APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2005; **19**: 440–450
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.771

Organotin compounds: from kinetics to stereochemistry and antitumour activities†

Marcel Gielen*, Monique Biesemans and Rudolph Willem

Vrije Universiteit Brussel, HNMR Unit, Room 8G512, Pleinlaan 2, B-1050 Brussels, Belgium

Received 26 June 2004; Revised 28 July 2004; Accepted 29 July 2004

An overview is given of the research performed by the authors at the Université Libre de Bruxelles and Vrije Universiteit Brussel, including the kinetics, stereochemistry and mechanism of S_E2 reactions at a saturated carbon atom, the synthesis of chiral organotin compounds and their configurational and optical stability, the fluxionality of trigonal bipyramidal metal atoms and the stereochemistry of S_N2 reactions at tetrahedrally substituted P, Si, Ge, Sn atoms, the cytotoxicity of many series of organotin compounds and the structure and reactivity of organotin salicylaldoximate clusters. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: kinetics; stereochemistry; mechanism; S_E2 reactions; mass spectrometry; fluxionality; cytotoxicity; organotin compounds; clusters

INTRODUCTION

This paper reports an overview of the research performed by the authors at the Université Libre de Bruxelles and the Vrije Universiteit Brussel. The kinetics, stereochemistry and mechanism of S_E2 reactions at a saturated carbon atom were first determined. In the first paper on the halodemetallation of tetraalkyltin compounds,[1] Colin Eaborn's (to the memory of whom this paper is dedicated) book *Organosilicon Compounds* was already cited as one of the references.

Mass spectrometric and NMR studies of organotin compounds were the topics of the subsequent research, followed by the synthesis of chiral organotin compounds and of their configurational and optical stability. The fluxionality of trigonal bipyramidal metal atoms and the stereochemistry of S_N2 reactions at tetrahedrally substituted atoms of the third, fourth or fifth period were then theoretically studied. The cytotoxicity of many series of organotin compounds was the next topic in which we got interested, as well as the mode of action of cytotoxic organotin compounds. Finally, the structure and reactivity of organotin salicylaldoximate clusters was experimentally investigated.

*Correspondence to: Marcel Gielen, Vrije Universiteit Brussel, HNMR Unit, Room 8G512, Pleinlaan 2, B-1050 Brussels, Belgium.
E-mail: mgielen@vub.ac.be
†Dedicated to the memory of Professor Colin Eaborn who made numerous important contributions to the main group chemistry.

S_E2 REACTION AT A SATURATED CARBON ATOM: KINETICS, STEREOCHEMISTRY AND MECHANISM

The conclusions of a series devoted to the determination of the mechanism of a bimolecular electrophilic substitution at a saturated carbon atom were described in a review.[2]

The first step consists of the addition of a nucleophile to the metal atom, either of X_2 if the reaction occurs in a non-polar solvent (Fig. 1, mechanism 1) or of a polar[3] (nucleophilic) solvent like methanol (Fig. 1, mechanism 2). The 'polarity' of a solvent for electrophilic (or nucleophilic) substitutions at a saturated carbon atom has been defined.[3]

The nucleophilic addition is necessary to be able to cleave a carbon–tin bond in a second step. The first mechanism, going through a four-center transition state, is characterized by retention of configuration at carbon, whereas the second mechanism occurs with Walden inversion at carbon, as proven experimentally.[2]

It must be mentioned that the S_E2 reaction is much more selective in polar solvents than in non-polar solvents. This may be due to the fact that, in non-polar solvents, an equatorial alkyl group is cleaved by E, whereas, in nucleophilic solvents, an apical carbon–tin bond is cleaved. This property was used to synthesize the first racemic tetraorganotin, in which the tin atom is linked to four different alkyl

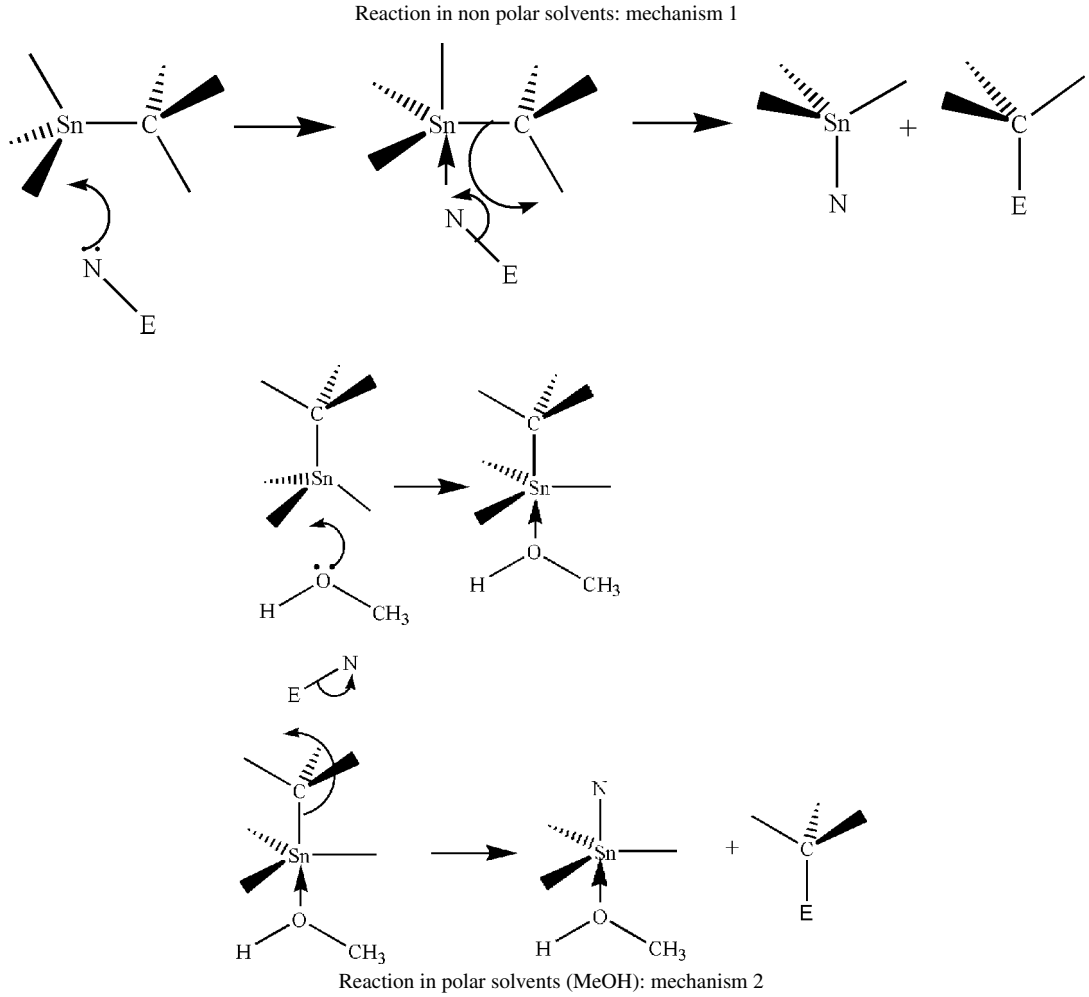


Figure 1. Mechanisms of S_E2 reactions in non-polar and polar solvents.

groups.[4] Starting from tetramethyltin, a bromodemetallation in methanol, that occurs like a titration, followed by the distillation of a methanol/benzene azeotrope, yields a benzene solution of very pure trimethyltin bromide that is then reacted with isopropylmagnesium bromide in diethylether. Evaporation of the solvent yields very pure isopropyltrimethyltin in very high yield that is treated as described above and reacted with cyclohexylmagnesium bromide, yielding very pure dimethylisopropylcyclohexyltin in very high yield, that is similarly reacted with ethylmagnesium bromide, yielding the first racemic tetraorganotin, methylethylisopropylcyclohexyltin. The reaction of that final compound with bromine in methanol gives only methyl bromide as detectable alkyl halide, as shown by GLC. The pure ethylisopropylcyclohexyltin bromide formed can be used to synthesize other racemic tetraorganotins containing no methyl group bound to tin by reaction with any Grignard reagent different from MeMgX, EtMgX, i-PrMgX or cy-HexMgX. A bromodemetallation of methylethylisopropylcyclohexyltin in chlorobenzene yields similar quantities of the four possible alkyl halides.

It is also possible to prepare other series of racemic tetraorganotins where not only alkyl but also aryl groups are bound to the metal.[5,6]

MASS SPECTROMETRIC AND NMR STUDIES OF ORGANOTIN COMPOUNDS

Mass spectrometry is a useful technique to characterize very easily tetraorganotin compounds[7–11] and other organotin derivatives. Indeed, tin is an element with many stable isotopes, two of which having a spin 1/2 that can be used for tin NMR. The characteristic pattern of tin fragment-ions containing one, two or three tin atoms makes the identification of these fragments very easy (see Fig. 2). The fragmentation pattern of tetraorganotin compounds is given schematically in Fig. 3.

Similarly (see Fig. 2), fragment-ions with two or more tin atoms[12] are also characterized by recognizable isotope patterns as well as tin halide fragment-ions.[13]

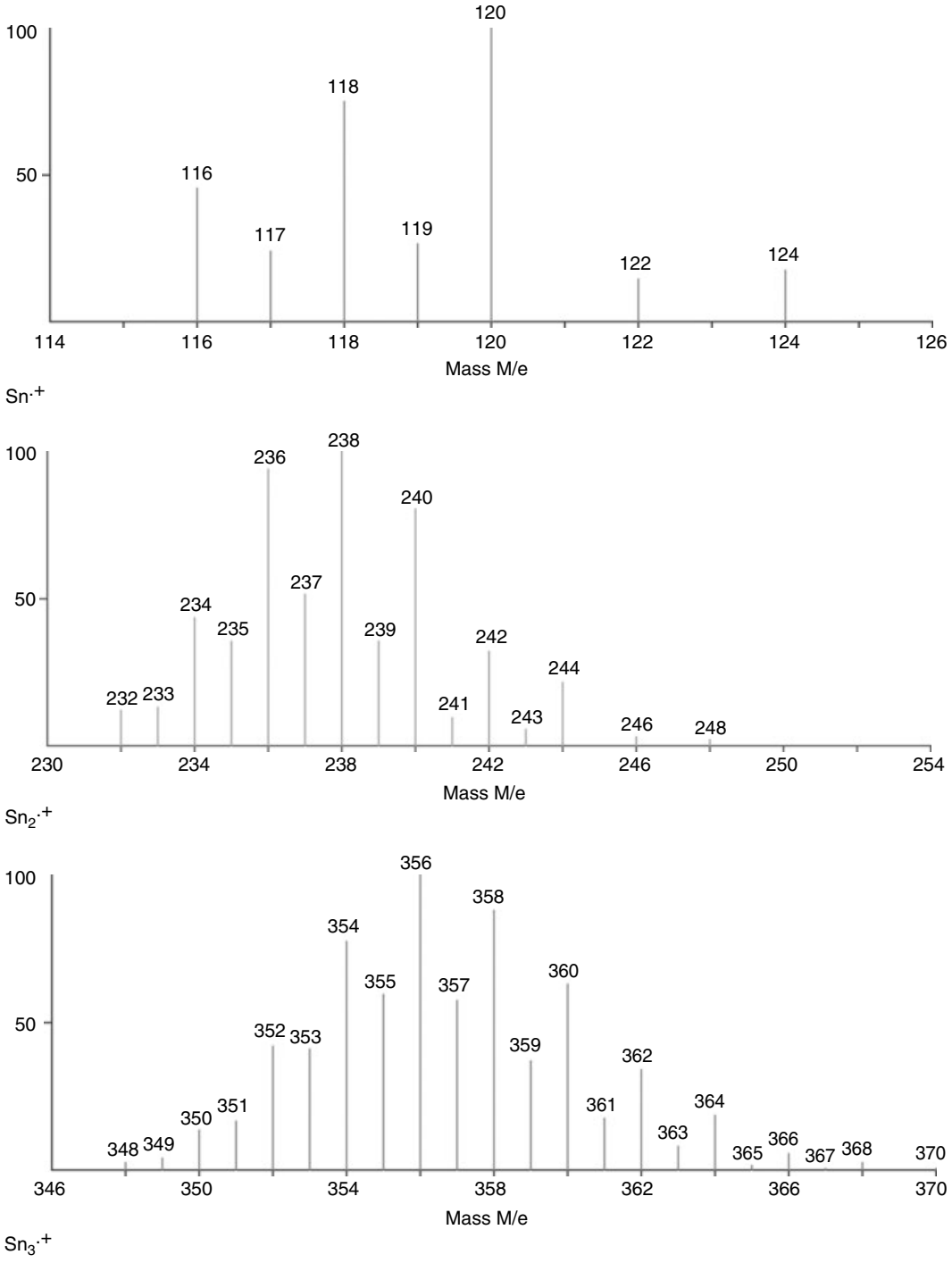


Figure 2. Isotopic distributions of Sn^+, Sn_2^+ and Sn_3^+.

CHIRAL ORGANOTIN COMPOUNDS AND THEIR CONFIGURATIONAL AND OPTICAL STABILITY

The study of the stereochemistry at tin of nucleophilic substitutions at the metal atom requires the synthesis of chiral organotin compounds. Chiral tetraorganotins in which the tin atom is the only chiral center were synthesized in 1975[14–16] and their optical stability has been proven. The optical stabilities of other classes of organotin derivatives were also examined.[2,17]

Triorganotin halides are not optically stable but bulky alkyl groups enhance their configurational stability.[18] The reason for this optical instability is the presence of nucleophiles in the

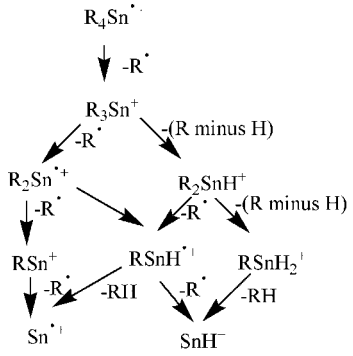


Figure 3. Mass spectrometric fragmentation of tetraorganotin compounds.

medium, the halide of the triorganotin halide being one of the nucleophiles that can induce configurational instability.[19,20]

The configurational stability of triorganotin hydrides, amines, phosphines and arsines was demonstrated,[21] as well as that of organotin compounds with a tin–germanium,[22] tin–tin[23] or tin–transition metal bond.[24–26] Chiral triorganotin hydrides, amines, phosphines and arsines, organotin compounds with a tin–germanium, tin–tin or tin–transition metal bond were then synthesized. The stereoselectivity of reactions converting an optically stable compound into another one could then be studied, and several stereoselective substitution reactions have indeed been observed, like the transformation of RR′R″SnH into RR′R″SnCH$_3$ with diazomethane or into RR′R″Sn–SnRR′R″ with palladium as catalyst.[27–35]

FLUXIONALITY AND STEREOCHEMISTRY OF S_N2 REACTIONS AT TETRAHEDRALLY SUBSTITUTED ATOMS OF THE THIRD, FOURTH OR FIFTH PERIOD

Several papers and books have appeared on the topological approach that can be used to explain the stereochemistry of S_N2 reactions at phosphorus.[36–38] The same approach has been used to explain the stereochemistry of S_N2 reactions at silicon and germanium[39] and might be used for similar reactions at the metal atom of organotin compounds, for instance to explain the retention of configuration observed when RR′R″SnD is converted to RR′R″SnH by a reaction with triphenyltin hydride.

CYTOTOXIC ORGANOTIN COMPOUNDS

When the antitumor activity of cisplatin, *cis*-$Cl_2Pt(NH_3)_2$, was discovered, several research groups started to investigate the possible therapeutic applications of other metal-based, often organometallic, compounds. The organotin compounds that were first tested were those that were available or easily synthesized, like tri- or diorganotin halides: these compounds can indeed routinely be prepared from tetraorganotin compounds R_4Sn and dihalogens X_2 [2] or HX:

$$R_4Sn + Y - X = R_3SnX + R - Y$$

$$\text{and } R_3SnX + Y - X = R_2SnX_2 + R - Y$$

$$Y = X \text{ or } H$$

Diorganotin halides can also be synthesized by direct synthesis in the presence of a suitable catalyst:[2]

$$2R - X + Sn = R_2SnX_2$$

The *in vivo* testing of tetraorganotin compounds showed that they are inactive, whereas organotin halides and their complexes with amines and other ligands exhibit borderline activities against P388 or L1210 leukemias.[41–46]

The *in vivo* pre-screenings against these two leukemias used initially by the National Cancer Institute (NCI) were later replaced by *in vitro* pre-screenings against a panel of human tumor cell lines.[47–59]

This is also the procedure that was used when organotin compounds were tested by the Rotterdam Cancer Institute. Seven human tumor cell lines were chosen for the panel that was used: MCF-7 and EVSA-T (two mammary cancers), WiDr (a colon cancer), IGROV (an ovarian cancer), M19 (a melanoma), MEL A498 (a renal cancer) and H226 (a lung cancer).

The main disadvantage of organotin halides for antitumor testings is that, when they are dissolved in water, the pH of the solution dramatically decreases because the Cl–Sn bonds are converted into water–tin bonds; the formed compounds then lose protons, yielding first organotin hydroxides that are afterwards possibly converted into insoluble bis(triorganotin) oxides or diorganotin oxides. Because di- or triorganotin carboxylates do not suffer from the same disadvantage, many series of these compounds were synthesized in order to determine their cytotoxic or antitumor properties. It has been shown that such derivatives, when dissolved in water, indeed remain intact for long periods.

Several recent reviews have been devoted to the antitumor properties of organotin compounds.[60–62] Therefore, only a few of the most typical compounds will be selected here.

The influence of the R and R′ groups of $R_2Sn(OCOR')_2$ or $\{[R_2(R'COO)Sn]_2O\}_2$ on the cytotoxicity has been determined.[63–65] The di-*n*-butyltin compounds are among the most potent ones. This result was felt to be very useful because di-*n*-butyltin oxide, a possible starting material to synthesize such di-*n*-butyltin derivatives, is commercially available and quite inexpensive. Di-*n*-butyltin derivatives have indeed found several industrial applications.[40] An inexpensive starting material is suitable when many series of

organotin compounds need to be synthesized and when only limited financial resources are available.

The conversion of insoluble polymeric $(R_2SnO)_n$ into $R_2Sn(OCOR')_2$ or $\{[R_2(R'COO)Sn]_2O\}_2$ is very easy: the suitable tin compound and R′COOH are placed in a mixture of ethanol and toluene and heated. Very quickly, the reaction mixture becomes a clear solution. The water–toluene–ethanol azeotrope is then distilled off and, when the concentrated remaining solution is cooled down, sometimes the reaction product precipitates. It can then be recrystallized and sometimes single crystals can be grown that can be analyzed by X-ray diffraction.

If the R_2SnO : R′COOH molar ratio is 1 : 1, then, generally, dimeric distannoxanes $\{[R_2(R'COO)Sn]_2O\}_2$ of type **1** are obtained (see Fig. 4).[66–70]

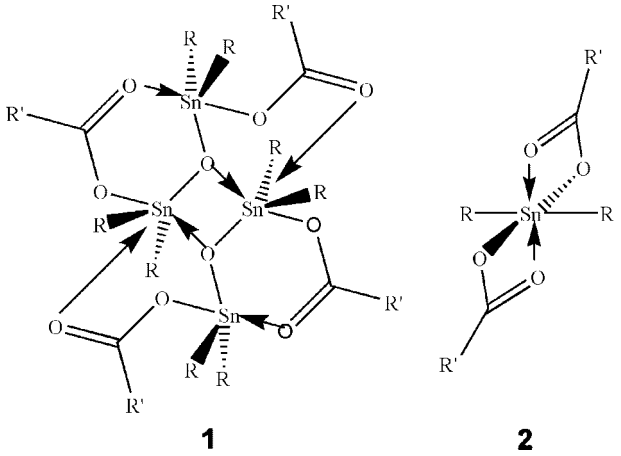
$$(R_2SnO)_n + nR'COOH = n\{[R_2Sn(OOCR')Sn]_2O\}_2 + H_2O$$

A 1 : 2 molar ratio generally yields diorganotin dihalides $R_2Sn(OCOR')_2$ of type **2** (see Fig. 4).[71–85].

$$(R_2SnO)_n + 2nR'COOH = nR_2Sn(OOCR')_2 + nH_2O$$

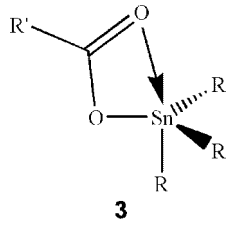
Triorganotin compounds (see Fig. 5) are quite well-known bactericides and fungicides.[86,87] Such compounds were prepared for that purpose and consequently screened for their cytotoxicities. Several of these were found to be quite potent.[88–90] Their cytotoxicities are comparable to that of doxorubicin, a clinically used anticancer drug.

Organotin steroidcarboxylates represent the first major development in this area.[91] Not only diorganotin (of type **1**) but also triorganotin steroidcarboxylates (of type **3**) have been studied. Triorganotin steroidcarboxylates are more potent than dimeric distannoxanes and appear to possess high *in vitro* cytotoxicities, but their poor water solubility still



1 **2**

Figure 4. Structures of tetraorganodicarboxylato distannoxane dimers $\{[R_2Sn(OOCR')Sn]_2O\}_2$ (type **1**) and diorganotin dicarboxylates $R_2Sn(OOCR')_2$ (type **2**) (see also Figs. 6 and 7).



3

Figure 5. Probable structure of triorganotin carboxylates (type **3**) in solution.

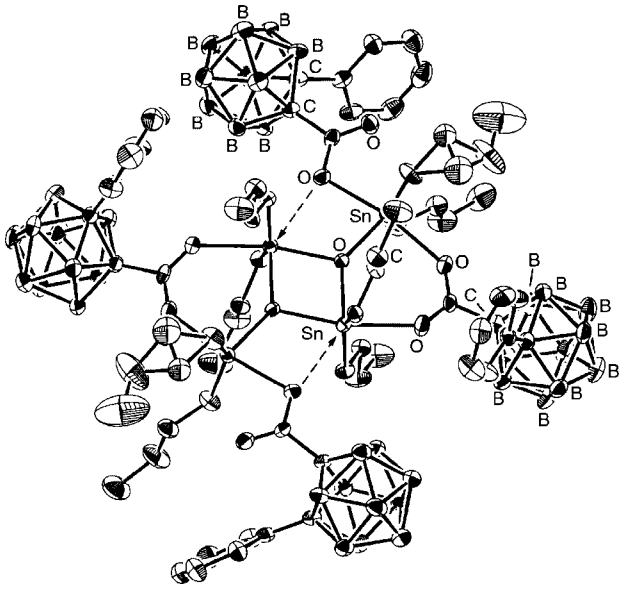


Figure 6. X-ray structure of the carborane-based organotin compound of type **1** $\{[Bu_2(2\text{-Ph-m-}C_2B_{10}H_{11}\text{-1-COO})Sn]_2O\}_2$.

remains a drawback,[94] that could probably affect their *in vivo* properties.

Several attempts were then made to try to synthesize organotin compounds characterized by improved water solubilities. The lipophilic/hydrophilic characteristics of the compounds are probably very important, their lipophilic properties being essential for crossing the cell membrane and their hydrophilic character for being accepted by the water-rich cell.

The first attempt to increase the water-solubility was to replace hydrogen atoms of phenyl rings of benzoato ligands with hydroxyl groups.[95] This did affect significantly neither their water solubility nor their cytotoxicity. Fluorine-substituted organotin compounds were also candidates. Already in 1984, such compounds were being synthesized to check whether the replacement of hydrogen by fluorine influenced their cytotoxicity.[96–101]

A peculiar property of fluorine-substituted compounds is indeed that they are more soluble in water than their hydrogen analogs and still soluble in non-polar solvents. Fluorine-containing organotin compounds are not significantly

more potent than their unfluorinated analogs.[97–101] Their cytotoxicities were not better than those of the starting compounds, and this route was rapidly abandoned.

Another possibility for increasing the hydrophilicity of organotin compounds is to prepare organotin salts, for instance stannates, by reacting organotin derivatives with an anionic ligand.[102–106] Carboranyl-based organotin compounds were also screened.[107–109] A carborane moiety $C_2B_{10}H_{11}$ has about the same size as a phenyl ring but is spherical instead of planar. The replacement of an aromatic phenyl ring by a hyper-aromatic carboranyl moiety is routinely used in the field of boron-based metallotherapeutic agents. In some compounds, the tin atom was linked directly to one of the boron or carbon atoms of the carbonanyl moiety. In other compounds, the carboranyl moiety was bound to a CO_2 or to a CH_2CO_2 linked to the tin atom of a distannoxane structure. Their cytotoxicity is comparable to that of organotin carboxylates without the carborane moiety.

An attempt to synthesize a carborane-based organotin compound with a polyoxaalkyl chain linked to the carboranyl moiety, in order to increase the water solubility (see below), produced a triphenylstannate[110] instead of the derivative of type **3** that was expected to be formed (see Figs. 8 and 9).

This triphenylstannate exhibited a cytotoxicity similar to that obtained for carboranyltin compounds of type **3**, whereas its water solubility was increased dramatically by the presence of the polyoxa substituent, and probably primarily by the fact that the compound was a salt.

The most promising development in the field of antitumor-active organotin compounds has been achieved by the synthesis and testing of organotin compounds that contain a polyoxaalkyl moiety linked to tin either by a carbon–tin or by a carbon–oxygen bond.[111–113] The polyoxaalkyl moiety can be either a linear or a cyclic one, a crown-ether. Many of these compounds, of which some are very soluble in water, exhibit exceptionally high cytotoxicities against the seven human cell lines studied (see Table 1). Of all the polyoxaalkyltin compounds tested, two distannoxanes of type **1** and two triorganotin derivatives of type **3** exhibited very pronounced cytotoxicities, as reported in table 1.

MODE OF ACTION OF CYTOTOXIC ORGANOTIN COMPOUNDS

The platinum antitumor drugs have been intensively studied and their probable mode of action, elucidated: their interaction with DNA is responsible for their property of inhibiting the cell division. The interaction of diorganotin halides with DNA or DNA fragments was studied,[114–121] but around pH 7 no effective interaction was detected.[122] Water-soluble cytotoxic organotin carboxylates were found not to interact significantly with DNA.[123] If cytotoxic organotin compounds interact, for instance, with proteins, they could be active due to this property but this is still an open question.

ORGANOTIN SALICYLALDOXIMATE CLUSTERS

Whereas the reaction of di-*n*-butyltin oxide with carboxylic acids yields tetra-*n*-butyldicarboxylato distannoxane dimers $\{[Bu_2Sn(OOCR')Sn]_2O\}_2$ or di-*n*-butyltin dicarboxylates $Bu_2Sn(OOCR')_2$, depending on the diorganotin oxide–carboxylic acid molar ratio, the reaction of $(Bu_2SnO)_n$ with salicylaldoxime H-OZNO-H (where Z represents C_6H_4-CH=) yields a stable crystalline cluster, **1**, containing two five-coordinate and one seven-coordinate tin atoms, independently of the molar ratio

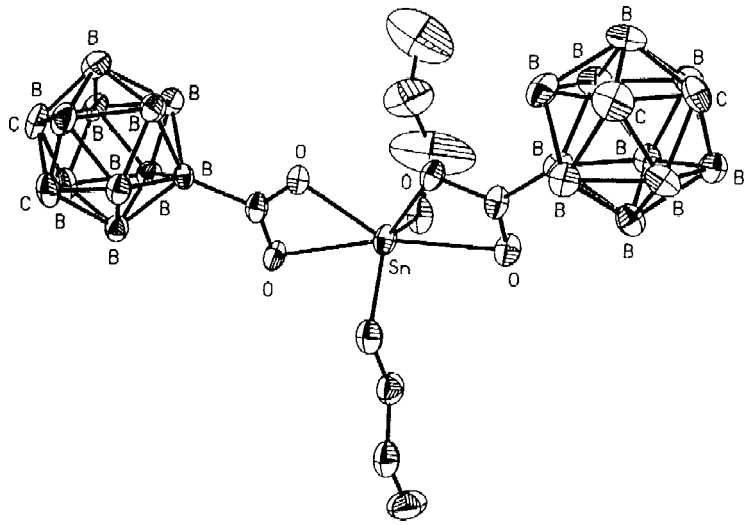


Figure 7. X-ray structure of the carborane-based organotin compound of type **2** bis(1,2-dicarbaclosododecaborane-9-carboxylato)di-*n*-butyltin, $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$.

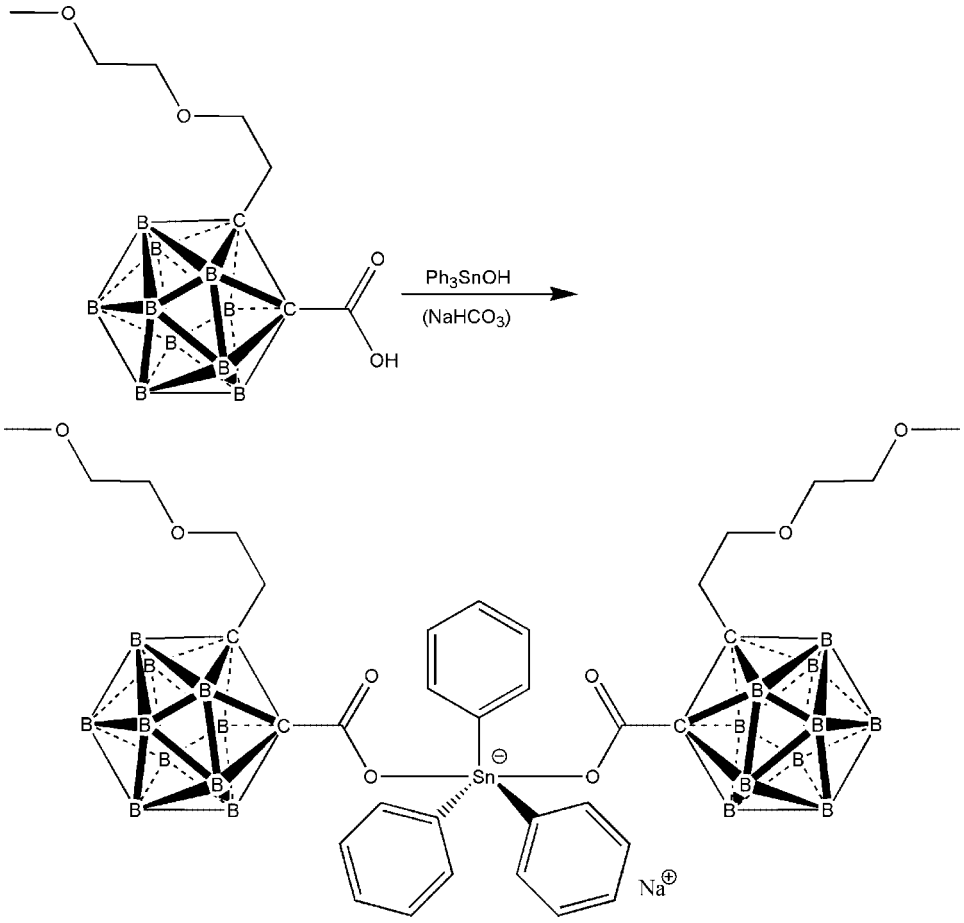


Figure 8. A boron-based triphenylstannate, sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-closo-dodecaborane-1-carboxylato] triphenylstannate, $[(CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2)(1,2\text{-}C_2B_{10}H_{10}\text{-}9\text{-}COO)_2SnPh_3]^-\ Na^+$, unexpectedly formed during the synthesis of the type **3** analog.

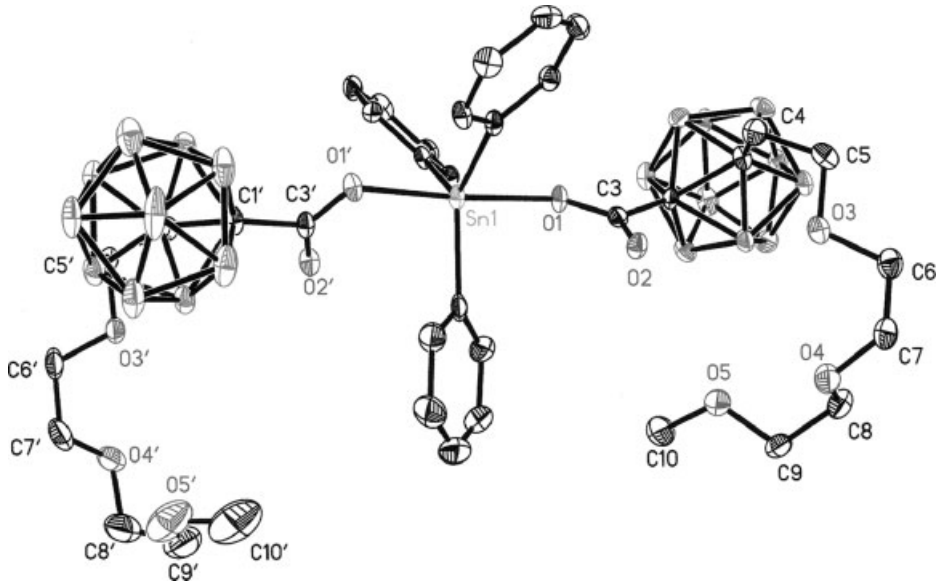


Figure 9. Crystal structure of sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-closo-dodecaborane-1-carboxylato]triphenylstannate, $[(CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2)(1,2\text{-}C_2B_{10}H_{10}\text{-}9\text{-}COO)_2SnPh_3]^-\ Na^+$.

used. Its solid state structure was determined by X-ray diffraction crystallography.[124,125] It can be described by $(Bu_2Sn)(Bu_2SnO)(Bu_2SnOH)(-OZNO-)(-OZNOH)$ (see Fig. 10).

$$2HOZNOH + 3/n(R_2SnO)_n \rightarrow H_2O + (Bu_2Sn)(Bu_2SnO)(Bu_2SnOH)(-OZNO-)(-OZNOH),\ \mathbf{1}$$

When dissolved in $CDCl_3$, this cluster undergoes reversible reactions that were revealed by one- and two-dimensional multinuclear (^1H, ^{13}C, ^{119}Sn) NMR techniques.[125] One of the clusters that is formed in solution, $(R_2SnO)(R_2Sn)_2(HOZNO-)(-ZNOH)(-OZNO-)$ (Fig. 11), can also be synthesized independently from $(R_2SnO)_n$ and salicylaldoxime.

$$3HOZNOH + 3/n(R_2SnO)_n \rightarrow 2H_2O + (R_2SnO)(R_2Sn)_2(HOZNO-)(-ZNOH)(-OZNO-),\ \mathbf{2}$$

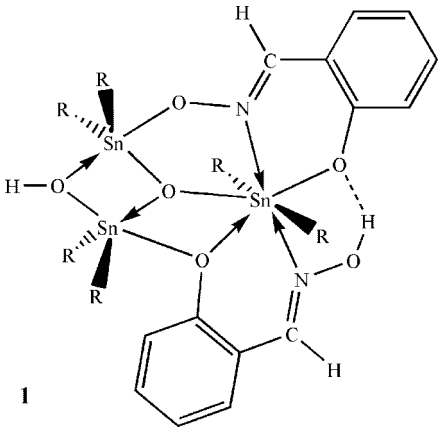


Figure 10. Structure of the organotin cluster $(Bu_2Sn)(Bu_2SnO)(Bu_2SnOH)(-OZNO-)(-OZNOH)$, **1**, in the crystalline state.

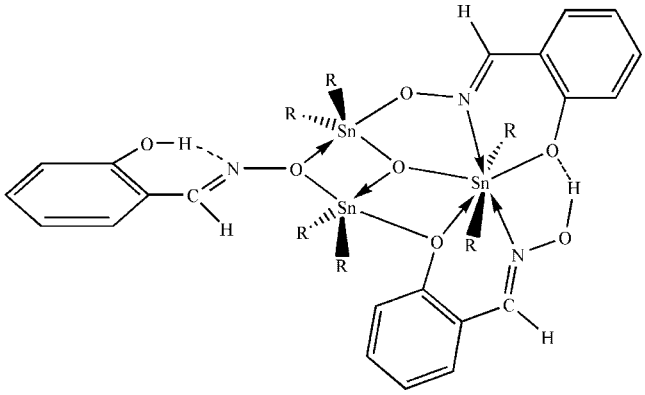


Figure 11. Structure of the organotin cluster $(R_2SnO)(R_2Sn)_2(HOZNO-)(-ZNOH)(-OZNO-)$, **2**.

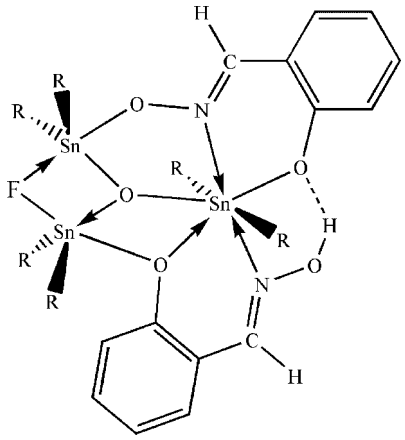
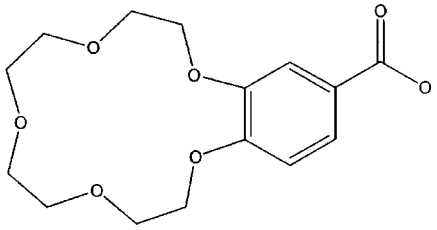


Figure 12. Structure of the organotin cluster $(Me_2Sn)(Me_2SnO)(Me_2SnF)(-OZNO-)(-OZNOH)$, **3**.

Table 1. ID_{50} values (ng/ml) of a few potent polyoxaalkyltin compounds tested against the seven human tumor cell lines

benzocrown-COO =



	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A 498	H 226
Type **1**, R = Bu, R′COO = $CH_3O(CH_2CH_2O)CH_2COO$	<1	<1	3.9	<1	<1	<1	3.3
Type **1**, R = Bu, R′COO = $CH_3O(CH_2CH_2O)_2CH_2COO$	<1	<1	<1.8	<1	<1	<1	<1
Type **3**, R = Ph, R′COO = benzocrownCOO	2.9	<2	<2	<2	<2	<2	<2
Type **3**, R = Bu, R′COO = benzocrownCOO	3.3	<2	<2	<2	<2	<2	<2
CPT	699	422	967	169	558	2253	3269
DOX	10	8	11	60	16	90	199

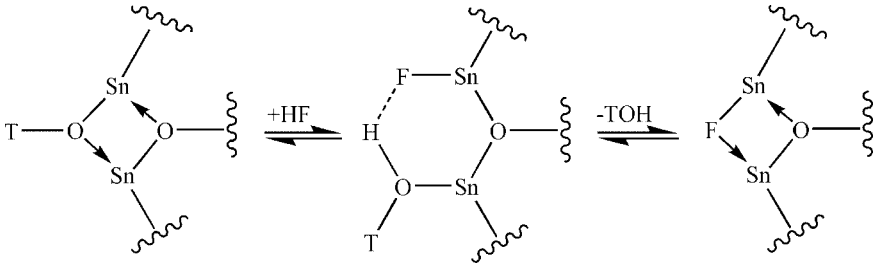


Figure 13. Addition–elimination mechanism for the replacement of TO^- by F^-.

The difference between clusters **1** and **2** can easily be expressed by the replacement of the HO-connecting the two five-coordinate tin atoms of cluster **1** with HOZNO- in cluster **2**. It has been shown that, in fact, the cluster that is formed when a diorganotin oxide reacts with salicylaldoxime is cluster **2**, and that it is then hydrolyzed by the water formed in solution to yield the cluster **1**.

$$(R_2SnO)(R_2Sn)_2(HOZNO-)(-ZNOH)(-OZNO-), \mathbf{2} + H_2O \rightarrow$$
$$(Bu_2Sn)(Bu_2SnO)(Bu_2SnOH)(-OZNO-)(-OZNOH), \mathbf{1}$$
$$+ HOZNOH$$

The water converts the μ^2-bridging ligand HOZNO-into the good nucleophilic leaving group, HOZNOH, through electrophilic assistance by a hydroxylic proton, which is needed for such a reaction to occur.

Because a review has recently been published on these clusters,[126] we will discuss only the reactions of clusters of type **1** with alcohols.

When **1** (with R = Me) is recrystallized from R′OH, a new cluster, $(Me_2Sn)(Me_2SnO)(Me_2SnOR')(-OZNO-)(-OZNOH)$, is formed in which the HO- of **1** is analogously replaced by R′O-. Phenols R′OH give similar reactions provided they are not too acidic.

It is well known that fluoride is the most nucleophilic agent towards tin. Therefore the reaction of cluster **1** with fluoride in the presence of a proton source (NH_4F) was studied, and yielded a new cluster $(Me_2Sn)(Me_2SnO)(Me_2SnF)(-OZNO-)(-OZNOH)$, **3**, in which the bridging HO- of cluster **1** is replaced by fluoride (Fig. 12).[127]

^{19}F and ^{119}Sn NMR, in particular the spectral patterns arising from $^1J(^{19}F-^{119/117}Sn)$ scalar couplings, unambiguously show that the substitution occurs through the addition–elimination reaction mechanism shown in Fig. 13.

REFERENCES

1. Gielen M, Nasielski J. *Bull. Soc. Chim. Belg.* 1962; **71**: 32–58.
2. Gielen M. *J. Braz. Chem. Soc.* 2003; **14**: 870–877 and the references cited therein.
3. Gielen M, Nasielski J. *J. Organometal. Chem.* 1967; **7**: 273–280.
4. Boué S, Gielen M, Nasielski J. *Tetrahedron Lett.* 1968; 1047–1048.
5. Gielen M, Nasielski J, Topart J. *Recl Trav. Chim. Pays-Bas* 1968; **87**: 1051–1052.
6. Boué S, Gielen M, Nasielski J, Lieutenant JP, Spielmann R. *Bull. Soc. Chim. Belg.* **78**: 135–146.
7. Gielen M, Nasielski J. *Bull. Soc. Chim. Belg.* 1968; **77**: 5–14.
8. Boué S, Gielen M, Nasielski J. *Bull. Soc. Chim. Belg.* 1968; **77**: 43–58.
9. Gielen M, Mayence G. *J. Organometal. Chem.* 1972; **46**: 281–288.
10. Gielen M, De Poorter B, Sciot MT, Topart J. *Bull. Soc. Chim. Belg.* 1973; **82**: 271–276.
11. Gielen M, Jurkschat K. *Org. Mass Spectrom.* 1983; **18**: 224–225.
12. Gielen M, Nasielski J, Vandendunghen G. *Bull. Soc. Chim. Belg.* 1971; **80**: 175–180.
13. Gielen M, Mayence G. *J. Organometal. Chem.* 1968; **12**: 363–368.
14. Gielen M, Mokhtar-Jamaï H. *Bull. Soc. Chim. Belg.* 1975; **84**: 197–202.
15. Gielen M. *Acc. Chem. Res.* 1973; **6**: 198–202.
16. Gielen M, Hoogzand C, Simon S, Tondeur Y, Vanden Eynde I, Van de Steen M. *Israel J. Chem.* **15**: 74–77.
17. Gielen M, Mokhtar-Jamaï H. *Ann. NY Acad. Sci* 1974; **239**: 208–212.
18. Gielen M, Mokhtar-Jamaï H. *Bull. Soc. Chim. Belg.* 1975; **84**: 1037–1043.
19. Gielen M, Mokhtar-Jamaï H. *J. Organometal. Chem.* 1975; **91**: C33–C36.
20. Gielen M, Mokhtar-Jamaï H. *J. Organometal. Chem.* **129**: 325–230.
21. Gielen M, Tondeur Y. *Bull. Soc. Chim. Belg.* 1975; **84**: 939–945.
22. Gielen M, Tondeur Y. *J. Chem. Soc., Chem. Commun.* 1978; 81–82.
23. Gielen M, Simon S. *Bull. Soc. Chim. Belg.* 1977; **86**: 589–594.
24. Gielen M, Hoogzand C, Vanden Eynde I. *Bull. Soc. Chim. Belg.* 1975; **84**: 933–938.
25. Gielen M, Vanden Eynde I. *Israel J. Chem.* 1980; **20**: 93–101.
26. Gielen M, Vanden Eynde I, Polet F, Meunier-Piret J, Van Meerssche M. *Bull. Soc. Chim. Belg.* 1980; **89**: 915–927.
27. Gielen M, Vanden Eynde I. *J. Organometal. Chem.* 1981; **217**: 205–213.
28. Vanden Eynde I, Gielen M, Stühler G, Mannschreck A. *Polyhedron* 1982; **1**: 1–7.
29. Gielen M, Tondeur Y. *J. Organometal. Chem.* 1975; **128**: C25–C26.
30. Gielen M, Tondeur Y. *Nouv. J. Chim.* 1978; **2**: 117–118.
31. Gielen M, Tondeur Y. *J. Organometal. Chem.* 1979; **169**: 265–281.
32. Gielen M. *Pure Appl. Chem.* 1980; **52**: 657–668.
33. Gielen M, Vanden Eynde I. *J. Organometal. Chem.* 1980; **198**: C55–C57.
34. Gielen M, Vanden Eynde I. *J. Organometal. Chem.* 1981; **218**: 315–319.
35. Gielen M. *Top. Curr. Chem.* 1982; **104**: 57–105.
36. Gielen M. *Mededelingen Vlaamse Chem. Veren.* 1969; **31**: 185–200.
37. Gielen M, Van Lautem N. *Bull. Soc. Chim. Belg.* 1970; **79**: 679–688.
38. Gielen M, Willem R. *Phosphorus Sulfur* 1977; **3**: 339–345.

39. Brocas J, Gielen MR, Willem R. *The Permutational Approach to Dynamic Stereochemistry*. Mc Graw-Hill: New York, 1983 and references cited herein.
40. Omae I. *Organotin Chemistry*. *Journal of Organometallic Chemistry Library*, Vol. 21. Elsevier: Amsterdam, 1989.
41. Haiduc I, Silvestru C, Gielen M. *Bull. Soc. Chim. Belg.* 1982; **91**: 187–189.
42. Gielen M, Jurkschat K, Atassi G. *Bull. Soc. Chim. Belg.* 1984; **93**: 153–155.
43. Penninks AH, Bol-Schoenmakers M, Gielen M, Seinen W. *Main Group Metal. Chem.* 1989; **12**: 1–15.
44. Zhang Z, Pan H. Hu C, Fu F, Sun Y, Willem R, Gielen M. *Appl. Organometal. Chem.* 1991; **5**: 183–190.
45. Silvestru C, Haiduc I, Tiekink ERT, de Vos D, Biesemans M, Willem R, Kovala-Demertzi D, Tauridou P, Russo U, Gielen M. *Inorg. Chim. Acta* 1995; **239**: 177–183.
46. Gielen M, de Vos D, Meriem A, Bouâlam M, El Khloufi A, Willem R. *In Vivo* 1993; **7**: 171–174.
47. Gielen M, Willem R. *Anticancer Res.* 1992; **12**: 257–268.
48. Gielen M, Willem R. *Anticancer Res.* 1992; **12**: 269–272.
49. Gielen M, Willem R. *Anticancer Res.* 1992; **12**: 1323–1326.
50. Gielen M, de Vos D, Pan H, Willem R. *Main Group Metal Chem.* 1992; **15**: 242–245.
51. Gielen MR, Willem R. *Metal Ions in Biolology and Medicine*, Anastassopoulou J, Collery P, Etienne JC, Theophanides T (eds). John Libbey Eurotext: Paris, Vol. II, 1992; 186–187.
52. Gielen M, Willem R. *Metal Ions in Biolology and Medicine*, Anastassopoulou J, Collery P, Etienne JC, Theophanides T (eds), Vol. II. John Libbey Eurotext: Paris, 1992; 188–189.
53. Gielen M, Willem R, Bouâlam M, El Khloufi A, de Vos D. *Metal Ions in Biolology and Medicine*, Anastassopoulou J, Collery P, Etienne JC, Theophanides T (eds), Vol. II. John Libbey Eurotext: Paris, 1992; 190–191.
54. Gielen M. *Metal-Based Drugs* 1994; **1**: 213–219.
55. Gielen M. *Metal Ions in Biolology and Medicine*, Anastassopoulou J, Collery P, Etienne JC, Theophanides T (eds), Vol. III. John Libbey Eurotext: Paris, 1994; 309–314.
56. Gielen M, Willem R. *Main Group Metal Chem.* 1994; **17**: 1–8.
57. Gielen M, Willem R. *Main Group Elements and their Compounds—Perspectives in Materials Science, Chemistry and Biology*, Das VGK (ed.). Springer/Narosa: Berlin, 1996; 446–452.
58. Gielen M, Willem R. *Cytotoxic, Mutagenic and Carcinogenic Potential of Heavy Metals Related to Human Environment*. NATO ASI Series 2: Environment, Vol. 26, Hadjiliadis ND (ed.). Kluwer Academic: Dordrecht, 1997; 445–455.
59. de Vos D, Gielen M, Willem R, van Wingerden KE, Nooter K. *Metal-Based Drugs* 1998; **5**: 179–188.
60. Gielen M. *Appl. Organometal. Chem.* 2002; **16**: 481.
61. de Vos D, Willem R, Gielen M, van Wingerden KE, Nooter K. *Metal-Based Drugs* 1998; **5**: 179–188.
62. Gielen M. *Coord. Chem. Rev.* 1996; **151**: 41–51.
63. Gielen M, El Khloufi A, Biesemans M, Mahieu B, Willem R. *Bull. Soc. Chim. Belg.* 1992; **101**: 243–248.
64. Bouâlam M, Willem R, Biesemans M, Gielen M. *Appl. Organometal. Chem.* 1991; **5**: 497–506.
65. Gielen M, De Clercq L, Willem R, Joosen E. *Tin and Malignant Cell Growth*, Zuckerman JJ (ed.). CRC Press: Boca Raton, PC, 1988; 39–46.
66. Bouâlam M, Willem R, Gelan J, Sebald A, Lelieveld P, de Vos D, Gielen M. *Appl. Organometal. Chem.* 1990; **4**: 335–343.
67. Meriem A, Biesemans M, Willem R, Mahieu B, de Vos D, Lelieveld P, Gielen M. *Bull. Soc. Chim. Belg.* 1991; **100**: 367–374.
68. Bouâlam M, Willem R, Biesemans M, Mahieu B, Meunier-Piret J, Gielen M. *Main Group Metal Chem.* 1991; **14**: 41–56.
69. Gielen M, Meunier-Piret J, Biesemans M, Willem R, El Khloufi A. *Appl. Organometal. Chem.*, 1992; **6**: 59–67.
70. Gielen M, Meunier-Piret J, Biesemans M, El Khloufi A, Willem R. *Polyhedron* 1992; **11**: 1861–1868.
71. Gielen M, Joosen E, Mancilla T, Jurkschat K, Willem R, Roobol C, Bernheim J, Atassi G, Huber F, Hoffmann E, Preut H, Mahieu B. *Main Group Metal Chem.* 1987; **10**: 147–167.
72. Gielen M, Joosen E, Mancilla T, Jurkschat K, Willem R, Roobol C, Bernheim J. *Platinum and other Metal Coordination Compounds in Cancer Chemotherapy*, Nicolini M (ed.). Martinus Nijhoff: Amsterdam, 1988; 662–665.
73. Meriem A, Gielen M, Willem R. *J. Organometal. Chem.* 1989; **365**: 91–101.
74. Gielen M, Willem R, Delmotte A, Meriem A, Mélotte M, Vanbellinghen C, Mahieu B, Joosen C, Lelieveld P, de Vos D, Atassi G. *Main Group Metal Chem.* 1989; **12**: 55–72.
75. Meriem A, Willem R, Meunier-Piret J, Gielen M. *Main Group Metal Chem.* 1989; **12**: 187–198.
76. Meriem A, Willem R, Meunier-Piret J, Biesemans M, Mahieu B, Gielen M. *Main Group Metal Chem.* 1990; **13**: 167–180.
77. Meriem A, Willem R, Biesemans M, Mahieu B, de Vos D, Lelieveld P, Gielen M. *Appl. Organometal. Chem.* 1991; **5**: 195–201.
78. Gielen M, Acheddad M, Mahieu B, Willem R. *Main Group Metal Chem.* 1991; **14**: 73–79.
79. Gielen M, Bouâlam M, Biesemans M, Mahieu B, Willem R. *Main Group Metal Chem.* 1991; **14**: 271–281.
80. Gielen M, Willem R, Biesemans M, Bouâlam M, El Khloufi A, de Vos D. *Appl. Organometal. Chem.* 1992; **6**: 287–291.
81. Gielen M, Bouâlam M, Meriem A, Mahieu B, Biesemans M, Willem R. *Heteroatom Chem.* 1992; **3**: 449–452.
82. Gielen M, Bouhdid A, Kayser F, Biesemans M, de Vos D, Mahieu B, Willem R. *Appl. Organometal. Chem.* 1995; **9**: 251–257.
83. Gielen M, Willem R, Bouhdid A, de Vos D, Kuiper M, Veerman G, Peters GJ. *In Vivo* 1995; **9**: 59–64.
84. Gielen M, Willem R, Bouhdid A, de Vos D, Kuiper CM, Veerman G, Peters GJ. *Oncol. Rep.* 1996; **3**: 583–587.
85. Gielen M, Willem R, Dalil H, de Vos D, Kuiper CM, Peters GJ. *Metal-Based Drugs* 1998; **5**: 83–90.
86. Dutrecq A, Willem R, Biesemans M, Bouâlam M, Meriem A, Gielen M. *Main Group Metal Chem.* 1992; **15**: 285–291.
87. Moens L, Maraite H, Mahieu B, El Khloufi A, Willem R, Gielen M. *Main Group Metal Chem.* 1992; **15**: 275–283.
88. Willem R, Bouhdid A, Mahieu B, Ghys L, Biesemans M, Tiekink ERT, de Vos D, Gielen M. *J. Organometal. Chem.* 1997; **531**: 151–158.
89. Gielen M, El Khloufi A, Biesemans M, Bouhdid A, de Vos D, Mahieu B, Willem R. *Metal-Based Drugs* 1994; **1**: 305–309.
90. Bouâlam M, Gielen M, El Khloufi A, de Vos D, Willem R, Pharmachemie BV, European Patent Publication no. 538 517, Application no. 91/202,746, 22 October 1991 [*Chem. Abstr.* 1993; **119**: 117548b.].
91. Gielen M, Lelieveld P, de Vos D, Pan H, Willem R, Biesemans M, Fiebig HH. *Inorg. Chim. Acta* 1992; **196**: 115–117.
92. Willem R, Dalil H, Broekaert P, Biesemans M, Ghys L, Nooter K, de Vos D, Ribot F, Gielen M. *Main Group Metal Chem.* 1997; **20**: 535–542.
93. Gielen M, Pan H, Willem R, de Vos D, Pharmachemie BV, European Patent Publication no. 484 596, Application no. 90/202,936.2, 6 November 1990 [*Chem. Abstr.* 1992; **117**: 111 807x.].
94. Atassi G. *Rev. Si, Ge, Sn Pb Cpds* 1985; **8**: 219–235.
95. Gielen M, Willem R, Bouhdid A, de Vos D, Pharmachemie BV, European Patent Publication no. 677 528 A1, Application no. 94/201012.5, 12 April 1994 [*Chem. Abstr.* 1996; **124**: 87376c.].
96. De Clercq L, Willem R, Gielen M. *Bull. Soc. Chim. Belg.* 1984; **93**: 1089–1097.
97. Gielen M, El Khloufi A, Biesemans M, Willem R. *Appl. Organometal. Chem.* 1993; **7**: 119–125.

98. Gielen M, El Khloufi A, Biesemans M, Kayser F, Willem R. *Appl. Organometal. Chem.* 1993; **7**: 201–206.
99. Gielen M, Biesemans M, El Khloufi A, Meunier-Piret J, Willem R. *J. Fluorine Chem.* 1993; **64**: 279–291.
100. Gielen M, El Khloufi A, de Vos D, Kolker HJ, Schellens HM, Willem R. *Bull. Soc. Chim. Belg.* 1993; **102**: 761–764.
101. Gielen M, Tiekink ERT, Bouhdid A, de Vos D, Biesemans M, Verbruggen I, Willem R. *Appl. Organometal. Chem.* 1995; **9**: 639–648.
102. Ng SW, Das VGK, Gielen M, Tiekink ERT. *Appl. Organometal. Chem.* 1992; **6**: 19–25.
103. Willem R, Biesemans M, Kayser F, Bouâlam M, Gielen M. *Inorg. Chim. Acta* 1992; **197**: 25–30.
104. Ng SW, Das VGK, Gielen M. *Appl. Organometal. Chem.* 1992; **6**: 489–492.
105. Willem R, Biesemans M, Bouâlam M, Delmotte A, El Khloufi A, Gielen M. *Appl. Organometal. Chem.* 1993; **7**: 311–317.
106. Ng SW, Das VGK, Holecek J, Lycka A, Gielen M, Drew MGB. *Appl. Organometal. Chem.* 1997; **11**: 39–45.
107. Gielen M, Kayser F, Zhidkova OB, Kampel VTs, Bregadze VI, de Vos D, Biesemans M, Mahieu B, Willem R. *Metal-Based Drugs* 1995; **2**: 37–42.
108. Tiekink ERT, Gielen M, Bouhdid A, Willem R, Bregadze VI, Ermanson LV, Glazun SA. *Metal-Based Drugs* 1997; **4**: 75–80.
109. Bregadze VI, Glazun SA, Petrovskii PV, Starikova ZA, Rochev VYa, Dalil H, Biesemans M, Willem R, Gielen M, de Vos D. *Appl. Organometal. Chem.* 2003; **17**: 453–457.
110. Bregadze VI, Glazun SA, Petrovskii PV, Starikova ZA, Buyanovskaya AG, Takazova RU, Gielen M, de Vos D, Kemmer M, Bieseman M, Willem R. *Appl. Organometal. Chem.* 2003; **18**: 191–194.
111. Kemmer M, Gielen M, Biesemans M, de Vos D, Willem R. *Metal-Based Drugs* 1998; **5**: 189–196.
112. Kemmer M, Ghys L, Gielen M, Biesemans M, Tiekink ERT, Willem R. *J. Organometal. Chem.* 1999; **582**: 195–203.
113. Gielen M, Willem R, Biesemans M, Kemmer M, de Vos D, Pharmachemie BV, World Patent Publication no. C07F 7/22, A61K 31/32, WO 00/06583, Application no. PCT/NL98/00429, 28/7/98, 10 February 2000.
114. Li Q, Yang P, Wang H, Guo M. *J. Inorg. Biochem.* 1996; **64**: 181–195.
115. Yang Z, Bakas T, Sanchez-Diaz A, Charalambopoulos C, Tsangaris J, Hadjiliadis N. *J. Inorg. Biochem.* 1998; **72**: 133–140.
116. Jancso A, Nagy L, Moldrheim E, Sletten E. *J. Chem. Soc., Dalton Trans.* 1999; 1587–1594.
117. Barbieri R, Silvestri A. *J. Inorg. Biochem.* 1991; **41**: 31–35.
118. Piro V, Di Simone F, Madonia G, Silvestri A, Giuliani AM, Ruisi G, Barbieri R. *Appl. Organometal. Chem.* 1992; **6**: 537–542.
119. Barbieri R, Silvestri A, Giuliani AM, Piro V, Di Simone F, Madonia G. *J. Chem. Soc., Dalton Trans.* 1992; 585–590.
120. Barone G, Cotta Ramusino M, Barbieri R, La Manna G. *J. Mol. Struct.* 1999; **469**: 143–149.
121. Barbieri R, Huber F, Silvestri A, Ruisi G, Rossi M, Barone G, Barbieri Paulsen A. *Appl. Organometal. Chem.* 1999; **13**: 595–603.
122. Ghys L, Biesemans M, Gielen M, Garoufis A, Hadjiliadis N, Willem R, Martins JC. *Eur. J. Inorg. Chem.* 2000; 513–522.
123. Casini A, Messori L, Orioli P, Gielen M, Kemmer M, Willem R. *J. Inorg. Biochem.* 2001; **85**: 297–300.
124. Bouâlam M, Biesemans M, Meunier-Piret J, Willem R, Gielen M. *Appl. Organometal. Chem.* 1992; **6**: 197–205.
125. Kayser F, Biesemans M, Bouâlam M, Tiekink ERT, El Khloufi A, Meunier-Piret J, Bouhdid A, Jurkschat K, Gielen M, Willem R. *Organometallics* 1994; **13**: 1098–1113.
126. Gielen M, Biesemans M, Willem R, Tiekink ERT. *Eur. J. Inorg. Chem.* 2004; 445–451.
127. Meddour A, Mercier F, Martins JC, Gielen M, Biesemans M, Willem R. *Inorg. Chem.* 1997; **36**: 5712–5715.

