	6.0	8.0	3.5				

Compound No. corresponds to Table 1.

TABLE 2b

ANTIFUNGAL ACTIVITY OF $Ph_3SnX.L$

Compound No.	Minimum inhibition concentration (μg/ml)		
	C. albicans	A. niger	T. mentagrophytes
2.	30	15	10
3.	25	15	15
4.	25	25	15
6.	30	20	10
7.	20	25	10
9.	25	15	5
10.	25	15	10
11.	25	30	10
14.	25	25	10
TBTO	15	15	5

TABLE 3

INSECTICIDAL ACTIVITY OF $Ph_3SnX.L$

Compound No.	K.D./hr at concentration	
	0.5%	0.1%
1.	10	12
2.	17	28
3.	10	12
4.	18	28
5.	8	10
6.	12	18
7.	22	24
8.	15	20
9.	18	30
11.	12	13
12.	22	24
13.	14	17
14.	12	14
15.	22	24
Acetone	40	40
Parathione	4	6

Compound No. corresponds to Table 1.

excepting those of $Ph_3SnNCS.DMF$ and $Ph_3SnNCS.DMSO$ which produce inhibitory effects on the enzyme upto 20–29% at 1×10^{-4}M concentration (Table 4).

TABLE 4

CNS ACTIVITY OF MOLECULAR ADDUCTS OF TRIPHENYLTIN PSEUDOHALIDES *IN VIVO* AND *IN VITRO*

Comp. No.	CNS Activity at 1/5th AL D_{50} i.p.					CNS Activity *in vttro*	
	SMA	Respiration	Reactivity	Other effects	ALD_{50} mg/kg i. p.	MAO% at 1×10^{4}M	AChE% inhibition activation at 1×10^{3}M
1.	—	—	—			−29	+56
2.	—	—	—	anoxic convulsions	72.6	—	+28
3.						—	+56
4.	—	—	—	strousl tail	200	−20	+27
5.	—	—	—			—	+47
6.	—	—	—	anoxic convulsions occurs	68.1	+20	+36
7.	—	—	—	—	—	+105	+6
8.	—	—	—	—	—	+89	e
9.	—	—	—	strousl tail	150	+72	+27
10.	—	—	—	anoxic convulsions occurs	68.1	+69	+e

Acetylcholinesterase Activity: The method of Parmar *et al.*[17] was employed to determine acetylcholinesterase activity in rat brain homogenate. The activity of the tested compound was observed at 1×10^{-3}M concentration in propylglycol using acetylcholine as substrate. The data tabulated in Table 3 show that the acetylcholinesterase inhibition activity has been lowered on complexation of Lewis bases with triphenyltin isocyanate. However, the per cent inhibition of the adducts with DMSO, HMPA and 1,10 phen remains at par with the parent compound (55 to 56%). The varying nature of (X) in Ph_3SnX has no marked effect on the per cent inhibition of the adducts.

CNS Activity: A few compounds have been tested for their grass effects on central nervous system at 1/5th of approx. LD_{50} value by employ-

ing the method of Weil[18]. The data for the said compounds have been recorded in Table 4. Compounds No. 2,4,6,9,10,14 were administered intraperitoneally to the group of 5 albino mice of either sex in doses of 68.1, 72.6, 200, 68.1, 150 and 46.4 mg/kg body weight at the approximately LD_{50} value and gross effects were observed at 1/5th of the LD_{50}. The adducts of Ph_3SnNCS stimulated the central nervous system with increased spontaneous motor activity (SMA), reactivity and respiration, while those of Ph_3SnNCO show depressant features with decreased SMA, reactivity and respiration. When compounds are administered to mice anoxic convulsions occur showing acute toxicity. After intraperitoneal injection to albino mice triphenyltin compounds might have degraded to diphenyl, monophenyl and finally inorganic tin compounds as metabolites[19] which are reported[20] to be non-toxic.

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