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Reactions of Triorganotin(IV) Compounds with L-Cysteine, L-Cysteine Ethyl Ester, N-Acetyl L-Cysteine and Glutathione Reduced

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Triorganotin(IV) compounds are potent inhibitors of mitochondrial oxidative phosphorylation [1]. The study of triethyltin binding to rat liver mitochondria has led to the assignment of two binding sites in the membrane: one of high affinity, the other low affinity [2]. These binding sites are considered to involve histidine and thiol groups respectively [2, 3]. No definite information exists, however, concerning the reactions of organotin compounds with thiol-containing amino acids and peptides. We have reported previously studies of organotin(IV) derivatives of L-cysteine and DL-penicillamine [4]. In this communication we report the reactions of some triorganotin(IV) compounds with L-cysteine, L-cysteine ethyl ester, N-acetyl L-cysteine, and glutathione reduced.

Bis(triphenyltin)oxide, $(Ph_3Sn)_2O$, reacted with L-cysteine at 70 °C in a water/ethanol solvent mixture. After the reaction mixture had been filtered, crystallization produced only bis(triphenyltin)sulfide as evidenced by the mass spectrum (m/z 734 = $(Ph_3Sn)_2S^+$; m/z 657 = $Ph_3SnSSnPh_2^+$) and the ^1H N.M.R. spectrum (peaks due only to phenyl ring protons, complex group at τ = 7.3). Both spectra were identical to those from an authentic sample of the sulfide.

L-cysteine ethyl ester hydrochloride and $(Ph_3Sn)_2O$ reacted in a water/ethanol mixture at pH 8–11. A product which was isolated by extraction with chloroform had a mass spectrum which showed the presence of Ph_3SnCl, $Ph_3SnSCH_2CH(NH_2)COOC_2H_5$, and $(Ph_3Sn)_2S$. The ^1H N.M.R. indicated that the product was predominantly the organotin–cysteine derivative, while microanalysis confirmed the presence of the chloride compound. It is surprising that triphenyl tin chloride can form in the presence of a strong base such as sodium hydroxide. The cysteine derivative slowly decomposes on standing, forming bis(triphenyltin)sulfide and other products. The presence of the sulfide in the product isolated is probably due to this decomposition.

Trimethyltin chloride reacted with L-cysteine ethyl ester hydrochloride at pH 9, in a water/ethanol mixture. The product, isolated by extraction with chloroform, was identified as $(CH_3)_3SnSCH_2CH(NH_2)COOC_2H_5$ by its mass spectrum, ^1H N.M.R. spectrum, and I.R. spectrum (Tables I and III). The mass spectrum also revealed the presence of small amounts of $[(CH_3)_3Sn]_2S$. On standing, the product decomposes, giving off a very pungent odor of NH_3 and H_2S. After this, a water-soluble portion can be separated, which does not contain the organotin moiety (as shown by the N.M.R. spectrum). The insoluble residue has an increased amount of the trimethyltin sulfide. An attempt to identify all the decomposition products is in progress.

The reaction between bis(tri-n-butyltin)oxide and L-cysteine ethyl ester hydrochlorodem under similar conditions leads to the formation of n-$Bu_3SnSCH_2CH(NH_2)COOC_2H_5$. Analysis of the product confirms the formula, and its mass, N.M.R., and I.R. spectra show it to be similar to the phenyl tin and methyl tin derivatives discussed above. *Anal.*: Calc. C, 46,59; H, 8.50; S, 7.32%. Found: C, 45.86; H, 7.62; S, 6.9%. This product also decomposes, but at a slower rate than the trimethyltin derivative.

Both $(CH_3)_3SnCl$ and $(n\text{-}Bu_3Sn)_2O$ form stable complexes with N-acetyl L-cysteine. The products are clear, 'plastic' materials which are soluble in chloroform and ethanol, and insoluble in water. The trimethyltin derivative shows two peaks in the ^1H and ^{13}C N.M.R. spectra, due to the organotin moiety. I.R. spectra indicate that both these compounds may be associated in the solid, via the C=O and NH groups.

$(n\text{-}Bu_3Sn)_2O$ and glutathione reduced react readily under relatively mild conditions to form a product which corresponds to:

$$\begin{array}{l}Bu_3SnSCH_2CHCONHCH_2COOSnBu_3\\ \qquad\qquad\quad |\\ \qquad\qquad HNCO(CH_2)_2CH(NH_3^+)CO_2^-\end{array}$$

Anal.: Calc, C, 46.13; H, 7.85; S, 3.62; Sn, 26.81; O, 10.84%. Found: C, 45.88; H, 7.99; S, 3.0; Sn, 27.25; O, 11.9%. The ^{13}C N.M.R. spectrum of the complex contains chemical shifts which correspond to the αC of the Bu_3Sn–S (13.8) and Bu_3Sn–O (17.1) moieties, and the ^1J values slow that these tin atoms may be four- and five-coordinated respectively. A preliminary Mössbauer spectrum also indicates that the two tins have similar isomer shifts and quadrupole splittings which are indicative of high and low coordination states.

A product is formed from the reaction between $(CH_3)_3SnCl$ and glutathione reduced, but it has not so far been purified because it is water soluble, and the NaCl and unreacted starting materials are difficult to separate.

Details of preparative methods and structural studies will be published shortly. It is clear at this stage that organotin(IV) compounds react readily with the thiol groups of amino acids and peptides. The stability of these compounds increases from L-cysteine to glutathione reduced. This is an indication

TABLE I. ^{1}H N.M.R. Spectra. Chemical shifts in ppm from T.M.S. are internal standard. Coupling constants in Hz, accurate to ±0.1 Hz, and are the average from at least three scans.

Compound	Organotin Moiety			Ligand Shifts
	Shift	$^{2}J(^{119}Sn-^{1}H)$	$^{2}J(^{117}Sn-^{1}H)$	
$Me_3SnCyst-Et$[a] ($CDCl_3$)	0.44	56.1	53.7	Ethyl = 4.19, 1.29. Cyst: four peaks at 3.54 and at 2.86.
$Ph_3SnCyst-Et$ ($CDCl_3$)	7.21–7.48	–	–	Ethyl = 4.01, 1.30. Cyst: four peaks at 3.35 and 2.77.
$Bu_3SnCyst-Et$ ($CDCl_3$)	0.80–1.69	–	–	Ethyl CH_2 = 4.14. A group at 2.62–3.20.
$(Me_3Sn)_2NAcet-L-Cyst$ ($CDCl_3$)	0.44 0.61	56.2 59.0	53.6 56.0	SCH_2 = 3.02(d), NCH = 4.70(q), NH = 6.56(d), CH_3 = 2.02
$(Bu_3Sn)_2NAcet-L-Cyst$ ($CDCl_3$)	0.80–1.69	–	–	SCH_2 = 3.06(d), NCH = 4.77(q), NH = 6.54(d), CH_3 = 2.06(s).
$(Me_3Sn)_2SG(D_2O)$	1.03	64.0	61.0	2.74(t), 3.09(t), 3.49(q), 4.29(s), 4.96 (t)

[a]Abbreviations used in this and the other tables are: Cyst-Et = L-cysteine ethyl ester; NAcet-L-Cyst = N-acetyl L-cysteine; SG = glutathione reduced.

TABLE II. ^{13}C N.M.R. Spectra.

Compound	Shifts of Organotin Moiety	$^{1}J(^{119}Sn-^{13}C$	$^{1}J(^{117}Sn-^{13}C)$	Ligand Shifts
$(Me_3Sn)_2NAcet-L-Cyst$ ($CDCl_3$)	−1.3, −5.3	443.0[a] 416.0[a]		CO = 174.2; 169.6; NCH = 54.8; SCH = 29.2; CH_3 = 23.2
$(Me_3Sn)_2SG$ (D_2O)	−1.5	439.0	418.0	CO = 177.2, 175.8, 175.1, 172.9; others = 57.5; 55.3, 44.7, 32.8, 29.0, 27.5
$(Bu_3Sn)_2SG$ ($CDCl_3$)	αC(Sn–O) = 17.1, βC = 28.0 γC = 27.2, δC = 13.8	366	349	CO = 170.6, 173.0, 174.3; others = 56.0, 54.4, 42.7, 33.0, 28.8 (28.4)
	αC(Sn–S) = 13.8	329	315	
HSG (D_2O)	–	–	–	CO = 173.6, 174.6, 175.9; others = 54.8, 56.8, 42.7, 32.2, 27.2, 26.6

[a]The peaks were not resolved into ^{119}Sn and ^{117}Sn isotope peaks.

TABLE III. I.R. Spectra.

Compound	$\nu(NH_2)$[a]	$\nu(C=O)$[a]	$\nu(Sn-C)$	$\nu(Sn-S)$	$\delta(NH_2)$[a]	$\nu(S-H)$[a]
Me_3Sn Cyst-Et	3378(m)[b] 3205(w)	1743(s)	540(s) 515(m)	343(m)	1590(m.br)	Absent
Bu_3Sn Cyst-Et	3370(w) 3200(v.w)	1743(s)	600(s) 513(m)	330(m)	1665(m)	Absent
Ph_3Sn Cyst-Et	3368(m) 3200(w)	1737(s)	270(m)	348(w)	1593(m.br)	Absent
$(Me_3Sn)_2NAcet-L-Cyst$	3400(w.br) 3280(w.br)	1628(s.br)	550(w) 510(w)	~335(w.br)		Absent
$(Bu_3Sn)_2NAcet-L-Cyst$	3270(m.br) 3090(w)	1625(s.br)	600(m) 515(m)	345(m.br)		Absent
NAcetyl-L-Cysteine	3372(s)	1723(s)	–	–	1585(s.br)	2548(s)
$(Bu_3Sn)_2SG$	3395(m.br) 3295(s.br)	1655(s.sh) 1635(s.br)	600(s) 518(m)	343(s)	~1600(br.sh)	Absent
Glutathione	3344(s) 3245(s) 3124(s) 3024(s)	1715(s) 1655(s)	–	–	~1600(s.br)	2525(s)

[a]Following Ref. 5. [b]Abbreviations: s = strong, m = medium, w = weak, sh = shoulder, br = broad.

that quite stable compounds may be formed by the interaction of organotin compounds with polypeptides and proteins containing thiol groups.

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