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Review

Biological chemistry of organotin compounds: Interactions and dealkylation by dithiols

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Abstract

In this paper, we review our past and current efforts toward the elucidation of the biological chemistry of organotin compounds. In particular, we cover two prominent aspects of organotin compounds: their reactivity toward biological dithiols, and their degradation (or metabolization) mechanism using a combination of experimental and computational techniques.

Keywords: Organotin(IV) compounds; Stannin; NMR; CD spectroscopy; ESI-MS; Fluorescence spectroscopy

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1. Introduction

Organotin compounds are amongst the most widely used organometallic compounds. Over the last several decades, they have been utilized for a variety of industrial and agricultural applications including pesticides, fungicides and anti-fouling agents [1]. Run-off from organotin compounds used for agriculture accounts for the largest source of organotin accumulation in the environment, and has increased concerns regarding their toxic effects toward living organisms. The adverse environmental effects of organotin compounds have surpassed their usefulness in day to day applications, prompting bans on compounds such as tributyltin chloride (TBT) in the Unites States during the late 1980s [2,3]. While similar bans in developed nations have helped to decrease the overall incorporation

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of certain organotin compounds into the environment, several foreign countries still produce and utilize vast quantities of these compounds [2,3].

Indeed, traces of trimethyltin salts (TMT), which have not been implemented in commercial applications due to their high level of toxicity, have been found in the urine of humans not exposed directly to TMT, reinforcing the concern of environmental contamination [4]. Accidental human exposure to TMT has resulted in the appearance of dramatic behavioral changes, including weakness, aggressive behavior, depression, disorientation, seizures, severe memory loss, and in some instances death [5–9]. A distinguishing feature of organotin toxicity is the high level of specificity these compounds exhibit toward their biological targets. For example, TBT and triphenyltin salts (TPT) are primarily immunotoxic, while triethyltin chloride (TET) and TMT exhibit neurotoxic activity. Furthermore, while TMT and TET are both neurotoxic, they behave differently, inducing selective damage to distinct regions of the central nervous system. TMT-induced toxicity is localized within the hippocampus and neocortex of the brain, while TET predominately affects regions of the spinal cord. The selective neurotoxic pattern of TMT has made it an ideal system for studying organotin effects [9,10], and in general, the high specificity and toxicity of all organotin compounds have made them excellent candidates for modeling the mechanisms of alkylmetal intoxication in mammalians, though little attention has been focused on their biological chemistry under near physiological conditions.

Organotin toxicity is directly linked to the number and nature of the organic moiety. Highly substituted organotin compounds are known to be the most toxic (tri- and disubstituted organotins), with their toxicity decreasing with increasing alkyl chain length in a manner independent of the counter ions [11]. Among the most interesting properties of organotin compounds is their environmental degradation (speciation) by physico-chemical factors (UV, pH) and metabolization carried out by prokaryotic and eukaryotic organisms. In spite of its relatively high dissociation energy (~190–220 kJ/mol), the covalent Sn–C bond can be cleaved by a number of environmental sources, including chemical attacks (nucleophilic or electrophilic), UV radiation, and dealkylation by bacteria [12]. In mammalian organs such as the brain, liver and kidneys, organotin compounds are systemically degraded to inorganic tin, with the extent of the dealkylation correlating inversely with the length and stability of the alkyl moiety [13]. This noted in vivo degradation may provide an explanation for the delayed toxic response to organotin compounds observed in mammals [14].

Given the important role of organotin compounds in pollution and toxicology, the literature concerning their binding to biological macromolecules is rather scarce. Most studies focus on organotin interactions with hemoglobin [15–18], liver mitochondria [19–23] and ATPases [24] at a macroscopic level. It is only very recently that attention has been focused on the possible molecular mechanisms of organotin toxicity. One mechanism postulated for protein–organotin interactions is the formation of covalent bonds between the tin(IV) atom and thiols present in proteins [2,17,25]. This mechanism has been corroborated by recent in vitro studies showing that vicinal dithiols rather than monothiols are responsible for mediating the biochemical effects of organotin compounds [25–28].

While the mediation of thiol groups seems to be a common theme in organotin–protein interactions, a more recent paper from Ballmoos et al. shows a different mechanism of interaction between TBT and F-ATP synthase [29]. According to these researchers, TBT interacts with the selectivity filter of the ion channel of subunit a of ATP synthase through non-covalent interactions without any explicit involvement of the thiols in the coordination of the tin atom. Moreover, a few papers have been published on the effects of di- and trialkyltin compounds on membrane stability [30,31] and on their interactions with carbohydrates and DNA fragments in the solid state [32–34] and in solution [35,36]. In particular, it has been observed that organotin compounds (i.e., TBT and TPT) do not modify the macroscopic organization of lipid bilayers; rather, they modify the degree of hydration by interacting preferentially with the lipid/water interface [30].

In the last few years, our laboratory has embarked on the characterization of the biological chemistry of the organotin compounds. Our final goal is to answer the following questions: What are the biological targets of organotin compounds? What is the physiological mechanism of their dealkylation? Which is the toxic species, the highly substituted organotins or their metabolic products? Not only will this knowledge make it possible to implement appropriate therapeutics for cases of accidental intoxication, but it will also be useful in the development of new bioremediation technologies. In this paper, we review our latest efforts to rationalize the mechanisms of interaction and degradation of organotin compounds with dithiols. We will begin by focusing on the experimental studies of interactions between organotin compounds and model peptides and then describe the mechanistic studies that we have carried out using computational methods.

2. Peptides containing dithiols as models for protein–organotin interactions

Studies of various organotin compounds with amino acids and proteins have underscored their avidity for histidine and cysteine residues. Specifically, TET and TMT bind strongly to the histidines present in mitochondrial membrane proteins of rat and guinea-pig liver [19,23] as well as to the cysteines and histidines of rat and cat hemoglobin [15–17]. Moreover, alkyltin compounds have a marked preference for vicinal thiols rather than monothiols. In particular, it has been shown that both tri- and dialkyltin compounds target dithiols present in mitochondrial proteins, inducing cellular apoptosis [28,37].

Billingsley and co-workers identified and localized a mitochondrial membrane protein named stannin (SNN; from *stannum*, latin for tin) that sensitizes neuronal cells to TMT intoxication [38]. SNN is largely expressed in the hippocampus region of the brain [39] and has two conserved vicinal cysteines (Cys-32 and Cys-34) that may constitute a TMT binding site. Since there is a direct correlation between TMT toxicity and the expression of SNN [40], we designed a nine amino acid peptide (SNN-PEP) corresponding to residues 29–37 of the SNN sequence and incorporating the CXC motif (ILG*CW-C*YLR) believed to be the putative TMT coordination site.

To determine the interaction between various organotins and dithiols, we used CD spectroscopy [41]. Our data show that upon titration with TMT, TET, and tripropyltin chloride (TPrT) at a pH of 4.0, SNN-PEP undergoes a radical conformational change from random coil to a β-turn structure, as demonstrated from the distinctive dichroic shift from a broad negative band centered at ~208 nm to a dichroic profile with a negative band centered at ~222 nm and a positive band centered at ~205 nm. Addition of TBT, monomethyltin trichloride (MMT) or $SnCl_4$ to the peptide resulted in no substantial dichroic shift. Interestingly, SNN-PEP in addition to the tri-substituted organotins also binds disubstituted alkyltins such as dimethyltin dichloride (DMT), and diethyltin dichloride (DET). K_d values obtained from the titration curves show that peptide has the following order of affinity: DMT > DET > TPrT > TET > TMT; which indicates a preference for coordinating tri- and disubstituted organotins, while no binding was observed for MMT or $SnCl_4$. Perhaps the most surprising observation was the rather significant preference of the peptide for coordinating DMT over TMT, since TMT was believed to be the toxic species interacting with SNN resulting in cellular apoptosis [39]. At a higher pH (~6.5), where cysteines residues are more reactive, we observed the same affinity scale, with an expected overall decrease in K_d values.

The stoichiometry of the SNN-PEP/organotin complexes formed was analyzed using electrospray ionization mass spectrometry (ESI-MS) [41]. Our data show unequivocally that SNN-PEP dealkylates TMT and coordinates the dealkylated product. Analysis of the peptide complexed with TET and TPrT also showed a progressive dealkylation to DET and dipropyltin (DPrT), respectively. As in the CD measurements, no complex formation (or dealkylation) was detected for TBT, MMT or $SnCl_4$. These findings indicate that the peptide is able to dealkylate trisubstituted organotin compounds up to three carbons in length, most likely resulting in the release of the corresponding alkane. Consequently, our proposed dealkylation reaction can be represented as follows:

$$R_3Sn^+ + \text{SNN-PEP} \rightarrow \text{SNN-PEP}\cdot SnR_2 + H^+ + RH$$

where the peptide thiols form two Sn–S bonds with the alkyltin cation losing one alkyl group.

To further define the binding mechanism, we used 1D ^1H NMR spectroscopy [42]. TMT and DMT titrations at pH 4.0 showed that the free and bound species of SNN-PEP were in a slow exchange regime on the NMR time scale, as indicated by the two distinct sets of resonances observed in the NMR spectra. Upon increasing the pH to 6.5 and saturating the peptide with either ligand, the NMR spectra converge to a single unique set of resonances, which was identical for both the TMT and DMT titrations. It is interesting to note, however, that the formation of the bound species upon titration of DMT occurs more rapidly than with the titration of TMT. These findings indicate that: (a) the complex formed is the same for both TMT and DMT, and (b) there is a marked preference for binding DMT over TMT, consistent with the observed CD data.

Given the preference of SNN-PEP for coordinating DMT, we used conventional 2D [^1H, ^1H] TOCSY and ROESY experiments to elucidate the three-dimensional structure of the SNN-PEP/DMT complex at a pH of 6.5 [42]. From the TOCSY spectra, the three residues most prominently influenced by the coordination of DMT were Cys-4, Cys-6, and Tyr-7 which showed considerable chemical shift perturbations, directly implicating these residues in the coordination and stabilization of the organotin moiety. From the ROESY spectra, 54 ROE distant constraints, including 35 intraresidue and 19 interresidue ROEs, were obtained for use in the structural calculations. Of the interresidue constraints, there were several ROEs that comprise an extensive distance constraint network with Tyr-7, and were pivotal in the overall folding of the peptide. In addition, two ROEs between the Trp-5-Hξ2 and the methyl protons of DMT, and between Tyr-7-Hε and the methyl protons of the second methyl group of DMT, indicate that both aromatic rings are in close proximity to the DMT methyl protons. To probe the local geometry of the tin(IV) atom in the SNN-PEP/DMT complex, the $^1J(^{119}Sn, ^{13}C)$ and $^2J(^{119}Sn, ^1H)$ scalar couplings, which have previously been correlated with the CH_3–Sn–CH_3 angle of the tin atom in methyltin compounds [43,44], were measured using a 2D [^1H, ^{13}C]-HMQC experiment and the values implemented in the structural calculations [43,44].

The 12 lowest energy conformers are depicted in Fig. 1A. An overlap of the residues involved in the well-defined β-turn consists of residues Cys-4 through Tyr-7, with a backbone RMSD of 0.77 Å. Analysis of the Ramachandran angles for the residues involved in the β-turn indicates that DMT causes SNN-PEP to fold into a type I β-turn. Furthermore, as predicted from the ROE patterns, the two aromatic side chains Trp-5 and Tyr-7 are positioned above and below the central tin atom, providing further stabilization for the β-turn (Fig. 1C). A similar aromatic stabilization has been observed in potential antitumor dipeptide/dimethyltin complexes [45]. The tin atom in the SNN-PEP/DMT complex from both the calculated structures and the *J*-coupling constant values indicates that the metal center adopts a slightly distorted T_h geometry.

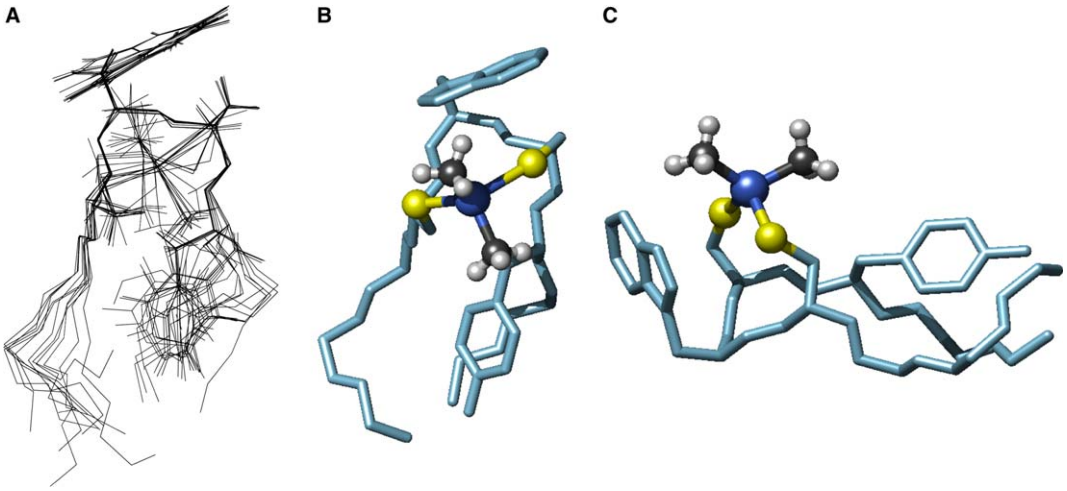


Fig. 1. (A) Overlap of the 12 lowest energy structures for the SNN-PEP/DMT complex (only the side chains for residues 4–7 are shown). (B) Single average structure of the peptide complex highlighting the DMT molecule. (C) Rotation of the average structure indicating the aromatic side chain orientations involved in stabilization of the DMT ligand. Reprinted with permission from [42]. Copyright 2004 American Chemical Society.

To unequivocally prove that both cysteines in the peptide model (Cys-4 and Cys-6) are necessary and sufficient for the coordination and dealkylation of trialkyl organotins, peptide variants replacing the cysteines with serines residues (C4S-SNN-PEP and C6S-SNN-PEP) were analyzed with various organotin compounds. Our results show no detectable dichroic shift by CD upon titration with the above described organotin compounds, demonstrating that the peptide was not able to coordinate any of the organotin compounds [41]. These results were confirmed by both ESI-MS as well as ^{1}H NMR analysis [41]. Together these results indicate that a dithiol, not a monothiol, is necessary for coordination of the organotin ligand to occur. In addition, a peptide variant replacing the tyrosine residue with a phenylalanine (Y7F-SNN-PEP) was utilized to provide evidence that the Tyr-7 side chain oxygen is not involved in coordination of the tin(IV) atom. Repetition of the CD, ESI-MS and ^{1}H NMR experiments with the various organotins indicated that Y7F-SNN-PEP behaves exactly as SNN-PEP confirming that only the cysteines are involved in the coordination of the tin(IV) atom [42].

In sum, our findings suggest that DMT acts as a ''molecular clip'', binding with relatively high affinity to the sulfhydryl groups of the cysteine side chains and inducing a stable β-turn conformation of the peptide backbone. Furthermore, peptide variant studies indicate that both cysteines in the peptide are necessary and sufficient to induce coordination of the tin(IV) atom and the subsequent organotin dealkylation reaction.

3. Is the mechanism of dealkylation of organotin compounds similar to organomercurial and organolead degradation?

The CXC motif is common among metalloproteins and has been found to coordinate a variety of different metal ions, including Cu^{2+}, Cd^{2+}, Ni^{2+}, and Hg^{2+} [46]. More importantly, vicinal cysteine residues have been implicated in the progressive dealkylation of organotin compounds in both bacteria and mammals [13,28,47,48], with a mechanism similar to the degradation of alkyllead and alkylmercury compounds [49,50]. In particular, the organotin dealkylation carried out by the dithiols of SNN-PEP shows similarities to the degradation of organomercurials into inorganic Hg(II) by organomercurial lyase (MerB) in bacteria resistant to organomercurial compounds [51–54]. Thiols located in the active site of MerB have also been shown to bind and dealkylate organotin compounds [54,55]. In addition, bacteria resistant to organotin compounds exhibit resistance to organomercurial compounds, further supporting a similar mechanism between the degradation of organomercurials and organotin compounds by biological dithiols [56]. Furthermore, dithiols have recently been implicated in the dealkylation and speciation of organomercurial compounds in humans [57]. The SNN-PEP model further emphasizes the importance of dithiols in structural proteins and enzymes for both coordinating the tin atom and dealkylating TMT to DMT.

4. Quantum mechanical modeling in support of structure and reactivity of organotin/peptide complexes

Protein structures determined from NMR inevitably involve the addition of a classical molecular mechanics force field to a number of distance constraints derived from nuclear Overhauser effect (NOE) measurements. In essence, a custom force field is created for a particular protein with unique force constants and equilibrium distances associated with each NOE data point. When a sufficient number of such points are available, the degree of structural precision that can be established is competitive with that available from single-crystal X-ray diffraction. In the case of metalloproteins, however, additional challenges arise. Modern force fields tailored to the modeling of proteins tend to be parameterized only for the 20 amino acid

residues from which the vast majority of non-metalloproteins are entirely constructed [58]. When it comes to including other elements, or even other organic functionalities not present in standard amino acids, parameters are typically not available for the computation of molecular structures and energies.

Of course, the extension of force field parameterizations is a well understood problem. Typically, one develops and validates new parameter sets, e.g., for Sn complexed to cysteine thiolate groups, by computing the energies of small model systems incorporating the requisite new functionality at very high levels of electronic structure theory, and parameterizing the force field to reproduce these calculations. In favorable instances, relevant experimental data will also be available against which to validate the parameterization process. However, while this is a tried and true technique in many instances, developing a robust set of parameters for a metal can be a particularly challenging task because of the potentially wide variety of low-energy coordination geometries available to a given metal. This is especially true for transition metals [59], but even for Sn there can be a subtle balance between T_h and trigonal bipyramidal coordination when the Sn is sufficiently Lewis acidic to interact with environmental Lewis bases, such as water. For example, Fig. 2 and Table 1 illustrate the substantial geometric differences that occur when $(CH_3)SnCl_2$ complexes H_2O both in the gas phase (cluster) and in aqueous solution (represented as a dielectric continuum). At the HCTH level [60] of density functional theory [58] with a polarized valence double-ζ basis set and an effective core potential on Sn, the CH_3–Sn–CH_3 angle is predicted to change by over 20° depending on whether or not the Lewis-acid complex with water is accounted for [42]. We have shown previously, however, that this complication does not seem to arise when thiolate ligands appear in place of chloride ligands. Under these conditions, the reduced Lewis acidity of the resulting Sn compound renders complexation with water unfavorable at the HCTH level of theory [42].

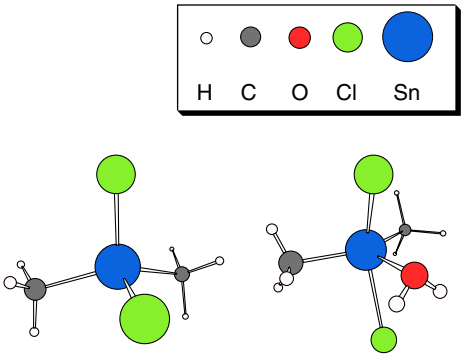


Fig. 2. Optimized structures for $(CH_3)SnCl_2$ and $(CH_3)SnCl_2 \cdot H_2O$; see Table 1 for structural and spectral details.

In addition to being useful for the benchmarking of force field parameters, modern computational protocols have become sufficiently powerful that small polypeptides incorporating non-standard elements like tin can simply be modeled *in their entirety* at the quantum mechanical level. Thus, for instance, a full optimization of SNN-PEP at the HCTH level using the efficient MIDI! basis set [61] for all elements other than Sn (a total of 902 basis functions) resulted in a final structure consistent with all measured NOE constraints except for one, which was externally maintained during optimization [61] (that one involved a non-bonded methyl/π interaction for which current density functional models are well known to be less than robust) [58]. Such a fully quantal approach obviates the need for a lengthy re-parameterization effort in instances when the size of the system is tractable.

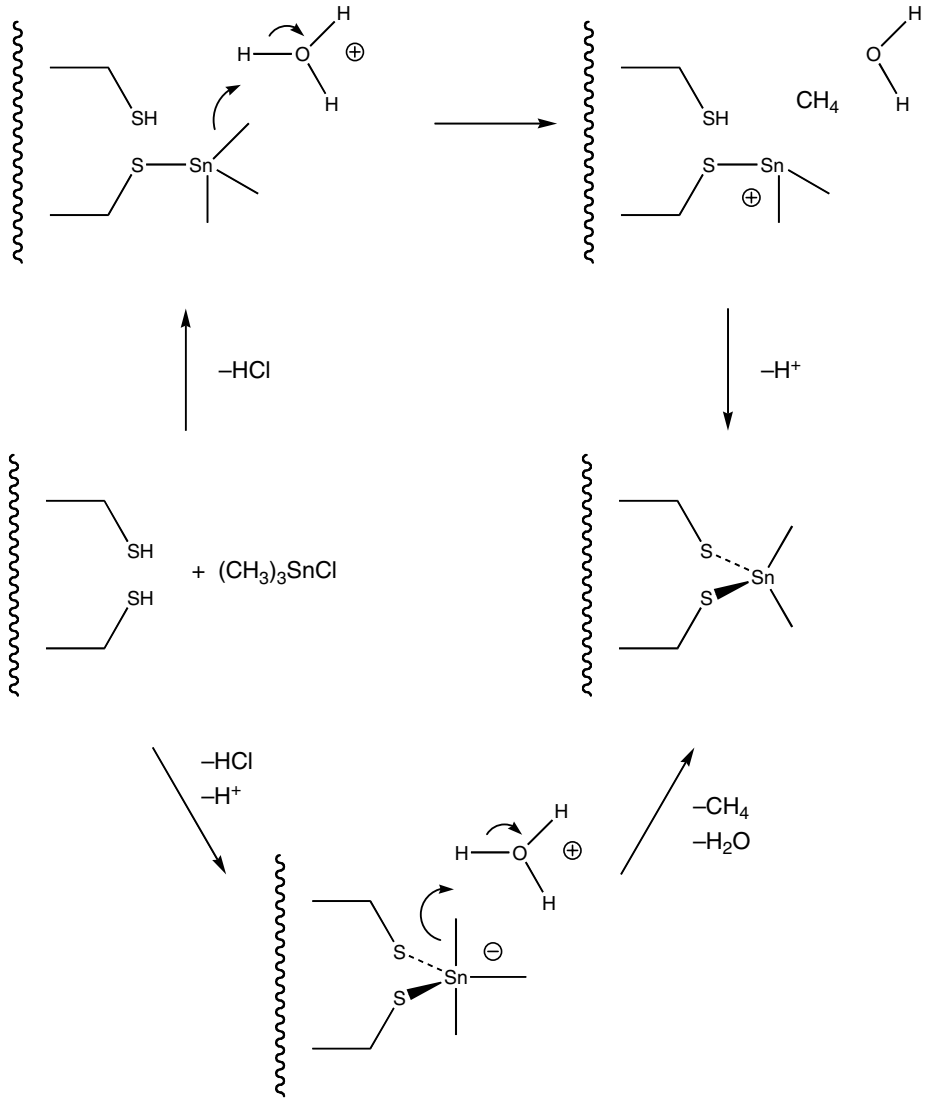
5. Quantum mechanical modeling in support of mechanistic studies

While classical force fields, particularly well parameterized ones, are vastly more efficient for structural modeling than are quantal methods, classical models are only very rarely applicable to the study of enzymatic reactions that involve the making and breaking of chemical bonds (indeed, in a standard harmonic force field, a bond *cannot* break!) Thus, an enormous amount of effort in the last 20 years has gone into the development and application of efficient quantum mechanical and mixed quantum mechanical/molecular mechanical (QM/MM) methods for the study of enzymatic reaction mechanisms [62–64].

To date, there have been few applications of these quantal technologies to metalloenzymes containing Sn. One example, which we take from ongoing research in our group, focuses on the dealkylation of trialkyltin halides by SNN. Plausible reaction mechanisms involve the hydrolytic proteolysis of a Sn–C bond after addition of one or two cysteine thiolate groups (Scheme 1). Preliminary studies at the B3LYP/6-31(d)(CEP-31G on Sn) quantum mechanical level [58] for the model systems $(CH_3)_3SnSCH_3$ and $[(CH_3)_3Sn(SCH_3)_2]^-$ reacting with H_3O^+ indicate that

Table 1
Selected structural and spectral data for $(CH_3)SnCl_2$ and $(CH_3)SnCl_2 \cdot H_2O$ at the HCTH/pVDZ level

Parameter	$(CH_3)SnCl_2$ (gas)	$(CH_3)SnCl_2 \cdot H_2O$ (gas)	$(CH_3)SnCl_2 \cdot H_2O$ (aq)
θ_{CSnC}, deg	121.1	131.9	143.7
$\delta\ ^{13}C$, ppm	4.2	13.8	16.5
$^1J_{SnC}$, Hz	474.0	562.5	621.1
$^2J_{SnH}$, Hz	62.0	69.0	80.0



Scheme 1.

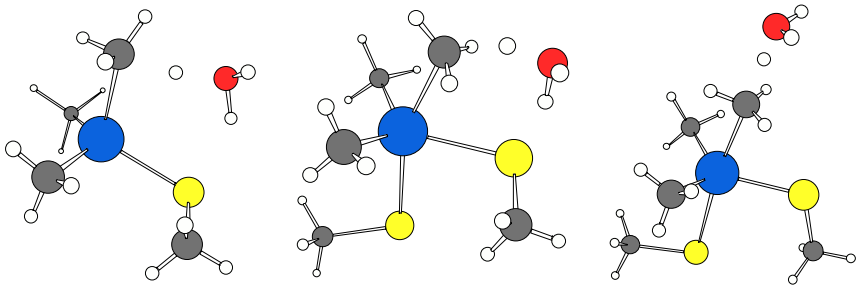


Fig. 3. B3LYP/6-31G* optimized transition-state structures for H_3O^+ hydrolytic proteolysis of $(CH_3)_3SnSCH_3$ in the gas phase (left), $[(CH_3)_3Sn(SCH_3)_2]^-$ in the gas phase (center), and $(CH_3)_3Sn(SCH_3)_2^-$ in aqueous solution (using the SM6 solvation model, right). Atoms are color-coded as in Fig. 2; yellow atoms are sulfur. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

transition-state structures for both reactions exist in the gas phase (Fig. 3). Free energies of activation computed for these structures including the effects of aqueous solvation from the SM6 implicit solvent model [65] are relatively high, 114.5 and 100.3 kJ mol^{-1}, respectively. However, reoptimization of the transition-state structure for the latter reaction leads to substantial geometric rearrangement. The solvated transition-state structure is well described as a

concerted addition/elimination (with general acid catalysis) at a Tbp center, as the incoming thiolate displaces the *trans*-diaxial methyl group that is in the process of being protonated (Fig. 3). This structural rearrangement in response to the surrounding implicit solvent is accompanied by substantial energy lowering; the free energy of activation is reduced to 54.8 kJ mol^{-1}. While further work is necessary to quantify the influence of the surrounding protein on the transition-state structure(s) and energetics for these various processes, the preliminary data certainly support their potential relevance from a mechanistic standpoint.

6. Conclusions

Using a combination of experimental and computational techniques, we have analyzed the structure and mechanism of organotin interactions with dithiol containing peptide models. In particular we have provided spectroscopic evidence that a nine residue peptide preferentially coordinates and dealkylates trialkyltin compounds to their dialkyltin counterparts through a CXC metal binding motif. In addition, new computational methods are being developed to further characterize the coordination state of the tin(IV) atom when complexed to the peptide as well as evaluate the specifics of the dealkylation reaction. The SNN-PEP model has provided great insight into the interaction of organotin compounds with biological targets, however, to fully understand how organotin compounds elicit their toxic response studies of the full SNN protein must be carried out. Toward that end, we have recently solved the high-resolution NMR structure of the mitochondrial protein SNN in detergent micelles [66]. The structure indicates that the protein contains a single transmembrane domain, a long unstructured linker region and a second cytosolic helix that is partially imbedded on the membrane surface. Interestingly, the CXC motif (Cys-32 and Cys-34 correspond to Cys-4 and Cys-6 in SNN-PEP) is located at the end of the transmembrane helix at the lipid/solvent interface making it accessible to organotin ligand binding. From this structure and our peptide model studies, we hypothesize that TMT enters the cell, binds to SNN and is dealkylated to DMT, which induces a structural change in the protein eliciting the toxic response. Further studies of SNN/organotin complexes such as those described in this review are being implemented to test this hypothesis and provide an overall mechanism for organotin neurotoxicity that can be used in the design of new therapeutics.

References

[1] K.E. Appel, Drug Metab. Rev. 36 (2004) 763.
[2] K. Fent, Crit. Rev. Toxicol. 26 (1996) 1.
[3] M.A. Champ, Sci. Total Environ. 258 (2000) 21.
[4] S.M. Jenkins, S. Barone, Toxicol. Lett. 147 (2004) 63.
[5] R.G. Feldman, R.F. White, I.I. Eriator, Arch. Neurol. 50 (1995) 1320.
[6] J. Gui-Bin, Z. Qun-fang, H.B. Bin, Environ. Contam. Tox. 65 (2000) 277.
[7] J. Gui-Bin, Z. Qun-Fang, H. Bin, Environ. Sci. Technol. 34 (2000) 2697.
[8] S. Kreyberg, A. Torvik, A. Bjorneboe, W. Wiik-Larson, D. Jacobson, Clin. Neuropathol. 11 (1992) 256.
[9] K.R. Reuhl, J.M. Cranmer, Neurotoxicology 5 (1984) 187.
[10] D.E. McMillin, G.R. Wenger, Pharmacol. Rev. 37 (1985) 365.
[11] S.M. Jenkins, K. Ehman, S. Barone Jr., Dev. Brain Res. 151 (2004) 1.
[12] M. Hoch, Appl. Geochem. 16 (2001) 719.
[13] Y. Arakawa, O. Wada, T.H. Yu, Toxicol. Appl. Pharm. 60 (1981) 1.
[14] V.C. Karpiak, C.L. Eyer, Cell Biol. Toxicol. 15 (1999) 261.
[15] M.S. Rose, Biochem. J. 111 (1969) 129.
[16] B.M. Elliott, W.N. Aldridge, Biochem. J. 163 (1977) 583.
[17] K.R. Siebenlist, F. Taketa, Biochem. J. 233 (1986) 471.
[18] G. Zolese, R. Gabbianelli, G.C. Caulini, E. Bertoli, G. Falcioni, Proteins 34 (1999) 443.
[19] W.N. Aldridge, B.W. Street, Biochem. J. 118 (1970) 171.
[20] K. Cain, D.E. Griffiths, Biochem. J. 162 (1977) 575.
[21] A.P. Dawson, M.J. Selwyn, Biochem. J. 138 (1974) 349.
[22] A.P. Dawson, B.G. Farrow, M.J. Selwyn, Biochem. J. 202 (1982) 163.
[23] M.S. Rose, E.A. Lock, Biochem. J. 120 (1970) 151.
[24] D.K. Apps, C.W. Lorna, Biochem. Biophys. Res. Co. 227 (1996) 839.
[25] H. Stridh, I. Cotgreave, M. Muller, S. Orrenius, D. Gigliotti, Chem. Res. Toxicol. 14 (2001) 791.
[26] M.F. Powers, A.D. Beavis, J. Biol. Chem. 266 (1991) 17250.
[27] M. Aschner, J.L. Aschner, Neurosci. Biobehav. R. 16 (1992) 427.
[28] A. Nishikimi, Y. Kira, E. Kasahara, E.F. Sato, T. Kanno, K. Utsumi, M. Inoue, Biochem. J. 356 (2001) 621.
[29] C. Ballmoos, J. Brunner, P. Dimroth, Proc. Natl. Acad. Sci. 101 (2004) 11239.
[30] J.J. Chicano, J. Ortiz, J.A. Teruel, F.J. Aranda, Biochim. Biophys. Acta 1510 (2001) 330.
[31] J. Sarapuk, H. Kleszczynska, S. Przestalski, Appl. Organomet. Chem. 14 (2000) 40.
[32] L. Nagy, B. Gyurcsik, K. Burger, S. Yamashita, T. Yamaguchi, H. Wakita, M. Nomura, Inorg. Chim. Acta 230 (1995) 105.
[33] L. Nagy, A. Szorcsik, J. Inorg. Biochem. 89 (2002) 1.
[34] L. Nagy, T. Yamaguchi, K. Yoshida, Struct. Chem. 14 (2003) 77.
[35] H. Barátné-Jankovics, l. Nagy, L. Pellerito, N. Buzás, R. Barbieri, J. Inorg. Chem. 92 (2002) 55.
[36] A. Jancsó, L. Nagy, E. Moldrheim, E. Sletten, J. Chem. Soc., Dalton Trans. 10 (1999) 1587–1594.
[37] H. Stridh, S. Orrenius, M.B. Hampton, Toxicol. Appl. Pharmacol. 156 (1999) 141.
[38] S.M. Toggas, J.K. Krady, M.L. Billingsley, Mol. Pharmacol. 42 (1992) 44.
[39] C.M. Patanow, J.R. Day, M.L. Billingsley, Neuroscience 76 (1997) 187.
[40] T.A. Thompson, J.M. Lewis, N.S. Dejneka, W.B. Severs, R. Polavarapu, M.L. Billingsley, J. Pharmacol. Exp. Ther. 276 (1996) 1201.
[41] B. Buck, A. Mascioni, L. Que Jr., G. Veglia, J. Am. Chem. Soc 125 (2003) 13316.
[42] B. Buck, A. Mascioni, C.J. Cramer, G. Veglia, J. Am. Chem. Soc. 126 (2004) 14400.
[43] T.P. Lockhart, W.F. Manders, Inorg. Chem. 25 (1986) 892.
[44] T.P. Lockhart, W.F. Manders, J. Am. Chem. Soc. 109 (1987) 7015.
[45] M.A. Girasolo, G. Guli, L. Pellerito, G.C. Stocco, Appl. Organomet. Chem. 9 (1995) 241.
[46] T.M. DeSilva, G. Veglia, F. Porcelli, A. Prantner, S.J. Opella, Biopolymers (Biospectroscopy) 64 (2002) 189.
[47] T.K. Misra, Plasmid 27 (1992) 4.
[48] G.M. Gadd, Sci.Total Environ. 258 (2000) 119.
[49] J.E. Casida, E.C. Kimmel, B. Holm, G. Widmark, Acta Chem. Scand. 25 (1971) 1497.
[50] L.W. Chang, J. Toxicol. Sci. 15 (1990) 125.

[51] T.P. Begley, A.E. Walts, C.T. Walsh, Biochemistry 25 (1986) 7192.
[52] K.E. Pitts, A.O. Summers, Biochemistry 41 (2002) 10287.
[53] S. Silver, Ann. Rev. Microbiol. 50 (1996) 753.
[54] A.E. Walts, C.T. Walsh, J. Am. Chem. Soc. 110 (1988) 1950.
[55] C.T. Walsh, M.D. Distefano, M.J. Moore, L.M. Shewchuk, G.L. Verdine, FASEB J. 2 (1988) 124.
[56] A. Pain, J.J. Cooney, Arch. Environ. Contam. Toxicol. 35 (1998) 412.
[57] H. Strasdeit, A. von Dollen, W. Saak, M. Wilhelm, Angew. Chem. Int. Ed. 39 (2000) 784.
[58] C.J. Cramer, Essentials of Computational Chemistry, second ed., Wiley, Chichester, 2004.
[59] P.O. Norrby, in: T. Cundari (Ed.), Computational Organometallic Chemisty, Marcel Dekker, New York, 2001, p. 7.
[60] F.A. Hamprecht, A.J. Cohen, D.J. Tozer, N.C. Handy, J. Chem. Phys. 109 (1998) 6264.
[61] R.E. Easton, D.J. Giesen, A. Welch, C.J. Cramer, D.G. Truhlar, Theor. Chim. Acta 93 (1996) 281.
[62] M.J. Field, J. Comp. Chem. 23 (2002) 48.
[63] J.L. Gao, D.G. Truhlar, Annu. Rev. Phys. Chem. 53 (2002) 467.
[64] U. Ryde, Curr. Opin. Chem. Biol. 7 (2003) 136.
[65] C.P. Kelly, C.J. Cramer, D.G. Truhlar, J. Chem. Theor. Comput. 1 (2005) 1133.
[66] B.A. Buck-Koehntop, A. Mascioni, J.J. Buffy, G. Veglia, J. Mol. Biol. 354 (2005) 652.