Organotin Compounds and Deoxyribonucleic Acid

Renato Barbieri, Arturo Silvestri, Anna M. Giuliani, Vincenzo Piro, Francesco Di Simone and Grazia Madonia
Dipartimento di Chimica Inorganica, Università di Palermo, I-90123 Palermo, Italy

The interaction of organotin(IV) moieties $Sn^{IV}R_2$ and $Sn^{IV}R_3$ (R = Me, Et, Bu^n, C_8H_{17} or Ph) with calf thymus deoxyribonucleic acid (DNA) has been studied. The experimental conditions have been determined for the formation of condensates $Sn^{IV}R_2$– and $Sn^{IV}R_3$–DNA by the reaction of ethanolic organotins [$SnR_2Cl_2(EtOH)_2$ and $SnR_3Cl(EtOH)$], as well as aqueous $Sn^{IV}Me_3$ species, with aqueous DNA. The nature of the condensates has been investigated by ^{119}Sn Mössbauer spectroscopy. The species $SnEt_2$(DNA phosphate)$_2$ and SnR_3(DNA phosphate) (R = Me or Et) have been assumed to occur, where the environment of the tin atoms would be *trans* octahedral and trigonal bipyramidal respectively. In the reaction with aqueous DNA of $SnR_2Cl_2(EtOH)_2$ and $SnR_3Cl(EtOH)$ (R = Bu^n, C_8H_{17} or Ph), stannoxanes $(SnR_2Cl)_2O$ and hydroxides $SnR_3(OH)$ would form too, being possibly the main reaction products for the moieties $Sn^{IV}(C_8H_{17})_2$, $Sn^{IV}(C_8H_{17})_3$ and $Sn^{IV}Ph_3$. Possible bonding situations have been advanced for $Sn^{IV}R_n$–DNA condensates, involving *e.g.* two vicinal phosphodiester groups (from the DNA double strand) *cis*-co-ordinated giving an octahedral geometry, as well as a phosphodiester residue axially binding $Sn^{IV}R_3$ to give a trigonal-bipyramidal structure.

Organotin compounds are widespread in the environment,[1] interacting with living organisms,[2] owing to their practical uses.[3] The interpretation of the consequent biological effects on molecular bases has been attempted. For example, the genotoxicity and mutagenicity of di-*n*-butyltin dichloride has been tentatively ascribed to complex formation with deoxyribonucleic acid (DNA).[4] It has been reported that di-*n*-octyltin dichloride induces mutagenesis by binding to DNA;[5] these assumptions have recently been questioned, and further investigation excluded covalent interactions of $Sn(C_8H_{17})_2Cl_2$ with nucleic acids.[6]

We have reported on the formation of condensates in dimethyltin(IV)–calf thymus DNA systems, consisting possibly of adducts $SnMe_2$·2(DNA monomer), where the structure of the organotin moiety involves a linear CSnC skeleton.[7] No interactions with DNA occur in the case of methyltin hydroxides, $SnMe_2(OH)_2$ and $SnMe_3(OH)(OH_2)$, which are the species occurring at physiological pH.[7,8] These studies have been extended to $Sn^{IV}R_2$ and $Sn^{IV}R_3$ (R = Et, Bu^n or C_8H_{17}), as well as to $Sn^{IV}Ph_2$ and $Sn^{IV}Ph_3$ moieties, which have wide application and induce a series of biological effects,[1–3] and the results obtained are reported in the present paper. The interaction of ethanol solutions of the organotin chlorides (as well as of aqueous methyltins) with calf thymus DNA in aqueous solution has been investigated, and the nature of the organotin species obtained is discussed, based on a study of the metal environment using ^{119}Sn Mössbauer spectroscopy of DNA pellets and solutions as well as of the reacting species in ethanol and water and of their hydrolysis products.

In the context of nucleic acid–metal ion systems,[9,10] inorganic divalent tin has been reported to interact with DNA[11,12] (not Sn^{IV}; eventual redox reactions have not been investigated). Tin(II) species enter human white blood cells (as shown by electron microscopy and X-ray spectrometry) and Chinese hamster ovary cells, extensively damaging DNA.[11,12] As far as organometallic-moiety DNA systems are concerned, a number of studies on $Hg^{II}Me$ have been reported.[13–15] Lastly, solid metal ion–nucleic acid phases have long been known, *e.g.* $Hg(NO_3)_2$– and $Hg(O_2CMe)_2$–DNA[16]. Coulomb interaction yields paracrystalline DNA condensates, and the related phenomena have been amply investigated and interpreted by appropriate theoretical approaches.[17,18]

Experimental and Results

Materials and Methods.—The organotin chlorides were gifts from Ciba-Geigy (Marienberg, Germany) and Schering (Bergkamen, Germany), or obtained commercially (Alfa, Karlsruhe, Germany; ICN Biomedical, Plainview, USA), which, whenever needed, were purified by recrystallization according to standard procedures. Calf thymus DNA, $M \approx 10^6$, was from Serva Feinbiochemica (Heidelberg, Germany). The buffer tris(hydroxymethyl)aminomethane (Tris) was from Sigma (St. Louis, MO, USA). Other reagents and solvents were from Carlo Erba (Milan, Italy).

The ^{119}Sn Mössbauer spectra were obtained at 77.3 K with the apparatus described earlier.[8,19,20] Conductivity was measured with a model CDM 83 (Radiometer, Copenhagen, Denmark) conductivity meter; the UV spectra were recorded by a model Lambda 15 (Perkin-Elmer, Norwalk, CT, USA) spectrometer, and the pH values by a model 2002 instrument (Crison, Barcelona, Spain). Elemental analyses were carried out at the Dipartimento di Chimica Organica e Industriale (Milan, Italy).

The experimental values reported in Tables 1–4 were extracted from at least duplicate experiments effected with samples from different stocks, and are averages.

Calculation of ΔE, the Nuclear Quadrupole Splitting.—The point-charge model rationalization of the Mössbauer parameter ΔE, and its correlation to the tin environment, was effected according to the following approaches. (*i*) The electric field gradient, e.f.g., tensor was taken as originating from the bond electrons in the Sn–C bonds only; ΔE_{calc} data were obtained by employing partial quadrupole splittings, p.q.s., inherent to the organic radicals bound to Sn, and are a function of the angles CSnC (in species SnR_2A_n, n = 3 or 4) and CSnA (in SnR_3A_n, n = 1 or 2; A are donor atoms from ligand molecules). The approach of Bancroft[21] and Parish[22] was followed. (*ii*) The e.f.g. tensor at Sn was considered to be dictated by all the valence electrons of bonds to Sn, regular structures being assumed for the tin environment; this procedure corresponds to the literal version of the point-charge model.[23]

Calculations were performed by employing p.q.s. parameters from the literature[8,19,22–25] and a computer program written by T. C. Gibb (Leeds University). Examples of the application of

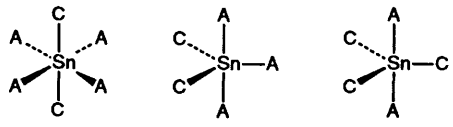


Table 1 ^{119}Sn Mössbauer parameters (mm s^{-1})[a] of SnR_nCl_{4-n} in ethanol solution

Compound	δ[b]	ΔE[c]	Γ_{av}[d]
$SnMe_2Cl_2$	1.35[e]	4.05[e]	0.94[e]
$SnEt_2Cl_2$	1.56	3.91	0.87
$SnBu^n_2Cl_2$	1.55	3.85	0.89
$Sn(C_8H_{17})_2Cl_2$	1.59	3.95	1.02
$SnPh_2Cl_2$	1.31	3.58	0.98
$SnMe_3Cl$	1.33	3.31	0.97
$SnEt_3Cl$	1.48	3.37	0.95
$SnBu^n_3Cl$	1.46	3.38	0.94
$Sn(C_8H_{17})_3Cl$	1.44	3.36	0.96
$SnPh_3Cl$[f]	1.29	3.07	0.88

[a] Absorber samples: *ca.* 2 cm^3 of solutions 0.1 mol dm^{-3} in dry, or 95% EtOH, frozen to 77.3 K. [b] Isomer shift with respect to room-temperature (r.t.) $Ca^{119}SnO_3$, ±0.02 mm s^{-1} (standard deviation). Average data. [c] Nuclear quadrupole splitting, ±0.02 mm s^{-1} (standard deviation). Average data. [d] Full width at half height of the resonant peaks at lesser and larger velocity than the spectrum centroid respectively. Average data. [e] Ref. 7. [f] A solution 0.35 mol dm^{-3} was also tested for Mössbauer spectroscopy.

approaches (*i*) and (*ii*) to organotin in model biological systems have been reported previously.[8,19,20]

Nature of Ethanol Solutions of SnR_nCl_{4-n}.—In the present research, methyltin compounds in aqueous solution and organotin chlorides in ethanol are treated with DNA. The 'reacting' species $Sn^{IV}Me_3$, as well as $Sn^{IV}Me_2$, formed in aqueous solution as a function of pH and monitored by ^{119}Sn Mössbauer spectroscopy, have been amply commented on in previous papers;[19,20,26] the structure of ethanolic organotin chlorides is discussed herein. The ^{119}Sn Mössbauer parameters reported in Table 1 suggest that single tin sites occur (narrow Γ), pertaining to linear CSnC and planar trigonal SnC_3 fragments in regular octahedral and trigonal-bipyramidal structures, respectively. Calculations according to approach (*i*), yielded the following ΔE_{calc} values: *trans*-SnR_2A_4, 4.12; *trans*-$SnPh_2A_4$, 3.80; SnR_3A_2, 3.39; $SnPh_3A_2$, 2.94 mm s^{-1}. These configurations apply to the compounds in glassy phases formed by rapid freezing, which would reflect the solution-phase structures, in line with literature reports.[19]

Molar conductances have been determined for systems such as those in Table 1, at 25 °C in dry EtOH. Representative ranges of data are as follows (uncorrected for solvent conductivity): (*a*) SnR_2Cl_2 (R = Me, Et or Bu^n), concentration 6.55 × 10^{-3}–7.0 × 10^{-5} mol dm^{-3}, Λ_M = 1.07–35.1 S cm^2 mol^{-1}; (*b*) $Sn(C_8H_{17})_2Cl_2$, 7.88 × 10^{-3}–8.0 × 10^{-5} mol dm^{-3}, Λ_M = 0.78–13.9 S cm^2 mol^{-1}; (*c*) $SnPh_2Cl_2$, 6.98 × 10^{-3}–7.0 × 10^{-5} mol dm^{-3}, Λ_M = 1.46–21.9 S cm^2 mol^{-1}; (*d*) SnR_3Cl, 8.49 × 10^{-3}–7.0 × 10^{-5} mol dm^{-3}, Λ_M = 0.61–23.7 S cm^2 mol^{-1}. These data are in the range typical for organotin chlorides in organic solvents,[27–29] and suggest very slight dissociation.

It is inferred that the species present in the ethanol stock solutions are mainly $SnR_2Cl_2(EtOH)_2$ and $SnR_3Cl(EtOH)$, where the ethanol would co-ordinate through its oxygen atom; owing to the low stability of Sn–Cl bonds,[30] the moieties SnR_2^{2+} and SnR_3^+, respectively, would be the species reacting with DNA as well as with H_2O.

Hydrolysis of Ethanolic SnR_nCl_{4-n} (R = Bu^n, C_8H_{17} *or* Ph; *n* = 2 *or* 3).—These compounds, very slightly soluble in water,[1] are employed as stock ethanol solutions, subsequently to be treated with aqueous DNA. Consequently, the species formed by the action of water on $SnR_nCl_{4-n}(EtOH)_m$ have been studied. The absorber samples subjected to Mössbauer spectroscopy were as follows: (*i*) 0.2 cm^3 of 0.1 mol dm^{-3} SnR_nCl_{4-n} in EtOH diluted to 1 cm^3 with EtOH, and 1 cm^3 of water added; (*ii*) 0.2–0.5 cm^3 of 0.1 mol dm^{-3} SnR_nCl_{4-n} in EtOH added to 1.8–1.5 cm^3 water. Absorbers (*i*) were mainly diorganotins and (*ii*) triorganotins, the percentage of ethanol reflecting that in the experimental organotin–DNA systems. The Mössbauer parameters for a given organotin were constant in absorbers (*i*) and (*ii*).

The results are reported in Table 2. It is clear that $SnR_2Cl_2(EtOH)_2$, *trans* octahedral, and $SnR_3Cl(EtOH)$, trigonal bipyramidal (Table 1) react with water forming products with a trigonal-bipyramidal geometry according to fingerprint criteria based on ΔE_{exptl},[24] as well as on point-charge ΔE_{calc} values and related data (Table 2). The point-charge model angles reported in Table 2 suggest the formation of $(SnR_2Cl)_2O$ and the hydroxides $SnR_3(OH)$ for the terms of the two congeneric series respectively. Other possible hydrolysis products, such as oxides SnR_2O (ΔE = 1.73–2.40[31]) and stannoxanes $(SnR_3)_2O$ (ΔE = 1.15–2.40[31,33]), which are tetrahedral species,[34–37] are not formed under the present conditions.

It is worth noting the excellent agreement of the point-charge model angles, Table 2, with crystallographic data, *e.g.* of congeneric stannoxanes $\{[SnMe_2(NCS)]_2O\}_2$, $[(SnMe_2Cl)_2O]_2$, $[(SnPh_2Cl)_2O]_2$, and related species which are ladder- or staircase-type polymers with five-co-ordinated tin and angles CSnC 133–141,[32,38–41] and $SnR_3(OH)$ (R = Me or Ph) which are polymers with oxygen (OH) bridges and quasi-regular trigonal-bipyramidal structure.[42,43]

The assumed formation of species $(SnR_2Cl)_2O$[44] in absorbers (*i*) has been confirmed by elemental analysis of the solid products obtained: $SuBu^n_2Cl_2(EtOH)_2 + H_2O$ (Found: C, 34.80; H, 6.40. Calc. for $C_{16}H_{36}Cl_2OSn_2$: C, 34.75; H, 6.55); $Sn(C_8H_{17})_2Cl_2(EtOH)_2 + H_2O$ (Found: C, 50.90; H, 8.50. Calc. for $C_{32}H_{68}Cl_2OSn_2$: C, 49.45; H, 8.80); and $SnPh_2Cl_2(EtOH)_2 + H_2O$ (Found: C, 45.75; H, 3.35. Calc. for $C_{24}H_{20}Cl_2OSn_2$: C, 45.55; H, 3.20%).

Interaction of Aqueous DNA with Organotin Compounds.—Stock solutions of calf thymus DNA in the range 15–20 mmol dm^{-3} (monomer units), in triply distilled water buffered to pH around 8 by 1 mmol dm^{-3} Tris, 0.1 mmol dm^{-3} ethylenediaminetetraacetate, were employed. The concentration was determined by UV spectrophotometry, using the absorption coefficient ε_{260} = 7000 dm^3 mol^{-1} cm^{-1}.[45] Aqueous DNA was interacted with ethanolic, as well as aqueous ($Sn^{IV}Me_3$), organotin compounds by procedures described previously[7] (see footnotes *a* to Table 3 and *m* to Table 4). The location of DNA in pellets (dissolved in Tris-edta) and in supernatants was monitored by UV spectrophotometry and $Sn^{IV}R_n$ by Mössbauer spectroscopy.

The macroscopic effects observed by addition of ethanolic organotins (0.1 mol dm^{-3} stock) to aqueous DNA (20–28 μmol), in the absence of any other reagent or condition causing the formation of solid DNA, are as follows. (*i*) $Sn^{IV}R_2$–DNA, *r* = [Sn]/[DNA phosphate] ≈ 0.5:1 and $Sn^{IV}R_3$–DNA, *r* ≈ 1.0:1. No pellet was obtained for R = Me[7] and C_8H_{17}; a solid phase not containing DNA occurred for $Sn(C_8H_{17})_2$. Pellets were formed for R = Et, Bu^n or Ph, consisting of DNA and organotin, minor amounts of DNA being found in the supernatants. (*ii*) $Sn^{IV}R_2$, *r* > 1.0:1 and $Sn^{IV}R_3$, *r* ≈ 2.0:1. Pellets were formed by all organotins. For R = Bu^n, C_8H_{17} or Ph, DNA was also found in the supernatant.

The system $[SnMe_3(OH_2)_2]^+$–DNA, obtained from aqueous $Sn^{IV}Me_3$,[26] behaves differently with respect to the corresponding $Sn^{IV}Me_2$ system.[7] No $SnMe_3$–DNA pellets were formed at *r* = 1.0–2.0:1, being obtained by the subsequent addition of H^+ (pH ≈ 2.5–3.5). Treatment of the solutions, *r* ≈ 1–2, with two to three volumes of EtOH, *I* = 0.1 mol dm^{-3} with NaCl,

Table 2 ^{119}Sn Mössbauer parameters of hydrolysed $Sn^{IV}R_2$ and $Sn^{IV}R_3$ (R = Bu^n, C_8H_{17} or Ph)

System[a] or compound[b]	δ[c] / mm s^{-1}	ΔE[c] / mm s^{-1}	Γ_{av}[c] / mm s^{-1}	Ref.	Angles (°)[d] CSnC in $Sn^{IV}R_2$ and CSnA in $Sn^{IV}R_3$
$SnBu^n_2Cl_2 + H_2O$	1.38	3.33	0.89	This work	129
$(SnBu^n_2Cl)_2O$	1.25–1.46	3.20–3.26	—	31, 32	125–127
$Sn(C_8H_{17})_2Cl_2 + H_2O$	1.42	3.26	0.85	This work	126
$SnPh_2Cl_2 + H_2O$	1.05	2.64	0.91	This work	122
$(SnPh_2Cl)_2O$	1.26	3.08	—	32	135
$SnBu^n_3Cl + H_2O$	1.43	3.37	0.96	This work	91
$SnBu^n_3(OH)$	1.37–1.46	2.99–3.24	—	31, 33	96.5–101.5
$Sn(C_8H_{17})_3Cl + H_2O$	1.50	3.55	0.88	This work	≈90
$Sn(C_8H_{17})_3(OH)$	1.35	2.95	—	33	102
$SnPh_3Cl + H_2O$	1.30	2.97	0.85	This work	≈90
$SnPh_3(OH)$	1.16–1.35	2.70–2.83	—	31, 33	96.5–99.5

[a] Absorber samples for systems indicated as '$SnR_nCl_{4-n} + H_2O$' consist of ethanolic SnR_nCl_{4-n} added to EtOH and water, or water. See Experimental and Results. [b] Stannoxanes, $(SnR_2Cl)_2O$, and hydroxides, $SnR_3(OH)$; literature data. [c] See footnotes *b–d* to Table 1. Average values of multiple determinations, and ranges of literature data. The parameters ε% (percent resonance effect) for $SnR_nCl_{4-n} + H_2O$ range from 0.1 to 1.0. [d] Refers to trigonal-bipyramidal species SnR_2A_3 and SnR_3A_2 respectively, with equatorial R groups. Data estimated by the point-charge model approach (*i*), see Experimental and Results.

Table 3 ^{119}Sn Mössbauer parameters of SnR_2–DNA systems[a]

	R in $SnR_2Cl_2(EtOH)_n$ + DNA[a]		r[b]	δ[c] / mm s^{-1}	ΔE[c] / mm s^{-1}	Γ_1[c] / mm s^{-1}	Γ_2[c] / mm s^{-1}
1	Me	Pellet[d]	0.4	1.26[e]	4.39[e]	0.90[e]	0.79[e]
2		Pellet[f]	1.0	1.33[e]	4.44[e]	0.91[e]	0.91[e]
		Supernatant[f]	1.0	1.25[e]	3.87[e]	1.15[e]	1.15[e]
3	ET	Pellet[d]	0.6	1.39	4.49	0.89	0.75
4		Pellet[g]	1.0	1.43	4.40	0.74	0.99
		Supernatant[g]	1.0	1.50	3.88	1.00	1.29
5		Pellet[h]	2.4	1.50	4.47	0.85	0.90
		Supernatant[h]	2.4	1.47	3.96	1.22	0.90
6	Bu^n	Pellet[d]	0.48[i]–0.6	1.41	3.80	1.31	1.17
7		Pellet[d]	1.0	1.44	3.84	1.20	1.11
8		Pellet[d]	2.4	1.43	3.41	0.92	0.92
9	C_8H_{17}	Pellet[d]	0.48[i]–0.50[i]	1.36	3.23	0.85	0.83
10		Precipitate[d]	0.50[j]	1.35	3.23	0.86	0.93
11		Precipitate[d]	2.4	1.61	3.33	1.00	0.93
12	Ph	Pellet[d]	0.48[k]	1.13	3.23	1.45	1.22
13		Pellet[d]	1.0	1.05	2.96	1.63	1.22
14		Pellet	2.4[l]	1.07	2.83	1.24	1.01
		Supernatant	2.4[l]	1.20	3.01	1.32	0.98

[a] At 77.3 K. Unless otherwise stated, the absorber samples were prepared by adding 0.1–0.2 cm^3 of 0.1 mol dm^{-3} SnR_nCl_{4-n} in EtOH to the appropriate volume of ≈20 mmol dm^{-3} DNA phosphate (≈1–2 cm^3). See *Materials and Methods*. An eventual resonance effect in the supernatants is expected for $Sn^{IV}Me_2$–, $Sn^{IV}Me_3$– and $Sn^{IV}Et_3$–DNA systems owing to the solubility in water of these organotin(IV) moieties. [b] r = mol $Sn^{IV}R_n$ per mol DNA phosphate. [c] See footnotes *b–d* to Table 1. Data are average values from multiple determinations. [d] The supernatants corresponding to entries 1, 3, 6 (r = 0.6:1), 7–13 do not show resonance effect (*i.e.*, ε% < 0.1). See text. [e] Ref. 7. [f] Per cent resonance effect data:[7] pellet, ε_1 = 0.46, ε_2 = 0.42; supernatant, ε_1 = 0.31, ε_2 = 0.33%. [g] ε% data: pellet, ε_1 = 0.63, ε_2 = 0.58; supernatant, ε_1 = 0.28, ε_2 = 0.30%. [h] ε% data: pellet, ε_1 = 1.54, ε_2 = 1.44; supernatant, ε_1 = 0.87, ε_2 = 1.05%. [i] Pellets obtained by addition of NaCl, I = 0.1 mol dm^{-3} and two to three volumes of EtOH (see ref. 7). [j] Precipitate, obtained by the procedure under *a*, which does not contain DNA. See text. [k] Pellets obtained by the procedure under *a*, as well as by diluting $SnPh_2Cl_2$ with EtOH (two to three volumes), and adding to DNA (I = 0.1 mol dm^{-3} with NaCl). [l] ε% data: pellet, ε_1 = 0.98, ε_2 = 1.29; supernatant, ε_1 = 0.33, ε_2 = 0.48%.

provoked the precipitation of pellets containing DNA only, while $Sn^{IV}Me_3$ was found in the solution.

Representative Mössbauer parameters of the organotin-DNA systems are reported in Tables 3 and 4.

Discussion

Diorganotin(IV)–DNA Systems.—(*i*) The environment of tin in $Sn^{IV}Me_2$–DNA[7] and $Sn^{IV}Et_2$–DNA pellets is *trans*-C_2 octahedral (see ΔE_{calc} data in *Nature of Ethanol Solutions* in Experimental and Results). A single tin site occurs, according to the narrowness of the linewidths Γ. The occurrence of $Sn^{IV}Et_2$ in the supernatant for r = 1.0:1, as for the related pellet, indicates the stoichiometry $Sn^{IV}Et_2$(DNA phosphate)$_2$ in the condensate. This corresponds perfectly to findings on $Sn^{IV}Me_2$–DNA.[7]

(*ii*) The $Sn^{IV}R_2$–DNA (R = Bu, C_8H_{17} or Ph) condensates show ΔE_{exptl} values tending to data for chlorodiorganodistannoxanes, especially for systems with r > 0.5:1. This would imply that $SnR_2Cl_2(EtOH)_2$ (R = Bu^n, C_8H_{17} or Ph) and related solvates, react with aqueous DNA originating in both DNA pellets and stannoxanes, the latter being localized in the solid phase too. This is in agreement with the large Γ values of the $Sn^{IV}Bu^n_2$– and $Sn^{IV}Ph_2$–DNA samples, which suggest the occurrence of multiple tin sites, while the narrow lines of $Sn^{IV}(C_8H_{17})_2$–DNA would imply the formation of a single main species, possibly the stannoxane.

(*iii*) The surprising presence of the highly water-insoluble $Sn^{IV}Ph_2$ moiety, as well as of $Sn^{IV}Ph_3$ to a lesser extent, in the supernatants from $SnPh_2$–DNA, r = 2.4:1 and $SnPh_3$–DNA, r = 2.0:1, together with minor amounts of DNA, would suggest a particular type of interaction between these species. Intercalation of the phenyl radicals between base pairs of the

Table 4 ^{119}Sn Mössbauer parameters of SnR_3–DNA[a] systems

	R in $SnR_3Cl(EtOH)_n$ + DNA[a]		r[b]	δ[c] / mm s^{-1}	ΔE[c] / mm s^{-1}	Γ_1[c] / mm s^{-1}	Γ_2[c] / mm s^{-1}
1	Me	Solution	0.96	1.30	3.71	0.88	0.95
2		Pellet[d,e]	2.4[f]	1.31	3.77	0.89	0.82
		Supernatant[e]	2.4	1.31	3.59	0.95	0.86
3	Et	Pellet[g]	1.0–1.2	1.49	3.86	0.85	0.88
4		Pellet[h]	2.4	1.47	3.83	0.86	0.82
		Supernatant[h]	2.4	1.47	3.61	0.87	1.16
5	Bu^n	Pellet[i]	0.96[j]	1.50	3.85	1.09	0.98
6		Pellet[i]	2.4	1.45	3.79	0.94	0.92
7	C_8H_{17}	Pellet[i]	1.0[k]–1.2	1.48	3.46	0.85	0.66
8		Pellet[i]	2.4	1.53	3.53	0.95	0.86
9	Ph	Pellet[i]	1.0–1.2	1.27	3.03	1.00	1.22
10		Pellet[i]	2.0–2.4	1.28	2.97	0.97	1.15
		Supernatant[i]	2.0	1.28	3.41	1.26	0.86
	$[SnMe_3(OH_2)_2]^{+m}$ + DNA						
11	Solution		1.20–1.56	1.32	3.80	0.89	0.78
12	Pellet[n]		2.4	1.38	3.84	0.93	0.75
	Supernatant[n]		2.4	1.34	3.86	0.86	0.88

[a] At 77.3 K. See footnote *a* to Table 3. Angles CSnA (A are axial ligand atoms) estimated by point-charge model calculations using ΔE parameters correspond to regular trigonal-bipyramidal structures. See text. [b] r = mol $Sn^{IV}R_n$ per mol DNA phosphate. [c] See footnotes *b–d* to Table 1. Data are average values from multiple determinations. [d] Pellets obtained, for r = 0.96–1.2:1, by separation from the mother-liquor soon after their formation (in order to prevent redissolution), as well as pellets precipitated by two to three volumes of EtOH (I = 0.1 mol dm^{-3} with NaCl), do not show any resonance effect. See text. [e] Per cent resonance effect data: pellet, ε_1 = 0.59, ε_2 = 0.63; supernatant, ε_1 = 0.38, ε_2 = 0.39%. [f] Pellets obtained by the procedure under *a*, Table 3, or by further addition of HCl or $HClO_4$. [g] Supernatants show $\varepsilon \approx 0.1\%$. [h] Per cent resonance effect data: pellet, ε_1 = 1.24, ε_2 = 1.33; supernatant, ε_1 = 0.40, ε_2 = 0.32%. [i] The supernatants corresponding to entries 5–9 do not show resonance effects. [j] No effect is detected in the pellets obtained by diluting $SnBu^n_3Cl$ with EtOH (two to three volumes), and adding to DNA (I = 0.1 mol dm^{-3} with NaCl). [k] Pellets obtained by addition of EtOH (two to three volumes) and NaCl (I = 0.1 mol dm^{-3}) to the system $Sn(C_8H_{17})_3Cl$–DNA. See Ref. 7. [l] Per cent resonance effect data: pellet, ε_1 = 2.11, 2.98, ε_2 = 2.04, 2.85; supernatant, ε_1 = 0.18, ε_2 = 0.15%. [m] Aqueous $SnMe_3Cl$, 20 mmol dm^{-3}, added to DNA (see ref. 7, the procedure for $Sn^{IV}Me_2$, and text, this paper). pH 3.5–5.0 after addition. [n] Per cent resonance effect: pellet, ε_1 = 0.17, ε_2 = 0.18; supernatant, ε_1 = 0.66, ε_2 = 0.63%.

nucleic acid is inferred. Alternatively, the formation of micelles by *e.g.* the hydrolysis products of $Sn^{IV}Ph_2$ and $Sn^{IV}Ph_3$ could be assumed.

Triorganotin(IV)–*DNA Systems.*—The reactant $SnR_3Cl(EtOH)$, and the possible products $Sn^{IV}R_3$–DNA and $Sn^{IV}R_3(OH)$, all show quasi-regular trigonal-bipyramidal structures with equatorial SnC_3 skeletons, according to the point-charge model angles and literature data.

(*i*) The $Sn^{IV}Me_3$– and $Sn^{IV}Et_3$–DNA condensates from $SnR_3Cl(EtOH)$ added to DNA, $r \approx 2:1$, or obtained by addition of H^+ to the systems $SnMe_3Cl(EtOH)$ + DNA and $[SnMe_3(OH_2)_2]^+$ + DNA, all with $r \approx 2:1$, consist of 1:1 species SnR_3(DNA phosphate), according to the order of magnitude of the ε parameters of the pellets and the related supernatants. This again corresponds to findings on the $Sn^{IV}Me_2$–DNA systems, where the species $SnMe_2$(DNA phosphate)$_2$ have been assumed to occur.[7] It seems worth recalling that such information may be extracted from $Sn^{IV}Me_2$–, $Sn^{IV}Me_3$– and $Sn^{IV}Et_3$–DNA systems where the free organotin species are consistently soluble in water even at neutral pH [the Mössbauer parameters of the hydrolysed species $SnMe_2(OH)_2$, $SnMe_3(OH)(OH_2)$, and $SnEt_3(OH)(OH_2)$ being on the other hand quite peculiar[19,20,26]].

(*ii*) The $Sn^{IV}Ph_3$– and $Sn^{IV}(C_8H_{17})_3$–DNA pellets could consist also of, or mainly of, $SnR_3(OH)$, according to the trends in ΔE values as well as to the multiple tin sites evidenced by the Γ values of $Sn^{IV}Ph_3$–DNA.

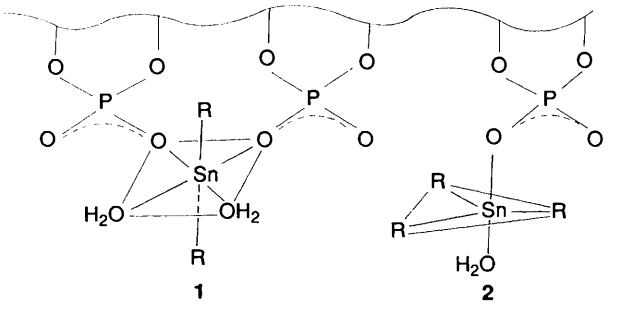
Conclusion

The findings and the assumptions regarding the di- and triorganotin–DNA systems, in conjunction with the conditions of formation of the condensates, suggest the occurrence of Coulomb interactions rather than covalent bonding, which would take place between the moieties $Sn^{IV}R_2$ and $Sn^{IV}R_3$ (formal charges +2 and +1 respectively, which would be available 'from' ethanol solutions, as well as in aqueous systems at acid pH for methyl- and ethyl-tins) and the phosphodiester group $^-O_2P(OR)_2$ of the nucleic acids.

Interactions between metal ions and DNA phosphate have been widely investigated.[17,18,46,47] For organotins, bonding to phosphate oxygens has been detected for a series of crystalline compounds.[8] Moreover, $Sn^{IV}R_2$ (R = Me or Bu^n) and $Sn^{IV}Me_3$ in aqueous, or aqueous methanol, solutions bind to phosphate fragments of the mononucleotides adenosine 5′-monophosphate and adenosine 3′:5′-cyclic monophosphate.[8,48] Aqueous $Sn^{IV}Me_3$ binds to phosphate of mononucleotides with stability constants of the order of those exhibited with inorganic phosphates.[49] Lastly, the nucleoside adenosine in methanol solution reacts with *e.g.* $SnMe_2O$ through the ribose hydroxyls;[50] bonding to purine bases, such as adenine and 6-thioxopurine, requires anhydrous organic solvents and eventual deprotonation of the bases by NaOMe.[51,52]

In conclusion, the species $SnR_2Cl_2(EtOH)_2$ and $SnR_3Cl(EtOH)$ (R = Me or Et), $[SnMe_2(OH_2)_4]^{2+}$,[7,26] and $[SnMe_3(OH_2)_2]^+$ (ref. 26) react with aqueous DNA, the larger macroscopic effect (*i.e.* the tendency to form organotin–DNA condensates) being detected for the ethyl derivatives. The more lipophilic organotins, $SnR_2Cl_2(EtOH)_2$ and $SnR_3Cl(EtOH)$ (R = Ph, Bu^n or C_8H_{17}), generally interact with DNA to an extent decreasing with the increasing lipophilicity of the radical R, the competing reaction with water yielding hydrolysis products. Fragments $Sn^{IV}R_2$ are more effective than $Sn^{IV}R_3$, for the same R, in binding to DNA.

Assuming the occurrence of bonding to tin by phosphodiester oxygen atoms, the formation of the species in Fig. 1 could be advanced. The ΔE_{calc} data for structure **1** closely correspond to the experimental values for the $Sn^{IV}Me_2$–[7] and $Sn^{IV}Et_2$–DNA



1 2

R = Alkyl, ΔE_{calc} = + 4.74 mm s^{-1} R = Alkyl, ΔE_{calc} = − 4.01 mm s^{-1}
R = Ph, ΔE_{calc} = + 4.42 mm s^{-1} R = Ph, ΔE_{calc} = − 3.56 mm s^{-1}

Fig. 1 Possible structures of tin sites in phosphate-bound $Sn^{IV}R_2$–DNA, r = 0.5:1 and $Sn^{IV}R_3$–DNA, r = 1.0:1. The values of ΔE were calculated by the literal version of the point-charge model[23–25] (see Experimental and Results)

condensates (Table 3), so that binding of Sn through two vicinal phosphodiester groups of a double strand could be advanced in the present context. The ΔE_{calc} data for **2** differ from ΔE_{exptl} of $Sn^{IV}R_3$–DNA (R = Me, Et or Bu^n) (Table 4) by less than the acceptable difference of 0.4 mm s^{-1}, and these fragments $Sn^{IV}R_3$ would accordingly be appended to the double strand through a phosphodiester. The nature of phosphate oxygen–metal bonds has been amply commented on for a number of aquated ion–nucleic acid systems (see *e.g.* ref. 47), mainly in connection with ribonucleic acid (RNA).[53–55]

It should be taken into account that metal environments other than those of **1** and **2** may be consistent with the structure and bonding from point-charge model calculation of ΔE values, as well as from ΔE data of organotin phosphates taken as model systems. The species $Sn^{IV}R_2(O_2PXY)_2$, *trans* octahedral with chelating phosphate,[8] and $Sn^{IV}R_3(O_2PXY)_2$, trigonal-bipyramidal polymers,[8] could be accounted for by interstrand DNA cross-linking. Moreover, according to the p.q.s. values of heterocyclic nitrogen and exocyclic oxygen, as well as of related atoms and groups,[24,25] ΔE_{calc} data for binding to Sn by nitrogen bases, in the context of known types of structures,[9,10,56] have been observed to be in some cases consistent with the experimental ΔE of Table 3. Further studies are clearly needed in order fully to understand the correct bonding situation.

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