ELSEVIER

Coordination Chemistry Reviews 224 (2002) 111–150

COORDINATION CHEMISTRY REVIEWS

www.elsevier.com/locate/ccr

Organotin(IV)$^{n+}$ complexes formed with biologically active ligands: equilibrium and structural studies, and some biological aspects

Lorenzo Pellerito [a], László Nagy [b,*]

[a] *Department of Inorganic Chemistry, University of Palermo, Viale delle Scienze, Parco dOrleans, 90128 Palermo, Italy*
[b] *Department of Inorganic and Analytical Chemistry, University of Szeged, PO Box 440, H-6701 Szeged, Hungary*

Received 30 October 2000; accepted 19 June 2001

This work is dedicated to the memory of Professor Kálmán Burger

Contents

Abstract

The organotin(IV) cations form complexes with ligands containing {O}, {N}, {S}, or {phosphorus(O)} donor atoms with various composition and stability. The emergence of new experimental techniques (EXAFS, multinuclear ^{1}H-, ^{13}C-, ^{119}Sn-NMR, ^{119}Sn Mössbauer, etc., spectroscopic techniques) provided useful information about the structure and stabilities of the complexes formed. We reviewed the literature on these type of complexes taking into account the biological aspects of the complexes discussed.

Keywords: Organotin(IV) cations; Complexes; Mössbauer spectroscopy; EXAFS; Multinuclear NMR spectroscopy; X-ray diffraction; Antitumour activities; Equilibrium measurements; Biological effects

* Corresponding author. Fax: +36-62-420505.
E-mail addresses: bioinorg@unipa.it (L. Pellerito), laci@chem.u-szeged.hu (L. Nagy).

0010-8545/02/$ - see front matter
PII: S0010-8545(01)00399-X

1. Introduction

The rapid rise in the industrial, agricultural and biological applications of organotin(IV) compounds during the last few decades has led to their accumulation in the environment and in biological systems.

Organotin(IV) compounds are characterized by the presence of at least one covalent C–Sn bond. The compounds contain tetravalent Sn centres and are classified as mono-, di-, tri- and tetraorganotin(IV)s, depending on the number of alkyl (R) or aryl (Ar) moieties. The anion is usually chloride, fluoride, oxide, hydroxide, a carboxylate or a thiolate.

It is well known that organotin(IV) compounds display strong biological activity. Most organotin(IV) compounds are generally very toxic, even at low concentration. The biological activity is essentially determined by the number and nature of the organic groups bound to the central Sn atom. It seems that the nature of the anionic group is of only secondary importance. The trialkyltin(IV) $[R_3Sn(IV)^+]$ and triaryltin(IV) $[Ar_3Sn(IV)^+]$ derivatives exert powerful toxic action on the central nervous system. Within the series of $R_3Sn(IV)^+$ compounds, the lower homologues (methyl, Me; ethyl, Et) are the most toxic when administrated orally, and the toxicity diminishes progressively from tri-*n*-propyl to tri-*n*-octyl, the latter not being toxic at all.

The moieties $R_nSn(IV)^{(4-n)+}$ ($n = 2$ or 3) may be bound to membrane proteins or glycoproteins, or to cellular proteins; e.g. $Et_2Sn(IV)^{2+}$ to ATPase and hexokinase [1], $Bu_2Sn(IV)^{2+}$ and $Bu_3Sn(IV)^+$ to ATPase and acetylcholinesterase of human erythrocyte membrane [2,3], while $Bu_2Sn(IV)^{2+}$ may also be bound to skeletal muscle membranes. It seems that the sulfur-coordinated complexes are very stable as compared with those coordinated by {O} or {N}. Some organotin(IV) compounds have antitumour activity [4]. The antitumoural mechanism remains unknown (see later).

Several surveys of organotin(IV) compounds have been published. Zuckerman reviewed much of the work published before 1978 [5], while in 1989 Saxena and Huber [4] covered the literature dealing with the biological, including the anticancer activities, of most of the compounds studied. In the same year, the results obtained in the wide field of bioorganotin(IV) compounds were surveyed by Molloy [6]. Later, Tsangaris and Williams [7] published a paper on Sn [including organotin(IV)], compounds in pharmacy and nutrition. A full listing of reports which have evaluated organotin(IV) compounds in agriculture is to be found in the two-part review by Crowe [8,9]. Detailed discussions of organotin(IV) wood preservatives are published in [10,11].

In 1985, two independently published reviews demonstrated the utility of organotin(IV) derivatives of (poly)alcohols in regioselective manipulations involving indirect acylation, alkylation and oxidation [12,13], while a very recent work by Grindley dealt with the applications of organotin(IV)-containing intermediates in carbohydrate chemistry [14].

Strong sugar-organotin(IV) cation complexation have been discussed by Burger and Nagy [15], Gyurcsik and Nagy [16], Verchére et al. [17], while Barbieri et al. [18] dealt mainly with the interactions of organotin(IV) cations and complexes with DNA and their derivatives. However, a comprehensive review of the properties of the organotin(IV) complexes formed with biologically active ligands is not yet available. The aim of the present work is to survey the results obtained by means of different equilibrium (mainly pH-metric, spectrophotometric and calorimetric) and structural [spectroscopic (multinuclear NMR, FTIR and Mössbauer), X-ray diffraction, extended X-ray absorption fine structure (EXAFS) and X-ray absorption near edge structure (XANES) measurements, etc.] methods on the complexes formed with the various organotin(IV) ions or compounds. The biological properties of some of the compounds in question are also discussed.

2. Physical methods for the study of organotin(IV) derivatives

2.1. ^{119}Sn-NMR spectroscopy

The most convenient technique used to study organotin(IV) derivatives in solution and in the solid state is ^{119}Sn-NMR spectroscopy. The ^{119}Sn nucleus has a spin of 1/2 and a natural abundance of 8.7%; it is about 25.5 times more sensitive than ^{13}C, taking into account the isotopic abundance. The isotope ^{117}Sn is slightly less sensitive (natural abundance 7.7%) and has not been used much. Both of these nuclei have negative magnetogyric ratios, and consequently the nuclear Overhauser enhancements are negative. Some examples of the applications of this method are mentioned later, in different sections.

2.2. ^{119}Sn Mössbauer spectroscopy

The effect discovered by R. Mössbauer in 1957 [19], the 'nuclear resonance fluorescence of gamma radiation', is analogous to the atomic fluorescence of UV–VIS light. The effect is now generally termed the recoil-free emission and resonant absorption of nuclear γ-rays [20]. The characteristic quantities measured are the isomer shift (δ), the quadrupole splitting (Δ) and the half-height line-width (Γ) in mm s^{-1}.

The information extracted from the ^{119}Sn Mössbauer spectroscopy of Sn compounds is essentially: (1) the valence state in the inorganic derivative; (2) the structure and bonding in the metal environment [(mainly in

organotin(IV)s]; and (3) the dynamics of the Sn nuclei, which possibly correlates with the nature of the substrate (mono- or polymeric). Measurements may be made on solids (crystalline or amorphous), gels and solutions (quickly frozen to a glassy state). Mössbauer spectroscopic measurements give information that is analogous or complementary to data obtained with other spectroscopic techniques, such as NMR spectroscopy, X-ray diffraction, neutron diffraction, EXAFS, etc. As usual, this method has both advantages and disadvantages.

Advantages:

1. The easy experimental procedures.
2. The relative simple and inexpensive instrumentation.
3. The possibility of obtaining information on the metal properties in high molecular weight systems.

Disadvantages:

1. In addition to the high cost of the Sn source, the time required to collect the spectra can also be excessive (about 1 day per spectrum).
2. The sample must contains Sn at the milligram level (about 0.5 mg $^{119}Sn\ cm^{-2}$).
3. The near impossibility of quantitative Sn analysis. This technical limit is shared by other widely employed spectroscopic techniques.

2.3. Extended X-ray absorption fine structure (EXAFS) method

The EXAFS method seems to be suitable for determination of the local structure of organotin(IV) complexes formed with biologically active ligands in solution or the solid state. A very high flux of X-rays produced by synchrotron radiation is usually applied the EXAFS method provides structural information relating to the radial distribution of atom pairs in a system: the number of neighbouring atoms around a central atom (the coordination number) in the first, second and sometimes third coordination spheres, the interatomic distances and their root mean square deviations. The XANES spectra should also be analysed, to obtain information on the coordination geometry, possible binding sites and the oxidation number of the metal ion in question. It should be noted, however, that additional, independently obtained information on the metal ion-binding sites and suitable structural models (in most cases) are needed to analyse EXAFS spectra.

Advantages of EXAFS as a structural probe:

1. No requirement for crystalline matter: gases, glasses, powders or liquids can be studied.
2. Element-specific for elements suitable for X-ray absorption.
3. For situations with a good contrast of the X-ray absorption edge over the background for the transition metal in a matrix of low atomic number, information can be obtained at a concentration of about one atom in 10^6.
4. Accurate interatomic distances can be obtained (± 20 pm) within 350 pm of the primary absorber.
5. Studies as a function of time are also possible.

Disadvantages of EXAFS as a structural probe:

1. No angular information can be obtained.
2. Reliable data are restricted to distances less than 350 pm from the primary absorber.
3. The requirement of sample homogeneity for the element of interest.
4. The possibility of radiation damage.
5. The validity of the interpretation involves the adjustment of several parameters within a theoretical model to reproduce the experimental data [21].

A few years ago, we used this method to determine the local structures of the complexes of $Et_2Sn(IV)^{2+}$ [22] and other moieties, mainly transition metal ions [23–32], with non-protected carbohydrates and their derivatives. The local structures of a large number of amorphous organotin(IV) complexes (including DNA and their constituents, haemoglobin and albumin as ligands) were recently measured by EXAFS; the data-processing and curve-fitting analysis are in progress [33].

2.4. X-ray diffraction method

X-ray crystallographic findings on of compounds containing a ligand and a metal salt in stoichiometric proportions do not constitute evidence of complex formation in solution. The well-defined crystal structure merely indicates that in the solid state the ligands, the metal ion and the anion fill the space in a regular packing, usually held together by coordination and by electrostatic and hydrogen bonding. When the crystals are dissolved in polar solvents (e.g. water), these hydrogen bonds may be broken and water or some other solvent molecule may displace one of the coordinated groups of the ligand from the coordination sphere of the metal ion. On the basis of the crystal structures, it is not possible to predict complex formation in solution. On the other hand, when complex formation is known to occur in solution from independent equilibrium measurements, or there is other spectroscopic evidence, it is very probable that the main binding sites are the same in the crystal and in solution. In the crystal, additional weak binding sites may also be present.

Table 1
Stability constants of species formed in the hydrolysis of $Me_2Sn(IV)^{2+}$ at 298 K in different ionic media

(p, r)	$\log \beta_{pr}$				
	Ref. [36] 0.1 M $NaClO_4$	Ref. [37] 0.1 M $NaNO_3$	Ref. [38] 0.1 M KNO_3	Ref. [39] 0.1 M NaCl	Ref. [39] 3 M $NaClO_4$
(1, −1)	−3.17	−3.18	−3.12	−3.25	−3.54
(1, −2)	−8.42	−8.42	−8.43	−8.54	−8.98
(1, −3)	−19.45	–	−19.45	–	–
(2, −2)	−4.96	−4.69	−5.05	−5.05	−4.60
(2, −3)	−9.71	−9.64	−9.74	−9.81	−9.76
(2, −4)	–	−15.44	–	–	–
(3, −2)	–	−3.21	–	–	–
(3, −4)	–		–	−11.52	−10.40
(4, −5)	–	−11.72	–	–	–
(4, −6)	–	−16.36	–	–	–

$p = Me_2Sn(IV)^{2+}$, $r = OH^-$.

3. Hydrolysis of organotin(IV)$^{n+}$

From environmental and equilibrium measurement aspects, the speciation of organotin(IV) species in water is very important if their reactivities are to be understood. It is necessary therefore, to obtain information relating to the hydrolysis and the structure of the hydrolysed species.

The species organotin(IV)$^{(4-n)+}$ are considered to be Lewis acids of different strengths, depending on the groups bound to the Sn(IV) [34]. Consequently, they display a strong tendency to hydrolysis in aqueous solution, as first demonstrated by Tobias et al. [35]. Later studies on the interactions of $Me_2Sn(IV)^{2+}$ with ligands containing different donor atoms (O, N, S, etc.) necessitated determination of the hydrolysis constants. The evaluation of such complex formation constants was based on the data obtained earlier from independent measurements. Some data are compared in Table 1.

Most of the reported thermodynamic parameters refer to a single ionic medium and a single ionic strength. Hydrolysis of $Me_2Sn(IV)^{2+}$ recently performed in different aqueous media (NaCl or $(Me)_4NCl$, $NaNO_3$, $NaClO_4$, and Na_2SO_4), in a wide range of ionic strength at 298 K. The same species were observed to form as earlier. The dependence on the ionic strength for different salt solutions was taken into account by using a Debye–Hückel equation. For exemplification purposes the dependences of (A) $\log \beta_{11}$ and (B) $\log \beta_{12}$ on the ionic strength are depicted in Fig. 1. Medium effects were explained by considering the formation of chloride and sulfate complexes too [40].

Despite their environmental relevance, relatively few studies have been performed on the solution chemistry of $R_3Sn(IV)^+$, though their structures have been extensively investigated both in the solid state and in solution. Studies on aqueous solutions of $Me_3Sn(IV)^+$ have been performed by ^{119}Sn-NMR measurements [41] and by potentiometry, in $NaClO_4$ medium (3 and 0.3 mol dm^{-3}) [34,42]. Investigations of the interactions of $Me_3Sn(IV)^+$ with carboxylic and amino acids have been performed in aqueous solution (total ionic strength adjusted to 0.3 mol dm^{-3}) [44]. Cannizzaro recently reinvestigated the system in different ionic media ($NaNO_3$ and NaCl), at different ionic strength (0–1.5 mol dm^{-3}) and at different temperatures (5–45 °C). Only two species could be detected throughout the whole pH range: Me_3SnOH and $\{Me_3Sn(OH)_2\}^-$. At higher chloride ion concentrations, the cation also forms a weak chloro complex [43]. For purpose of comparison the $-\log \beta_{11}$ values are collected in Table 2.

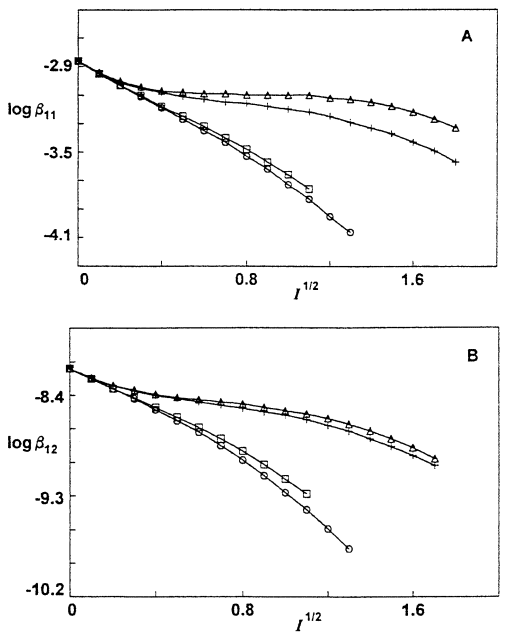

Fig. 1. Dependence of (A) the $\log \beta_{11}$ and (B) the $\log \beta_{12}$ values of the hydrolysis products of $Me_2Sn(IV)^{2+}$ on the ionic strength [40].

Table 2
Literature data on the hydrolysis constants of $Me_3Sn(IV)^+$

Ionic medium	Method	$-\log \beta_{11}$	Refs.
KNO_3, 0.5 M	NMR	6.35	[41]
KCl, 0.5 M	NMR	6.38	[41]
$NaClO_4$, 3 M	Potentiometry	6.59	[34]
KCl, 2 M	Potentiometry	6.40	[42]
$NaNO_3$, 0.5 M	Potentiometry	6.21	[43]
NaCl, 0.5 M	Potentiometry	6.25	[43]
$NaClO_4$, 0.3 M	Potentiometry	6.26	[44]

All measurements were performed at 298 K [43].

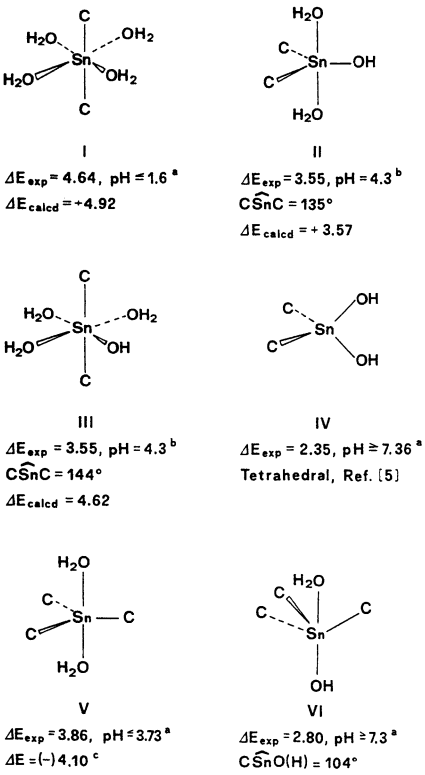

Fig. 2. Point-charge model estimates of the possible structures of $Me_2Sn(IV)^{2+}$ and $Me_3Sn(IV)^+$ as a function of the extent of hydrolysis: (I) → [(II) or (III)] → (IV); (V) → (VI). The angles C–Sn–C and C–Sn–O have been estimated via the correlation Δ-angle from the partial nuclear quadrupole splitting due to Sn–C bonds only [45].

According to Rizzarelli et al. [38], there is no significant difference in the acidities of $Me_2Sn(IV)^{2+}$ and $Et_2Sn(IV)^{2+}$. This result is in contrast with earlier findings by Tobias, which pointed to an acidity increase in the series $Me_2Sn(IV)^{2+}$, $Et_2Sn(IV)^{2+}$ and $Pr_2Sn(IV)^{2+}$, with log K values of -3.54, -3.40 and -2.92, respectively [34]. The latter trend [34], which is opposite to that observed for $Me_3Sn(IV)^+$ and $Et_3Sn(IV)^+$, and to that expected simply on the basis of inductive effects, was explained by invoking a decreasing degree of solvation of the acid with increase in size of the alkyl groups. It is likely that the difference between these results and the results published in [34] is attributable to an incomplete model that considered only the formation of $[R_2Sn(OH)]^+$ and $[(R_2Sn)_2(OH)_2]^{2+}$.

In addition to the equilibrium studies on the hydrolysis of $Me_2Sn(IV)^{2+}$, the structures of the main species formed have also been determined. In ethanol solution the *trans* Me_2 species is formed, with composition $Me_2SnCl_2(EtOH)_2$. This species has an octahedral structure [45,46]. In aqueous solution, the gradual hydrolysis of $Me_2Sn(IV)^{2+}$ has been followed by potentiometric titration and Mössbauer spectroscopic measurements (Fig. 2). The results show that the structure varies from octahedral in the aquated species $Me_2Sn(H_2O)_4$ to tetrahedral in $Me_2Sn(OH)_2$. The latter species is present at neutral and basic pH, and reacts with aqueous phosphate and D-ribose-phosphate, yielding mainly 1:1 and 1:2 complexes where the $Me_2Sn(IV)^{2+}$ moiety is embedded into a trigonal-bipyramidal or octahedral (probably distorted) species [47,48].

The ^{1}H-NMR spectra of Me_2SnCl_2 [49] and Et_2SnCl_2 [50] solutions present a sharp signal with satellite peaks, as a result of heteronuclear couplings [$^2J(^{117}Sn^1H)$ and $^2J(^{119}Sn^1H)$] with the two NMR active isotopes of Sn as already mentioned above. In the $Me_2Sn(IV)^{2+}$ system, both the chemical shift and the coupling constants decrease with increasing pH. The $^2J(^{119}Sn^1H)$ values can be used to determine the C–Sn–C angle, providing information on the structure of the species formed in solution [51]. From the ^{1}H-NMR spectra of $Me_2Sn(IV)Cl_2$ solutions recorded at different values of pH, taking into account the known species distribution of hydroxo complexes in fast mutual exchange, it is possible to calculate the individual NMR parameters (δ, ^2J) for the different species. The values calculated for the different hydrolytic species are collected in Table 3. These data suggest an octahedral structure for

Table 3
Individual NMR parameters (δ, ^2J) calculated for different hydrolytic species of $Me_2Sn(IV)^{2+}$ [49] and $Et_2Sn(IV)^{2+}$ [50]

	$\delta(CH_3)$ (ppm)	$\delta(CH_2)$ (ppm)	^2J(Sn–H) (Hz)	∠C–Sn–C (°)
$Me_2Sn(IV)^{2+}$	0.89	–	106	175
$Me_2Sn(OH)^+$	0.87	–	95	154
$Me_2Sn(OH)_2$	0.64	–	81	175
$[Me_2Sn(OH)_3]^-$	0.41	–	81	132
$Me_2Sn_2(OH)_2$	0.74	–	80	132
$Me_2Sn_2(OH)_3$	0.79	–	82	132
$Et_2Sn(IV)^{2+}$	1.244	1.582	90.8	146
$Et_2Sn(OH)^+$	1.289	1.536	73.5	123
$Et_2Sn(OH)_2$	1.213	1.320	71.0	120
$Et_2Sn(OH)_3$	1.205	1.153	70.7	120
$Et_2Sn_2(OH)_2$	1.143	1.319	88.2	142
$Et_2Sn_2(OH)_3$	1.188	1.343	70.3	120

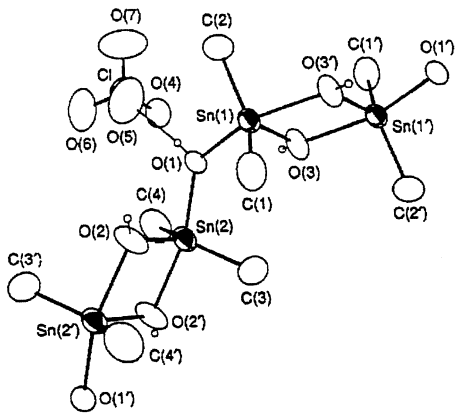

Fig. 3. An ORTEP diagram of the polymer of $[(Me_2Sn)_2(OH)_3]ClO_4$. All H atoms have been omitted for clarity [37].

the aqua ion, a trigonal-bipyramidal structure for the complexes $M(OH)_2$, $M(OH)_3$, $M_2(OH)_2$ and $M_2(OH)_3$, [where $M = Me_2Sn(IV)^{2+}$ or $Et_2Sn(IV)^{2+}$], for $M(OH)_2$, more probably a tetrahedral [52], while for MOH an intermediate value is determined, probably as a results of (1) the coexistence of both octahedral and trigonal-bipyramidal structures in fast mutual exchange, or (2) a very distorted structure.

A rhombic crystal of the perchlorate of $[(Me_2Sn)_2(OH)_3]^+$ was obtained [37]. The results of crystal structure analysis showed, that the polymer structure consists of penta-coordinate Sn(IV) units with di- and monohydroxo bridging. The coordination geometry of the Sn unit is a distorted trigonal-bipyramid with two Me groups and one μ-hydroxo group in *equatorial* positions and the other two μ-hydroxo groups in *axial* positions. Each di-μ-hydroxo bridge has two different Sn-O bond lengths, 203.0 and 222.0 pm for Sn(1)–O(3) and Sn(1)–O(3′) and 201.9 and 223.6 pm for Sn(2)–O(2) and Sn(2)–O(2′). The shorter and longer bonds correspond to the equatorial ($Sn–O_{eq}$) and axial bonds ($Sn–O_{ax}$), respectively. This di-μ-hydroxo structure is quite similar to that of the nitrate dimer, di-μ-hydroxo-bis[dimethylnitratotin(IV)] [53], in which the two bridging bond lengths are 206 and 218 pm. On the other hand, the mono-μ-hydroxo O(1) bridges Sn(1) and Sn(2), via their *axial* positions, with similar bond lengths, 213.9 and 213.2 pm, respectively (Fig. 3).

4. Interactions of organotin(IV)$^{n+}$ with biologically active ligands

4.1. Interactions of organotin(IV)$^{n+}$ with amino acids and peptides

The most widely studied interactions between biologically active ligands and organotin(IV) cations relate to the amino acids and their derivatives (*N*- or *S*-protected amino acids and peptides), though data on several of the most commonly occurring amino acids are still outstanding. This is especially true for speciation in aqueous solution. A nice and very detailed review was published on this area by Molloy [6].

In aqueous solutions at pH 7, there is little evidence of complex formation between $Me_3Sn(IV)^+$ and Gly [44,54]. A number of equilibrium data, among them data on amino acid ligands, were published on $R_2Sn(IV)^{2+}$ complexes [36,38,55–59]. These studies revealed the 'chameleon' nature of the $R_2Sn(IV)^{2+}$, since strong affinity was reported towards ligands containing {O}, {S,O,N} or {O,N} donor sites.

Equilibrium and spectroscopic studies on L-Cys and its derivatives (*S*-Me-Cys, *N*-Ac-Cys) and the $Et_2Sn(IV)^{2+}$ system showed that these bioligands are coordinated to the metal ion via carboxylic {O} and the thiol {S} donor atoms in acidic media [57]. In the case of *S*-Me-Cys, the formation of a protonated complex MLH was also detected, due to the stabilizing effect of additional thioether coordination.

In the solid state, the di- and triorganotin(IV)-amino acid compounds are readily formed in the reaction between the free ligand and an organotin(IV) oxide or hydroxide [60]. FTIR [ν_a(COO)] and Mössbauer data ($\Delta = 3.14–3.73$ mm s^{-1}) showed that organotin(IV) derivatives of Gly are *N*-bridged polymers [61,62]. This structure has been confirmed crystallographically and extensively evaluated by Mössbauer spectroscopy [63]. The N:-Sn interaction apparently occurs in Gly derivatives, because the carbonyl {O} is involved in the hydrogen bonding network C=O···H–N. In *N*-protected Gly complexes, polymerization occurs through bidentate carboxylate groups, or by bridging through the amide {O} [64–66]. $Me_3Sn(IV)^+$ and $Me_2Sn(IV)^{2+}$ complexes of *N*-Bz-Gly display antitumour activity against the leukaemia P-388 cell line [67].

Several alkyltin(IV) complexes of peptides have been prepared and studied in the solid state (or dissolved in different solvents) [68–71], e.g. Me-*N*-Bz-Leu-His was found to be a useful model to mimic alkyltin(IV) binding of proteins through imidazole {N}. The metal binding by amide {N(s)} is particularly important in peptide complexes. X-ray diffraction studies of some crystalline $R_2Sn(IV)$–peptide complexes and NMR measurements on the same complexes dissolved in aqueous solution, provided definite evidence for formation of the $Sn–N^-$ bond [69,72]. Recent pH-metric and spectroscopic results have confirmed, that the $Me_2Sn(IV)^{2+}$ does not interact with Histm and Gly-Histm which contain only {N} donor atoms. Hydrolysed species of the $Me_2Sn(IV)^{2+}$ always predominate over the complexes with Gly-Histm, imidazole-4-acetic acid, Gly and β-Ala-His, while the Gly-Gly and Gly-His coordinate through {COO^-, N^-, NH_2} donor sites at neutral pH and trigonal-bipyramidal species are formed [49]. Very

similar species are formed between $Me_2Sn(IV)^{2+}$ and Gly-Asp and Asp-Gly as ligands as mentioned above [73].

In consequence of their structural variability, organotin(IV) derivatives of *N*-substituted amino acids and-peptides have been extensively studied in recent decades. It is of particular interest to examine the structural variations caused by organic substituents on the Sn and protecting groups on the amino N of the ligand.

The spectroscopic data have revealed that in the $R_3Sn(IV)^+$ derivatives of *N*-Ac dipeptides the carboxylate groups of the latter are bound in a monodentate manner [60,67]. The amide –C=O group coordinates to another $R_3Sn(IV)^+$ unit in these compounds, resulting in a polymeric structure. In contrast, $R_3Sn(IV)^+$ derivatives of *N*-Ac-Gly and *N*-Ac-L-Cys are believed to contain bidentate $-COO^-$ donor groups [74].

In the *N*-Bz derivatives of Gly [64,65] and Gly-Gly [75], the planar $R_3Sn(IV)^+$ moieties are bridged by carboxylate groups. Because of the negative inductive effect of the Ph group, which reduces the donor ability of {O}, coordination of the amide –C=O in the latter compounds could be ruled out.

The influence of the length of the peptide chain on the coordination mode in $R_3Sn(IV)^+$ complexes has recently been studied [76]. The Gly-Gly-Gly moiety proved to be long enough to shade the $-I$ effect of the Bz group in its *N*-Bz derivatives: $R_3Sn(IV)^+$ complexes of *N*-Bz-Gly-Gly-Gly were considered to be polymeric, with monodentate carboxylate and –C=O coordination similar to that in the corresponding complexes of *N*-acetylated peptides [60,76,77].

$R_2Sn(IV)^+$ derivatives of *N*-Bz-Gly-Gly [75] and *N*-Bz-Gly-Gly-Gly [76] were found to involve both dicarboxylate binding to yield hexacoordinated Sn(IV) centres, and dimeric tetraorganodistannoxanes in which the carboxylates bind alternatively as monodentate and bridging bidentate groups. In these compounds, the involvement of amide groups in the coordination has been totally excluded.

$Ph_3Sn(IV)^+$ complexes of *N*-Ac-Gly, *N*-Ac-L-Leu, *N*-Ac-L-Asp and *N*-Acl-L-Tyr were prepared by two procedures and characterized by means of different spectroscopic methods (FTIR, multinuclear, ^{1}H-, ^{13}C- and ^{119}Sn-NMR and ^{119}Sn Mössbauer spectroscopy).

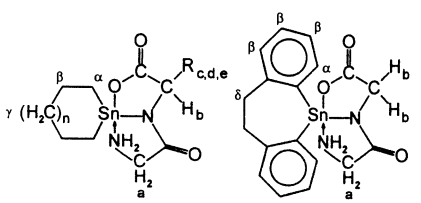

Fig. 4. Structures of stannacyclohexyl and stannacycloheptyl derivatives (AA) [79].

The data indicated that the *N*-Ac-Gly complex adopts a trigonal-bipyramidal structure in which the monodentate carboxylate and the amide –C=O group are bound to the same organotin(IV) moiety. The other three complexes are linear oligomers in which the planar $Ph_3Sn(IV)^+$ is coordinated axially by a monodentate carboxylate and an amide –C=O from two different ligands. At the C-terminal end of the oligomer chain, there is a tetracoordinated Sn(IV) with a monodentate carboxylate as donor group [78].

Stannacyclohexyl and stannacycloheptyl derivatives of dipeptides (AA) were prepared and investigated by Barbieri et al. In these compounds, Sn is a member of a ring system (Fig. 4). IR and ^{119}Sn Mössbauer data on the solid compounds indicate that the AA acts as a tridentate {O,N,N} ligand and the Sn has a trigonal-bypiramidal environment. An analogous structure has been found for the undissociated molecules in methanol solution [79]. This work clearly demonstrated that there are no basic restrictions for Sn(IV) to extend its coordination sphere (at least to attain pentacoordination) when it is an integral part of a cycloalkyl system. These results are confirmed by an X-ray structure determination of the Schiff-base complex ($H_2SAT = 2$-(*O*-hydroxyphenyl)benzothiazolidine) in which the Sn is pentacoordinated.

Diorganotin(IV) derivatives of *N*-Bz-Gly-Gly were suggested to be dimeric tetraorganodistannoxanes in which the carboxylate groups alternatively act as monodentate and bridging bidentate ligands, the Sn atoms being essentially pentacoordinated. Any involvement of peptide/amide groups in the bonding to the central atom was ruled out [75]. On the other hand, in triorganotin(IV) derivatives of *N*-Bz-Gly-Gly [75] and *N*-Bz-Gly [64,65], planar $R_3Sn(IV)^+$ units are bridged by carboxylate groups. A different coordination mode is observed in triorganotin(IV) derivatives of amino acids and *N*-acetylated dipeptides: X-ray diffraction studies on $Me_3Sn(IV)^+$ glycinate [80] and vibrational and Mössbauer spectroscopic data for the other derivatives [60,77] showed that the carboxylate group acts essentially as a monodentate ligand, and that the amino [80] or amide –C=O group [60,77] coordinates to another $R_3Sn(IV)^+$ unit. In this way pentacoordination of the Sn and polymeric structure resulted. The amide –C=O group seems not to be able to coordinate to the central Sn atom in the *N*-Bz derivatives, presumably as a consequence of the reduced donor power of the {O} atom, due to the inductive effect ($-I$) of the Ph group. On the other hand, in the triorganotin(IV) derivatives of *N*-Bz-Gly-Gly-Gly and *N*-Ac-Gly-Gly-Gly the Sn atom is in a trigonal-bipyramidal environment, where the planar $R_3Sn(IV)^+$ unit is bound by a monodentate carboxylate and a donor group, presumably the amide –C=O. The diorganotin(IV) compounds gave both dicarboxylates R_2SnL_2, containing hexacoordinated Sn,

and dimeric tetraorganodistannoxanes $\{[R_2SnL]_2O\}_2$, in which the Sn atoms are essentially pentacoordinated [76].

4.2. Interactions of organotin(IV) with carbohydrates and their derivatives

Organotin(IV) compounds have been used widely in synthetic carbohydrate chemistry [11,81–83], the reason being the regioselective directing power of the organometal cation towards further reactivity of the sugar substrate. They provide reliable, high-yielding methods for obtaining monosubstituted derivatives of diols or polyols, often with high selectivity. Moreover, the reactions occur under milder conditions or at rates that are much higher than those for the parent alcohols. For further reading, extended references for such applications are to be found in several reviews [10,11] and books [12,85,86].

The presence of organic ligands in organotin(IV) complexes, among them carbohydrates, modifies the biological properties of the system [87]. For example, the D-saccharose-$Ar_3Sn(IV)^+$ conjugates have been demostrated to be effective in marine antifouling paints [88]. This property modification is the reason for the increasing interest in interactions between organotin(IV) compounds and carbohydrate derivatives [11].

The literature contains only a few reports on equilibrium studies of the interactions of organotin(IV)-carbohydrates or carbohydrate derivatives. ^{13}C-NMR spectroscopy and mass spectrometry showed that D-glucopyranosiduronic acid (GlupA) forms complexes $Ar_3Sn(IV)$-GlupA upon reaction with bis[$(Bu_3Sn(IV)]_2O$ but surprisingly not with $Bu_3Sn(IV)Cl$ or $Me_3Sn(IV)Cl$ in Me_2SO or with $Me_3Sn(IV)Cl$ in water. Primarily the O-4 hydroxy and to a lesser extent the ring {O} at C-1 are coordinated to the organotin(IV) cation [89]. It was recently also shown that the interactions of $Et_2Sn(IV)Cl_2$ and 2-polyhydroxyalkylthiazolidine-4-carboxylic acid (PHTAc) derivatives (formed by the reaction of L-Cys and aldoses under mild conditions) led to formation of the complexes MLH, ML and MLOH [where $M = Et_2Sn(IV)^{2+}$], including of the hydrolysis products of the organotin(IV) cation [58]. Furthermore, $Et_2Sn(IV)^{2+}$ coordinated the *N*-D-gluconyl-α-amino acids (formed in the reactions between D-gluconic acid-δ-lactone and amino acids) via deprotonated carboxylate, amine and alcoholic hydroxy groups, while the β-amino acid derivatives were coordinated through carboxylate and deprotonated sugar hydroxy groups only [59]. ^{13}C-NMR measurements have confirmed that the amine group in the ligands does not participate in complex formation. The structures of species present in quick-frozen solution have been determined by Mössbauer measurements.

To study the effect of the conformation of the sugar hydroxy groups on metal complexation processes, the complex formation of eight saccharides (D-fructose, L-sorbose, L-arabinose, D-arabinose, D-glucose, D-sorbitol, 2-deoxy-D-glucose and D-saccharose) with $Me_2Sn(IV)^{2+}$ was investigated in aqueous solution by potentiometric equilibrium measurements, ^{13}C-NMR, polarimetry and Mössbauer spectroscopy. The experimental results revealed that deprotonation of D-fructose and L-sorbose is caused by the coordination of $Me_2Sn(IV)^{2+}$ in the unusually low pH interval 4–6, in contrast with the other saccharides, which are deprotonated in an analogous way at pH > 8. Increase of the pH of the solution resulted in the formation of further complexes that differed from each other only in deprotonation state. ^{13}C-NMR measurements led to the assignment of the sugar hydroxy groups participating in the processes. Mössbauer spectroscopic investigations of the quick-frozen solutions permitted determination of the stereochemistry of the Sn(IV) in the complexes [36]. Evaluation of the pH-metric titration curves for the systems $Me_2Sn(IV)^{2+}$–polyhydroxyalkylcarboxylic acids confirmed the formation of several 1:1 metal-to-ligand species differing only in protonation state. Besides these complexes, the hydrolysis products of the organometallic cation are also detectable. At low pH, the anchor group is the carboxylate. In alkaline solutions, of the alcoholic hydroxy groups undergo stepwise deprotonation, similarly as in the carbohydrate-$Me_2Sn(IV)^{2+}$ systems already studied [90].

Dialkylstannylene acetals (or, more properly, 2,2-dialkyl-1,3,2-dioxastannolanes, if the ring is five-membered; 2,2-dialkyl-1,3,2-dioxastannanes, if the ring is six-membered; and 2,2-dialkyl-1,3,2-dioxestannepanes, if the ring is seven-membered) are easily prepared by the reactions of vicinal diols with R_2SnO or $R_2Sn(OH)_2$ [91–98], or $R_2Sn(IV)$ diethoxide [99,100] under conditions of azeotropic dehydration in benzene or toluene. Molecular weight measurements in solution indicated that the main reaction product is a dimeric species [99,101,102]. Where more than one unprotected hydroxy group is available for reaction, both partially and fully stannylated products are formed [103–106]. Early work established the regioselectivity of tributylstannylation of carbohydrates, wich is related to the ease reaction with which Sn can coordinate a neighbouring {O} atom. Thus, C-6(O) is the most reactive, followed by

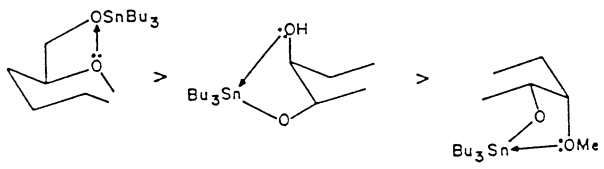

Fig. 5. The possible coordination sites of carbohydrates for $Bu_3Sn(IV)^+$ [107].

the secondary hydroxy groups, all of which are capable of coordinating to Sn by a second, *cis*-O [107] (Fig. 5). Triorganotin(IV)$^+$ carbohydrate complexes are easily distilled as oils, which are rapidly hydrolysed upon exposure to air, though the aerobic stability increases if free hydroxy groups are retained in the product [108].

The regioselectivity of alcoholic hydroxy group reactivity towards diorganotin(IV)$^{2+}$ compounds is also dictated by the ability of the system to allow the formation of additional O:→Sn bonds. Thus, two vicinal, secondary alcoholic hydroxy groups in a *cis*-(*axial*, *equatorial*) position are the most reactive, and another favourable combination for further coordination is a secondary hydroxy groups in conjunction with a *cis*-(*axial*) alkoxy moiety. Least favourable is a pair of a *trans*-(*equatorial*, *equatorial*) hydroxy groups [107], though the overall order of reactivity is partially dependent on the reaction conditions.

In general the carbohydrate organotin(IV) complexes have been studied by ^{1}H- and ^{13}C-NMR [97,103], or, especially recently, by multinuclear NMR (^{119}Sn, ^{1}H and ^{13}C) spectroscopy [104,109–111]. The nice series of papers by Grindley et al. demostrated that these compounds are present in solution as dimers and/or higher oligomers in which the central Sn atoms are penta- or hexacoordinated [110,111]. ^{119}Sn-NMR chemical shift ranges have also been established for the Sn nuclei in 2,2-dibutyl-1,3,2-dioxastannolanes; pentacoordinate Sn nuclei absorb in the region from −115 to −150 ppm with respect to Me_4Sn(IV), while hexacoordinate Sn nuclei absorb between −220 and −300 ppm in solution [110,111]. The ^{119}Sn-NMR spin-lattice relaxation rates in solution for a number of 1,3,2-dioxastannolanes in which the central Sn atoms are in either penta- or hexacoordinate environments have also been measured [111]. The relaxation times in these compounds were found to be very short, and the major mechanism of spin-lattice relaxation at 8.48 T was due to chemical shift anisotropy. In solution, the chemical shift anisotropies for the hexacoordinate sites are approximately 1.6 times higher than those for the pentacoordinate sites. It was subsequently shown that these observations also held true for solid compounds [112,113]. These results supported the previous conclu-

Table 4
Typical ^{119}Sn-NMR chemical shifts for dialkylstannylene compounds

Compounds	Solvent used	N	Structure	Chemical shift (ppm)	Ref.
1	Chloroform	5	Dimer	−126.8	[111]
	–	5,6	Trimer	−126.8, −283.0	–
	–	5,6	Tetramer	−131.4, −266.0	–
	Solid state	6	Polymer	−231.0	[113]
2	$CHCl_3$:CCl_2F_2 = 3:1	5	Dimer	−141.5	[111]
	–	5,6	Trimer	−142.5, −291.8	–
3	Chloroform	5	Dimer	−139.8	[111]
4	Chloroform	5	Dimer	–	[118]
	Solid state	5	Dimer	–	[113]
5	Chloroform	5	Dimer	−127.9	[119]
	–	4	Monomer	80	–
6	Chloroform	4	Monomer	−20.4	[119]
7	Chloroform	5	Dimer	−187.8	[112]
	–	5,6	Trimer	−195.1, −346.1	–
	Solid state	6	Polymer	−279.5, −281.8	–
8	Chloroform	5	3,3-Dimer	−125.4, −124.9	[120,110]
	Toluene	5	–	−131.6	[104]
	Solid state	5	3,3-Dimer	−126.8, −128.6	[113]
9	Chloroform	5	3,3-Dimer	−132.6	[110]
	–	–	2,3-Dimer	–	–
10	Chloroform	5	2,2-Dimer	−145.1, −143.8	[120,110]
	Solid state	5	2,2-Dimer	−141	[113]
11	Chloroform	5	Dimer	−125.6	[120]
12	Chloroform	5	Dimer	−123.4	[119]
	–	5,6	Trimer	−117.4, −122.5 −283.3	–
	Toluene	5,6	Trimer	−116.8, −124.0, −287	–
	–	–	Tetramer	−124.1, −243.4	–
13	Chloroform	5	6,6-Dimer	−119.6	[121]
14	Chloroform	5	6,6-Dimer	−180	[120]
15	Chloroform	5	Dimer	−217.7	[113]
16	Chloroform	5	Dimer	−150.8	[120]
17	Chloroform	5	Dimer	−160.2	[97]

Compounds **1**–**17** are $Bu_2Sn(IV)^{2+}$ derivatives of different protected carbohydrates. For details, see the references cited.

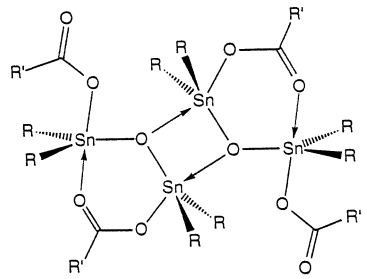

Fig. 6. Basic structure of dimeric tetraorganodicarboxylatodistannoxanes [114].

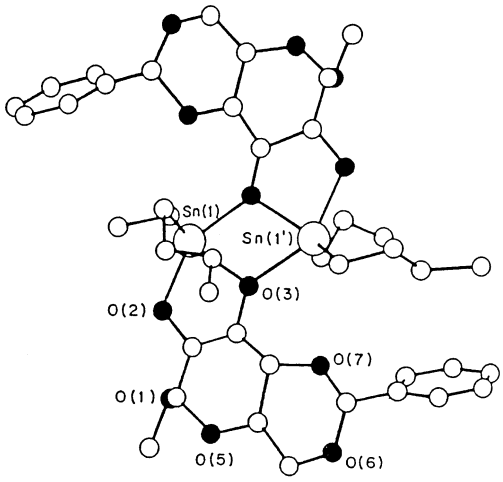

Fig. 7. The dimeric structure of the di-*n*-butylstannylene derivative of 4,6-di-*O*-benzylidene-α-D-glucopyranoside [116].

sion [110] that the antisymmetric terms of the chemical shift tensor make only a small or negligible contribution to the rate of ^{119}Sn spin-lattice relaxation in these compounds.

Typical ^{119}Sn-NMR chemical shifts for dialkylstannylene compounds are collected in Table 4.

The solid-state structure of tetrabutylbis(2,3:4,6-diisopropylidene-2-keto-L-gulonato)distannoxane has been determined [114], and is shown in Fig. 6. The $Bu_2Sn(IV)^{2+}$ complex of D-lactobionic acid also proved to be oligomeric, containing octa- (within the chain) and pentacoordinated (at the end of the chain) Sn(IV) centres in a ratio of 2:4 [115].

In some cases, when partially protected sugars were used as ligands, single crystals suitable for X-ray diffraction measurements were successfully prepared. To date, only a few crystallographic studies have been reported. In 1979, David et al. [116] showed that the di-*n*-butylstannylene derivative of 4,6-di-*O*-benzylidene-α-D-glucopyranoside has a dimeric structure, in which every tin atom exhibits distorted trigonal-bipyramidal geometry (Fig. 7).

The structure of the same complex was redetermined by Cameron et al. [117]. Data were collected at −70 °C because the previous assignment had involved a large *R* (fitting parameter) value. The results showed, similarly to the previous findings, that the Sn atom is pentacoordinated in a severely distorted trigonal-bipyramid. The *n*-Bu {C} atoms are *equatorial*, but the average C–Sn–C bond angle is large, 131.0°. The two *n*-Bu groups adopt different conformations and are still significantly disordered even at −70 °C. The Sn–O bond lengths inside the monomer units are shorter (average 207 pm) than those between the monomer units (average 223.7 pm).

In contradiction with the results discussed above, Holzapfel et al. [92] reported that 4,6-*O*-benzylidene-2,3-*O*-di-*n*-butylstannylene-α-D-mannopyranoside has a pentameric structure containing two penta- and three hexacoordinated central Sn(IV) atoms. The intramolecular Sn–O distances are similar (209 pm), and the intermolecular Sn–O distances (223 pm) in this dimer (both Sn atoms are pentacoordinated) are equivalent to the 223 and 227 pm that separate the two terminal tin atoms from their respective neighbouring {O} atoms in the pentamer. The average intermolecular Sn–O distance in hexacoordinated Sn moieties, is 248 pm. The reasons for oligomerization have been elegantly discussed in terms of steric interaction between the sugar residues (Fig. 8) shown in the structure of the pentamer. Finally, Davis et al. [94] indicated on the basis of the Mössbauer spectra of 2,2-di-*n*-butyl-D-mannose-stannolane that this compound contains penta- and hexacoordinated Sn atoms in a ratio of 2:3. The X-ray measurements demonstrated average Sn–O bond lengths of 204 pm within each monomer unit, and of 251 pm between the units. The endocyclic O–Sn–O angle was shown to be 79.9°, and the exocyclic C–Sn–C angle 138.6°.

The two hydroxy groups in 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol and its di-*O*-isopropylidene analogue are *trans*. The X-ray crystal structure [122] of the latter compound suggests that the ring is in a skew conformation with the O-3 and O-4 hydroxy groups both in *axial* orientations, but NMR studies [123] and ab initio calculations [124] indicate that a mixture of the skew and chair conformations, with O-3 and O-4 both in equatorial orientations, is present. Formation of a dibutylstannylene acetal presumably locks these two compounds in the latter conformation.

Mössbauer spectroscopy has also been widely used to investigate the structures of dialkylstannylene derivatives of carbohydrates in the solid state [89,94–96,98,125–127,364]. The usual magnitude of $\Delta = 2.78–3.07$ mm s^{-1} indicated a coordination number greater than four, with Sn(IV) centres in a penta- or hexacoordinated environment.

Comparison of the experimental quadrupole splitting values with those calculated on the basis of the partial quadrupole splitting (pqs) concept revealed that the

complexes formed are of three types, with central $Et_2Sn(IV)^{2+}$ or $Bu_2Sn(IV)^{2+}$ present (a) in a purely trigonal-bipyramidal *cis*-R_2SnO_3 unit within a polymeric framework, (b) in a purely octahedral environment, and (c) in both octahedral and trigonal-bipyramidal arrangements in a ratio of approximately 1:1 [96,98]. For $Bu_2Sn(IV)^{2+}$, a tetrahedral complex of D-mannitol is detectable [96,98]. It was also possible to distinguish between the different structural isomers (*equatorial* or *axial* arrangements of the two organo substituents) for the complexes $Et_2Sn(IV)^{2+}$- [96], $Bu_2Sn(IV)^{2+}$- [98] and $Bz_2Sn(IV)^{2+}$- [127] carbohydrates and $Bu_2Sn(IV)^{2+}$-PHTAc [58]. The formation of different structural isomers has been discussed in terms of different steric requirements of the organo substituents. The Goldanskii–Karyagin effect for $Bu_2Sn(IV)^{2+}$ complexes has been observed and discussed [98]. Thermal decomposition pathways for several $R_2Sn(IV)^{2+}$ carbohydrate complexes have been reported in [95,96]. In order to increase the water solubility of the organotin(IV) derivatives, a large number of organotin(IV) complexes of polyhydroxyalkylcarboxylic acids (containing only {O,O} donor atoms) have recently been prepared in the solid state. The compositions of the complexes were determined by the ICP method. The bonding sites of the ligands were determined by means of FTIR, Raman and in some cases ^{13}C-NMR spectroscopy. Via *pqs* calculations, the coordination geometry around the Sn(IV) centre was determined by Mössbauer measurements. The results showed that oligomeric complexes are formed, where the carboxylate group coordinates as a bidentate bridging ligand through the organometallic cations. The Sn atoms are in both trigonal-bipyramidal and octahedral surroundings [90].

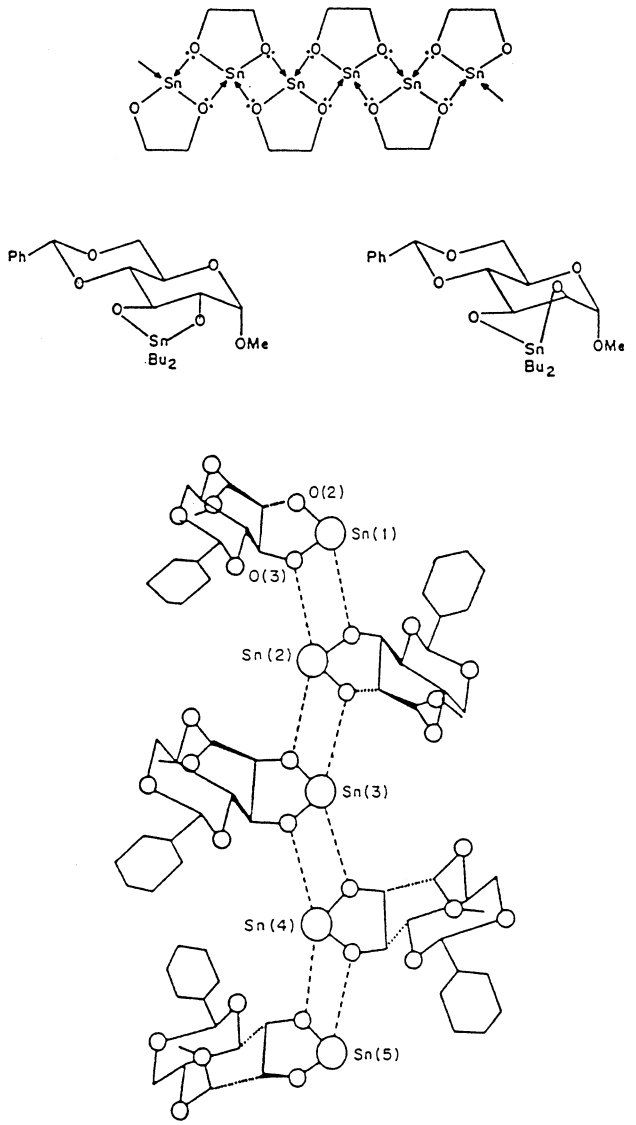

Fig. 8. The structure of pentameric 4,6-*O*-benzylidene-2,3-*O*-di-*n*-butylstannylene-α-D-mannopyranoside [92].

The $R_2Sn(IV)^{2+}$ carbohydrates and other derivatives have also been investigated as possible antitumour agents [128].

As shown above, the organotin(IV) complexes formed with unprotected sugars, are oligomeric in the solid state, and it is very difficult, or even impossible, to obtain them as single crystals suitable for X-ray diffraction measurements. The first structural information on this type of complexes [formed with $Et_2Sn(IV)^{2+}$], was obtained by means of EXAFS method in the solid state [22]. Structural data on $Bu_2Sn(IV)^{2+}$ and $Et_2Sn(IV)^{2+}$ carbohydrate complexes, obtained by X-ray diffraction [92,116] and EXAFS [22] methods, are summarized in Table 5. The results demonstrate that the dioxastannolane units are associated into an infinite ribbon polymer, in which the Sn(IV) is bound by two {C} atoms and three or four {O} atoms. Within each unit, the average Sn–O and Sn–C bond lengths in the first coordination shell are 206–210 and 213 pm, while the intermolecular bond distances display a somewhat larger variation (246–255 pm). The Sn···C and Sn···Sn distances in the third and fourth shells are in the range 277–323 and 324–362 pm, respectively, similarly to X-ray diffraction data obtained on complexes formed with protected sugars and discussed above. The endocyclic Sn–O–Sn angles fall in the range 80–98° and are comparable with the value of 79° published in [94]. These EXAFS investigations proved the correctness of the structural information derived from Mössbauer studies based on the *pqs* concept of the symmetry and coordination sphere of diorganotin(IV) complexes.

Wardell et al. studied the preparation, reactivities, and structures of C(carbohydrate)–Sn bonded mono-, or di-*O*-isopropylidene or -*O*-benzylidene triphenylstannyl-carbohydrate derivatives by means of X-ray crystallography, and ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy [13,129–132]. It was found that in most cases the Sn atoms are in a slightly distorted tetrahedral

Table 5
Structural data for $Bu_2Sn(IV)^{2+}$ and $Et_2Sn(IV)^{2+}$ carbohydrate complexes, obtained by X-ray diffraction [92,116] and EXAFS [22] methods

Bond length (pm) and angles (°)	CN	1	2	3	4 [22]	5 [22]
Intramolecular	5	77, 82	79.1, 80.0	–	206	208
O–Sn–O	6	–	77.6, 78.3	79.0	–	–
Intermolecular	5-5	67, 70	–	–	246	255
O–Sn–O	5-6	–	69.6, 70.6	–	–	–
–	6-6	–	65.5, 69.2	65.2, 66.8	–	–
Intermolecular	6	–	142.0, 150.5	149	–	–
O–Sn–O	–	–	–	–	–	–
Exocyclic	5	126, 139	124.2, 127.4	–	–	–
C–Sn–C	6	–	134.7, 142.7	138.6	–	–
Intramolecular	5	213, 209	202, 207	–	–	–
Sn–O	6	–	206, 213	198, 210	–	–
Intermolecular	5	229, 217	223, 227	–	–	–
Sn–O	6	–	243, 260	250, 252	–	–
Exocyclic	5	223, 226	204, 225	213, 214	–	–
Sn–C	6	–	214, 220	–	213, 323	213, 307
Sn···Sn	1	–	–	–	324	362

CN, coordination number. A CN of 5-6 means that the compound contains the Sn central atom in two different environments. 1, $Bu_2SnOCH_2CH_2O$; 2, (methyl-4,6-*O*-benzylidene-α-D-glucopyranoside); 3, (methyl-4,6-*O*-benzylidene-α-D-mannopyranoside); 4, D-lactobionic acid; 5, D-galactose.

environment [13,129,131,132], but a distorted trigonal-bipyramidal arrangement with {I} and {O} atoms in axial positions (Sn–O = 268 pm), has also been observed [130]. In cases involving a tetrahedral structure [358], the shortest Sn···O separation is about 335 pm, an interaction that appears to have no effect on the stereochemistry of the metal. In the crystals of the chiral carbohydrates, the hydroxy groups are held together by an intermolecular hydrogen bonding network. Due to the large number of hydrophilic hydroxy groups, this phenomenon is quite characteristic for carbohydrate metal ion complexes [13,14].

The wood preservation properties of $Bu_3Sn(IV)^+$ compounds are strongly related to the interactions between cellulose (polysaccharides) and the organotin(IV) cation and are based on the good fungicidal activity and low mammalian toxicity of these complexes. Tbto [$(Bu_3Sn)_2O$]-treated wood is effectively preserved for up to 25 years, although there is some concern as to the long-term stability of the organotin(IV) with respect to dealkylation to less effective $R_2Sn(IV)$ compounds [133]. Some fungi which colonize wood, for example, are capable of causing this dealkylation process [134,135].

The basic question of nature of Tbto within the cellulose matrix is still not fully resolved. Early work suggested that the $Bu_3Sn(IV)^+$ moiety condenses with the terminal hydroxy groups of wood cellulose [136], but this was queried on the basis of electron microscopy studies [359]. Mössbauer spectra of Tbto-impregnated pine (experimental parameters: $\delta_{Tbto} = 1.17$ mm s^{-1}, $\Delta_{Tbto} = 1.46$ mm s^{-1}) point strongly to the presence of $(Bu_3Sn)_2CO_3$ (characteristic parameters: $\delta = 1.38$ and 1.43, $\Delta = 2.70$ and 3.79 mm s^{-1}); formed by reaction with atmospheric CO_2 [138], for $(Bu_3Sn)_2CO_3$ in wood; $\delta = 1.39$ and 1.44, $\Delta = 2.64$ and 3.66 mm s^{-1}, while for Tbto in wood $\delta = 1.39$ and 1.46, $\Delta = 2.84$ and 3.59 mm s^{-1} [137].

4.3. Interaction of organotin(IV)$^{n+}$ with nucleic acids and DNA

Many organometallic compounds exhibit interesting antitumour activity against several human cancer cell lines [139]. The well-known complex cisplatin, $Pt(NH_3)_2Cl_2$, used clinically in cancer chemotherapy, proved to interact with the N-7 atoms of two adjacent guanines in the same DNA strand [140–142]. In contrast with Pt compounds, very little is known of the origin of the antitumour activity of organotin(IV) compounds, though the structural similarity to cisplatin suggests that DNA could be the target [143]. In this section we survey the most important literature data published to date on this subject.

Diorganotin(IV) bis(adenine) was obtained by reaction performed ar N_2 atmosphere. The Mössbauer data ($\Delta = 1.91$–2.21 mm s^{-1}) are consistent with tetrahedral geometry around the central Sn atom, though a *cis*-R_2SnN_4 configuration cannot be excluded [144]. When adenine or 9-methyladenine is refluxed in methanol with Me_2SnCl_2, only simple adducts are formed. Under similar conditions, R_2SnCl_2 does not generally react with guanine, cytosine, thymine, uracil or theophylline [145]. Crystallization of Me_2SnCl_2 and purine from acetone leads to a product in which hydrated Me_2SnCl_2 is coordinated to four purine molecules via a hydrogen bonding network [146].

The interactions between different organotin(IV) compounds and 6-thiopurine, an antitumour metabo-

lite, are more complex. At 0 °C, a polymeric mixture is formed, with {N,S} or {N,N} donor atoms coordinated. At >0 °C, only {N,N}-bound product is observed [147,148].

Ten complexes of adenosine and related compounds (adenosine-5′-monophosphate, adenosine-5′-triphosphate, adenosine-N′-oxide, 1-methyladenosine, pyridoxal-5-phosphate and β-nicotinamide-adenine-dinucleotide-phosphoric acid) with R_2SnO and/or R_2SnCl_2 were prepared in the solid state. The compositions of the complexes were determined by standard analytical methods. It was found that the complexes contain the organotin(IV) moiety and the ligand in a ratio of 1:1 or 2:1. The FTIR spectra demonstrated that R_2SnO reacts with the D-ribose moiety of the ligands, while R_2SnCl_2 is coordinated by the deprotonated phosphate group. The basic part of the ligands does not participate directly in complex formation. Comparison of the experimental Mössbauer Δ values with those calculated on the basis of the *pqs* concept revealed that the organotin(IV) moiety has trigonal-bipyramidal, octahedral, or in some cases tetrahedral geometry. Some of the complexes contain the organotin(IV) cation in two different surroundings [149]. Very similar conclusions were obtained earlier on the complexes formed between Bu_2SnCl_2 or Bu_3SnCl and 5′-AMP, 5′-GMP

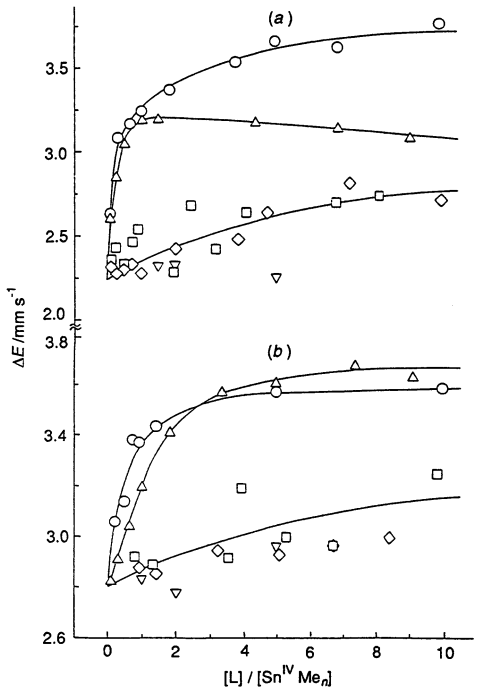

Fig. 9. ^{119}Sn Mössbauer titration of (a) $Me_2Sn(OH)_2$ and (b) $Me_3Sn(OH)(OH_2)$, with ligands $L = H_nPO_4^{(3-n)}$ ($n = 1$ or 2), D-ribose-5-phosphate (△), adenosine 3′:5′-cyclic monophosphate (□), dimethylphosphinate (G) or DNA (▽). The experimental nuclear quadrupole splitting, Δ, is plotted vs. the mole ratio [L]/[$Me_{2,3}Sn$(IV)]. The data points at [L] = 0.0, taken as the origin of the curves, refer to $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(OH_2)$, respectively (adapted from Ref. [48]).

and their 3′-5′ cyclic analogues. The stoichiometry of the compounds of 5′-AMP and 5′-GMP with Bu_3SnCl was 1:2, while that with Bu_2SnCl_2 was 1:1. Only 1:1 compounds were formed with the 3′-5′ cyclic nucleotides. Most of the compounds are polymeric and differ in the environments of the two *n*-Bu groups. For all the $Bu_3Sn(IV)^+$ complexes, ^{31}P-NMR chemical shifts indicate that the Sn(IV) is bonded to the phosphate group, but probably not chelated by it. A much larger ^{31}P-NMR upfield shift in $(Bu_3Sn)_2$(5′-GMP) is an indication of phosphate chelation. The D-ribose conformation is different within the $Bu_3Sn(IV)^+$ and $Bu_2Sn(IV)^{2+}$ complexes [150].

Mössbauer titration of $Me_2Sn(IV)^{2+}$ and $Me_3Sn(IV)^+$ hydroxides with ligands mimicking nucleic acid phosphate sites and with native DNA was the aim of work by Barbieri et al. [48]. A series of aqueous solutions of each system, formed by the organotin(IV) hydroxides and the phosphate ligands used [$H_nPO_4^{(3-n)-}$ ($n = 1$ or 2, phosphate buffer), D-ribose-5-phosphate, dimethylphosphinate, adenosine 3′:5′-cyclic monophosphate (Ado-3′:5′-P) and DNA], with varying ligand:organotin(IV) molar ratios, frozen at 77.3 K, were monitored by ^{119}Sn Mössbauer spectroscopy (Fig. 9).

On the basis of the point-charge model formalism of the experimental nuclear quadrupole splitting, Δ, the results obtained were interpreted in terms of strong complex formation by either $Me_2Sn(OH)_2$ or $Me_3Sn(OH)(H_2O)$ with $H_nPO_4^{(3-n)-}$ ($n = 1$ or 2, obtained in phosphate buffer) and D-ribose-5-phosphate. On the basis of the trend of the isomer shift, δ, along the titration, gradual opening of the C–Sn–C was proposed from tetrahedral in $Me_2Sn(OH)_2$, to octahedral *trans*-Me_2Sn(IV) in $Me_2Sn(OH)_2$-ligand. As far as the $Me_3Sn(OH)(H_2O)$-ligand was concerned, the invariance of its δ with respect to that of $Me_3Sn(OH)(H_2O)$ ($\delta = 1.24$ mm s^{-1}) [151] suggested that the distorted trigonal-bypiramidal configuration of $Me_3Sn(OH)(H_2O)$ was maintained in the complexes $Me_3Sn(OH)(H_2O)$-ligand. Such distortions were quantified by rationalization of the experimental Δ according to the point-charge model formalism (Fig. 10), which permitted estimation of the C–Sn–C angles in the $Me_2Sn(IV)^{2+}$ derivatives and of the angle C–Sn–A in the Me_3SnA moieties (A being a ligand atom) [152,153]. Quite limited effects were reported for the interactions of $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(H_2O)$ with dimethylphosphinate and adenosine 3′:5′-cyclic monophosphate (Ado-3′:5′-P). Native DNA did not induce any interaction.

Barbieri et al. [45,46,157] investigated the interactions between ethanolic diorgano(IV)$^{2+}$ and triorganotin(IV)$^+$ [$R_2SnCl_2(EtOH)_2$ and $R_3SnCl(EtOH)$, R = Me, Et, *n*-Bu, *n*-Oct or Ph] and aqueous $[Me_2Sn(H_2O)_n]^{2+}$ and $[Me_3Sn(H_2O)_2]^{2+}$ species with aqueous DNA from calf thymus by ^{119}Sn Mössbauer

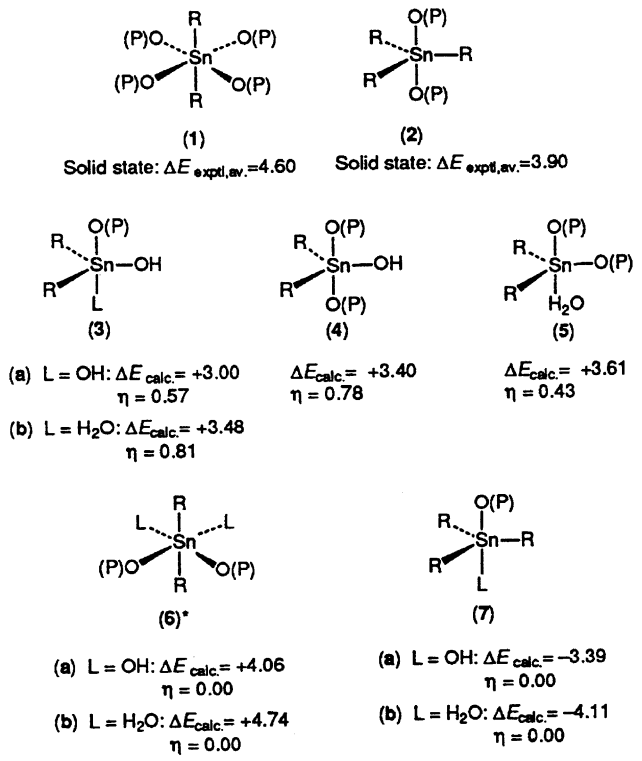

Fig. 10. Schemes of the environments in phosphate complexes in the solid state, (1) and (2), and in species possibly formed in aqueous solutions of organotin(IV)s and ligands, (1)–(7). Idealized regular configurations are generally considered. Calculated values of the nuclear quadrupole splittings, Δ, and the asymmetry parameter $\eta = (V_{xx} - V_{yy})/V_{zz}$, were obtained by the literal point-charge model approach, using tabulated values for *pqs* [52,154–156] in conjunction with pqs data extracted from the cited work for phosphate ligands. * Equatorial ligands in a *trans* configuration yield slightly larger Δ_{calc} values.

spectroscopy. In particular, the Mössbauer data (Table 6) showed that the solids obtained by adding solvated $[R_2SnCl_2(C_2H_5OH)_n]$ and $R_3SnCl(EtOH)$ to DNA (R = Me, Et, Bu) were possibly R_2Sn(DNA phosphate)$_2$ and R_3Sn(DNA phosphate). In these complexes, the environment of the Sn atoms would be *trans*-octahedral, with a linear CH_3–Sn–CH_3 skeleton, and trigonal-bipyramidal, respectively. Possible structures of the Sn sites in phosphate-bound R_2Sn(IV)-DNA and R_3Sn(IV)-DNA (R = Me, Et, *n*-Bu) are reported in Fig. 11.

According to Barbieri et al., on the basis of the point-charge model formalism, by using *pqs* values of heterocyclic {N}, exocyclic {O} and related atoms and groups, it can not be excluded that some of the coordination sites are occupied by {N} atoms of the nucleic acid constituents [45,46]. The precipitate obtained from $Ph_2Sn(IV)^{2+}$ would contain both the $R_2Sn(IV)^{2+}$-DNA complex and distannoxane $[(Ph_2SnCl)_2O]$. The main products of the interactions of aqueous DNA with *n*-Oct$_2SnCl_2(EtOH)_2$ and $R_3SnCl(EtOH)$ (R = *n*-Oct, Ph) were possibly stannoxanes $[(R_2SnCl)_2O]$ and hydroxides (R_3SnOH). Finally, no interaction at all was detected when the water-soluble hydrolysed species $[Me_2Sn(OH)(H_2O)_n]^+$, $Me_2Sn(OH)_2$ and $Me_3Sn(OH)(H_2O)_2$ were added to native DNA. Such results imply that organotin(IV) moieties may interact in vivo with cellular DNA only if they are weakly solvated [45]. Finally, a quantitative structure–activity relationship (QSAR) [158–160] treatment of Δ data (Fig. 12) was applied to rationalize the Coulomb interactions in conjunction with effects originating from the radicals R, according to the equation:

$$BA = a + b\pi + c\pi^2 + d\sigma + eE_s + gS \quad (1)$$

where BA is the biological activity of the assumed complex, π is a hydrophobic parameter, σ is an electronic parameter (which depends on the extent of the acid–base interaction $Sn^{2+,1+}$–O^{-1}, and is an increasing function of the ratio r = [Sn]/[DNAphosphate]), E_s is a steric factor and S is a structural parameter [157].

According to Eq. (1), the authors explained the tendency to obtain, or not, condensed R_nSn(IV)-DNA as a function of the lipophilicity parameter π, which increases in the series Me < Et < Ph < *n*-Bu < *n*-Oct [158]. As a consequence, hydrophilic $Me_2Sn(IV)^{2+}$ and $Me_3Sn(IV)^+$ remain in solution, even at low r values, while the lipophilic $R_2Sn(IV)^{2+}$ and $R_3Sn(IV)$ (R = *n*-Bu, *n*-Oct, Ph) give hydrolysis products [157].

The interactions between ethanolic solutions of $Me_2SnCl(SPy)$ or $Me_2SnCl(SPym)$ (HSPy = 2-mercaptopyridine; HSPym = 2-mercaptopyrimidine) and aqueous calf-thymus DNA have been the subject of a recent report from Barbieri et al. [161]. They concluded that the 1:1 complex/DNA condensates are derived from an electrostatic interaction between the cations $Me_2SnCl(SPy)^+$ and $Me_2SnCl(SPym)$ and the phosphate {O} of phosphodiester groups.

Semiempirical calculations on the interaction between $Me_2Sn(IV)^{2+}$ and a dinuclide triphosphate duplex (DD), mimicking a DNA model system, were performed by the semiempirical PM3 method and recently published by Barbieri et al. [162]. The results indicate that, the $Me_2Sn(IV)^{2+}$ moiety binds to two adjacent phosphate.

{O} atoms, allowed by the presence of water molecules coordinating to the Sn atom, are in agreement with the ^{119}Sn Mössbauer and X-ray data. Fig. 13 shows the probable geometry of the Sn environment, in good agreement with the available experimental data.

Small-angle X-ray scattering (SAXS), circular dichroism (CD) and UV spectroscopy at different temperatures were used to investigate the nature of calf thymus DNA in aqueous solution, in the presence of $Me_nSn^{(4-n)}+$ (n = 1–3) species [163]. The results demonstrate that the $MeSn(IV)^{3+}$ moiety does not influence the structure and conformation of the DNA double helix, and does not degrade DNA, as indicated by

Table 6
^{119}Sn Mössbauer parameters of $R_2Sn(IV)^{2+}$ systems [a] [46]

System	Organotin compounds reacted with DNA [b]	r [c]	δ [d] (mm s^{-1})	Δ [d] (mm s^{-1})	Γ_1, Γ_2 [c] (mm s^{-1})
(A)	$R_2SnCl_2(C_2H_5OH)_2$; pellets				
1	Me_2SnCl_2 [e]	0.40; 1.00	1.26; 1.33	4.39; 4.44	0.79–0.91
2	Et_2SnCl_2 [f]	0.60–2.40	1.39–1.50	4.40–4.49	0.74–0.99
3	n-Bu_2SnCl_2	0.48–1.00	1.37–1.45	3.72–3.88	1.08–1.32
4	n-Bu_2SnCl_2	2.4	1.43	3.41	0.92; 0.92
5	n-Oct_2SnCl_2 [g]	0.50	1.35	3.23	0.86; 0.93
6	n-Oct_2SnCl_2	2.40	1.61	3.33	1.00; 0.93
7	Ph_2SnCl_2	0.48	1.13	3.23	1.44; 1.22
8	Ph_2SnCl_2	1.00	1.05	2.96	1.63; 1.22
9	Ph_2SnCl_2	2.40	1.07	2.83	1.24; 1.01
(B)	$R_3SnCl(C_2H_5OH)$; pellets	–	–	–	
10	Me_3SnCl [h]	2.40	1.31	3.77	0.89; 0.82
11	Et_3SnCl [i]	1.00–2.40	1.47–1.50	3.83–3.89	0.80–0.90
12	n-Bu_3SnCl	0.96; 2.40	1.50; 1.45	3.85; 3.79	0.92–1.09
13	n-Oct_3SnCl	1.00–2.40	1.39–1.56	3.42–3.53	0.66–0.97
14	Ph_3SnCl	1.00–2.4	1.24–1.29	2.85–3.08	0.94–1.22
(C)	$[Me_2Sn(OH)(OH_2)_n]^+$ and $[Me_3Sn(OH)_2]^+$ [j,k,l]	–	–	–	
15	$Me_2Sn(IV)$; solution	0.38; 1.00	1.15; 1.14	3.44; 3.11	0.94; 1.51
16	$Me_3Sn(IV)$; solution	1.20–1.56	1.25–1.37	3.75–3.88	0.65–0.96
17	$Me_3Sn(IV)$; pellets	2.40	1.38	3.84	0.93; 0.75
(D)	$Me_2Sn(OH)_2$ and $[Me_3Sn(OH)(OH)_2$; solutions	–	–	–	
18	$Me_3Sn(IV)^{2+}$	0.20–0.66	0.92–0.96	2.24–2.33	0.79–1.41
19	$Me_3Sn(IV)^+$	0.20–1.00	1.22–1.26	2.83–2.96	0.69–0.93

[a] Measured at liquid nitrogen temperature. Data from Refs. [45,46,48].
[b] The absorber samples 1–19 were prepared as described in the experimental section of [157]. See Table 2 of Ref. [46] for the parameters of the reactant organotin(IV) species in ethanol and aqueous solution.
[c] r = [Sn]/[DNA phosphate].
[d] See Table 1, footnotes c, d, and Table 2, footnote d in Ref. [46]. Γ values are working values from computer fitting.
[e] Percent resonance effect data, ε%, $r = 1.0$; pellet, $\varepsilon_1 = 0.46$, $\varepsilon_2 = 0.42$; supernatant, $\varepsilon_1 = 0.31$, $\varepsilon_2 = 0.33$%.
[f] ε% data, $r = 1.0$; pellet, $\varepsilon_1 = 0.63$, $\varepsilon_2 = 0.58$; supernatant, $\varepsilon_1 = 0.28$, $\varepsilon_2 = 0.30$%.
[g] The precipitate does not contain DNA.
[h] ε% data; pellet, $\varepsilon_1 = 0.59$, $\varepsilon_2 = 0.63$; supernatant, $\varepsilon_1 = 0.38$, $\varepsilon_2 = 0.39$%.
[i] ε% data, $r = 2.4$; pellet, $\varepsilon_1 = 1.24$, $\varepsilon_2 = 1.33$; supernatant, $\varepsilon_1 = 0.40$, $\varepsilon_2 = 0.32$%.
[j] Aqueous Me_2SnCl_2 or Me_3SnCl 20 mmol dm^{-3}, pH $\approx$ 5, is added to DNA; pH 3.5–5.0 after addition.
[k] ε% data; pellet, $\varepsilon_1 = 0.17$, $\varepsilon_2 = 0.18$; supernatant, $\varepsilon_1 = 0.66$, $\varepsilon_2 = 0.63$%.
[l] Aqueous Me_2SnCl_2 or Me_3SnCl, adjusted to pH 7.4 with NaOH, is added to DNA.

agarose gel electrophoresis. Inter alia, the radii of gyration, R_c, of the cross-section of native calf thymus DNA, determined by SAXS in aqueous solution in the presence of $Me_nSn^{(4-n)+}$ ($n = 1$–3) species are constant and independent of the nature and concentration of the $Me_nSn^{(4-n)+}$ species. The results are summarized in Table 7.

Model compounds of DNA have also been studied. For example, the coordination of $Me_2Sn(IV)^{2+}$ to 5′-GMP, 5′-ATP and 5′-[d(CGCGCG)$_2$] and to their sugar constituents (D-ribose and 2-deoxy-D-ribose) was investigated in aqueous solution by means of potentiometric titration and ^{1}H- and ^{31}P-NMR spectroscopic methods. The results showed that the phosphate groups can provide suitable sites for metal ion coordination in acidic medium, while in the higher pH range the hydroxy groups of the studied sugars or the sugar moieties of the two nucleotides play a role in this process. The base moieties of 5′-GMP and 5′-ATP were not coordinated to $Me_2Sn(IV)^{2+}$. The stability constants of the complexes formed in the above systems were determined by pH-metric titration. The data revealed a

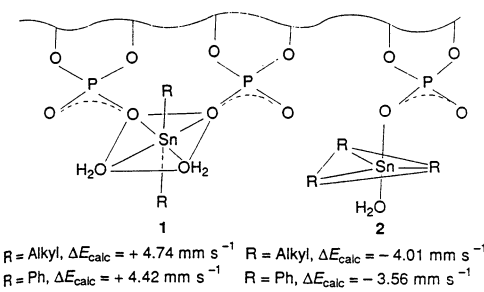

Fig. 11. Possible structures of Sn sites in phosphate-bound $R_2Sn(IV)$-DNA, $r = 0.5{:}1$ and $R_3Sn(IV)$-DNA, $r = 1{:}1$. The values of $\triangle$ were calculated by the literal version of the point-charge model (adapted from Ref. [46]).

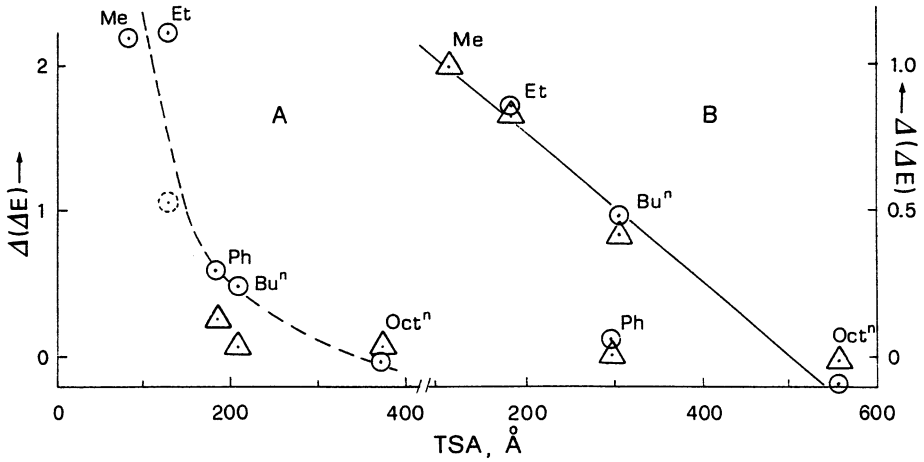

Fig. 12. The correlation of normalized nuclear quadrupole splitting data, $\Delta(\Delta)$, of condensates: (A) $R_2Sn(IV)^{2+}$-DNA; (B) $R_3Sn(IV)^{+}$-DNA, with the total surface area, TSA, of the $R_nSn(IV)$ moieties. $\Delta(\Delta)$ values are obtained from Δ_{exp} of pellet $R_nSn(IV)$-DNA, by subtracting Δ_{exp} for the corresponding (same R) hydrolysed (or water-insoluble) species (adapted from Ref. [157]).

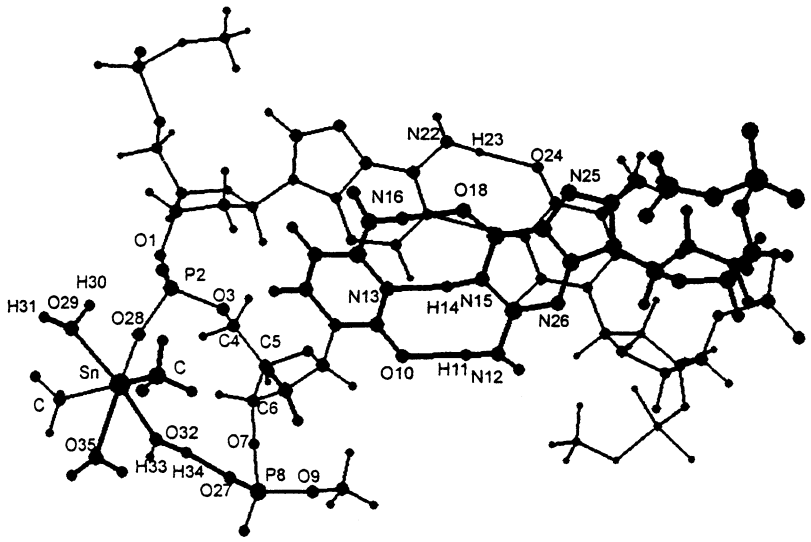

Fig. 13. Geometrical structure of the DD–$Me_2Sn(IV)^{2+}$ complex (adapted from Ref. [162]).

stronger coordination ability of the triphosphate compared with that of the monophosphate. The compari son of the stability constants of the D-ribose and 2-deoxy-D-ribose complexes showed that more stable species were formed when the neighbouring alcoholic hydroxy groups were available for the coordination of metal ions. The observed chemical shift changes of the ^{31}P-NMR resonances, compared with those measured for the metal-free systems, demonstrated that the phosphate groups of the DNA fragment [5′-*d*(CGCGCG)$_2$] chains act as binding sites for $Me_2Sn(IV)^{2+}$ between pH 4.5 and 7. The 1D and 2D ^{1}H-NMR spectra indicated that the base and sugar moieties do not participate in the coordination process under these conditions [164].

Li et al. [165] investigated the interaction of Et_2SnCl_2(phen) with 5′-dGMP in aqueous medium, using [*trans*-en$_2$Os(η-H$_2$)](CF$_3$SO$_3$)$_2$, a versalite ^{1}H-NMR probe. The AA also studied solid mixtures of the same Et_2SnCl_2 complex with 5′-AMP, 5′-CMP, and 5′-GMP dissolved in DMSO, using ^{1}H- and ^{31}P-NMR and UV spectroscopy. Recently, Hadjiliadis et al. [166] studied the interactions of purine nucleotides 5′-IMP and 5′-GMP with Et_2SnCl_2, using various techniques, including ^{1}H-, ^{13}C- and ^{31}P-1D-NMR and Mössbauer spectroscopy. Finally, one paper has dealt with the interactions between Et_2SnCl_2 + 5′-CMP, 5′-dCMP, and 5′-UMP, using multinuclear (^{119}Sn, ^{15}N and ^{31}P) 1D- and 2D-NMR techniques. These studies were combined with electrospray mass spectrometry, IR spectroscopy, solid-state ^{13}C-, ^{31}P- and ^{117}Sn-CP-MAS-NMR and elemental analysis [360]. Others studied the interactions of $Me_2Sn(IV)^{2+}$ 5′-AMP, D-ribose-5-phosphate, D-glucose-6-phosphate and D-glucose-

1-phosphate [167]. All these authors concluded that at low pH values (pH <4) the organotin(IV) cations interact with pyrophospate {O}. At intermediate pH values (4–9.5) no interaction takes place (in the systems depending on the concentration of metal ion and the ligand to metal ratio a precipitate is formed), while at pH >9.5 the sugar O′-2 and O′-3 atoms are the preferred coordination sites. Additionally two oligomeric complexes were obtained, containing Sn centres in trigonal-bipyramidal or octahedral geometry.

Thus, the basic question of how the organotin(IV) cations interact with DNA and influence the growth of tumour cells is still open. Except for the phosphate group and in alkaline solution the sugar moieties, no any specific interactions between the basic part of DNA or DNA constituents and organotin(IV) cations were found. It seems that the mechanism of antitumour action of organotin(IV) complexes (if the target is the DNA) differs substantially from that of cisplatin.

4.4. Interaction of organotin(IV)$^{n+}$ with other bioligands

Several complexes of $Bu_2Sn(IV)^{2+}$ with flavonoid glycosides (rutin, hesperidin and 2′,4′,3-trihydroxy-5′,4-dimetoxychalcone 4-rutinoside) and flavonoid aglycones (quercetin, morin, hesperitin and other flavones) were prepared. The analytical data indicated the formation of complexes containing the diorganotin(IV)$^{2+}$ moiety and the ligand in a ratio of 1:1, 2:1 or 3:1. The FTIR spectra were consistent with the presence of Sn–O (phenolic or alcoholic {O} atom) vibrations in the compounds. Comparison of the experimental Δ with those calculated on the basis of the *pqs* concept revealed that the complexes are of four types: with the central Sn atoms surrounded by donor atoms in a purely trigonal-bipyramidal, octahedral + trigonal-bipyramidal, trigonal-bipyramidal + tetrahedral or octahedral + tetrahedral arrangement [168]. This procedure also distinguished the different structural isomers of both trigonal-bipyramidal and octahedral complexes. These properties are similar to those of the organotin(IV) carbohydrate complexes discussed above.

To date only a few papers have been published on the structures of organotin(IV) complexes formed with carboxylate compounds containing {O,S} donor sites [50,169–173].

Four $Bu_2Sn(IV)^{2+}$ complexes have been prepared with mercaptoacetic, 2-mercaptopropionic, mercaptosuccinic and *m*-2,3-dimercaptosuccinic acid (DMSA) by means of two different procedures. The compounds were characterized by elemental analysis, FTIR, Raman, ^{119}Sn Mössbauer, ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy. The IR and Raman data indicate the presence of bidentate coordinated carboxylate groups, non-linear C–Sn–C bonds, and Sn–S bonds. The results of Mössbauer spectroscopic measurements, based on point-charge model calculations, revealed the general occurrence of Sn(IV) in trigonal-bipyramidal environments. A multinuclear NMR study also suggested {O,S} coordination of the $Bu_2Sn(IV)^{2+}$ fragment, within the cyclic oligomeric complexes. In strongly donor solvent (DMSO) the depolymerization occured [173].

Table 7
Radii of gyration, R_c, of the cross-section and extrapolated intensity at zero angle, $I(0)$, of native calf thymus DNA [a] in aqueous solutions, in the presence of $Me_nSn(IV)$ species ($n = 1$–3), as determined by SAXS

$Me_nSn(IV)$ species ($n = 1$–3) [b]	r [c]	pH [d]	Tris–HCl [d] (mmol dm^{-3})	R [c] (nm)	$I(0)$ [e]
[d,f]	0.00	7.0	1.0	1.00 ± 0.03	12.2 ± 1.8
[f]	0.00	8.1	150.0	0.97 ± 0.04	10.9 ± 2.8
$SnMe_3^+$; $SnMe_3(OH)$	0.05	6.6	1.0	0.98 ± 0.04	11.6 ± 2.7
$SnMe_3^+$; $SnMe_3(OH)$	0.10	6.3	1.0	0.99 ± 0.04	12.4 ± 2.6
$SnMe_3(OH)$	0.10	8.1	150.0	0.96 ± 0.05	10.0 ± 3.5
$SnMe_3(OH)$	0.80	7.9	150.0	0.94 ± 0.04	9.5 ± 2.4
$SnMe_2(OH)^+$; $[(SnMe_2)_2(OH)_3]^+$	0.01	6.7	1.0	0.99 ± 0.04	11.6 ± 2.2
$SnMe_2(OH)^+$; $[(SnMe_2)_2(OH)_3]^+$	0.05	6.0	1.0	0.97 ± 0.05	12.1 ± 2.7
$SnMe_2(OH)_2$	0.10	8.0	150.0	0.94 ± 0.03	10.3 ± 2.9
$SnMe_2(OH)_2$	0.70	7.7	150.0	0.94 ± 0.04	10.9 ± 2.6
$SnMe_n$, Sn–O–Sn bridges	0.01	6.6	1.0	0.98 ± 0.04	11.9 ± 3.4
$SnMe_n$, Sn–O–Sn bridges	0.70	7.4	150.0	1.05 ± 0.05	15.9 ± 2.3
$SnMe(OH)_3$; $SnMe_n$, Sn–O–Sn bridges	0.10	8.0	150.0	0.94 ± 0.04	10.6 ± 3.7

[a] Calf thymus DNA: 5 mg cm^{-3} in monomeric units.
[b] Dominant species, as estimated via $Me_nSn(IV)$ hydrolysis constants (see Ref. [163], Results and discussion section) at the indicated solution pH, hydrated species being formed.
[c] $Me_nSn(IV)$/DNA phosphate (mol/mol).
[d] DNA solutions [without added $Me_nSn(IV)$].
[e] $I(0)$ (relative units proportional to the mass per unit length of the DNA rod; see Ref. [163], Experimental part.
[f] In the presence of NaCl (150.0 mmol dm^{-3}); $R_c = 0.99 \pm 0.05$ nm.

On the other hand, the $Bu_2Sn(IV)^{2+}$ complexes of the O analogues of the above-mentioned ligands (glycolic, 2-hydroxypropionic, succinic and malic acids) are linear oligomers. The IR and Raman data indicated the presence of bidentate and/or monodentate carboxylate groups, non-linear C–Sn–C bonds, and Sn–O bonds within the complexes. The results of Mössbauer spectroscopic measurements, based on point-charge model calculations, demonstrated a trigonal-bipyramidal arrangement around the central Sn(IV) atom, in addition to the octahedral and tetrahedral structures [174].

The complex formation of $Et_2Sn(IV)^{2+}$ with glycolic, lactic, succinic, malic, tartaric, mercaptoacetic, 2-mercaptopropionic, mercaptosuccinic and dimercaptosuccinic acids has been investigated in aqueous solution. The formation constants of the complexes and of the hydrolysis products of $Et_2Sn(IV)^{2+}$ were determined by potentiometric equilibrium measurements and (for the thiocarboxylic acids) by spectrophotometry. The structures of the complexes formed were studied by Mössbauer spectroscopic measurements on fast-frozen solutions, and by ^{1}H- and ^{13}C-NMR spectroscopy. The thiocarboxylic acids yielded very stable complexes. The formation of hydrolytic species was suppressed throughout the whole pH range (Fig. 14a) Complexes displaying slow ligand exchange were detected. In the systems with hydroxycarboxylic acids, both mixed hydroxo complexes and hydrolytic species were observed. The formation of complexes participating in slow ligand exchange and the significant shift of the CH (situated adjacent to the hydroxy group) signals indicated coordination of the deprotonated alcoholic hydroxy group. Evaluation of the Mössbauer spectroscopic data on the basis of pqs calculations on the $Et_2Sn(IV)^{2+}$-malic acid, -thioacetic acid, -mercaptosuccinic acid and -dimercaptosuccinic acid systems demonstrated that dimeric species were formed in which trigonal-bipyramidal and octahedral arrangements of the donor atoms around the organotin(IV) ion occurred [50] (Fig. 14b, c).

Organotin(IV) compounds are strong neurotoxins and induce thymus atrophy and bile duct damage. The metabolism involves subsequent dealkylation reactions; accordingly, $R_3Sn(IV)^+$, or $R_4Sn(IV)$ exposure results in systematic exposure to the $RSn(IV)^{3+}$, and $R_2Sn(IV)^{2+}$ compounds. Although dimercaptosuccinic acid did not reduce the $Bu_2Sn(IV)^{2+}$-induced mortality in mice, it reduced thymus and bile duct damage more efficiently than did 2,3-dimercaptopropanol (DMP) and it was also an antidote in rats [175–177].

Two women were poisoned by drinking red wine containing $Me_3Sn(IV)^+$ added for homicidal purposes. One woman died after 1 week, with multiorgan failure despite intravenous dimercaptosuccinic acid chelation. The other gradually recovered from severe neuropsychiatric symptoms over several months. She had been chelated for several weeks with oral dimercaptosuccinic acid, apparently improving her clinical condition [177].

A set of six tris(1-Bu)Sn(IV) citrates and three tris(1-Bu)Sn(IV) 1,2,3-propanetricarboxylates of the general formula $R^1C(CH_2)_2(COOR^2)_3$, where $R^1 = OH$ or H, and $R^2 = H$, $(1\text{-}C_4H_9)_3Sn$, $C_6H_{11}NH_3^+$, $(C_6H_{11})_2NH_2^+$ or $(CH_2)_5NH_2^+$, were prepared and their structures were studied in the solid state and in solutions of different types of solvent by IR, ^{1}H-, ^{13}C- and ^{119}Sn-NMR, ^{13}C- and ^{119}Sn-CP/MAS-NMR and ^{119}Sn Mössbauer spectroscopy. Isolated molecules or 'ionic' or 'pseudo-ionic' pairs with a pseudotetrahedral Sn atom neighbourhood were found in solutions of non-coordinating solvents. Similar isolated particles enriched by one solvent molecule bound to each of the Sn atoms were present in solutions of coordinating solvents, forming a *trans*-trigonal-bipyramidal arrangement around the Sn atoms with 1-Bu substituent situated in the equatorial plane and a donor atom of the coordinating solvent and {O} atom of the monodentate carboxylic group in axial positions. A part of the tris(1-Bu)Sn(IV) groups, together with some bidentate bridging carboxylate groups, form polymeric chains in the solid state in citrates and 1,2,3-propanetricarboxylates. Stannadioxacycles with the participation of α-hydroxycarboxylate fragments and one of the tris(1-Bu)Sn(IV) groups probably occur in the solid state in some citrates [178].

The reaction of $Me_2Sn(IV)^{2+}$ with pyridoxine [3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridine, PN, vitamin B_6] yielded three complexes, one with the composition $[SnMe_2(PN\text{-}H)]NO_3{\cdot}2H_2O$. This complex is a polymer: each monoprotonated pyridoxine coordinates to one Sn atom via the phenolic {O} and a deprotonated CH_2OH group {O}, and to the other via the latter group alone. In each dimeric unit, the Sn atom is coordinated to two Me groups, the phenolic {O} atom, the {O} atoms of two deprotonated CH_2OH groups, and the {O} atom of the non-deprotonated CH_2OH group [179]. Further work on the interaction of the same ligand and $Et_2Sn(IV)^{2+}$ in an 80:20 (v/v) ethanol–water mixture containing different anions in various molar ratios, was published in Ref. [180]. In this system, three complexes were formed. The structure of one of the compounds was determined by X-ray diffraction, and was found to consist of dimeric $[SnEt(PN\text{-}H)]_2^{2+}$ units [n which two bridged-chelating hydrogenpyridoxinate anions link the Sn(IV) ion with coordination number five] and hydrogen-bonded Cl^-. This is similar to the system discussed above. Other work on similar systems was reported in [181,182].

Organotin(IV) compounds are a widely studied class of metal-based antitumour drugs [183–185]. Their intensive investigation has led to the discovery of compounds with excellent in vitro antitumour activity, but, in many cases, disappointingly low in vivo potency or high in vivo toxicity [183–186]. The design of improved

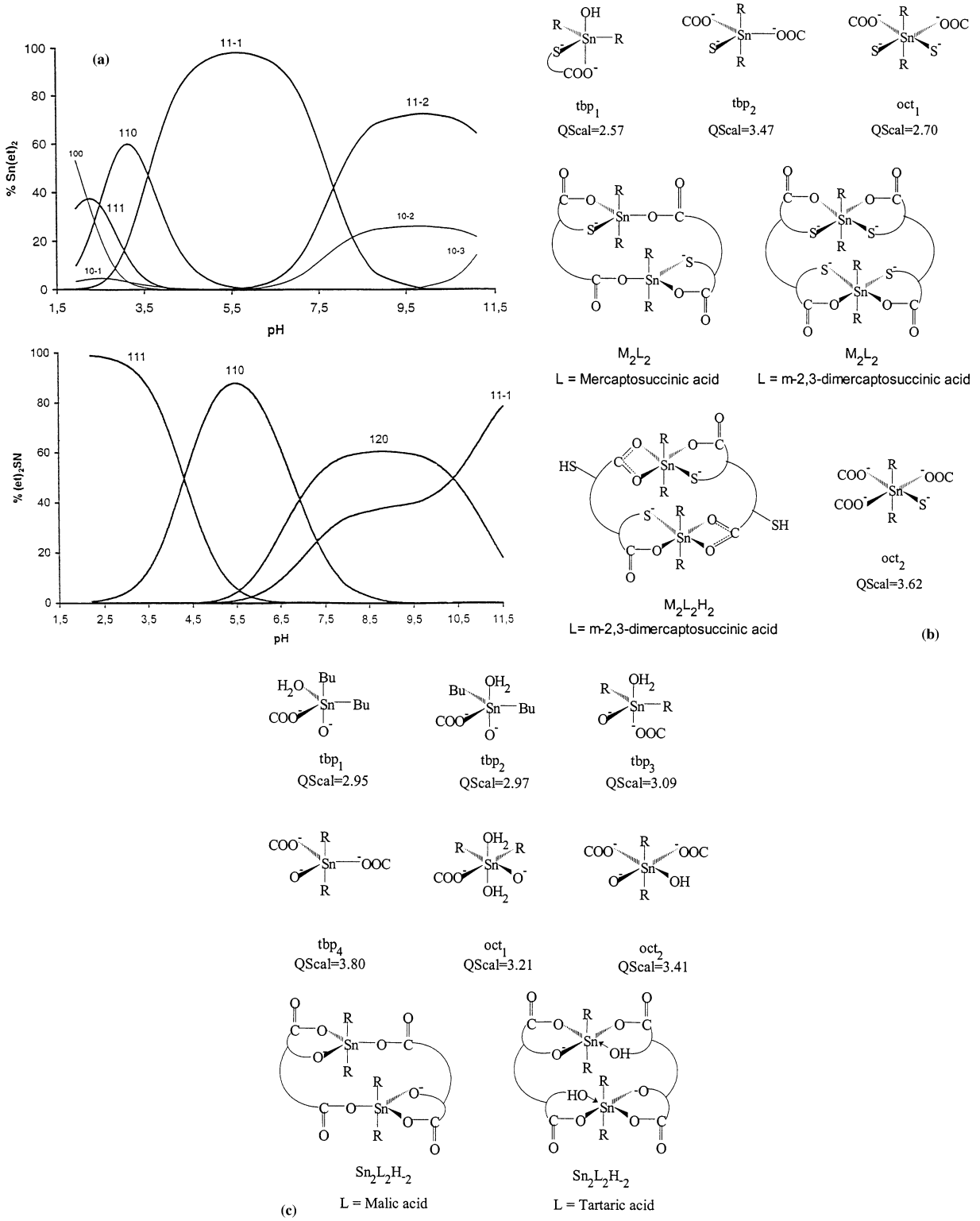

Fig. 14. (a) Species distribution curves of $Et_2Sn(IV)^{2+}$-malic acid (A) and -mercaptosuccinic acid (B) systems. (A: [M] = [L] = 0.01 mol dm^{-3}; B: 2[M] = [L] = 0.01 mol dm^{-3}). Hydrolytic species are shown by thin lines. The notation of the different species corresponds to the *pqr* values of the corresponding complex $M_pL_qH_r$ [50]. (b, c) Proposed local environments of $Et_2Sn(IV)^{2+}$ within the complexes formed with hydroxycarboxylic acids (A) and with mercaptocarboxylic acids (B), as suggested by the results of Mössbauer and other spectroscopic measurements [50].

organotin(IV) antitumour agents is unfortunately hampered by the paucity of information concerning the cellular targets of these compounds and their mechanism of action, although inhibition of mitochondrial oxidative phosphorylation appears to be an important mode of toxicity [184,185].

A review of the extensive literature in this field reveals two classes of organotin(IV) compounds with exceptionally high antitumour potency. $Ph_3Sn(IV)^+$ benzoates exhibit an in vitro antitumour activity higher than that of cisplatin and comparable with that of mitomycin C [187]. The most active such of these compounds have been patented [188]. However, Ng et al. recently reported that, while $Ph_3Sn(IV)$ esters have a greater in vitro activity against four human tumour cell lines, this activity is independent of the structure of the ester moiety and comparable with that of $Ph_3Sn(IV)$ hydroxide, suggesting that hydrolysis is a common, cytotoxic intermediate [189].

A large number of structurally diverse $Bu_2Sn(IV)^{2+}$ carboxylates and other Sn–O bound $Bu_2Sn(IV)^{2+}$ derivatives exhibit consistently high in vitro antitumour activity and some possess low mammalian toxicity and greater in vivo activity than those of cisplatin (selected examples can be found in [190–195]). This antitumour potency is, in general, structure-dependent, although for some compounds there is evidence of prior hydrolysis to a common $Bu_2Sn(IV)^{2+}$ equivalent species which is responsible for the comparable activity [194]. It was recently reported that di-*n*-butylstannylene alkoxides (including enantiomeric pairs prepared from $Bu_2Sn(IV)$ D- or L-tartrate) also exhibited greater in vivo antitumour activity than that of cisplatin in a variety of human tumour cell lines. The first step in the mechanism of action is hydrolysis to a common cytotoxic intermediate, and this intermediate targets the mitochondria [196]. The $Bu_2Sn(IV)^{2+}$ dihydroxybenzoates are also active against different human tumour cell lines [191,193]. All dihydroxybenzoates with an *ortho*-hydroxy group are more active against MCF-7 cells than are the substituted salicylates screened previously [186].

The $Bu_2Sn(IV)^{2+}$ complexes formed with ligands containing a carboxylate group(s) are easily prepared by a one-pot method described by Davies et al. [169]. In a first step, tetra-*n*-butyl-di-*n*-propoxydistannoxane is prepared from Bu_2SnO and *n*-propanol by refluxing in benzene or in toluene. This distannoxane subsequently reacts at room temperature with carboxylates. This method appears to have two advantages over that [190,197] in which Bu_2SnO reacts with the carboxylic acid in refluxing ethanol/toluene, methanol/toluene; first, as the carboxylic acid is added at room temperature, organotin(IV) carboxylates that are unstable at higher temperature can also be prepared; second, tetra-*n*-butyl-di-*n*-propoxydistannolane is synthesized in water-free medium because the water is eliminated through a water/propanol/benzene azeotrope; hence, water-sensitive organotin(IV) carboxylates can conveniently be prepared.

$Ph_3Sn(IV)^+$ and $Bu_3Sn(IV)^+$ derivatives of carboxylates could be obtained by the reaction of the latter with $Ph_3Sn(OH)$ and $Bu_3Sn(Ac)$, respectively [187,198,199].

Mono-organotin(IV) compounds, considered the least toxic among organotin(IV) derivatives ($R_3Sn(IV)^+ > R_2Sn(IV)^{2+} > RSn(IV)^{3+} > Sn^{4+}$, toxicity scale), have not achieved as much commercial application as diorgano- and triorganotin(IV) derivatives. However, they are often used as hydrophobic agents for building materials and cellulosic matter [9] and can be present in the aquatic environment as the first step in the alkylation of inorganic Sn [200].

The behaviour of $RSn(IV)^{3+}$ compounds in aqueous solution has not been investigated widely. The majority of studies, performed many years ago, concern the complex formation with N-donor atom-containing molecules [201] and with Cl^- [202–204] and F^- ions [205,206]. Raman measurements showed the formation of the species $[CH_3SnCl_2(OH)_2]^{2-}$ in the presence of a high concentration of Cl^-. The results of NMR measurements in very concentrated solutions of $CH_3Sn(IV)^{3+}$ (from 210 up to 830 mmol dm^{-3}) indicated the formation of mixed chloro-hydroxo complexes $[CH_3SnCl_x(OH)_y]$, with x decreasing in dilute solutions. Analogous behaviour was found by Tobias [35] and more recently by Gianguzza et al. [40] in the interactions of $Me_2Sn(IV)^{2+}$ in Cl^--containing solutions. Luijten [207] investigated the hydrolysis products of Et-, Bu- and $OctSnCl_3$ and reported their properties and preparation in the solid state. Some potentiometric studies on the hydrolysis [208–210] and complex formation with S^{2-} [211] of $EtSnCl_3$ in mixed water/methanol solutions have been performed by Devaud et al., in the concentration range organometallic compounds 6–60 mmol dm^{-3}. The results obtained by these authors are partially in contrast with the earlier findings on $MeSnCl_3$, probably because of the different solvent and concentration ranges used. Results of ^1H- and ^{119}Sn-NMR and ^{119}Sn Mössbauer spectroscopic studies on the hydrolysis of Me- and $BuSnCl_3$ (0.5 mol dm^{-3}) have been reported by Blunden et al. [212,213]. In the very recent and detailed publication of De Stefano et al. [214], it was found that at low $MeSnCl_3$ concentration only five different species could be detected (with metal to OH^- ion ratios 1:1, 1:2, 1:3, 1:4 and 2:5). The first hydrolysis step takes place at very low pH. The equilibrium constants obtained are given in Table 8. According to the species distribution curves, the amount of the dimeric species gradually increases with increasing concentration of $MeSn(IV)^{3+}$. Among the triply charged cations, $MeSn(IV)^{3+}$ is the most hydrolysed: undergoes hydrolysis at lower pH values than those for Fe(III) and Al(III).

Table 8
Equilibrium constants and standard deviations for the hydrolysis of $MeSn(IV)^{3+}$ at 25 °C and $I = 0$ mol dm^{-3} [214]

Reactions	log β
$MeSn(IV)^{3+} + H_2O = MeSn(IV)(OH)^{2+} + H^+$	-1.5 ± 0.5
$MeSn(IV)^{3+} + 2H_2O = MeSn(IV)(OH)_2^+ + 2H^+$	-3.36 ± 0.05
$MeSn(IV)^{3+} + 3H_2O = MeSn(IV)(OH)_3^0 + 3H^+$	-8.99 ± 0.04
$MeSn(IV)^{3+} + 4H_2O = MeSn(IV)(OH)_4^- + 4H^+$	-20.27 ± 0.06
$2MeSn(IV)^{3+} + 5H_2O = Me_2(Sn(IV)OH)_5^+ + 5H^+$	-7.61 ± 0.08
$MeSn(IV)^{3+} + OH^- = MeSn(IV)(OH)^{2+}$	-1.5 ± 0.5
$MeSn(IV)^{3+} + OH^- = MeSn(IV)(OH)_2^+$	22.64
$MeSn(IV)^{3+} + 3OH^- = MeSn(IV)(OH)_3^0$	33.01
$MeSn(IV)^{3+} + 4OH^- = MeSn(IV)(OH)_4^-$	35.73
$2MeSn(IV)^{3+} + 5OH^- = Me_2Sn(IV)OH)_5^+$	62.38

Acetate can form only one species, $[SnMe_2(O_2CMe)_2]$, with $Me_2Sn(IV)^{2+}$, while malonate and succinate form a set of species. The thermodynamic parameters confirm the rearrangement of the two Me groups from the *trans* to the *cis* position during formation of the bis complex [55,56]. Subsequently, the results of equilibrium studies on the system $Me_2Sn(IV)$–acetate, –malonate, –1,2,3-propanetricarboxylate and –1,2,3,4-butanetetracarboxylate have shown that this cation forms quite stable complexes with carboxylic-group containing ligands, with formation constants comparable to those of transition metals [somewhat higher than those of analogous complexes of Cu(II)], except for the hydrolytic species $ML(OH)^{1-n}$. The hydrolytic species and the mixed species have to be taken account in the course of the curve- fitting analysis. The stability of $Me_2Sn(IV)$-carboxylic ligand species follows a regular trend of $z^{2/3}$, which makes it possible to estimate the formation constants of other systems [361]. The results obtained on the acetate and malonate systems in the same ionic medium are in agreement with previous findings [55,56].

The results on the complex formation of $Me_2Sn(IV)^{2+}$ with aminodiacetate (ida), oxyacetate and thiodiacetate ligands have revealed the conformational flexibility of this cation in its complexes. Such flexibility is manifested not only in the variability of the Me–Sn–Me angle, but also in the ability to give rise to unusual asymmetric stereochemistry. In the ida complex, the skew disposition of the Me groups and the different bond lengths of equivalent donor atoms were observed [215].

The complex formation of $Me_3Sn(IV)^+$ with succinate, 1,2,3-propanetricarboxylate (tricarballylate), 1,2,3,4-propanetetracarboxylate and benzenehexacarboxylate (mellitate) has also been studied [216]. In all systems investigated formation of the species ML and MH_jL was detected. For the tetra- and hexacarboxylates, the binuclear species M_2L was also found. The stabilities of these complexes are quite relevant, and for $ML^{(1-z)}$ a simple relationship was obtained: $\log K = z^{0.86}$ (where z is the charge on the ligands).

Three primary factors are involved: in the structure–activity relationships for organotin(IV) derivatives $(L)_xR_nSnX_{4-n}$: the natures of the organic group R, of halide or pseudohalide X, and of donor ligand. Examination of the structures of Sn(IV) compounds containing a N-donor atom and tested for antitumour activity revealed that in the active Sn complexes the average Sn–N bond lengths were > 239 pm, whereas the inactive complexes had Sn–N bonds < 239 pm, which implies that predissociation of the ligand may be an important step in the mode of action of these complexes, while the coordinated ligand may favour transport of the active species to the site of action in the cells, where they are released by hydrolysis.

With regard to the data published on all the Sn(IV) derivatives, it can be concluded that $R_2Sn(IV)^{2+}$ compounds generally exhibit higher antitumour activity than those of corresponding mono-, tri- and tetraorganotin(IV) or the inorganic Sn(IV) derivatives, and within the diorganotin(IV) class, the highest activity is exerted by the $Et_2Sn(IV)^{2+}$ and $Ph_2Sn(IV)^{2+}$ complexes.

In a series of publications Pettinari et al. [217–221] investigated a large number of organotin(IV) complexes formed with mono- or bidentate N-donor ligands. The ligands were mainly substituted imidazole derivatives. In some cases, the ligand imidazole-2-thione was also used. The complexes were characterized by their analytical and spectral data. The behaviour in solution was investigated by conductivity, molecular weight determinations, and ^{1}H-, ^{119}Sn- and sometimes ROESY-NMR experiments. It was found that the reactivities of these imidazoles towards organotin(IV) acceptors depended not only on the electronic and steric features of the groups bound to the Sn, but also on the position of the alkyl or aryl substituent in the imidazole moiety and on the nature of the counterion. The combined spectral data suggest that the triorganotin(IV) adducts have a trigonal-bypiramidal structure, whereas a distorted octahedral or pseudo-octahedral structure is likely for all the other derivatives.

Organotin(IV) derivatives of 2,2′-bisimidazole [222], *N*-methyl-2,2′-bisimidazole [223] and *N*,*N*′-dimethylbisimidazole [224,225] were studied by Sordo et al. Conductivity measurements in acetonitrile showed that the adducts behave as non-ionogens in this solvent. The spectroscopic data suggest that all the complexes have analogous pseudo-octahedral geometry, with bidentate ligands, and the R groups are in *trans* positions. The $Bu_2Sn(IV)^{2+}$ derivatives proved to be the most active compounds against the well-established cell line KB.

When reacted with tetraalkylammonium halides, hydrated $Me_2Sn(IV)^{2+}$, $Bu_2Sn(IV)^{2+}$ [226] $Ph_2Sn(IV)^{2+}$ [227] and $EtPhSn(IV)^{2+}$ [228], ester derivatives of 2,6-pyridinedicarboxylic acid yield tetraalkylammonium diorganohalogeno(2,6-pyridinedicarboxylato)stannates.

Table 9
Overview of ID_{50} values in vitro of condensation compounds of Bu_2SnO with F^--containing carboxylic acids against MCF-7 and WiDr

Organotin(IV) compound	ID_{50} (ng cm^{-3})		Ref.
	Against MCF-7	Against WiDr	
{[(4-F-$C_6H_4CO_2$)-$Bu_2Sn]_2O$}$_2$	81	360	[277]
(4-F-$C_6H_4CO_2$)$SnBu_2$	90	309	[277]
{[(2,3-F_2-$C_6H_2CO_2$)-$Bu_2Sn]_2O$}$_2$	9	120	[280]
(2,3-F_2-$C_6H_3CO_2$)$SnBu_2$	23	283	[280]
{[(2,3,6-$F_3C_6H_2CO_2$)-$Bu_2Sn]_2O$}$_2$	13	200	[281]
{[(2,3,4,5-$F_4C_6HCO_2$)-$Bu_2Sn]_2O$}$_2$	35	250	[281]
{[(2-F-C_6H_4CH=$CHCO_2$)$Bu_2Sn]_2O$}$_2$	28	368	[228]
{[(4-F-$C_6H_4CH_2CO_2$)-$Bu_2Sn]_2O$}$_2$	38	268	[228]
(1,2-$F_4C_6(CO_2)_2$)Bu_2Sn	51	68	[282]
{[($F_5C_6CO_2$)$Bu_2Sn]_2O$}$_2$	44	214	[190]
{[(F_5C_6CH=$CHCO_2$)-$Bu_2Sn]_2O$}$_2$	10	145	[190]
[*n*-Bu_2Sn(5-Cl-2-OH–$C_6H_3CO_2)_2$] [(cyclo-$C_6H_{11})_2NH_2]_2$	319	89	[192]
[($C_4H_9)_2$Sn-($O_2CC_5H_3NCO_2)_2$]	46	172	[229]
[2,3-$(OH)_2$-$C_6H_3COO)_2SnBu_2$]	7	90	[191]
[2,4-$(OH)_2$-$C_6H_3COO)_2SnBu_2$]	16	120	[191]
[2,5-$(OH)_2$-$C_6H_3COO)_2SnBu_2$]	4	115	[191]
[2,6-$(OH)_2$-$C_6H_3COO)_2SnBu_2$]	15	130	[191]
[2,6-$(OH)_2$-$C_6H_3COO)_2SnBu_2$]	130	500	[191]
Salicylaldoxime/*n*-Bu_2SnO	67	215	[283]
Salicylaldoxime/*tert*-Bu_2SnO	49	121	[283]
Salicylaldoxime/Ph_2SnO	1643	4565	[283]
Et_2Sn[2,6-$(O_2C)_2$-$C_5H_3N]\cdot H_2O$	822	1290	[284]
{Et_2Sn[2,6-$(O_2C)_2$-C_5H_3N]F}$^-$[NEt_4^+]	1002	2495	[284]
n-Bu_2Sn[2,6-$(O_2C)_2$-$C_5H_3N]\cdot H_2O$	54	76	[284]
{*n*-Bu_2Sn[2,6-$(O_2C)_2$-C_5H_3N]F}$^-$[NEt_4^+]	118	220	[284]
Etoposide	187	624	[285]
Mitomycin C	3	17	[285]
Carboplatin	5500	1500	[285]
Cisplatin	800	650	[285]
5-Fluorouracil	210	260	[285]
Methroterxate	150	140	[285]
Doxorubicin	8	20	[285]

The compounds already used in clinical practice are given in italics.

Both classes of compounds exhibit high in vitro antitumour activity.

Bis(dicyclohexylammonium) bis(2,6-pyridinedicarboxylato)dibutylstannate is concluded to have sevenfold coordination at the Sn on the basis of its ^{119}Sn-CP/MAS-NMR chemical shift ($\delta = -424.9$ ppm). The assignment has been corroborated by crystal structure determination of its monohydrate, in which the Sn atom has *trans*-C_2SnNO_4 pentagonal-bipyramidal geometry (Sn–C = 204.0, 206.7 pm, C–Sn–C = 168.9°). One 2,6-pyridinedicarboxylato group chelates to the Sn atom (Sn–O = 223.4, 226.0 pm; Sn–N = 227.9 pm), whereas the other binds through only one carboxyl end (Sn–O = 241.6, 244.1 pm). The anhydrous compound display higher in vitro antitumour activity than those of cisplatin and carboplatin (Table 9) [229].

Several investigations have shown that the salicylaldimine complexes (Fig. 15) with X = H are effective ligands for both inorganic and organotin(IV) species. Replacement of X by a methoxy group, radically altered the nature of the metal salicylaldimine complexes as ligands, transforming them from bidentate to extremely effective tetradendate ligands. Much more surprising, however, was the finding that the behaviour of the complexes as ligands is markedly and dramatically influenced by the nature of the bridging group B in Fig. 15a. When the number of {C} atoms linking the imine {N} atoms is increased beyond three, the effectiveness of the metal salicylaldimines as ligands is greatly reduced. For example, practically no organotin(IV) Lewis acids react with the complex of *N*,*N*-bis(3-methoxysalecylidene)pentane-1,5-diamine [230,231]. ^{119}Sn Mössbauer parameters indicated that all of the adducts of di- and triorganotin(IV) halides are organotin(IV) aqua adducts with the donor water engaged in hydrogen bonding with Schiff-base {O} atoms. Ph_3SnCl, Ph_2SnBr_2 and $Bz_2Sn(IV)^{2+}$ complexes contained pentacoordinated Sn. The Δ value of 3.20–3.29 mm s^{-1} for the Bu_2SnCl_2 adducts may reflect pseudo-octahedral coordination geometry around tin central atoms as a result of weak intermolecular Sn–Cl, interactions such as those in $SnMe_2Cl_2\cdot H_2O$[Ni(3-MeOsal,3pn)] [232].

Equimolar reactions of Bu_2SnO with Schiff bases derived from amino acids led to the formation of a new series of $Bu_2Sn(IV)^{2+}$ complexes of general formula Bu_2SnL (L = dianion of tridentate Schiff bases derived from the condensation of 2-hydroxy-1-naphthaldehyde or acetyl acetone with Gly, L-β-Ala, DL-Val, DL-4-aminobutyric acid, L-Met, L-Leu and PhGly). The central Sn(IV) ions in all these complexes are pentacoordinated with a monodentate carboxylic group. The complexes have been tested against various bacteria, and exhibited moderate activity. The cytotoxicities of the complexes were higher than those observed for cisplatin and carboplatin [233].

Diorganotin(IV)$^{2+}$ complexes with general formula R_2SnL (R = Ph, *n*-Bu and Me) were recently prepared

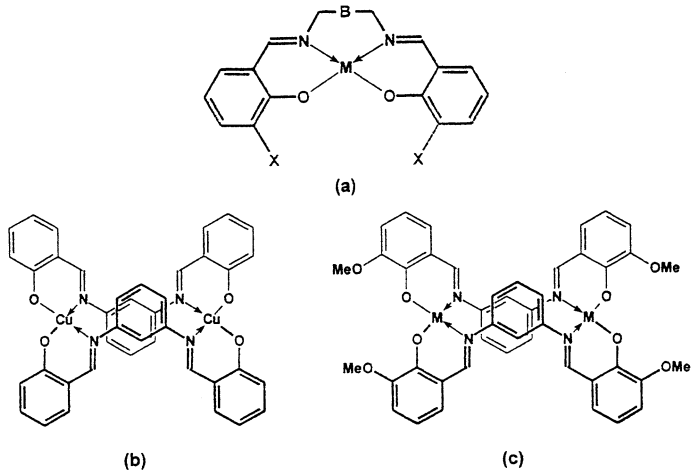

Fig. 15. Structures of metal salicylaldimine complexes [230,231].

by reacting R_2SnCl_2 and tetradentate Schiff bases (H_2L) containing N_2O_2 donor atoms in the presence of triethylamine (as base) in benzene. In the $Bu_2Sn(IV)^{2+}$ complexes formed with 3-methoxysalicyladehyde derivatives, the Sn atom has a distorted octahedral structure, where the donor atoms of the Schiff base ligand occupy the four equatorial positions and the organo moieties are in *trans* axial positions [234]. Similarly, biologically active, hexacoordinated organotin(IV) complexes, with the two *n*-Bu groups in *trans* axial positions are formed with Schiff bases derived from heterocyclic ketones and sulfa drugs [235].

Further results on organotin(IV)-amino acid or 2-amino-2-methyl-1-propanol Schiff base complexes were reported in [236–243].

The reactions of mercaptopyrimidine derivatives with Ph_2SnCl_2 or $Ph_3Sn(OH)$ yielded the species Ph_3SnL, Ph_2SnL_2 or Ph_2SnClL. The species containing only one anionic ligand are stable in most of the solvents they dissolve in, the Ph_2SnClL whereas complexes interact with strong O-donors, such as DMSO, yielding the corresponding species Ph_2SnL_2 and Ph_2SnCl_2. Except for two complexes, for which an octahedral geometry with *trans* arrangement of the Ph groups was proposed these products, have severely distorted trigonal-bipyramidal structures [244] (Fig. 16).

A large number of Ge-substituted $Bu_2Sn(IV)^{2+}$ dipropionates with the formula $(R^3GeCHR^2CHR^1\text{-}COO)_2SnBu_2{\cdot}H_2O$ [R_3OPh_3, $N(OCH_2CH)_3$, $R^2 = H$, Me, aryl, $R^1 = H$, Me] have been synthesized and characterized by FTIR, NMR, MS and in one case X-ray diffraction All these compounds display antitumour activity, despite their low solubility in water [245].

Multifunctional di- and triorganotin(IV) carboxylates derived from bioorganic acids such as steroid carboxylic acids [246], terebic acid [247], 2,3:4,6-di-isopropylidene-2-keto-L-gulonic acid [114] and gibberellic acid [251] (Fig. 17) were found to exhibit antitumour properties in vitro. On the other hand, numerous other organotin(IV) carboxylates have likewise been shown to exhibit high antitumour activity [198,199,248,249]. Very recently, the $Bu_2Sn(IV)^{2+}$ $Ph_3Sn(IV)^{+}$ and $Bu_3Sn(IV)^{+}$ derivatives of 3*S*,4*S*-3-[(*R*)-1-(*terc*-butyldimethylsyloxy)ethyl-4-[*R*-1-carboxyethyl]-2-azetidinone have been synthesized and characterized. They also posses antitumour activity [250].

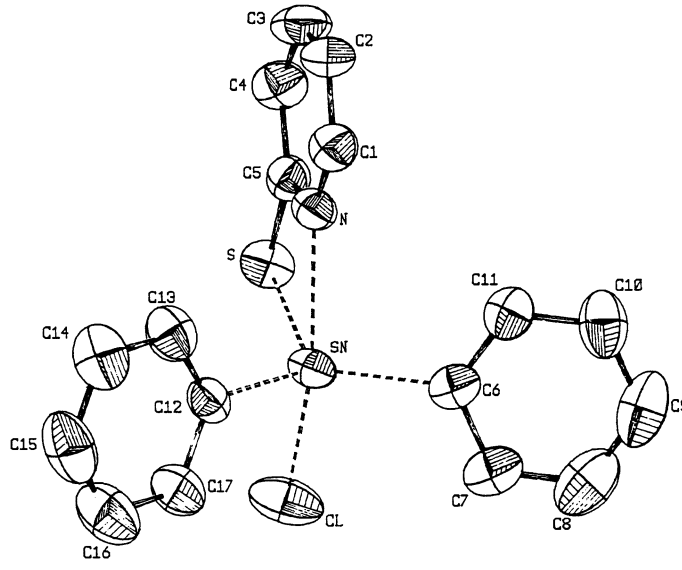

Fig. 16. Molecular structure of $Ph_2SnCl(MP)$ with the atom numbering scheme [244].

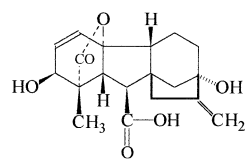

Fig. 17. The structure of gibberellic acid [251].

Gibberellic acid (Fig. 17) complexes of $Bu_2Sn(IV)^{2+}$, $Bu_3Sn(IV)^+$ and $Ph_3Sn(IV)^+$ have been prepared. The monomeric $Bu_3Sn(IV)^+$ derivative has the strongest antitumour activity [251].

Triorganotin(IV) compounds appear to inhibit the mitochondrial function in at least three ways: by (1) causing large-scale swelling at high concentrations, (2) mediating Cl^-/OH^- exchange across membranes, and (3) inhibiting oxidative phosphorylation or ATP hydrolysis, like oligomicyn [252]. The last process is usually assumed to be the most significant one, although binding of $Ph_3Sn(IV)^+$ to the cell wall was concluded to be responsible for the toxicity of *Ceratocystis ulmi* (*C. ulmi*) [253]. The triorganotin(IV)-mediated anion exchange across the mitochondrial membrane, which is electro-silent, i.e. it involves neutral R_3SnX species, may also interfere with ATP synthesis or hydrolysis.

Dutch elm disease continues to devastate the diminishing population of American elm trees. The pathogenic fungus responsible for the disease, *C. ulmi* causes a blockage in the vascular tissue, which can lead to the eventual death of the elm. In explorations of the expectation that the incorporation of biologically active entities into a triorganotin(IV) system would lead to the formation of potent biocides [254], a number of $Ph_3Sn(IV)^+$ compounds with simple biologically active anionic groups were synthesized and first investigated spectroscopically [255]. The abiguous spectroscopic data led to further crystallographic investigations on two of the Sn–S bound compounds; these complexes have been shown to be especially active against *C. ulmi* [256]. The results of the studies on the complexes of several $Ph_3Sn(IV)^+$ carboxylates and of some 1:1 addition compounds of Ph_3SnCl and 2,3-disubstituted thiazolidin-4-ones indicate that the carboxylates in the solid state are monomeric with a tetrahedral Sn atom (Δ = 2.14–2.54 mm s^{-1}) the only exception being the furan-2-carboxylic acid derivative, which is polymeric. The Ph_3SnCl adducts are trigonal-bipyramidal ($\Delta = 2.97$–3.08 mm s^{-1}) with the three phenyl groups in a not coplanar equatorial plate. These complexes are effective inhibitors of *C. ulmi* [257].

The structure of $[Ph_3Sn(O_2CCH_2N(H)C(O)NH_2]$ (hydantoic acid) is polymeric in consequence of the bridging property of the ligand: each ligand coordinates to one Sn atom via one of the carboxylate O atoms, and to a symmetry-related Sn atom via a carbonyl group at the other end of the molecule. The structure is distorted trigonal-bipyramidal around the Sn atom, with a *trans*-R_3SnO_2 motif characteristic of triorganotin(IV) complexes. The structure of $[c\text{-}Hex_3Sn(O_2CCH_2N(H)C(O)NH_2]$, by contrast, is monomeric with monodentate carboxylate group. Fungitoxicity and phytotoxicity studies indicate that the *n*-Bu derivative is the most active compound [258].

The 2,3-disubstituted thiazolidin-4-ones [259] are compounds with a wide range of biological activity. Several $Ph_3Sn(IV)^+$ complexes of these type of ligands have a trigonal-bipyramidal structure with the three Ph groups in the equatorial plane in non-coplanar positions. These complexes are effective inhibitors of *C. ulmi* [260].

Several triorganotin(IV) esters of *N*-arylidene-ω-amino acid complexes have also been prepared. These complexes have a *trans*-R_3SnO_2 pentacoordinated structure with bridging carboxylate or phenolic O atoms. The compounds are active against *C. ulmi* [261]. The $Bu_2Sn(IV)^{2+}$ complexes of the same ligands were tested against the panel of 60 cell lines of the National Cancer Institute. The complexes have only moderate activity, probably because of the presence of the N-bearing ligand, which increases the stability of the compounds [262]. In the crystal structures of the $Ph_3Sn(IV)^+$ derivatives of *N*-(2-carboxybenzylidene)aniline, the Sn atom in both of the molecules comprising the asymmetric unit exists in distorted tetrahedral geometry owing to an intramolecular acyl O···Sn contact. These complexes exhibit high fungicidal activity [263]. Other arylamine complexes of diorganotin(IV) with general formula R_2SnCl_2L [R = Me, Et, Vin, *t*-Bu, *n*-Bu or Ph; L = *N*-(2-pyridylmethylene)arylamine] have also been prepared. These complexes adopt a distorted *trans*-octahedral structure and have a significant cytogenetic effect [264].

$Ph_3Sn(IV)^+$ compounds of *p*-ethoxybenzoic acid and acetylsalicylic acid contain molecular units with Sn–O bonds and distorted tetrahedral Sn centres. The phthalic acid derivative contains two tetracoordinated Sn atoms with a phthalic acid unit bridging them. The salicylaldehydato compound is polymeric with trigonalbypiramidal Sn centres in which the Ph groups take equatorial positions. The polymerization occurs via the aldehyde {O} atom bonding to a neighbouring Sn atom [265]. These complexes have significant activity against a range of fungi [266].

The fungicidal activity of a number of ArSn(IV) compounds, $(p\text{-}ZC_6H_4)_3SnX$ [where X = $^-$OAc, $^-$OH or 1/2O, Z = F^-, Cl^-, CH_3, CH_3O^-, C_2H_5 or $(CH_3)_3C$)] are reported in [267]; the results are compared with those on the Ph_3SnOAc and Ph_3SnOH archetypes. It was found that, in most cases, *para*-substitution reduces the biocidal activity only slightly, but with *p*-CH_3O the ArSn(IV) is completely ineffective. A model for the fungicidal action was proposed.

In the context of studies on the coordination of organotin(IV) moieties by thiol S and heterocyclic N, diorganotin(IV) complexes of 2-mercaptopyridine (HSPy), $R_2Sn(SPy)_2$ and $R_2SnCl(SPy)$, have been characterized in the solid state and in solution [268]. The structure of the latter complex (R = Ph) was determined by X-ray diffraction (Fig. 18). The crystal is monoclinic in the space group $P2_1/n$. With the bidentate ligand

SPy, Sn forms a four-membered chelate ring with a short N–Sn–N bite angle of 64.8(1)°, leading to a heavily distorted trigonal-bipyramidal environment around the Sn. The related complexes have analogous structures. The compounds $R_2Sn(SPy)_2$ are distorted octahedra with R in the *trans* position, and S- and N-donor atoms in *cis* positions. The solid-state molecular structures are retained in chloroform solution.

The solid-state structures of the complexes $R_2SnHal(SPym)$, (R = *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, Cy, Ph, SPym = 2-mercaptopyrimidine) are of trigonal-bipyramidal type, but distorted, with the angles C–Sn–C larger than 120° for the $R_2Sn(IV)^{2+}$ and $Cy_2Sn(IV)^{2+}$ derivatives. The complexes $R_2Sn(Spyr)_2$ have *trans*-R_2 octahedral, or possibly skew-trapezoidal structures, with *cis*-S,S and *cis*-N,N atoms in the equatorial plane. The complex $Me_2SnCl(SPym)$ could be assumed to be a monomeric, trigonal-bipyramidal species with the C–Sn–C angle around 134–145°, or a monodimensional polymer with a *trans*-R_2 octahedral-type Sn environment [269].

Mono-organotin(IV) complexes of the above ligands with the compositions $MeSn(SPy)_3$ and $PhSn(Spy)_3 \cdot 1.5CHCl_3$ are monoclinic. In the discrete monomeric $RSn(Spy)_3$ units, three bidentate SPy ligands together with R form a distorted pentagonal-bipyramid around the Sn. One {S} and one {C} atom are in the axial positions. Two {S} atoms and three {N} atoms form the pentagonal plane [270].

The structure and dynamics for some representatives of the series of $Me_2Sn(IV)^{2+}$, $MeSn(IV)^{3+}$ and inorganic Sn(IV) complexes with {S,N}-containing donors have been determined by ^{119}Sn Mössbauer spectroscopy and are reported in [271].

A series of di- and triorganotin(IV) complexes of 2-thionaphthalene have also been prepared. All the complexes have tetrahedral geometry and moderate biological activities against various bacteria and fungi [272].

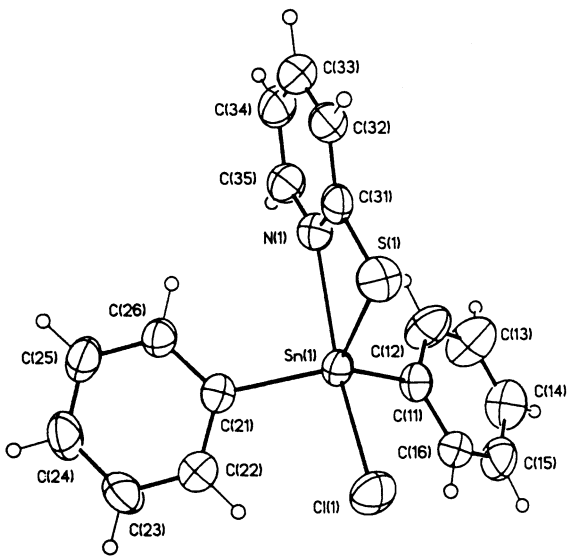

Fig. 18. Structure of diphenyl pyridine-2-thiolatochlorotin(IV) [268].

The coordination behaviour of the diorganotin(IV) compounds R_2SnCl_2 (where R = Me, Ph) with 4*H*-pyrido[1,2-*a*] pyrimidin-4-one derivatives (L) has been described. The ligands are coordinated in a monodentate fashion, mainly via the {O} atom of the 4-one group or possibly via the N atom of the –C=N linkage to give pentacoordinated Sn complexes [273].

Bis{3-methoxysalicylato[di(*n*-butyl)]tin(IV)} oxide, obtained by the condensation of Bu_2SnO and 3-methoxysalicylic acid, exhibits higher antitumour activities in vitro against, two human tumour cell lines, MCF-7, a mammary tumour, and WiDr, a colon carcinoma, than those of the 5-Me and 4-MeO analogues [186] (see Table 9). The position of the MeO substituent also influences the antitumour activity of the di(*n*-butyl)tin bis(methoxysalicylate)s, $(CH_3O\text{-}2\text{-}OH\text{–}C_6H_3COO)_2SnBu_2$: for the 4-MeO derivative, the ID_{50} values are 131 and 1182 ng ml^{-1}, whereas for the 5-MeO derivative, they are 54 and 611 ng ml^{-1}, respectively. On the other hand, di(*n*-butyltin(IV)-bis(4-hydroxy-3-metoxy-benzoate), $(4\text{-}OH\text{-}3\text{-}CH_3O\text{–}C_6H_3COO)_2SnBu_2$, are characterized by excellent ID_{50} values (44 and 82 ng ml^{-1}, respectively) [186], as compared with the former compounds. The di(*n*-butyl)tin(IV) bis(dihydroxybenzoate)s have skew-trapezoidal-bipyramidal or bicapped tetrahedral structures in the solid state (Δ = 3.6–3.8 mm s^{-1}) [191], comparable with those of dimethyltin(IV) diacetate [274] and di(*n*-butyl)-bis(*o*-aminobenzoato)- or di(*n*-butyl)bis(5-chloro-2-hydroxybenzoato)tin(IV) [192,275]. The much larger Δ value (4.7 mm s^{-1}) for $(2,6\text{-}(OH)_2C_6H_3COO)_2SnBu_2$ is consistent with a heptacoordinated structure, like that of $Me_2Sn(IV)^{2+}$ dipicolinate in the solid state [276]. The antitumour activities of these compounds are presented in Table 9.

The substitution of H by F^- influences the biological activity of organic molecules markedly. Although the van der Waals radii of F^- (135 pm) and H (120 pm) are comparable, the substituent F^- is very resistant to metabolic transformations because of the strength of the C–F bond. The much higher electronegativity of F^- also strongly affects the electronic density distribution in the molecule. Accordingly Gielen et al. synthesized a series of organotin(IV) carboxylates containing mono- or polyfluorophenyl groups, and screened them for antitumour activity against MCF-7 and WiDr (Table 9) [190].

The $Bu_2Sn(IV)^{2+}$ monofluorobenzoates [277] are characterized by ID_{50} values roughly half those of etoposide. The 2,3-difluorobenzoates are more active than the 4-monofluorobenzoates, which shows that the activity is enhanced when the number of F^- atoms on the benzoate moiety is increased. The {[(2,3-

$F_2C_6H_2CO_2)Bu_2Sn]_2O\}_2$ compound provides an ID_{50} value against MCF-7comparable with that of mitomycin C. The ID_{50} value of the corresponding 2,3,6-trifluorobenzoate is of the same order of magnitude, while that of the 2,3,4,5-tetrafluorobenzoate is lower. Against WiDr, all fluorobenzoates exhibit comparable activities, again except $\{[(2,3\text{-}F_2C_6H_2CO_2)Bu_2Sn]_2O\}_2$, which is significantly more active. The activities of Bu_2Sn(IV) fluorocinnamate and fluorophenylacetate are similar, while di-*n*-butyltin(IV) tetrafluorophthalate is characterized by a quite low ID_{50} value against WiDr cells. As far as the cell lines MCF-7 and WiDr are concerned, the pentafluorobenzoates have activities comparable with those of the tri- and tetrafluorobenzoates and the monofluorophenyl-acetates and -cinnamates [190].

The crystal structure of [*n*-Bu_2Sn(5-Cl-2-OH–$C_6H_3CO_2)_2$] [dibutylbis(5-chloro-2-hydroxybenzoato)-tin(IV)] shows that in the monomeric species the hexacoordinated Sn atom exists in skew-trapezoidal bypiramidal geometry in which the four {O} donor atoms, derived from two asymmetrically chelating carboxylate ligands, define the basal plane. Additionally, the *n*-Bu substituents lie over the weaker Sn–O interactions, determining a C–Sn–C angle of 147.6°. The in vitro antitumour activity of the compound is shown in Table 9 [192].

The sarcosine $Ph_3Sn(IV)^+$ complexes with compositions $[Ph_3Sn(OCOCH_2NH_2CH_3)_2]X$ ($X = Cl^-$, SCN^-) were studied by Khoo et al. [278]. Sarcosine reacts in a zwitterionic form, and behaves as a monodentate ligand via coordination through the carboxylate O. All data support the *trans*-R_3SnO_2 (trigonal-bipyramidal) structure of the complexes. The cyclosarcosylsarcosine complexes of $RSn(IV)^{3+}$ and $R_2Sn(IV)^{2+}$ have also been studied. The $Ph_2Sn(IV)^{2+}$ derivative forms zigzag polymeric chains of *trans*-$Ph_2Sn(IV)^{2+}$ bridged by ketonic {O} atoms. Each Sn(IV) atom is surrounded by two C atoms (Sn–C = 212.9 and 214.6 pm, C–Sn–C 160.1°), two Cl^- (Sn–Cl = 245.5 pm, Cl–Sn–Cl = 98.5°) and two {O} atoms (Sn–O = 237.0, and 246.8 pm, O–Sn–O 86.1°) [279].

Triorganotin(IV) and diorganotin(IV) halides and pseudohalides form molecular adducts with zwitterions such as *N*-alkyl and *N*-arylsalicylides [286–289], picolinic acid [290,291] and quinaldic acid [292]. With Schiff bases, the 1:1 and 1:2 adducts normally have trigonal-bipyramidal and octahedral structures, respectively, though some unusual structures have also been reported [293,294]. With carboxylic acids, hydrated complexes are generally obtained. The acid in its zwitterion form binds to the $Ph_3Sn(IV)^+$ moiety and generates trigonal-bipyramidal geometry around the Sn atom. Hydrogen bonding involving non-coordinated water molecules serves to bind the pentacoordinated units together in the form of a dimer. These compounds display a most unusual structure [290–294], and show promising fungicidal activity. In $Me_2HNCH_2COOPh_3$-SnX ($X = Cl^-$, NCS^-), the Sn atom is also found to be pentacoordinated and the ligand in the form of the zwitterion binds to the metal ion through the monodentate carboxylate group. Surprisingly, the NCS^- is bound through the N atom. The fungicidal activities slightly better than that of the parent compound, Ph_3SnCl [295]. The structure of [*n*-Bu_3(*N*-phthaloylglycinate)(H_2O)] is similar to the structure discussed above. Instead of a halide ion, a water molecule is coordinated to the Sn centre. These complexes also have fungicidal activity [296].

Di- and tri-organotin(IV) derivatives of thiophene-2-carboxylic acid and aminobenzoic acid complexes have octahedral and trigonal-bypiramidal geometry [297,298]. Diphenic acid (A) also forms diorganotin(IV) complexes, which are tetrahedral with two monodentate carboxylic groups. On the other hand, soluble dinuclear triorganotin(IV) complexes (where the organo moieties are Me and Ph) contain symmetrically bound carboxylates, while the less soluble compound $(Cyh_3Sn)_2A$ has two asymmetrically bonded carboxylates. All have trigonal-bipyramidal structures with $R_3Sn(IV)^+$ units remote from each other [299].

The preparation and spectroscopic characterization of [$R_3Sn(O_2CCH_2SC_5H_4N$-4)] (R = Ph, Bz, *c*-Hex and *n*-Bu) and [$R_3Sn(O_2CCH_2SC_4H_3N_2$-2,6)] (R = Me, Ph, *n*-Bu) have been reported in [300] (Fig. 19). The 2-pyrimidyl compounds feature trigonal-bypiramidal Sn centres with *trans*-R_3SnO_3 geometry as confirmed by X-ray diffraction measurements on [$Ph_3Sn(O_2CCH_2$-SC_5N_2-2,6)]. By contrast, 4-pyridyl complexes have trigonal-bypiramidal geometry in the solid state (arising from the intermolecular Sn···N interaction) and a tetrahedral structure in solution [300].

The antitumour activity of salicylaldoxime complexes of *n*-$Bu_2Sn(IV)^{2+}$, *terc*-$Bu_2Sn(IV)^{2+}$ and Ph_2Sn(IV) complexes have been tested. The results are collected in Table 9 [283].

Ascorbic acid coordinates $Me_2Sn(IV)^{2+}$, and $Bu_2Sn(IV)^{2+}$ in aqueous solution via O-1, O-2 and O-3 of the lactone ring. Other weak interactions of Sn complexes in the solid state are also possible [181].

Diorganotin(IV) 2,6-pyridinedicarboxylates exhibit in vitro antitumour activities [301]. Atassi assumed that water-soluble organotin(IV) compounds are probaly more active than complexes soluble only in organic solvents [302]. Therefore, Gielen et al. [229,284] (Fig. 20) prepared some tetraethylammonium (diorgano)-halogeno(2,6-pyridinecarboxylato)-stannates (halogeno = Cl^-, F^-), whose water solubilities under physiological conditions are higher than those of their parent compounds. The desired compounds were obtained by using a similar procedure as in the case of the analogous tetraethylammonium diorgano(halogeno)-

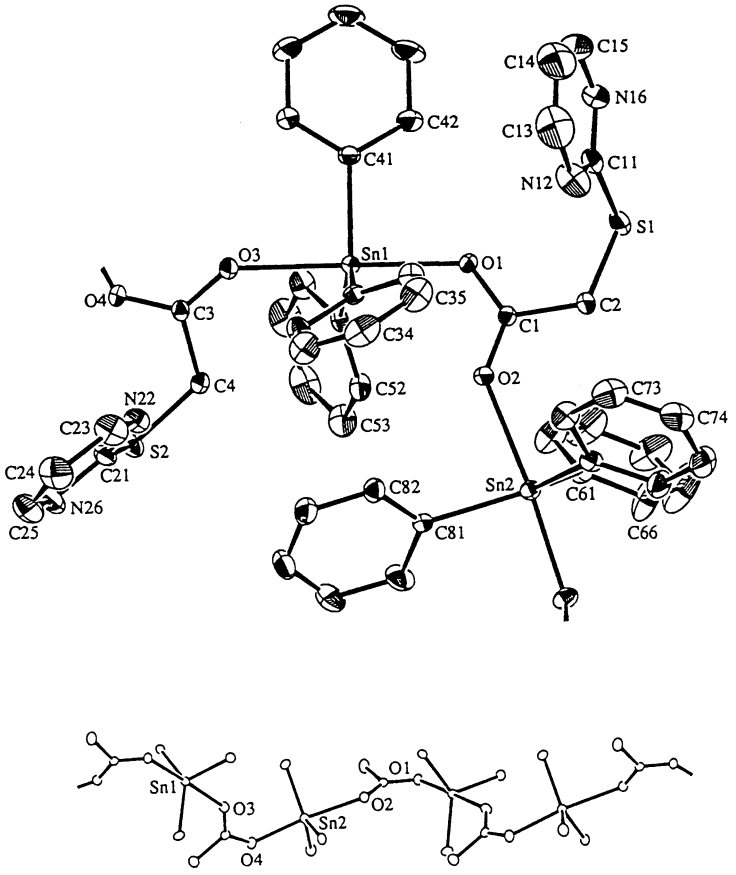

Fig. 19. Molecular structure and crystallographic numbering scheme for the two molecules comprising the asymmetric unit in $[Ph_3Sn(O_2CCH_2SC_4H_3N_2\text{-}2,6)]$. The lower view shows the polymeric structure; R′ and all but the *ipso* carbon atoms of the phenyl rings have been omitted for clarity [300].

thiosalicylatostannates [283] (Fig. 21). The Mössbauer parameters ($\Delta = 3.50$–4.23 mm s^{-1}) suggested that the heptacoordination around the Sn atom in the parent compounds [226,301] is maintained in the salts.

The inhibition doses, ID_{50}, for the compounds and the parent $Bu_2Sn(IV)^{2+}$ derivatives are presented in Table 9. These data do not support the hypothesis of Atassi that water-soluble Sn compounds might exhibit higher antitumour activity, at least for the cell lines studied. It should be outlined that the $Bu_2Sn(IV)^{2+}$ compounds exhibit a much higher activity than the corresponding $Et_2Sn(IV)^{2+}$ compounds, in contrast with most Sn compounds tested in vivo against P338 mouse leukaemia cells [302]. Furthermore, the $Bu_2Sn(IV)^{2+}$ complex is quite active against WiDr cells, which is not the case for most $Bu_2Sn(IV)^{2+}$ derivatives as they mainly exhibit promising activity against MCF-7 cells [186].

As a consequence of their practical importance, particular attention has been paid to studies of synthesis, properties, structures and reactivities of triorganotin(IV) monocarboxylates. Similar triorganotin(IV) di- and polycarboxylates have been studied much less intensively. For triorganotin(IV) carboxylates involving different degrees of the substitution of the carboxylic group {H} atoms, it is possible to prepare a diverse

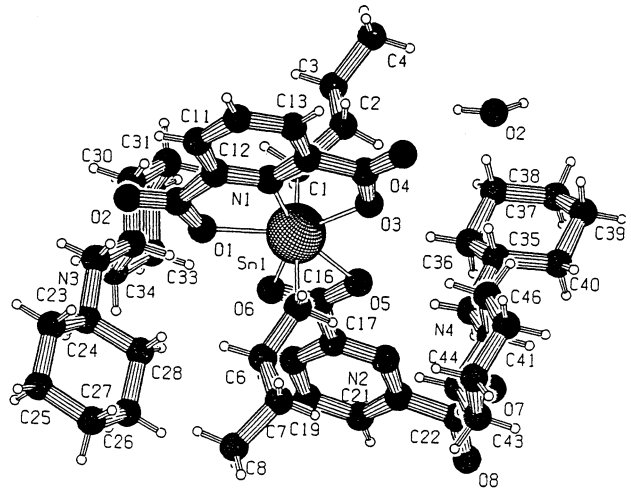

Fig. 20. Atomic labelling scheme for bis(dicyclohexylammonium) bis(2,6-pyridinecarboxylato)dibutylstannate hydrate. The water molecule is disordered over two positions [229].

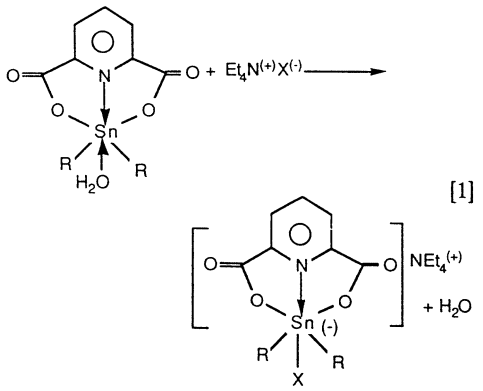

Fig. 21. Preparation of tetraethylammonium (diorgano)halogeno-(2,6-pyridine-dicarboxylato)stannates [284].

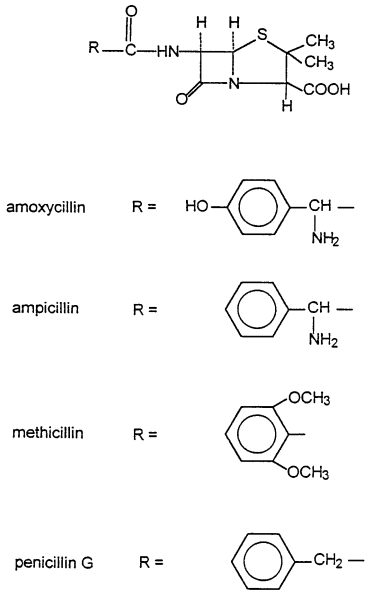

Fig. 22. Structures of penicillins studied here.

palette of mixed esters or ionic salts, in which some {H} atoms are substituted by organic or organometallic groups, and/or by ions. The current knowledge on the crystal and molecular structures of this class of organotin(IV) compounds relates to triorganotin(IV) carboxylates derived from dicarboxylic acids. As far as we are aware, the compounds derived from tricarboxylic acids have not been studied. When dicarboxylic acids react with a diorganotin(IV) oxide, they generally lead to a cyclic structure containing one Sn atom [228,282]. The reaction of hexafluoro-2,2-bis(4-carboxyphenyl)-propane with tetrabutyldipropoxydistannoxane, formed in situ from Bu_2SnO and *n*-propanol in benzene, yields a compound whose structure is a strained macrocycle with a single dicarboxylate moiety [303]. The ^{117}Sn-NMR spectrum exhibits a single resonance at -142.3 ppm, typical of the usual trapezoidal bipyramidal geometry of diorganotin(IV) dicarboxylate [191].

Several novel derivatives of 6-[D(−)-β-amino-*p*-hydroxyphenylacetamido]penicilline (amoxicillin) (Fig. 22) [304], D(−)-α-aminobenzylpenicillin (ampicillin) [305], 2,6-dimethoxyphenylpenicillin (methicillin) [305] and 4-thia - 1 - azabicyclo[3.2.0]heptane - 2 - carboxylate,3,3–dimethyl-7-oxo-6(2-phenylacetamido)penicillin (penicillin G) [306] with diorgano- and triorganotin(IV) moieties have been prepared.

The stoichiometries of the compounds obtained were $R_2Sn(IV)Cl(antib)\cdot nH_2O$, $R_3Sn(IV)Cl(antib)Na\cdot nH_2O$ ($antib^{-1}$ = amoxicillinate^{-1}, $n=2$; $antib^{-1}$ = ampicillinate^{-1} or methicillinate^{-1}, $n=1$; $antib^{-1}$ = penicillinate^{-1}, $n=0$; R = Me, Bu, Ph) and $R_2Sn(IV)(antib)_2\cdot 2H_2O$ ($antib^{-1}$ = amoxicillinate^{-1} and ampicillinate^{-1}; R = Me, Bu, Ph). For $R_2Sn(IV)Cl(antib)\cdot nH_2O$ and $R_3Sn(IV)Cl(antib)Na\cdot nH_2O$, the IR data suggest penta-coordination around the Sn(IV) atom, whereas $R_2Sn(IV)(antib)_2\cdot 2H_2O$ most probably involves hexacoordination. In all of the compounds, thermogravimetric analysis excludes any coordination of Sn(IV) of water molecules. On the basis of IR and Mössbauer data, trigonal-bipyramidal configurations are proposed for both $R_2Sn(IV)Cl(antib)\cdot nH_2O$ and $R_3Sn(IV)Cl(antib)Na\cdot nH_2O$ ($antib^{-1}$ = amoxicillinate^{-1}, ampicillinate^{-1} or methicillinate^{-1}) in the solid state.

As far as the compounds $R_2Sn(IV)(antib)_2\cdot 2H_2O$ are concerned, the coordination geometry of the Sn could be skew-trapezoidal bipyramidal, with the monoanionic bidentate amoxicillin or ampicillin residues in the trapezoidal plane, and bent *axial* organic groups.

In order to estimate the partial atomic charge on the Sn atoms, Q_{sn}, electronegativity equalization procedures have been applied to idealized trigonal-bipyramidal structures for $R_2Sn(IV)Cl(antib)nH_2O$ and $R_3Sn(IV)Cl(antib)NanH_2O$ ($antib^{-1}$ = amoxicillinate^{-1}, ampicillinate^{-1} or methicillinate^{-1}) (Fig. 23a, b), and to octahedral *trans*-R_2 for $R_2Sn(IV)(antib)_2\cdot 2H_2O$ (Fig. 23c). The values obtained have been correlated to the Mössbauer parameter, isomer shift, δ (Table 10, Figs. 24 and 25).

Diorganotin(IV) derivatives of D-(−)*threo*-2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-β-(4-nitrophenyl)ethyl]acetamide (chloramphenicol, Fig. 26a) and of γ-4-amino-3-isoxazolidone (D-cycloserine, Fig. 26b) with formulae $R_2Sn(IV)Cl(antib)$ and $R_2Sn(IV)(antib)_2$ (antib = chloramphenicol, R = Me, Ph; antib = D-cycloserine, R = Me) were obtained and their solid-state and solution configurations were investigated by conventional IR, Mössbauer, ^{1}H- and ^{13}C-NMR spectroscopy [307].

FTIR and Mössbauer spectroscopic measurements lead to tetrahedral structures being proposed for $R_2Sn(IV)Cl(chloramphenicol)$ and $R_2Sn(IV)(chloramphenicol)_2$ in the solid state. In DMSO-d_6 solution, complete or partial dissociation is inferred for the Me

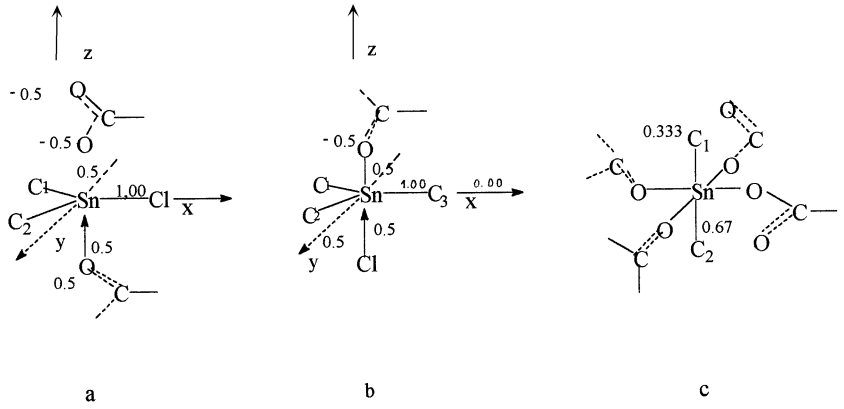

Fig. 23. Regular structures of Sn assumed fot estimation of the partial atomic charge on the Sn atom, Q_{Sn}. The reported bond orders and formal charges are taken as input in the calculation of Q_{Sn} (adapted from Refs. [304–306]).

and the Ph derivatives, as shown by the ^{1}H- and ^{13}C-NMR spectroscopic results. Two different Sn(IV) sites occur. One involves a Sn(IV) atom tetrahedrally coordinated by a monoanionic monodentate cycloserinate group, through the {O} atom of the resonance stabilized hydroxamate anion, furnishing Me_2SnClO and Me_2SnO_2 polyhedra in Me_2SnCl(D-cycloSer) and Me_2Sn(D-cycloSer)$_2$, respectively (Fig. 27a, b). The second site corresponds to Sn(IV) in a polymeric octahedral configuration with Me_2SnCl_2ON and $Me_2SnO_2N_2$ environments in Me_2SnCl(D-cycloSer) and Me_2Sn(D-cycloSer)$_2$ (Fig. 27c–f).

In diorganotin(IV)chloro-protoporphyrin IX complexes, with the general formula $(R_2SnCl)_2$protoporphyrin IX (R = Me, Bu and Ph), the ligand (Fig. 28a) coordinates to the $R_2Sn(IV)Cl^+$ moieties via bridging carboxylate, forming pentacoordinated *cis*-R_2 trigonalbypiramidal structures, as inferred from the FTIR and Mössbauer spectroscopies data [308].

The spectral features of the complexes $(R_2SnCl)_2$-protoporphyrin IX are in agreement with the monomeric character of protoporphyrin IX (Fig. 29).

meso-Tetra(4-carboxyphenyl)porphine (= H_6TPPC, Fig. 27b) interacts with diorgano and triorganotin(IV) moieties to afford complexes with the formulae $(R_2Sn)_2H_2TPPC$ and $(R_3Sn)_4H_2TPPC$, respectively. Pentacoordination of the Sn(IV) atom in both compounds is attained through coordination of the carboxylate O of the carboxyphenyl group. In $(R_2Sn)_2H_2TPPC$, two different carboxylate coordination types (bridging and monodentate types) are indicated the IR spectra, whereas in $(R_3Sn)_4H_2TPPC$ only bridging carboxylate groups are present, with the {O} atoms in axial positions (Fig. 30a, b) [309]. ^{1}H- and ^{13}C-NMR data, on DMSO solutions, point to the pentacoordinated monomeric structures of the above complexes.

Diorgano and triorganotin(IV) derivatives of *meso*-tetra(4-sulfonatophenyl)porphine (= H_6TPPS, Fig. 27c) with the formulae $(R_2Sn)_2H_2TPPS$ and $(R_3Sn)_4H_2TPPS$ (R = Me, Bu, Ph) have been studied by FTIR and Mössbauer spectroscopy in the solid state, while ^{1}H- and ^{13}C-NMR spectroscopy have been applied to DMSO-d_6 solutions [310]. The coordination mode of the sulfonate groups towards the organotin(IV) moieties has been established on the basis of the S–O vibrations present in the IR spectra of the complexes. In the IR spectrum of the free ligand *meso*-tetra(4-sulfonatophenyl)porphine, six S–O vibrations are found (three A_1 and three E). According to Yeats et al. [311], these are due to the RSO_3^- groups present as an ionic species with C_{3v} symmetry in all the complexes. Follow-

Table 10
Experimental Mössbauer parameter, isomer shift, δ (mm s^{-1}), and calculated partial atomic charge on the Sn atom, Q_{Sn}(CHELEQ), for a homologous series of pentacoordinated triorgano- and diorganotin(IV) derivatives

Compound [a]	δ [c]	Q_{Sn} [c]	Point N [b]	Ref.
$R_2SnCl(amox)\cdot 2H_2O$	1.24	0.270	1	[304]
$Ph_2SnCl(amox)\cdot 2H_2O$	1.20	0.317	2	[304]
$R_3SnCl(amox)Na\cdot 2H_2O$	1.36	0.128	3	[304]
$Ph_3SnCl(amoxNa)\cdot 2H_2O$	1.26	0.208	4	[304]
$R_2SnCl(penG)$	1.28	0.270	5	[306]
$Ph_2SnCl(penG)$	1.21	0.317	6	[306]
$R_3SnCl(penG)Na$	1.40	0.128	7	[306]
$Ph_3SnCl(penG)Na$	1.30	0.208	8	[306]
$R_2SnCl(ampic)\cdot H_2O$	1.27	0.270	9	[305]
$Ph_2SnCl(ampic)\cdot H_2O$	1.07	0.317	10	[305]
$R_3SnCl(ampic)Na\cdot H_2O$	1.33	0.128	11	[305]
$Ph_3SnCl(ampic)Na\cdot H_2O$	1.17	0.208	12	[305]
$R_2SnCl(methic)\cdot H_2O$	1.32	0.270	13	[305]
$Ph_2SnCl(methic)\cdot H_2O$	1.19	0.317	14	[305]
$R_3SnCl(methic)Na\cdot H_2O$	1.38	0.128	15	[305]
$Ph_3SnCl(methic)Na\cdot H_2O$	1.28	0.208	16	[305]

[a] Amox$^-$, amoxicillin^{-1}; penG$^-$, penicillinG^{-1}; ampic$^-$, ampicillin^{-1}; methic$^-$, methicillin^{-1}.
[b] Identification numbers of the points in Fig. 25.
[c] Average of the δ and Q_{Sn}(CHELEQ) values reported in the cited references.

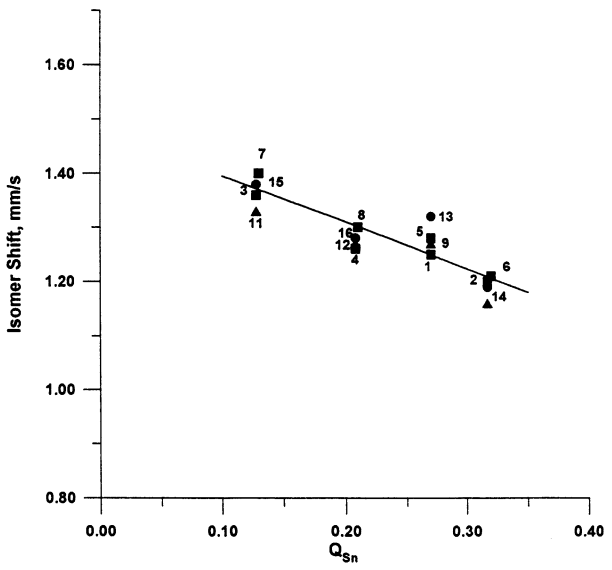

Fig. 24. Isomer shifts, δ, vs. atomic charge, Q_{Sn}, for $R_2Sn(IV)Cl(antib)\cdot nH_2O$ and $R_3Sn(IV)Cl(antib)Na\cdot nH_2O$ derivatives (Table 10) ($antib^{-1}$: amoxicillin^{-1}, $n=2$; penicillinG^{-1}, $n=0$; ampicillin^{-1}, methicillin^{-1}, $n=1$; R = Me, Bu, Ph). Full lines are the least-squares fits of data points (adapted from Refs. [304–306]).

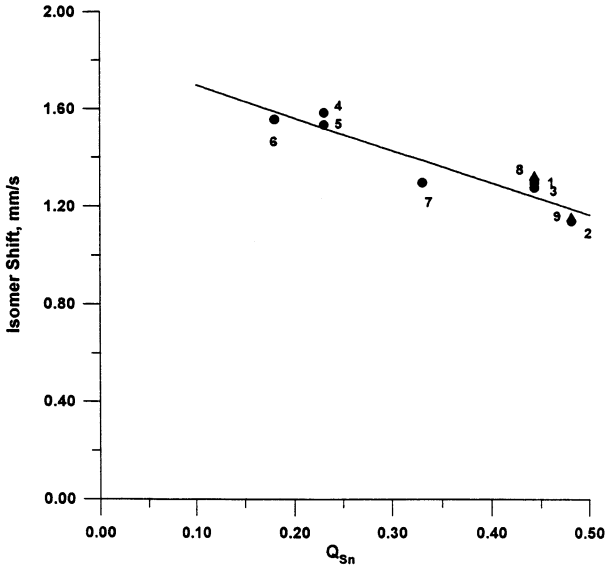

Fig. 25. Isomer shifts, δ, vs. atomic charge, Q_{Sn}, for $R_2Sn(antib)_2\cdot 2H_2O$ and related derivatives in Table 10 ($antib^{-1}$ = amoxicillin^{-1}, ampicillin^{-1}; R = Me, Bu, Ph). The full line is the least-squares fit of data points (adapted from Refs. [304–306]).

ing coordination and the formation of a more or less covalent bond, the symmetry decrease to C_s, removing the degeneracy of the three modes and increasing the number of fundamentals to nine (six A′ and three A″). The preceding findings have been interpreted as reflecting a bidentate bridging behaviour of the sulfonate groups. Consequently, in the diorganotin(IV) [*meso*-tetra(4-sulfonatophenyl)porphinate]s, the Sn(IV) atom should be hexacoordinated in a polymeric structure, as shown in (Fig. 31a), while in triorganotin(IV) [*meso*-tetra(4-sulfonatophenyl)porphinate]s, the Sn(IV) atom should be pentacoordinated in an *eq*-$R_3Sn(IV)$ polymeric configuration with axial RSO_3^- groups (Fig. 31b).

The ^{1}H- and ^{13}C-NMR spectra of the complexes in DMSO-d_6 solution led to the conclusion that the octahedral and the trigonal-bipyramidal configurations of $(R_2Sn)_2H_2TPPS$ and $(R_3Sn)_4H_2TPPS$ (R = Me, Bu, Ph),

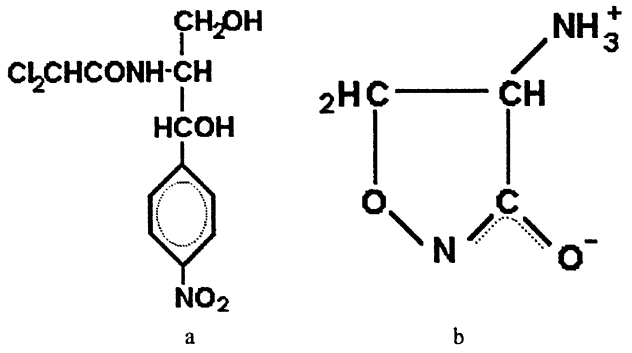

Fig. 26. The ligands chloramphenicol (a) and D-cycloserine (b) (adapted from Ref. [307]).

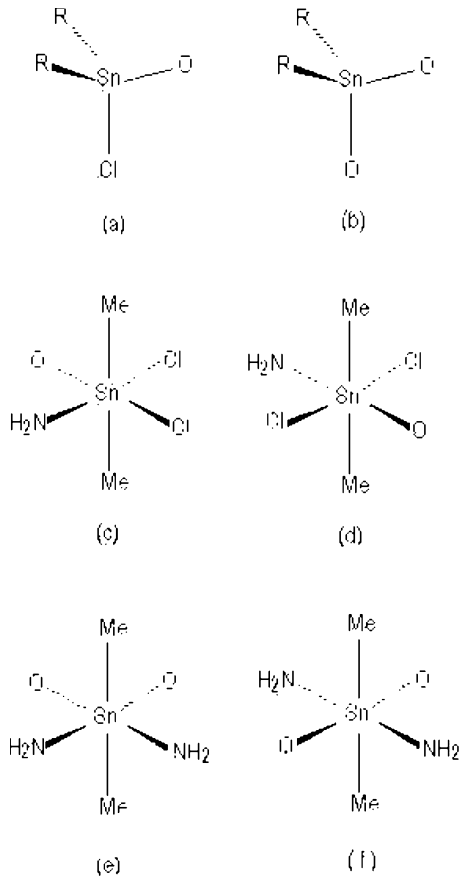

Fig. 27. Sn(IV) environments proposed for $R_2Sn(IV)Cl(antib)$ and $R_2Sn(IV)(antib)_2$ (antib = chloramphenicol, a, b; D-cycloSer, c–f) (adapted from Ref. [307]).

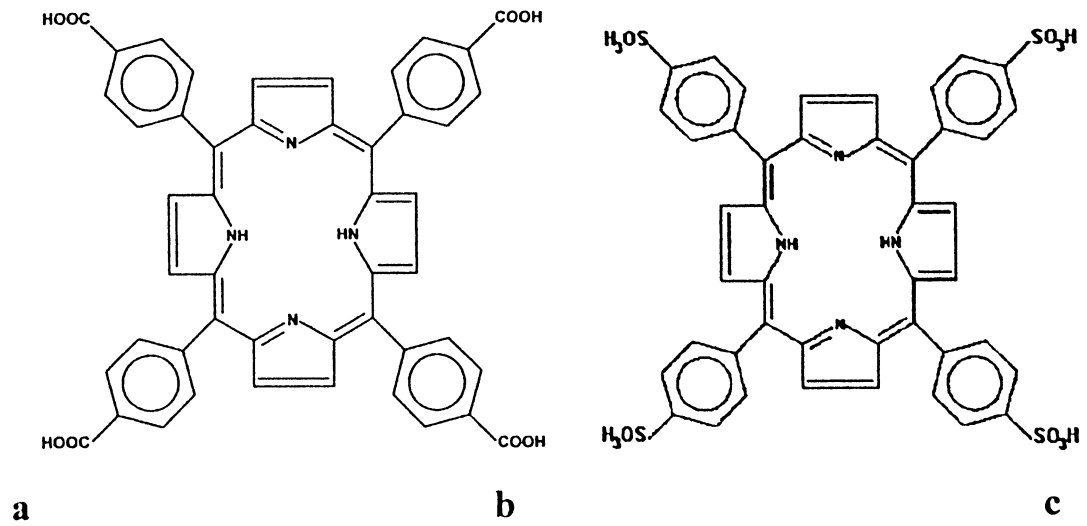

Fig. 28. Structures of protoporphyrin IX (a), *meso*-tetra(4-carboxyphenyl)porphine (b) and *meso*-tetra(4-sulfonatophenyl)porphine (c) (adapted from Refs. [308–310]).

respectively, in the solid state, are maintained in solution.

Pentacoordination, in a trigonal-bypiramidal configuration, *eq*-R_3, has been proposed for $R_3Sn(IV)$ derivatives of L-homocysteic acid, (Fig. 32) on the basis of IR and Mössbauer spectroscopy. The SO_3^- and NH_3^+ groups of L-homocysteic acid are not involved in the coordination.

The $\Delta\nu = [\nu_{as}(COO^-) - \nu_s(COO^-)]$ values extracted from the FTIR data ranged from 117 cm^{-1} for Ph_3SnL-homocysteate up to 140 cm^{-1} for Me_3SnL-homocysteate, suggesting bidentate bridging behaviour of the carboxylate group in a polymeric network. Furthermore, the pentacoordination around the Sn(IV) was preserved in solution, as verified through ^1H- and ^{13}C-NMR in DMSO-d_6. From IR and Mösbauer investigations in the solid state [312] it was hypothesized that orotic acid, 6-uracilcarboxylic acid (H_3Or) (Fig. 33), coordinates $R_2Sn(IV)^{2+}$ moieties to yield two different classes of derivatives with formulae $R_2SnHOr{\cdot}nH_2O$, and $R_2Sn(H_2Or)_2{\cdot}nH_2O$ (R = Me, $n = 0$; R = Bu, $n = 1$). In $R_2SnHOr{\cdot}nH_2O$, the orotic acid behaves as a dianionic tridentate ligand (Fig. 33). In $R_2Sn(H_2Or)_2{\cdot}nH_2O$, two different Sn(IV) sites have been evidenced by Mössbauer spectroscopy in the solid state, and by ^1H- and ^{13}C-NMR in DMSO-d_6 solution (Fig. 34a, b). Complexes with the formula R_3SnH_2Or (R = Me, Bu) were obtained with the $R_3Sn(IV)^+$ moieties, in which orotic acid behaves as a monoanionic bidentate bridging ligand and furnishes trigonal-bipyramidal *eq*-R_3 complexes (Fig. 34c).

Organotin(IV) compounds of the potentially ambidentate ligand *O*-cholesteryl-*O*-phenyl phosphorothionate were prepared according to [313] and formulated as $Me_3SnOSPR'R''$, $Ph_3SnOSPR'R''$, $O(CH_2CH_2S)_2Sn$-(*n*-Bu)$OSPR'R''$ or $S(CH_2CH_2S)2Sn$(*n*-Bu)$OSPR'R''$

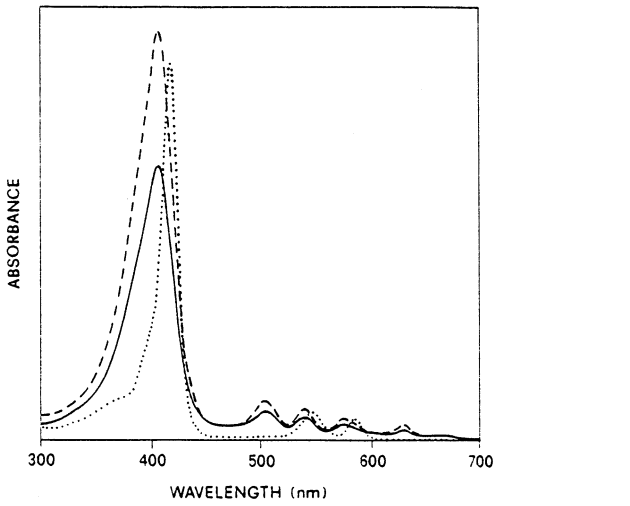

Fig. 29. Absorption spectra of: protoporphyrin IX (2.2×10^{-6} mol dm^{-3}, solid line; absorbance $\varepsilon_{max} = 0.319$); $(Me_2SnCl)_2$protoporphyrin IX (3.7×10^{-6} mol dm^{-3}, broken line; $\varepsilon_{max} = 0.470$); and $SnCl_2$ protoporphyrin IX (6.6×10^{-6} mol dm^{-3}, dotted line; $\varepsilon_{max} = 1.290$). Solvent: DMSO (adapted from Ref. [308]).

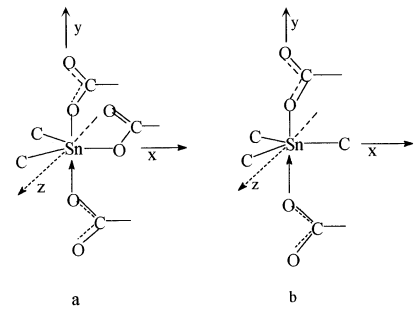

Fig. 30. Regular trigonal-bypiramidal structures proposed for $(R_2Sn)_2H_2TPPC$ and $(R_3Sn)_4H_2TPPC$ (R = Me, Bu, Ph) on the basis of FTIR and Mössbauer data (adapted from Ref. [309]).

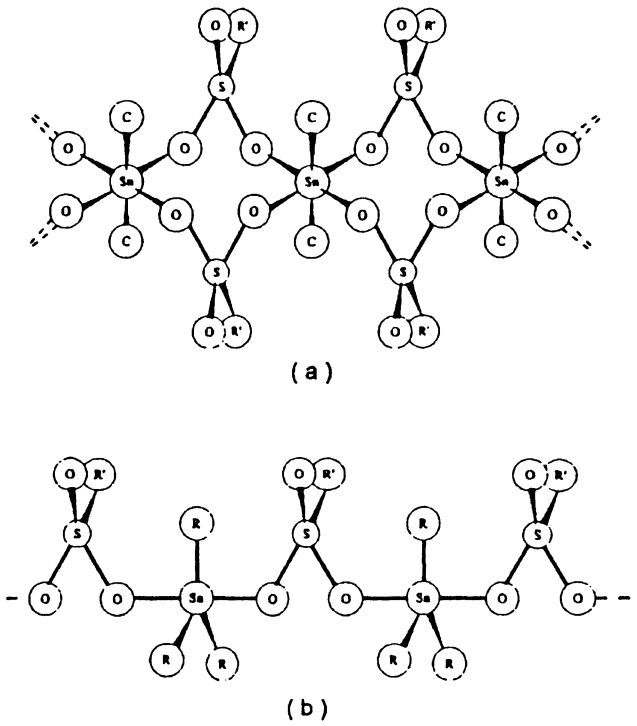

Fig. 31. Proposed polymeric structures for (a) $(R_2Sn)_2H_2TPPS$ and $(R_3Sn)_4H_2TPPS$, (b) R = Me, Bu, Ph (adapted from Ref. [310]).

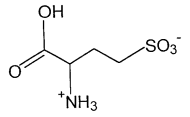

Fig. 32. Structure of L-homocysteic acid.

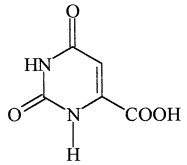

Fig. 33. The structure of orotic acid, H_3Or (adapted from [312]).

(where: R′ = O–Ph; R″ = O-cholesteryl). The spectroscopic data are consistent with bonding of the phosphorothionate ligand through both {S} and {O} donoratoms to the organotin(IV) centre [314].

A prominent feature of organotin(IV) coordination chemistry is the acceptor property associated with mono-, di- and triorganotin(IV) compounds containing strongly electron-withdrawing groups such as halide or pseudohalide attached to Sn [5]. In contrast, tetraorganotin compounds, R_4Sn(IV), show little tendency to expand their covalency beyond four. Thus, spectroscopic studies in the solid state of R_4Sn(IV) compounds containing intramolecular donor sites attached to the α- or β-carbon atom [315] and in donor solvents of compounds containing relatively electronegative moieties such as furyl [316,317], pyridyl [318–320], perhalogenoaryl [321–323] and thienyl [316,317] have generally not provided unequivocal evidence for higher than tetracoordination at the metal centre. However, for one class of tetraorganotins, namely the stannatrane derivatives represented by $Me_2Sn(CH_2CH_2CH_2)_2NMe$ and $MeSn(CH_2CH_2CH_2)_3N$, a multinuclear (^1H, ^{13}C, ^{119}Sn) NMR study has been reported [324] which strongly favours transannular N → Sn interactions in these compounds. The pentacoordinated structure of the triptych compound, $MeSn(CH_2CH_2CH_2)_3N$, has been confirmed [325]. The literature also contains two references to isolable pentacoordinated compounds in $Me_3SnCF_3{\cdot}P(NMe_2)_3$ [326] and lithium 1,1-bis(η^1-cyclopentadienyl) - 1 - halo - 2,3,4,5 - tetraphenylstannole [327], but the structures have not been rigorously clarified.

Kumar Das et al. [328] obtained a unique hexacoordinated tetraorganotin compound, bis{*C*,*N*-[3-82-pyridyl)-2-thienyl]}diphenyltin(IV). The crystal structure of this compound revealed the pseudo-octahedral environment of the Sn, with the coordinating pyridyl N atoms located *cis* to each other (Sn–N 256 pm, N–Sn–N 77.1°) along with the Ph groups (C–Sn–C 101.9°), and the *ipso*-thienyl {C} atoms arranged approximately *trans* to each other (C–Sn–C 144.4°). Later, a number of additional R_4Sn(IV) compounds containing the novel 2-(3-thienyl)pyridine ligand as one of the R groups were synthesized [328]. X-ray structure analysis of one of the complexes shows a pseudo-trigonal-bipyramidal arrangement, involving a weak interaction Sn–N bond of distance 284.1 pm (Fig. 35). The Mössbauer parameters are in the range ($\delta = 1.03–1.35$, $\Delta = 0.57–0.96$ mm s^{-1}) range. Further structural data (bond distances and ^{119}Sn-NMR data) are summarized in Tables 11 and 12.

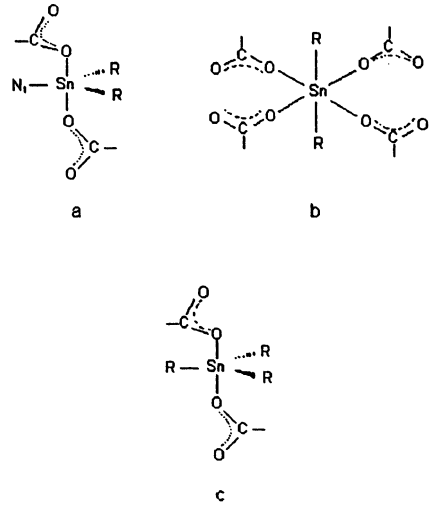

Fig. 34. Proposed coordination polyhedra around the Sn(IV) in (a) $R_2SnHOr{\cdot}nH_2O$, (b) $R_2Sn(H_2Or)_2{\cdot}nH_2O$, (R = Me, $n = 0$; R = Bu, $n = 1$) and (c) R_3SnH_2Or (R = Me, Bu) (adapted from Ref. [312]).

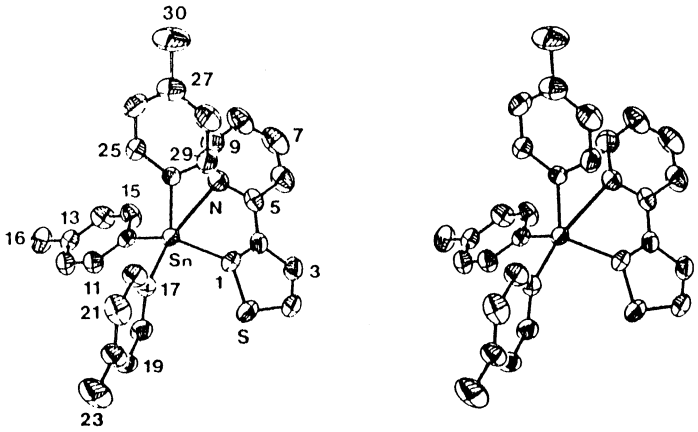

Fig. 35. ORTEP plot (35% thermal ellipsoids) (with atom labelling) of {*C*,*N*-[3-(2-pyridyl)-2-thienyl]}tri(*p*-tolyl)tin(IV) [328].

5. Applications

Organotin(IV) compounds have a range of *pharmacological* applications. The use of organotin(IV) halides as anti-inflammatory agents against different types of oedema in mice is of fundamental interest [337,338]. Compounds such as $Bu_2Sn(IV)Cl_2$ or $Ph_3Sn(IV)Cl$ can inhibit oedema as effectively as hydrocortisones. Organotin(IV) complexes with Schiff bases are of potential use as amoebicidal agents, displaying activity against axenically grown *Entamoeba histolytica* and *tropozoites* [339].

Another pharmaceutical application of organotin(IV) complexes is in the chemotherapy of leishmaniasis and helminthes, a parasitic infection of the skin, where $Oct_2Sn(IV)^{2+}$ maleate has shown promisingly high activity [340]. The $Bu_2Sn(IV)^{2+}$ dilaurate, distearate, diolate, phenylethyl acetate and dipalmitate act as antihelminthic agents in cats suffering from dipulidiosis.

Hyperbilirubinaemia is an abnormality observed mainly in neonates in whom the liver is insufficiently developed to be able to detoxify the bile pigment bilirubin. This situation is known as neonatal jaundice and can sometimes become a serious disease causing neurotoxic symptoms. Bilirubin is produced by the degradation of haem [the Fe(II) complex of protoporphyrin IX] by haem oxygenase to give biliverdin, which is reduced by biliverdin reductase to bilirubin. The Sn-haem complex [dichloro(protoporphyrin IX)tin(IV)] is a potential inhibitor of haemoxidase (see, for examples: [341–346]).

Table 11
Comparison of Sn–N bond lengths in selected organotin(IV) compounds containing N donor ligands

No.	Compound	Sn–N (pm)	Ref.
1	$Me_3SnCl{\cdot}py$	226	[329]
2	$(p\text{-}ClC_6H_4)_2SnCl_2{\cdot}4,4'\text{-}Me_2bipy$	–	[330]
	cis isomer	229.4, 232.2	
	trans isomer	240.6	
3	$(p\text{-tolyl})_2SnCl_2bipy$	230.6, 237.4	[331]
4	$Ph_2SnCl_2{\cdot}bipy$	234.4, 237.5	[332]
5	$ClSn(CH_2CH_2CH_2)_3N$	237.2	[324]
6	$Cl_2Sn(CH_2CH_2CH_2)_2NMe$	244.0	
7	$n\text{-}Pr(Et)Sn(quin)_2$	254.2, 259.7	[333]
8	$Ph_2SnCl_2{\cdot}SC_7H_5N$	254.8	[334]
9	$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]_2SnPh_2$	256.0	[328]
10	$MeSn(CH_2CH_2CH_2)_3N$	262.0	[326]
11	$Ph_3SnSC_5H_4N$	262.0*	[335]
12	$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]Sn(p\text{-tolyl})_3$	284.1	[328]
13	$(Ph_2SnCl_2{\cdot}pyz)_n$	296.5, 278.2	[336]

Abbreviations: py, pyridine; bipy, bipyridyl; Hquin, 2-methylquinolin-8-ol; pyz, pyrazine. * Reported as intermolecular Sn–N distance.

Table 12
^{119}Sn-NMR chemical shifts for organotin(IV) compounds containing different donor atoms

Compound	Concentration (w/w) [a]	δ (ppm) [b]	Ref.
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]Sn(p\text{-tolyl})_3$	0.12/1.5	−176.3	[328]
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]SnPh_3$	0.08/1.03	−181.6	[328]
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]\text{-}Sn(p\text{-}ClC_6H_4)_3$	0.08/1.3	−180.0	[328]
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]\text{-}Sn(cyclo\text{-}C_5H_9)_3$	0.4/1.5	−57.8	[328]
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]\text{-}Sn(cyclo\text{-}C_6H_{11})_3$	0.11/1.3	−105.9	[328]
$[3\text{-}(2\text{-py})\text{-}2\text{-}C_4H_2S]SnPh_2$	0.1/1.5	−245.5	[328]
$(3\text{-}C_4H_3S)Sn(p\text{-tolyl})_3$	10^3	−157.8	[84]
$(3\text{-}C_4H_3S)_2Sn(p\text{-tolyl})_3$	0.1/1.5	−146.3	[328]
$(2\text{-}C_4H_3S)SnPh_3$	0.08/2.0	−135.5	[328]
$(2\text{-}C_4H_3S)_2Sn(p\text{-tolyl})_2$	0.07/1.5	−138.0	[328]
$(2\text{-}C_4H_3S)_2SnPh_2$	0.13/1.5	−140.8	[328]
$(2\text{-}C_4H_3S)_2SnMe_2$	0.4/1.5	−62.7	[328]
$(2\text{-}C_4H_3S)_4Sn$	7 [c]	−147.0	[315]
Ph_4Sn	Saturated	−128.1	[362,363]
$cyclo\text{-}C_5H_9Sn$	0.13/1.5	−18.3	[328]

[a] All measurements were performed in $CDCl_3$.
[b] Relative to Me_4Sn.
[c] Concentration in w/v%.

Hyperbilirubinaemia is also a symptom of other diseases such as congenital anaemia, thalassaemia and liver abnormalities. Sn-haem has been tested in animals [343] and humans [346–348] and has been found successful in suppressing formation of the toxic metabolite bilirubin and in curing neonatal jaundice. In extensive toxicological studies on neonates (human or animal) and adults, Sn-haem proved to be essentially innocuous. Pharmacological studies of this therapeutic agent are in progress.

In recent years, the most active bioinorganic chemistry research area as concerns organotin(IV) compounds is the investigation of their *antitumour activity*. It has been established that the $R_2Sn(IV)^{2+}$ compounds which exhibit maximum antitumour activity combined with low mammalian toxicity are adducts of the type $R_2SnX_2L_2$ (X = halogen, pseudohalogen, L = O- or N-donor ligand). Some results are presented in Table 13. A large number of compounds have now been screened against a variety of tumour cell lines, and several reviews have been published [10,185,302,349,350].

Attempts to improve the bioavailability of the organotin(IV) cations by the formation of water-soluble complexes [351] or by their inclusion into β-cyclodextrin [352] have also been reported. In spite of their widespread activity, these antitumour organotin(IV) complexes, have not yet been subjected to extensive clinical trials in humans.

Organotin(IV) complexes are also used in *agriculture*. They are efficient fungicides and bactericides. Six triorganotin(IV) compounds are currently marketed. Although these complexes have broad-spectrum activity, in practice their usage is restricted to a limited area. Unfortunately, the high phytotoxicity [353] of these compounds towards many plants has restricted their practical use. Organotin(IV) compounds are also powerful insecticides, but since the most effective compounds contains the mammalian-toxic $Me_3Sn(IV)^+$, this property has not been commercialized. The fungicidal properties of $Bu_3Sn(IV)^+$ compounds have been utilized throuh their application as wood preservatives since the early 1950s [354,355]. The details of the action are not well understood and are still under discussion. Some comments on this subject have been made in Section 4.2 of this review. A complete listing of reports on the evaluation of organotin(IV) chemicals in agriculture is to be found in the two-part review by Crowe [8,9].

Marine fouling is the attachment of marine species (animals, plants, etc.) to the surface of immersed structures, mainly ships, hulls, buoys, sonar equipment, or sea-water conduits, e.g. cooling pipes. The fouling of ships can lead to inefficient travel through the water because of drag, with dramatic increases in fuel consumption. The development of organotin(IV)-based antifouling systems dates back to the early 1960s. The compounds employed for this purpose are usually Ph_3SnX ($X = OH^-$, F^-, Cl^-, ^-OAc), Bu_3SnX ($X = F^-$, Cl^-), and $(Bu_3Sn)_2O$, although many other systems have been developed [356,357]. It is important, that the working life-time of such systems is typically 1–2 years before repainting becomes necessary. Organotin(IV)-based anti-fouling paints are ca. ten times more effective than the formerly used conventional Cu_2O-based paints.

Despite the widespread use of organotin(IV)-based anti-fouling paints, in recent years there has been increasing concern regarding the impact of these chemicals on the environment. Particular concern has been expressed as concerns the effect of aqueous $Bu_3Sn(IV)^+$ on oyster farming. This topic has been reviewed by Tsangaris et al. [7].

6. Concluding remarks

This survey of the literature data on the interactions of organotin(IV) cations with biologically active ligands demonstrates that this is still a very open field. Above all, it is necessary to emphasize that usage of such complexes to treat humans is not permitted at present. Consequently, all compounds examined and discussed here (although with promising anticancer activity) are in the exploratory research stage.

Table 13
Antitumour activities of organotin(IV) compounds against two types of leukaemia cell lines (adapted from [4])

Structure	No. of compounds studied	P338	P338 (active%)	L1210	L1210 (active%)
Altogether	1554	680	25	696	1.0
$R_4Sn(IV)$	339	166	2	144	0.4
$R_3Sn(IV)X$	358	132	9	203	0.0
$R_2Sn(IV)X_2$	327	129	48	136	1.0
$RSn(IV)X_3$	33	11	9	11	0.0
$Sn(IV)X_4$	45	15	7	10	0.0
$R_2Sn(IV)X_3$, $R_2Sn(IV)X_4$	160	143	50	35	0.0

Equilibrium data on the different systems are largely missing. Systematic studies must be undertaken to understand the species distribution in the systems studied or in the environment.

The use of recently developed sophisticated experimental methods (e.g. EXAFS, mass spectrometry) or developments in the already used and widespread methods (multinuclear ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy in solution or in the solid state), will greatly accelerate progress. The comparison of solid versus solution structures is also needed. The effects of drugs are exerted in biological (mainly in aqueous) systems, and consequently the development of carriers of organotin(IV) cations with relatively high water solubility is at the forefront of recent research.

The mode of biological action of organotin(IV) complexes, or even the parent organotin(IV) compounds, has not yet been completely clarified and may vary from one compound to another.

Finally, more and more experimental data must to be collected in order to understand the biological (including antitumour) activity of organotin(IV) complexes [365,366].

Acknowledgements

This work was supported financially by the Hungarian Research Foundation (OTKA and T 029554), by the Foundation for the Development of Research and Education at Universities (FKFP 0015/1999) in Hungary, by the Ministero della Ricerca Scientifica e Tecnologica (M.U.R.S.T., Rome) and by the Universitá di Palermo, in Italy. The authors would like to thank Dr. Margit Véber (University of Szeged, Hungary) for her careful reading of the manuscript.

References

[1] K.R. Siebenlist, F. Taketa, Toxicol. Appl. Pharmacol. 58 (1981) 67.
[2] A.A. Ali, R.K. Upreti, A.M. Kidway, Toxicol. Lett. 38 (1987) 13.
[3] A.A. Ali, R.K. Upreti, A.M. Kidway, Bull. Environ. Contam. Toxicol. 44 (1990) 29.
[4] A.K. Saxena, F. Huber, Coord. Chem. Rev. 95 (1989) 109.
[5] J.A. Zubieta, J.J. Zuckerman, Prog. Inorg. Chem. 24 (1978) 251.
[6] K.C. Molloy, Bioorganotin compounds, in: F.R. Hartley (Ed.), The Chemistry of Metal–Carbon Bond, vol. 5, John Wiley and Sons, London, 1989, p. 465.
[7] J.M. Tsangaris, D.R. Williams, Appl. Organomet. Chem. 6 (1992) 3.
[8] A.J. Crowe, Appl. Organomet. Chem. 1 (1987) 143.
[9] A.J. Crowe, Appl. Organomet. Chem. 1 (1987) 331.
[10] S.J. Blunden, P.A. Cusack, R. Hill, The Industrial Use of Tin Compounds, Royal Society of Chemistry, London, 1985.
[11] A.J. Crowe, R. Hill, P.J. Smith, Laboratory Evaluation of Tributyltin(IV) Compounds as Wood Preservatives, Publication 559, International Tin Research Institute, London, 1979.
[12] S. David, S. Hanessian, Tetrahedron 41 (1985) 643.
[13] A. Patel, R.C. Poller, Rev. Sil. Ger. Tin Lead Comps. 8 (1985) 263.
[14] T.B. Grindley, Adv. Carbohydr. Chem. Biochem. 53 (1998) 17.
[15] K. Burger, L. Nagy, Chapter VI, in: K. Burger (Ed.), Biocoordination Chemistry, Metal Complexes of Carbohydrates and Sugar-type Ligands, Ellis Horwood, London, 1990, p. 236.
[16] B. Gyurcsik, L. Nagy, Coord. Chem. Rev. 203 (2000) 81.
[17] J.-F. Verchére, S. Chapelle, F. Xin, D.C. Crans, Prog. Inorg. Chem. 47 (1998) 837.
[18] R. Barbieri, L. Pellerito, G. Ruisi, A. Silvestri, A. Barbieri-Paulsen, G. Barone, S. Posante, M. Rossi, ^{119}Sn Mössbauer spectroscopy studies on the interaction of organotin(IV) salts and complexes with biological systems and molecules. Chapter 12, in: A. Gianguzza, E. Pelizetti, S. Sammartano (Eds.), Chemical Processes in Marine Environments, Springer, Berlin, 2000, pp. 229–244.
[19] R.L. Mössbauer, Z. Physik. 151 (1958) 124.
[20] G.K. Wertheim, Mössbauer Effect, Principles and Applications, Academic Press, New York, 1964.
[21] L. Nagy, Theoretical Background of EXAFS and XANES Spectroscopies. Application in Inorganic and in Bioinorganic Chemistry. Novel Results in Chemistry. Az EXAFS módszer elméleti alapjai. Szervetlen és bioszervetlen kémiai alkalmazások. A kémia újabb eredményei, Akadémiai Kiadó, Budapest, 1999, pp. 63–211.
[22] L. Nagy, B. Gyurcsik, K. Burger, S. Yamashita, T. Yamaguchi, H. Wakita, M. Nomura, Inorg. Chim. Acta 230 (1995) 105.
[23] L. Nagy, T. Yamaguchi, M. Nomura, H. Ohtaki, Inorg. Chim. Acta 159 (1989) 201.
[24] T. Yamaguchi, L. Nagy, M. Nomura, H. Ohtaki, Photon Factory Activity Report 7 (1989) 82.
[25] L. Nagy, T. Yamaguchi, L. Korecz, K. Burger, Trace Elements Med. 7 (1990) 99.
[26] L. Nagy, S. Yamashita, T. Yamaguchi, H. Wakita, M. Nomura, Photon Factory Activity Report 8 (1990) 141.
[27] L. Nagy, T. Yamaguchi, T. Mitsunaga, H. Wakita, Photon Factory Activity Report 11 (1993) 225.
[28] L. Nagy, T. Yamaguchi, T. Mitsunaga, H. Wakita, Photon Factory Activity Report 11 (1993) 135.
[29] K. Burger, L. Nagy, B. Gyurcsik, J. Mol. Liquid 65/66 (1995) 213.
[30] L. Nagy, T. Yamaguchi, T. Páli, M. Nomura, H. Ohtaki, ACH Models Chem. 135 (1998) 129.
[31] L. Nagy, T. Yamaguchi, T. Mitsunaga, H. Wakita, M. Jezowska-Bojczuk, M. Nomura, H. Kozlowski, ACH Models Chem. 135 (1998) 941.
[32] L. Nagy, T. Yamaguchi, T. Mitsunaga, P. Sipos, M. Nomura, H. Wakita, J. Inorg. Biochem. 72 (1998) 49.
[33] L. Nagy, T. Yamaguchi, L. Pellerito, M. Nomura, (2001) in preparation.
[34] R.S. Tobias, H.N. Farrer, M.B. Hughes, B.A. Nevett, Inorg. Chem. 5 (1966) 2052.
[35] R.S. Tobias, Organomet. Chem. Rev. 1 (1966) 93.
[36] N. Buzás, T. Gajda, L. Nagy, E. Kuzmann, A. Vértes, K. Burger, Inorg. Chim. Acta 274 (1998) 167.
[37] T. Natsume, S.-i. Aizawa, K. Hatano, H. Funahashi, J. Chem Soc. Dalton Trans. (1994) 2749.
[38] G. Arena, R. Purrello, E. Rizzarelli, A. Gianguzza, L. Pellerito, J. Chem. Soc. Dalton Trans. (1989) 773.
[39] R.S. Tobias, M. Yasuda, Can. J. Chem. (1964) 42.
[40] C. De Stefano, C. Foti, A. Gianguzza, M. Martino, L. Pellerito, S. Sammartano, J. Chem. Eng. Data 41 (1996) 511.
[41] M.J. Hynes, J.M. Keely, J. McManus, J. Chem. Soc. Dalton Trans. (1991) 3427.

[42] M. Asso, G. Carpeni, Can. J. Chem. 46 (1968) 1795.
[43] V. Cannizzaro, C. Foti, A. Gianguzza, F. Marrone, Ann. Chim. 88 (1998) 45.
[44] M.J. Hynes, M. O'Dowd, J. Chem. Soc. Dalton Trans. (1987) 563.
[45] R. Barbieri, A. Silvestri, J. Inorg. Biochem. 188 (1991) 95.
[46] R. Barbieri, A. Silvestri, A.M. Giuliani, V.S. Piro, G. Madonia, J. Chem. Soc. Dalton Trans. (1992) 585.
[47] H.S. Cheng, C.M. Hsu, J. Chin. Chem. Soc. 31 (1984) 101.
[48] R. Barbieri, A. Silvestri, V. Piro, J. Chem. Soc. Dalton Trans. (1990) 3605.
[49] P. Surdy, P. Rubini, N. Buzás, B. Henry, L. Pellerito, T. Gajda, Inorg. Chem. 38 (1999) 346.
[50] K. Gajda-Schrantz, L. Nagy, T. Gajda, L. Pellerito, J. Chem. Dalton Trans. (2001) in press.
[51] T.P. Lockhart, W.F. Manders, Inorg. Chem. 25 (1986) 892.
[52] R. Barbieri, M.T. Musmeci, J. Inorg. Biochem. 32 (1988) 89.
[53] A.M. Domingos, G.M. Sheldrick, J. Chem. Soc. Dalton Trans. (1974) 475.
[54] M.J. Hynes, J.M. O'Dowd, Biochem. Soc. Trans. 13 (1985) 490.
[55] G. Arena, A. Gianguzza, L. Pellerito, S. Musumeci, R. Purrello, E. Rizzarelli, J. Chem. Soc. Dalton Trans. (1990) 2603.
[56] G. Arena, R. Cali, A. Contino, A. Musumeci, S. Musumeci, R. Purello, Inorg. Chim. Acta 237 (1990) 187.
[57] N. Buzás, T. Gajda, E. Kuzmann, L. Nagy, A. Vértes, K. Burger, Main Group Met. Chem. 18 (1995) 641.
[58] N. Buzás, B. Gyurcsik, L. Nagy, Y-x. Zhang, L. Korecz, K. Burger, Inorg. Chim. Acta 218 (1994) 65.
[59] B. Gyurcsik, N. Buzás, T. Gajda, L. Nagy, E. Kuzmann, A. Vértes, K. Burger, Z. Naturforsch. 50b (1995) 515.
[60] G. Roge, F. Huber, H. Preut, A. Silvestri, R. Barbieri, J. Chem. Soc. Dalton Trans. (1983) 595.
[61] Y.K. Ho, J.J. Zuckerman, Inorg. Chem. 12 (1973) 1552.
[62] W.T. Hall, J.J. Zuckerman, Inorg. Chem. 16 (1977) 1239.
[63] Y.K. Ho, K.C. Molloy, J.J. Zuckeman, F. Reidinger, J.A. Zubieta, J. Organomet. Chem. 187 (1985) 211.
[64] G. Roge, F. Huber, H. Preut, A. Silvestri, R. Barbieri, Atti Congr. Naz. Chim. Inorg. 15 (1982) 241.
[65] G. Roge, F. Huber, A. Silvestri, R. Barbieri, Z. Naturforsch. Teil B. 37 (1982) 1456.
[66] F. Huber, G. Roge, R. Barbieri, F. Di Bianca, J. Organomet. Chem. 233 (1982) 185.
[67] F. Huber, G. Roge, G. Carl, G. Atassi, F. Spreafico, S. Filippeschi, R. Barbieri, A. Silvestri, E. Rivarola, G. Ruisi, F. Di Bianca, G. Alonzo, J. Chem. Soc. Dalton Trans. (1985) 523.
[68] P.G. Harrison, N.W. Sharpe, Appl. Organomet. Chem. 3 (1989) 141.
[69] H. Preut, M. Vornefeld, F. Huber, Acta Crystallogr. C47 (1991) 264.
[70] G. Ruisi, A. Silvestri, M.T. Lo Giudice, R. Barbieri, G. Atassi, F. Huber, K. Gratz, L. Lamartina, J. Inorg. Biochem. 25 (1985) 229.
[71] G. Guli, G. Gennaro, L. Pellerito, G.C. Stocco, Appl. Organomet. Chem. 7 (1993) 407.
[72] M.T. Musmeci, G. Madonia, M.T. Lo Giudice, A. Silvestrí, G. Ruisi, R. Barbieri, Appl. Organomet. Chem. 6 (1992) 127.
[73] A. Jancsó, B. Henry, P. Rubini, Gy. Vankó, T. Gajda, J. Chem. Soc. Dalton Trans. (2000) 1941.
[74] M.A. Mesubi, U.B. Eke, T.T. Bamgboye, Appl. Organomet. Chem. 2 (1988) 121.
[75] G. Ruisi, M.T. Lo Giudice, Appl. Organomet. Chem. 5 (1991) 385.
[76] G. Ruisi, M.T. Lo Giudice, F. Hubert, M. Vornefeld, Appl. Organomet. Chem. 10 (1996) 779.
[77] F. Huber, M. Vornefeld, G. Ruisi, R. Barbieri, Appl. Organomet. Chem. 7 (1993) 243.
[78] N. Buzás, L. Nagy, H. Jankovics, R. Krämer, E. Kuzmann, A. Vértes, K. Burger, J. Radioanal. Nucl. Chem. 241 (1999) 313.
[79] J. Koch, F. Huber, G. Ruisi, R. Barbieri, Appl. Organomet. Chem. 8 (1994) 113.
[80] Y.K. Ho, K.C. Molloy, J.J. Zuckerman, F. Reidinger, J.A. Zubieta, J. Organomet. Chem. 187 (1980) 213.
[81] T. Ogawa, Y. Takahashi, M. Matsui, Carbohydr. Res. 102 (1982) 207.
[82] A. Patel, R.C. Poller, E.B. Rathbone, Appl. Organomet. Chem. 1 (1987) 325.
[83] S. Jarosz, B. Fraser-Reid, J. Org. Chem. 54 (1989) 4011.
[84] D.W. Allen, D.J. Derbyshire, I.W. Nowell, J.S. Brooks, J. Organomet. Chem. 260 (1984) 263.
[85] M. Pereyre, J.-P. Quintard, A. Rahm, Tin in Organic Synthesis, Butterworths, London, 1987.
[86] S. David, Chapter 4, in: S. Hanessian (Ed.), Preparative Carbohydrate Chemistry, Marcel Dekker, New York, 1996.
[87] R. Barbieri, L. Pellerito, G. Ruisi, M.T. Lo Giudice, Inorg. Chim. Acta 66 (1982) 39.
[88] P. Smith, L. Smith, Chem. Ber. (1975) 208.
[89] H.E. Guard, W.M. Coleman III, M.M. Ross, Carbohydr. Res. 235 (1992) 41.
[90] A. Szorcsik, B. Gyurcsik, L. Nagy, R. Kramer, Gy. Vankó, A. Vértes, J. Inorg. Biochem. (2001) submitted.
[91] D. Wagner, J.P.H. Verheyden, J.G. Moffat, J. Org. Chem. 39 (1974) 74.
[92] C.W. Holzapfel, J.M. Kockemoer, C.M.. Marais, G.J. Kruger, J.A. Pretorius, S. Afr. J. Chem. 35 (1982) 81.
[93] G. Ruisi, M.T. Lo Giudice, L. Pellerito, Inorg. Chim. Acta 93 (1984) 161.
[94] A.G. Davies, A.J. Price, H.M. Dawes, M.B. Hursthouse, J. Chem. Soc. Dalton Trans. (1986) 297.
[95] J.D. Donaldson, S.M. Grimes, L. Pellerito, M.A. Girasolo, P.J. Smith, A. Cambria, M. Fama, Polyhedron 6 (1987) 383.
[96] L. Nagy, L. Korecz, I. Kiricsi, L. Zsikla, K. Burger, Struct. Chem. 2 (1991) 231.
[97] S. Köpper, A. Brandenburg, Libeigs Ann. Chem. (1992) 933.
[98] K. Burger, L. Nagy, N. Buzás, A. Vértes, H. Mehner, J. Chem. Soc. Dalton Trans. (1993) 2499.
[99] (a) R.C. Mehrota, V.D. Gupta, J. Organomet. Chem. 4 (1965) 145;
(b) R.C. Mehrota, V.D. Gupta, J. Radioanal. Nucl. Chem. 227 (1998) 89.
[100] J.C. Pommier, J. Valade, Bull. Soc. Chim. France (1965) 1257.
[101] W.J. Considine, J. Organomet. Chem. 5 (1966) 263.
[102] J.C. Pommier, J. Valade, J. Organomet. Chem. 12 (1968) 433.
[103] T. Ogawa, M. Matsui, Carbohydr. Res. 56 (1977) C1.
[104] S.J. Blunde, P.J. Smith, P.J. Beynon, D.G. Gilles, Carbohydr. Res. 88 (1981) 9.
[105] K.M. Taba, R. Köster, W.V. Dahlhoft, Synthesis (1984) 399.
[106] S. David, A. Thieffry, A. Vayrieres, J. Chem. Soc. Perkin Trans. 1 (1981) 1796.
[107] Y. Tsuda, M.E. Haque, K. Yoshimoto, Chem. Pharm. Bull. 31 (1983) 1612.
[108] A.J. Crowe, P.J. Smith, J. Organomet. Chem. 110 (1976) C57.
[109] T.B. Grindley, R.D. Curtis, R. Thangarasa, R.E. Wasylishen, Can. J. Chem. 68 (1990) 2102.
[110] T.B. Grindley, R. Thangarasa, Can. J. Chem. 68 (1990) 1007.
[111] T.B. Grindley, R. Thangarasa, J. Am. Chem. Soc. 112 (1990) 1364.
[112] T.B. Grindley, R. Thangarasa, P.K. Bakshi, T.S. Cameron, Can. J. Chem. 70 (1992) 197.
[113] T.B. Grindley, R.E. Wasylishen, R. Thangarasa, W.P. Power, R. Curtis, Can. J. Chem. 70 (1992) 205.
[114] H. Dalil, M. Biesemans, R. Willem, M. Gielen, Main Group Met. Chem. 21 (1998) 741.

[115] A. Szorcsik, J. Sletten, L. Nagy, A. Lakatos, E. Kuzmann, A. Vértes, ACH Models Chem. 137 (2000) 22.
[116] S. David, C. Pascard, M. Cesario, Nouv. J. Chim. 3 (1979) 63.
[117] T.S. Cameron, P.K. Bakshi, R. Thangarasa, T.B. Gridley, Can. J. Chem. 70 (1992) 1623.
[118] P.A. Bates, M.B. Hursthouse, A.G. Davies, S.D. Slater, J. Organomet. Chem. 363 (1989) 45.
[119] R. Thangarasa, T.B. Grindley, unpublished results, 2001.
[120] S. David, A. Thieffry, A. Forchioni, Tetrahedron Lett. 22 (1981) 2647.
[121] X. Kong, T.B. Grindley, Can. J. Chem. Soc. 72 (1994) 2405.
[122] S.-K. Chung, Y. Ryu, Y.-T. Chang, D. Whang, K. Kim, Carbohydr. Res. 253 (1994) 13.
[123] S.-K. Chung, Y.H. Ryu, Carbohydr. Res. 258 (1994) 145.
[124] S.J. Lee, S.J. Cho, K.S. Oh, C. Cui, Y. Ryu, Y.-T. Chang, K.S. Kim, S.-K. Chung, J. Phys. Chem. 100 (1996) 10111.
[125] P.J. Smith, R.F.M. White, L. Smith, J. Organomet. Chem. 40 (1972) 341.
[126] R.H. Herber, A. Shanzer, J. Libman, Organometallics 3 (1984) 586.
[127] N. Buzás, M.A. Pujar, L. Nagy, A. Vértes, E. Kuzmann, H. Mehner, J. Radioanal. Nucl. Chem. 189 (1995) 237.
[128] F. Caruso, M. Bol-Schoenmakers, A.H. Penninks, J. Med. Chem. 36 (1993) 1168.
[129] O.J. Taylor, J.L. Wardell, Recl. Trav. Chim. Pays-Bas 107 (1988) 267.
[130] P.J. Cox, M.S.V. Doidge-Harrison, R.A. Howie, I.W. Nowell, O.J. Taylor, J.L. Wardell, J. Chem. Soc. Perkin Trans. 1 (1989) 2017.
[131] S.M.S.V. Doidge-Harrison, I.W. Nowell, P.J. Cox, R.A. Howie, O.J. Taylor, J.L. Wardell, J. Organomet. Chem. 401 (1991) 273.
[132] L.A. Burnett, S.M.S.V. Doidge-Harrison, S.J. Garden, R.A. Howie, O.J. Taylor, J.L. Wardell, J. Chem. Soc. Perkin Trans. (1993) 1621.
[133] R. Hill, S.J. Blunden, Appl. Organomet. Chem. 2 (1988) 251.
[134] D. Barug, Chemosphere 10 (1981) 1145.
[135] R.J. Orsler, G.E. Holland, Int. Biodeterior. Bull. 18 (1982) 95.
[136] B.A. Richardson, Rec. Annu. Conv. Br. Wood Preserv. Assoc. (1970) 37.
[137] R. Hill, International Research Group on Wood Preservation, Doc. No. IRG/WP/3312, 1984.
[138] P.J. Smith, A.J. Crowe, D.W. Allen, J.S. Brooks, R. Formstone, Chem. Ind. (London) (1977) 874.
[139] B.K. Keppler, Metal Complexes in Cancer Chemotheraphy, Weinheim, VCH, 1993.
[140] A.T.M. Tullius, S.J. Lippart, J. Am. Chem. Soc. 103 (1981) 4620.
[141] S.J. Lippart, Science 218 (1982) 1075.
[142] M. Bloemink, J. Reedijk, in: A. Sigel, H. Sigel (Eds.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1996.
[143] A.J. Crowe, Drugs Future 12 (1987) 255.
[144] L. Pellerito, G. Ruisi, N. Bertazzi, M.T. Lo Giudice, R. Barbieri, Inorg. Chim. Acta 58 (1976) L9.
[145] C.J. Cardin, A. Roy, Inorg. Chim. Acta 107 (1985) 57.
[146] G. Valle, G. Plazzogna, R. Ettore, J. Chem. Soc. Dalton Trans. (1981) 1271.
[147] R. Barbieri, E. Rivarola, F. Di Bianca, F. Huber, Inorg. Chim. Acta 57 (1982) 37.
[148] R. Barbieri, F. Di Bianca, E. Rivarola, F. Huber, Inorg. Chim. Acta 108 (1985) 141.
[149] K. Gajda-Schrantz, L. Nagy, E. Kuzmann, A.A. Christy, H. Barátné-Jankovics, E. Sletten, A. Vértes, J. Radioanal. Nucl. Chem. 247 (2001) 42.
[150] A. Atkinson, M.D. Rodriguez, T.E. Shewmaker, J.A. Walmsley, Inorg. Chim. Acta 285 (1999) 60.
[151] R. Barbieri, A. Silvestri, M.T. Lo Giudice, G. Ruisi, M.T. Musmeci, J. Chem. Soc. Dalton Trans. (1989) 519.
[152] T.K. Sham, G.M. Bancroft, Inorg.Chem. 14 (1975) 2281.
[153] R.V. Parish, in: G.J. Long (Ed.), Mössbauer Spectroscopy Applied to Inorganic Chemistry, vol. I, Plenum, New York, 1984, pp. 527–575.
[154] G.M. Bancroft, R.H. Platt, Adv. Inorg. Chem. Radiochem. 15 (1972) 59.
[155] M.G. Clark, A.G. Maddock, R.H. Platt, J. Chem. Soc. Dalton Trans. (1972) 281.
[156] G.M. Bancroft, V.G. Kumar Das, T.K. Sham, M.G. Clark, J. Chem. Soc. Dalton Trans. (1976) 643.
[157] V. Piro, F. Di Simone, G. Madonia, A. Silvestri, A.M. Giuliani, G. Ruisi, R. Barbieri, Appl. Organomet. Chem. 6 (1992) 537.
[158] R.F. Rekker, The Hydrophobic Fragmental Constant, Elsevier, Amsterdam, 1977.
[159] C. Hansch, A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979.
[160] S.P. Gupta, Chem. Rev. 87 (1987) 1183.
[161] R. Barbieri, F. Huber, A. Silvestri, G. Ruisi, M. Rossi, G. Barone, A. Paulsen, Appl. Organomet. Chem. 13 (1999) 595.
[162] G. Barone, M. Cotta Ramusino, R. Barbieri, G. La Manna, J. Mol. Struct. (Theochem.) 469 (1999) 143.
[163] G. Barone, R. Barbieri, G. La Manna, M.H.J. Koch, Appl.Organomet. Chem. 14 (2000) 189.
[164] A. Jancsó, L. Nagy, E. Moldrheim, E. Sletten, J. Chem. Soc. Dalton Trans. (1999) 1587.
[165] Q. Li, P. Yang, H. Wang, T. Bakas, A. Sanchez-Diaz, C. Charalambopoulos, J. Tsangaris, N. Hadjiliadis, J. Inorg. Biochem. 64 (1996) 181.
[166] Z. Yang, T. Bakas, A. Sanchez-Diaz, C. Charalampopoulos, J. Tsangaris, N. Hadjiliadis, J. Inorg. Biochem. 72 (1998) 133.
[167] H. Barátné-Jankovics, L. Nagy, L. Pellerito, R. Barbieri, Appl. Organomet. Chem. (2001) in press.
[168] L. Nagy, H. Mehner, A.A. Christy, E. Sletten, F.T. Edelmann, Q.M. Anderson, J. Radioanal. Nucl. Chem. 227 (1998) 89.
[169] A.G. Davies, D.C. Kleinschmidt, P.R. Palan, S.C. Vasistha, J. Chem. Soc. (C) (1971) 3972.
[170] C.H. Stapferand, R.H. Herber, J. Organomet. Chem. 56 (1973) 175.
[171] C.-G. Hager, F. Huber, A. Silvestri, A. Barbieri, R. Barbieri, Gazz. Chim. Ital. 123 (1993) 583.
[172] G.K. Sandhu, N. Sharma, Appl. Organomet. Chem. 7 (1993) 33.
[173] K. Gajda-Schrantz, L. Nagy, E. Kuzmann, A. Vértes, J. Holecek, A. Lycka, J. Chem. Soc. Dalton Trans. (1997) 2201.
[174] K. Gajda-Schrantz, L. Nagy, E. Kuzmann, A. Vértes, J. Radioanal. Nucl. Chem. 232 (1998) 151.
[175] J. Merkord, G. Henninghause, Pharmazie 39 (1984) 572.
[176] G. Henninghause, J. Merkord, G. Krönig, Plzen. Lek. Sborn. Suppl. 56 (1988) 89.
[177] S. Kreyberg, A. Torvik, A. Bjorneboe, E. Wiik-Larsen, D. Jacobsen, Clin. Neuropath. 11 (1992) 256.
[178] J. Holecek, A. Lycka, D. Micak, L. Nagy, Gy. Vankó, S.W. Ng, J. Brus, Collect. Czech Chem. Commun. 64 (1999) 1028.
[179] J.S. Casas, E.E. Castellano, F. Condori, M.D. Couce, F. Sánchez, J. Sordo, J.M. Varela, J. Zuckerman-Schpector, J. Chem. Soc. Dalton Trans. (1997) 4421.
[180] J.S. Casas, A. Castineiras, F. Condori, M.D. Couce, U. Russo, A. Sánchez, J. Sordo, J.M. Valera, Polyhedron 19 (2000) 813.
[181] J.S. Casas, M.V. Castano, M.S. Garcia-Tasende, T. Perez-Alverez, A. Snachez, J. Sordo, J. Inorg. Biochem. 61 (1996) 97.
[182] J. Casas, A. Castineiras, M.D. Couce, G. Martinez, J. Sordo, J.M. Varela, J. Organomet. Chem. 517 (1996) 165.
[183] V.L. Narayanan, M. Nash, K.D. Paull, in: M. Gielen (Ed.), Tin Based Antitumor Drugs. NATO ASI Series, vol. H37, Spinger Verlag, Berlin, 1990, p. 201.

[184] A.J. Crowe, in: M. Gielen (Ed.), Metal Based Antitumour Drugs, vol. 1, Freund, London, 1988, pp. 103–149.
[185] A.K. Saxena, Appl. Organomet. Chem. 1 (1987) 39.
[186] M. Gielen, P. Lelieveld, D. de Vos, R. Willem, in: M. Gielen (Ed.), Metal Based Antitumour Drugs, vol. 2, Freund, Tel Aviv, 1992, pp. 29–54.
[187] M. Gielen, R. Willem, M. Biesemans, M. Boualam, A. El. Khloufi, D. de Vos, Appl. Organomet. Chem. 6 (1992) 287.
[188] M. Boualam, M. Gielen, A. El Khloufi, D. de Vos, R. Willem, (Pharmachemie B.V.) European Patent 91 202 746.3 (October), 1991.
[189] C.J. Traanter, S.J. Berners-Price, J. Cutts, P.G. Parsons, G. Rintoul, D.J. Young, Main Group Chem. 1 (1995) 165.
[190] M. Gielen, E.R.T. Tiekink, A. Bouhdid, D. de Vos, M. Biesemans, I. Verbruggen, R. Willem, Appl. Organomet. Chem. 9 (1995) 639.
[191] M. Gielen, A. Bouhdid, F. Kayser, M. Biesemans, D. de Vos, B. Mahieu, R. Willem, Appl. Organomet. Chem. 9 (1995) 251.
[192] M. Gielen, M. Boualam, B. Mahieu, E.R.T. Tiekink, Appl. Organomet. Chem. 8 (1994) 19.
[193] M. Gielen, R. Willem, Anticancer Res. 12 (1992) 257.
[194] A.H. Penninks, M. Bol-Schoenmakers, M. Gillen, W. Sienen, Main Group Met. Chem. 12 (1989) 1.
[195] M. Takahashi, F. Furukawa, T. Kokubo, Y. Kurata, Y. Hayashi, Cancer Lett. 20 (1983) 271.
[196] S.C. Ng, P.G. Parsons, K.Y. Sim, C.J. Tranter, R.H. White, D.J. Young, Appl. Organomet. Chem. 11 (1997) 577.
[197] M. Gielen, A. Bouhdid, E.R.T. Tiekink, Main Group Met. Chem. 18 (1995) 199.
[198] R. Willem, A. Bouhdid, M. Biesemans, J.C. Martins, D. de Vos, E.R.T. Tiekink, M. Gielen, J. Organomet. Chem. 514 (1996) 203.
[199] R. Willem, A. Bouhdid, B. Mahieu, L. Ghys, M. Biesemans, E.R.T. Tiekink, M. Gielen, J. Organomet. Chem. 531 (1997) 151.
[200] Y. Arakawa, O. Wada, Biological properties of alkyltin(IV) compounds, in: H. Sigel, A. Siegel (Eds.), Metal Ions in Biological Systems, Marcel Dekker, New York, Basel, 1993, p. 10, 29.
[201] M. Gielen, N. Sprecher, Organomet. Chem. Rev. 1 (1966) 455.
[202] H. Kriegsmann, S. Pauly, Z. Anorg. Allg. Chem. 330 (1964) 275.
[203] H.N. Farrer, M.M. Mc Grady, R.S. Tobias, J. Am. Chem. Soc. 20 (1965) 5019.
[204] E.V. Van den Bergue, G.P. Van der Kelen, Bull. Soc. Chim. Belges 74 (1965) 479.
[205] A. Cassol, L. Magon, R. Barbieri, J. Chromatogr. 19 (1965) 57.
[206] A. Cassol, Gazz. Chim. Ital. 96 (1966) 1764.
[207] J.G.A. Luijten, Recueil 85 (1966) 873.
[208] M. Devaud, J. Chim. Phys. 66 (1969) 302.
[209] M. Devaud, J. Chim. Phys. 67 (1970) 302.
[210] M. Devaud, J. Chim. Phys. 69 (1972) 460.
[211] M.C. Langlois, M. Devaud, Bull. Soc. Chim. France 5/6 (1974) 789.
[212] S.J. Blunden, P.J. Smith, D.G. Gillies, Inorg. Chim. Acta 60 (1982) 105.
[213] S.J. Blunden, R. Hill, Inorg. Chim. Acta 177 (1990) 219.
[214] C. De Stefano, C. Foti, A. Gianguzza, F. Marrone, S. Sammartano, Appl. Organomet. Chem. 13 (1999) 805.
[215] V. Cucinotta, A. Gianguzza, G. Maccarrone, L. Pellerito, R. Purrello, E. Rizzarelli, J. Chem. Soc. Dalton Trans. (1992) 2299.
[216] C. De Stefano, C. Foti, A. Gianguzza, Ann. Chim. 89 (1999) 147.
[217] C. Pettinari, Main Group Metal Chem. 22 (1999) 661.
[218] C. Pettinari, M. Pellei, F. Marchetti, C. Santini, M. Miliani, Polyhedron 17 (1998) 561.
[219] C. Pettinari, M. Pellei, C. Santini, I. Natali, F. Accorroni, A. Lorenzotti, Polyhedron 17 (1998) 4487.
[220] C. Pettinari, F. Marcheti, A. Cinglina, S. Bartolini, Polyhedron 15 (1996) 1263.
[221] C. Pettinari, F. Marchetti, M. Pellei, A. Cingolani, L. Barba, A. Cassetta, J. Organomet. Chem. 515 (1996) 119.
[222] A.S. Gonzales, J.S. Casas, J. Sordo, U. Russo, M.I. Lareo, B.J. Reguiero, J. Inorg. Biochem. 39 (1990) 227.
[223] P.A. Boo, J.S. Casas, M.D. Couce, E. Freijanes, A. Furlani, V. Scarcia, J. Sordo, U. Russo, M. Varela, Appl. Organomet. Chem. 11 (1997) 963.
[224] C. Lopez, A.S. Gonzales, M.E. Garcia, J.S. Casas, J. Sordo, R. Gracianai, U. Casellato, J. Organomet. Chem. 434 (1992) 261.
[225] M.P. Leal, A.S. Gonzales, M.E. Garcia, J.S. Casas, J. Sordo, Appl. Organomet. Chem. 7 (1993) 421.
[226] F. Huber, H. Preut, E. Hoffman, M. Gielen, Acta Crystallogr. C45 (1989) 51.
[227] M. Gielen, M. Acheddad, B. Mahieu, R. Willem, Main Group Met. Chem. 14 (1991) 73.
[228] M. Gielen, M. Acheddad, E.R.T. Tiekeink, Main Group Met. Chem. 16 (1993) 367.
[229] S.W. Ng, V.G. Kumar Das, J. Holecek, A. Lycka, M. Gielen, M.B.G. Drew, Appl. Organomet. Chem. 11 (1997) 39.
[230] M. Boyce, B. Clarke, D. Cunningham, J.F. Gallanger, T. Higgins, P. McArdle, N. Cholchuin, M. Ogara, J. Organomet. Chem. 498 (1995) 241.
[231] B. Clarke, N. Clarke, D. Cunningham, T. Higgins, P. McArdle, M. Cholchuin, M. Ogara, J. Organomet. Chem. 559 (1998) 55.
[232] D. Cunningham, J.F. Gallanger, T. Higgins, P. McArdle, J. McGinley, M. Ogara, J. Chem. Soc. Dalton Trans. (1993) 2473.
[233] M. Nath, R. Yadav, M. Gielen, H. Dalil, D. de Vos, G. Eng, Appl. Organomet. Chem. 11 (1997) 727.
[234] D.K. Dey, M.K. Saha, M.K. Das, N. Bhartiya, R.K. Bansal, G. Rosair, S. Mitra, Polyhedron 18 (1999) 2687.
[235] H.L. Singh, S. Varshney, A.K. Varshney, Appl. Organomet. Chem. 13 (1999) 637.
[236] F. Maggio, R. Bosco, N. Cefalú, R. Barbieri, Inorg. Nucl. Chem. Lett. 4 (1968) 389.
[237] A. van-der Bergen, R.J. Cozens, K.S. Murray, J. Chem. Soc. (A) (1970) 3060.
[238] B.N. Ghose, Synth. React. Inorg. Met. Org. Chem. 12 (1982) 835.
[239] M. Nath, C.L. Sharma, N. Sharma, Synth. React. Inorg. Met. Org. Chem. 21 (1991) 807.
[240] H.P.S. Chauban, A. Bhargava, R.J. Rao, Ind. J. Chem. 32A (1993) 157.
[241] S. Gopinathan, M.P. Degaonkar, A.M. Hundekar, C. Gopinathan, Appl. Organomet. Chem. 7 (1993) 63.
[242] J. Wang, Y. Zhang, Y. Xu, Z. Wang, H. Youji, Heteroatom. Chem. 13 (1993) 289.
[243] S.G. Teoh, G.Y. Yeap, C.C. Loh, L.W. Foong, S.B. Teoh, H.K. Fun, Polyhedron 16 (1997) 2213.
[244] M.D. Couce, V. Cherchi, G. Faraglia, U. Russo, L. Sindellari, G. Valle, N. Zancan, Appl. Organomet. Chem. 10 (1996) 35.
[245] S. Xueqing, Y. Zhiqiang, X. Qinglan, L. Jinshan, J. Organomet. Chem. 566 (1998) 103.
[246] R. Willem, H. Dalil, P. Broekaert, M. Biesemans, L. Ghys, K. Nooter, D. de Vos, F. Ribot, M. Gielen, Main Group Met. Chem. 20 (1997) 535.
[247] M. Gielen, H. Ma, A. Bouhdid, H. Dalil, M. Biesemans, R. Willem, Metal-Based Drugs 4 (1997) 193.
[248] M. Gielen, Coord. Chem. Rev. 151 (1996) 41.
[249] D. de Vos, R. Willem, M. Gielen, K.E. van Wingerden, K. Nooter, Metal-Based Drugs 4 (1998) 179.
[250] M. Gielen, H. Dalil, M. Biesemans, B. Mahieu, D. de Vos, R. Willem, Appl. Organomet. Chem. 13 (1999) 515.
[251] M. Gielen, H. Dalil, B. Mahieu, M. Biesemans, R. Willem, Appl. Organomet. Chem. 12 (1998) 855.

[252] W.N. Aldridge, B.W. Street, J.G. Noltes, Chem. Biol. Interact. 34 (1981) 223.
[253] L. May, G. Eng, S.P. Coddington, J.G. Noltes, Hyperfine Interact. 42 (1988) 909.
[254] B.D. James, S. Gioskos, S. Chandra, R.J. Magee, J.D. Cashion, J. Organomet. Chem. 436 (1992) 155.
[255] B.D. James, R.J. Magee, W.C. Patalinghug, B.W. Skelton, A.H. White, J. Organomet. Chem. 467 (1994) 51.
[256] G. Eng, D. Whalen, Y.Z. Zhang, A. Kirksey, M. Otieno, L.E. Khoo, B.D. James, Appl. Organomet. Chem. 10 (1996) 501.
[257] G. Eng, D. Whalen, P. Musingarimi, J. Tierney, M. DeRosa, Appl. Organomet. Chem. 12 (1998) 25.
[258] S.K. Kamruddin, T.K. Chattophadhyaya, A. Roy, E.R.T. Tiekink, Appl. Organomet. Chem. 10 (1996) 513.
[259] J. Tierney, Heterocyclic Chem. 26 (1989) 997.
[260] G. Eng, D. Whalen, Y.Z. Zhang, J. Tierney, X. Jiang, L. May, Appl. Organomet. Chem. 10 (1996) 495.
[261] N.K. Goh, C.K. Chu, L.E. Khoo, D. Whalen, G. Eng, F.E. Smith, R.C. Hynes, Appl. Organomet. Chem. 12 (1998) 457.
[262] N. Ogwuru, L.E. Khoo, G. Eng, Appl. Organomet Chem. 12 (1998) 409.
[263] L.E. Khoo, N.K. Goh, L.L. Koh, Y. Xu, D.J. Whale, G. Eng, Appl. Organomet. Chem. 10 (1996) 459.
[264] S.B. Baul, T.S.B. Baul, E. Rivarola, D. Dakternieks, E.R.T. Tiekink, C. Syng-ai, A. Chatterjee, Appl. Organomet. Chem. 12 (1998) 503.
[265] B.D. James, L.M. Kivlighon, B.W. Skelton, A.H. White, Appl. Organomet. Chem. 12 (1998) 13.
[266] S. Chandra, S. Gioskos, B.D. James, B.J. Macauley, R.J. Magee, J. Chem. Tech. Biotechnol. 56 (1993) 41.
[267] I. Wharf, H. Lamparski, R. Reeleder, Appl. Organomet. Chem. 11 (1997) 969.
[268] R. Schmiedgen, F. Huber, H. Preut, G. Ruisi, R. Barbieri, Appl. Organomet. Chem. 8 (1994) 397 and references cited therein.
[269] R. Schmiedgen, F. Huber, A. Silvestri, G. Ruisi, M. Rossi, R. Barbieri, Appl. Organomet. Chem. 12 (1998) 861.
[270] F. Huber, R. Schmiedgen, M. Schurmann, R. Barbieri, G. Ruisi, A. Silvestri, Appl. Organomet. Chem. 11 (1997) 869.
[271] A. Barbieri, A.M. Giuliani, A. Silvestri, R. Barbieri, Z. Anorg. Allg. Chem. 621 (1995) 89 and references cited therein.
[272] A. Kalsoom, M. Mazhar, S. Ali, M.F. Mahon, K.C. Molloy, I. Chaudry, Appl. Organomet. Chem. 11 (1997) 47.
[273] T.A.K. Al-Allaf, R.I.H. Al-Bayati, L.J. Rashan, R.F. Khuzaie, Appl. Organomet. Chem. 10 (1996) 47.
[274] T.P. Lockhard, J.C. Calabrese, F. Davidson, Organometallic 6 (1987) 2479.
[275] A. Meriem, R. Willem, J. Menuier-Piret, B. Mahiue, M. Gielen, Main Group Met. Chem. 13 (1990) 167.
[276] T.P. Lockhard, J.C. Calabrese, F. Davidson, Organometallic 6 (1987) 2471.
[277] M. Gielen, A. El Khloufi, M. Biesemans, R. Willem, Appl. Organomet. Chem. 7 (1993) 119.
[278] L.E. Khoo, N.K. Goh, G. Eng, J. Whalen, A. Hazell, Appl. Organomet. Chem. 9 (1995) 699.
[279] D. Kovala-Demertzi, P. Tauridou, A. Moukarika, J.M. Tsangaris, C.P. Raptopoulou, A. Terzis, J. Chem. Soc. Dalton Trans. (1995) 123.
[280] M. Gielen, M. Biesemans, A. El Khloufi, J. Meunier-Piret, F. Kayser, R. Willem, J. Fluorine Chem. 64 (1992) 279.
[281] M. Gielen, A. El Khloufi, D. de Vos, J. Kolker, J.H.M. Schellens, R. Willem, Bull. Soc. Chim. Belg. 102 (1993) 761.
[282] M. Gielen, M. Boualam, A. Meriem, B. Mahieu, M. Biesemans, R. Willem, Heteroatom. Chem. 3 (1992) 449.
[283] M. Boualam, M. Biesemans, J. Menuier-Piret, R. Willem, M. Gielen, Appl. Organomet. Chem. 6 (1992) 197.
[284] R. Willem, M. Biesemans, M. Boualam, A. Delmotte, A. El Khloufi, M. Gielen, Appl. Organomet. Chem. 7 (1993) 311.
[285] R. van Lambalgen, P. Lelieveld, Invest. New Drugs 5 (1987) 161.
[286] T.N. Srivastava, A.K.S. Chauhan, P.C. Kamboj, J. Indian Chem. Soc. 60 (1983) 625.
[287] F.L. Lee, E.J. Gabe, L.E. Khoo, G. Eng, F.E. Smith, Polyhedron 9 (1990) 653.
[288] L.E. Khoo, F.E. Smith, Polyhedron 4 (1985) 447.
[289] L.E. Khoo, J.P. Charland, E.J. Gabe, F.E. Smith, Inorg. Chim. Acta 128 (1987) 139.
[290] L. Prasad, E.J. Gabe, F.E. Smith, Acta Crystallogr. 38B (1982) 1325.
[291] E.J. Gabe, F.L. Lee, L.E. Khoo, F.E. Smith, Inorg. Chim. Acta 112 (1986) 41.
[292] E.J. Gabe, F.L. Lee, L.E. Khoo, F.E. Smith, Inorg. Chim. Acta 105 (1985) 103.
[293] J.P. Charland, F.L. Lee, E.J. Gabe, L.E. Khoo, F.E. Smith, Inorg. Chim. Acta 130 (1987) 55.
[294] J.P. Charland, E.J. Gabe, L.E. Khoo, F.E. Smith, Polyhedron 8 (1989) 1897.
[295] L.E. Khoo, N.K. Goh, M.A. Otieno, R.A. Lucero, G. Eng, B.S. Luo, T.C.W. Mak, Appl. Organomet. Chem. 8 (1994) 33.
[296] S.W. Ng, A.J. Kuthubutheen, V.G. Kumar Das, A. Linden, E.R.T. Tiekink, Appl. Organomet. Chem. 8 (1994) 37.
[297] G.K. Sandhu, N.S. Boparoy, Synth. React. Inorg. Met. Org. Chem. 20 (1990) 975.
[298] G.K. Sandhu, S.P. Verma, L.S. Moore, R.V. Parish, J. Organomet. Chem. 321 (1987) 15.
[299] G.K. Sandhu, R. Hundal, Appl. Organomet. Chem. 9 (1995) 121.
[300] A. Chakrabarti, S. Kamruddin, T.K. Chattophadhyaya, A. Roy, B.N. Chakraborty, K.C. Molloy, E.R.T. Tiekink, Appl. Organomet. Chem. 9 (1995) 357.
[301] M. Gielen, T. Joosen, T. Mancilla, K. Jurkschat, R. Willem, C. Roobol, J. Bernheim, G. Atassi, F. Huber, E. Hoffman, H. Preut, B. Mahieu, Main Group Met. Chem. 10 (1987) 147.
[302] G. Atassi, Rev. Si Ge Sn Pb Comp. 8 (1985) 821.
[303] R. Willem, H. Dalil, M. Biesemans, J.C. Martins, M. Gielen, Appl. Organomet. Chem. 13 (1999) 605.
[304] L. Pellerito, F. Maggio, M. Consiglio, A. Pellerito, G.C. Stocco, S. Grimaudo, Appl. Organomet. Chem. 9 (1995) 227.
[305] L. Pellerito, F. Maggio, T. Fiore, A. Pellerito, Appl. Organomet. Chem. 10 (1996) 393.
[306] F. Maggio, A. Pellerito, L. Pellerito, S. Grimaudo, C. Mansueto, R. Vitturi, Appl. Organomet.Chem. 8 (1994) 71.
[307] A. Pellerito, T. Fiore, C. Pellerito, A. Fontana, R. Di Stefano, L. Pellerito, M.T. Cambria, C. Mansueto, J. Inorg. Biochem. 72 (1998) 115.
[308] L. Pellerito, A. Pellerito, F. Maggio, M. Beltramini, B. Salvato, F. Ricchelli, Appl. Organomet. Chem. 7 (1993) 79.
[309] M.G. Mirisola, A. Pellerito, T. Fiore, G.C. Stocco, L. Pellerito, A. Cestelli, I. Di Liegro, Appl. Organomet. Chem. 11 (1997) 499.
[310] A. Pellerito, T. Fiore, A.M. Giuliani, F. Maggio, L. Pellerito, C. Mansueto, Appl. Organomet. Chem. 11 (1997) 707.
[311] P.A. Yeats, J.R. Poh, B.F.E. Ford, J.R. Sams, F. Aubke, J. Chem. Soc. (A) (1970) 2188.
[312] S. Lencioni, A. Pellerito, T. Fiore, A.M. Giuliani, L. Pellerito, M.T. Cambria, C. Mansueto, Appl. Organomet.Chem. 13 (1999) 145.
[313] M. López-Cardoso, P. Garcia y Garcia, V. Garcia-Montalvo, R. Cea-Olivares, Heteroatom. Chem. 11 (2000) 6.
[314] M. López-Cardoso, P. Garcia y Garcia, A. Rogers-Sakuma, R. Cea-Olivares, Polyhedron 19 (2000) 1539.
[315] T. Chivers, J.R. Sams, J. Chem. Soc. Chem. Commun. (1969) 249.

[316] D.W. Allen, D.J. Derbyshire, J.S. Brooks, S.J. Blunden, P.J. Smith, J. Chem. Soc. Dalton Trans. (1889) 1984.
[317] R. Barbieri, F. Taddei, J. Chem. Soc. Perkin Trans. 2 (1972) 1323.
[318] J.E. Philips, R.H. Herber, J. Organomet. Chem. 268 (1984) 39.
[319] D.G. Anderson, D.E. Webster, J. Chem. Soc. (B) (1968) 765.
[320] D.G. Anderson, J.R. Chipperfield, D.E. Webster, J. Organomet. Chem. 12 (1968) 323.
[321] M. Cordey-Hayes, J. Inorg. Nucl. Chem. 26 (1964) 915.
[322] M. Cordey-Hayes, I.R. Harris, J. Organomet. Chem. 322 (1987) 163.
[323] R.V. Parish, R.H. Platt, J. Chem. Soc. Chem. Commun. (1968) 1118.
[324] K. Jurkschat, A. Tzschach, J. Organomet. Chem. 290 (1985) 285.
[325] A. Tzschach, K. Jurkschat, Pure Appl. Chem. 58 (1986) 639.
[326] V.S. Petrosyan, O.A. Reutov, Pure Appl. Chem. 37 (1974) 147.
[327] W.A. Gustavson, L.M. Principe, W.-Z. Min Rhee, J.J. Zuckermann, J. Am. Chem. Soc. 103 (1981) 4126.
[328] V.G. Kumar Das, L.K. Mun, C. Wei, S.J. Blunden, T.C.W. Mak, J. Organomet. Chem. (1987) 163.
[329] R. Hulme, J. Chem. Soc. (1993) 1524.
[330] V.G. Kumar Das, C.K. Yap, P.J. Smith, J. Organomet. Chem. C17 (1985).
[331] V.G. Kumar Das, C.K. Yap, C. Wei, T.C.W. Mak, J. Organomet. Chem. 299 (1986) 41.
[332] P.G. Harrison, T.J. King, J.A. Richards, J. Chem. Soc. Dalton Trans. (1974) 1723.
[333] V.G. Kumar Das, C.K. Yap, C. Wei, E. Sinn, J. Chem. Soc. Chem. Commun. (1984) 1418.
[334] P.J. Harrison, K.C. Molloy, J. Organomet. Chem. 152 (1978) 63.
[335] N.G. Bokii, Yu.T. Struchkov, D.N. Kravstsov, E.M. Rokhlina, J. Struct. Chem. (Engl. Transl.) 14 (1973) 458.
[336] D. Cunningham, T. Higgins, P. McArdle, J. Chem. Soc. Chem. Commun. (1974) 833.
[337] Y. Arakava, O. Wada, Igaku no Agumi 136 (1986) 177.
[338] Y. Arakava, O. Wada, Biochem. Biophys. Commun. 125 (1989) 59.
[339] A.K. Saxena, J.K. Koacher, J.P. Tandom, S.R. Das, J. Toxicol. Environ. Health 10 (1982) 709.
[340] W. Peters, E.R. Trotter, B.L. Robinson, Ann. Trop. Med. Parasitol. 74 (1980) 321.
[341] J.M. Keyes Jr., J. Carey, D. Moses, W. Beierwaltes, Manual of Nuclear Medicine Procedures, 2nd ed., CRC Press, Cleveland, 1973.
[342] E. Deutsch, R.C. Elder, B.A. Lange, M.J. Vaal, D.G. Lay, Proc. Natl. Acad. Sci. USA 73 (1976) 4287.
[343] H.R. Maxon, E.A. Deutsch, S.R. Thomas, K. Lisbon, S.J. Ludas, C.C. Williams, S. Ali, Radiology 166 (1988) 501.
[344] C.E. Cornelius, P.A. Rodgers, Pediat. Res. 18 (1984) 728.
[345] A. Kappas, G.S. Drummond, BioEssay 3 (1986) 256.
[346] A. Kappas, G.S. Drummond, C.S. Simionato, K.E. Anderson, Hepatology 4 (1984) 336.
[347] A. Kappas, G.S. Drummond, T. Manola, S. Petmezaki, T. Valaes, Pediatrics 81 (1988) 485.
[348] L. Berglund, B. Angelin, R. Blomstrand, G. Drummond, A. Kappas, Hepatology 8 (1988) 625.
[349] A. Saxena, J.P. Tandon, Cancer Lett. 19 (1983) 73.
[350] N.F. Cardinelli (Ed.), Tin as a Vital Nutrient, CRC Press Boca Raton, FL, 1985
[351] M. Gielen, in: N.F. Cardinelli (Ed.), Tin as a Vital Nutrient, CRC Press, Boca Raton, FL, 1985.
[352] J. Szejtli, Cyclodextrins and Their Inclusion Complexes, Akadémiai Kiadó, Budapest, 1982.
[353] S. Balabaskaran, K. Tilakavita, V.G. Kumar Das, Appl. Organomet. Chem. 1 (1987) 347.
[354] G.J.M. van der Kerk, J.G.A. Luijten, J. Appl. Chem. 4 (1954) 314.
[355] G.J.M. van der Kerk, J.G.A. Luijten, J. Appl. Chem. 6 (1954) 56.
[356] R.H. Chandler, J. Chandler, Fungicides, Perspectives and Anti-fouling Agents for Paints. Technical Note, R.H. Chandler Ltd, London, 1977.
[357] J.H. Russel, Bibliography on Anti-fouling Uses of Organotins, International Tin Research Library Bibliography No. 8, International Tin Reserach Institute, London, 1981.
[358] P.J. Cox, R.A. Howie, O.A. Melvin, J.L. Wardell, J. Organomet. Chem. 489 (1995) 161.
[359] A. Bravery, N. Parameswaran, W. Liese, Mater. Org. 10 (1975) 31.
[360] L. Ghys, M. Biesemans, M. Gielen, A. Garoufis, N. Hadjiliadis, R. Willem, J.C. Martins, Eur. J. Inorg. Chem. (2000) 513.
[361] C. De Stefano, A. Gianguzza, F. Marrone, D. Piazzese, Appl. Organomet. Chem. 11 (1997) 683.
[362] J. Holecek, M. Nadvornik, K. Handlir, A. Lycka, J. Organomet. Chem. 241 (1983) 177.
[363] J. Holecek, M. Nadvornik, K. Handlir, A. Lycka, J. Organomet. Chem. 258 (1983) 147.
[364] A. Vértes, K. Süveghi, E. Kuzmann, K. Burger, L. Nagy, K. Schrantz, N. Buzás, J. Radioanal. Nucl. Chem. 203 (1996) 399.
[365] P.J. Smith, Chemistry of Tin, Blackie Academic and Professional, Chapman and Hall, London, 1998.
[366] A.G. Davies, Organotin Chemistry, VCH, Weinheim and New York, 1997.