Complexes of Terminally-protected Dipeptides with Trimethyltin as Models for Triorganotin–Protein Interactions

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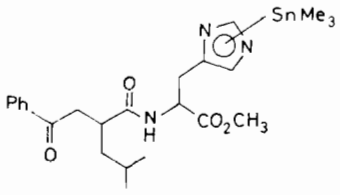
Abstract

The two trimethyltin–dipeptide complexes, PhCO·Leu·His·OMe($SnMe_3$) and PhCO·His·Cys·OMe($SnMe_3$), have been synthesised and characterised.

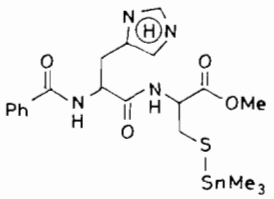
Introduction

Most notable amongst the protein systems to which triorganotin fragments are known to bind are the haemoglobins [1a–e] and the adenosine triphosphotase system [2a–e]. Both histidine (via the imidazole ring) and cysteine (via the sulphydryl group) residues have been implicated in the binding of triethyltin to cat and rat haemoglobins, with two triorganotin residues bound at identical sites on the alpha-chain sub-unit of the haemoglobin tetramer, and also in the low-affinity site of the ATPase system. In both cases the coordination number at tin was considered from Mössbauer data to be five in a *cis*-trigonal bipyramidal arrangement [1d, 2c, 2d]. However, the binding at the high-affinity ATPase site appears to involve only a histidyl imidazole residue resulting in four-coordination for tin, although a *cis* trigonal bipyramidal geometry could not be unequivocally excluded [2c, 2d].

Although other workers have previously characterised triorganotin derivatives of simple amino acids, their N-acyl derivatives, glycylglycine, methyl cysteinate and glutathione [3a–i], these compounds do not represent accurate models for triorganotin–protein interactions of these types, since they take little or no account of the additional terminal amino and carboxyl functions, which in the proteins themselves would be involved in peptide-link formation along the protein backbone. In order to overcome this shortcoming in modelling strategy, we have synthesised the trimethyltin derivatives of two terminally-protected dipeptides, methyl N-benzoyl-*l*-leucyl-*l*-histidinate (**I**) and methyl N-benzoyl-*l*-histidyl-*l*-cysteinate (**II**) as models for the interaction of trimethyltin with, respectively, the high-affinity site of ATPase (histidine only), and the low-affinity site of ATPase and haemoglobins (histidine and cysteine).



I



II

Both complexes are off-white, non-crystalline solids which are soluble in dmso, although complex **I** is also soluble in methanol and chlorinated hydrocarbons. In the solid, **I** exhibits both antisymmetric and symmetric $\nu(SnC_3)$ vibrations (infrared (KBr disc): 549 cm^{-1} and 519 cm^{-1}; Raman: 548 cm^{-1} and 514 cm^{-1}], characteristic of a non-planar [Me_3-Sn] moiety. The value of the Mössbauer quadrupole splitting (3.16 mm s^{-1}) is, however, significantly higher than might be expected for ideal tetrahedral [SnC_3N] coordination and indicates disortion towards trigonal bipyramidal geometry. Confirmation of this inference is afforded by the observation of fragments in the mass spectrum resulting from cleavage of the leucine α-carbon-to-peptide carbonyl bond for both dipeptide ligands either side of the [Me_3Sn] moiety along a one-dimensional polymeric chain, formed by a long interaction between the

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terminal amide oxygen of one molecule and the tin of an adjacent molecule. That the intermolecular association is very weak is indicated by the very small lowering of the amide ν(C=O), and also by the high negative value of the Mössbauer recoil-free fraction temperature coefficient, a, (-1.91×10^{-2} K^{-1}) which is of the same magnitude as those previously determined for organotin compounds known from crystallographic data to possess molecular lattices [4].

In contrast, complex **II** exhibits only the antisymmetric $\nu(SnC_3)$ mode in the infrared at 551 cm^{-1} (the compound decomposes in the laser precluding Raman measurement), whilst Mössbauer quadrupole splitting and a values of 3.35 mm s^{-1} and -1.69×10^{-2} K^{-1}, respectively, are indicative of a more tightly bound one-dimensional chain structure in which planar [Me_3Sn] moieties are bridged by the dipeptide, and resulting in a *trans* trigonal bipyramidal geometry at tin. That the axial ligands at tin are imidazole nitrogen and sulphydryl sulphur, is apparent from the observation of fragments in the mass spectrum at m/e values of 554, 524, 360 and 345 which contain a central [(imidazole)–Sn–S–CH–] unit.

Upon dissolution the solid-state chain structure of both complexes is broken down. However, the nature of the solution species is complex. In d_4-methanol, the ^{13}C NMR spectrum of complex **I** exhibits a single $Sn^{13}CH_3$ resonance with clearly resolved satellites ($^1J(^{117,119}Sn-^{13}C) = 471{,}2$, 493.1 Hz), showing that five-coordination is retained in solution, presumably by coordination of a solvent molecule. Chemical shift data for the imidazole ring carbon atoms indicate that the tin is bound to N1 of the ring. In addition, the spectrum shows the presence of *cis* and *trans* isomers resulting from restricted rotation about both the amide and peptide bands. Only one type of $Sn^{13}CH_3$ resonance may be distinguished in $CH_2Cl_2/CDCl_3$, although the two $SnC\underline{H}_3$ resonances (separated by 0.01 ppm) are observed in the ^1H spectrum (in $CDCl_3$). Both single-bond $^1J(^{117,119}Sn-^{13}C)$ (475 Hz, unresolved) and two-bond $^2J(^{117,119}Sn-^1H)$ (61.2, 63.9 Hz) confirm five-coordination for tin, whilst the *trans* amide conformer of the dipeptide skeleton is favoured. In contrast to the situation in d_4-methanol, the imidazole ^{13}C chemical shift pattern in the chlorinated methane solvent mixture shows the occurrence of a dynamic equilibrium between both ring nitrogen atoms as binding sites for the trimethyltin group. These data, therefore, tend to support a 'head-to-tail' dimeric structure in this non-donor solvent system, in which the tin atoms are bridged by amide carbonyl and rotating imidazole groups. A similar situation also appears to occur in dmso solution.

The ^{13}C spectrum of complex **II** in dmso is very complex, but some inferences may be made. The single $Sn^{13}\underline{C}H_3$ resonance is flanked by unresolved satellites with the exceptionally large one-bond $^1J(^{117,119}Sn^{13}C)$ (unresolved) coupling of 520 Hz. The two-bond $^2J(^{117,119}Sn-C-^1H)$ (also unresolved) coupling constant is similarly unusually high (96 Hz) and these values may reflect the presence of tin atoms which are six-coordinated by the three-methyl groups, the dipeptide imidazole nitrogen and sulphur atoms, as well as a dmso solvent molecule. Only the *trans*-amide-*trans*-peptide conformer of the dipeptide is apparent.

Two principal conclusions may be drawn from these data: (i) the tin atom of a trimethyltin residue bound solely to an imidazole ring as in complex **I** still possesses substantial Lewis acidity, and shows a distinct tendency towards *trans* trigonal bipyramidal five-coordination, thus casting some doubt on the proposed four-coordinated nature of the high-affinity binding site of the ATPase system, and (ii) in complex **II**, even though the juxtaposition of the histidyl and cysteinyl residues in the dipeptide might be expected to favour chelation of the dipeptide to tin leading to a *cis* trigonal bipyramidal geometry of tin, the nitrogen and sulphur donors prefer axial sites of a *trans* trigonal bipyramidal arrangement, at least in the solid-state. As such, this structure may provide a reasonable model for the bonding of the triorganotin residues by the 13α cystein and 20α histidine residues in cat haemoglobin as proposed by Taketa and his coworkers [1e].

Acknowledgements

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