Tetraethylammonium (diorgano)halogeno(thiosalicylato)stannates: synthesis, characterization and *in vitro* antitumor activity

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Abstract

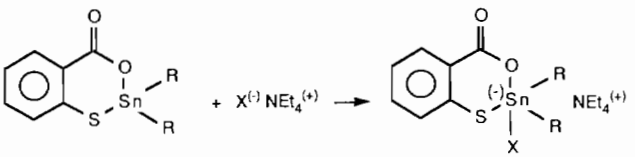
Some tetraethylammonium adducts of diorganotin thiosalicylates were prepared and characterized by Mössbauer, ^{1}H, ^{13}C, ^{19}F and ^{119}Sn NMR spectroscopy. Their solution chemistry in DMSO at equilibrium is discussed on the basis of ^{119}Sn NMR data. These data are explained in terms of the complex being six-coordinate with one DMSO ligand and existing as a mixture of at least five isomers. These adducts appear to be only slightly more active *in vitro* than the parent diorganotin thiosalicylates against MCF-7, a mammary tumor, and especially against WiDr, a colon carcinoma. The ionic character of the species, resulting in higher solubility, did not provide higher antitumor activities.

Introduction

Diorganotin thiosalicylates exhibit *in vitro* antitumor activities [1] against two human tumor cell lines, MCF-7, a mammary tumor, and WiDr, a colon carcinoma. Atassi [2] suggested that the generally low antitumor activity of organotin compounds arises from their usually low water solubility. Therefore ionic adducts of such organotin compounds could exhibit an improved activity with respect to their parent diorganotin thiosalicylates. This prompted us to prepare some tetraethylammonium adducts of diorganotin thiosalicylates already found to exhibit some activity *in vitro*.

The molecular structure of tetraethylammonium dimethyl(halogeno)thiosalicylatostannate was determined through X-ray diffraction analysis by Holmes and co-workers [3]. The two methyl groups and the sulfur atom were shown to occupy the equatorial positions of a trigonal bipyramid, while the oxygen and the halide span the apical positions, as expected.

The diorgano(halogeno)thiosalicylatostannates, prepared in the present work in acetonitrile, (with R = Ph, X = F, compound **1**; R = Ph, X = Cl, compound **2**; R = Ph, X = Br, compound **3**; and R = Et, X = F, compound **4**), have other organic substituents because the dimethyltin compounds tested until now are inactive [4, 5]. The compounds **1**–**4** were characterized by Mössbauer, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy.



Results and discussion

Physical properties and Mössbauer parameters

The melting points, recrystallization solvents, yields and Mössbauer parameters of compounds **1**–**4** are given in Table 1. The quadrupole splitting (*QS*) increases when the size of the halogen increases, which is in agreement with the increasing distortion observed by Holmes and co-workers [3] for the dimethyltin compounds in the crystalline state. The isomer shift (*IS*) decreases with increasing electronegativity of the halogen, as already reported [7].

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TABLE 1. Physical properties and Mössbauer parameters of the $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)X]^{(-)}[NEt_4]^{(+)}$ salts **1–4** and of the parent diorganotin thiosalicylates **5** and **6**[a]

Compound (R, X)	Melting point (°C)	Recrystallization solvent	Yield (%)	*IS* (mm/s)	*QS* (mm/s)	Γ_1 (mm/s)	Γ_2 (mm/s)
1 (Ph, F)	95–97	acetone/hexane	74	1.02	2.31	0.93	1.04
2 (Ph, Cl)	123–124	acetone/hexane	76	1.17	2.57	0.96	0.96
3 (Ph, Br)	116–117	acetone/benzene	78	1.19	2.67	1.12	1.16
4 (Et, F)	250–251	acetonitrile	69	1.26	2.73	0.86	0.87
5, $Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)$ [1]				1.19	2.75	0.85	1.02
6, $Et_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)$ [6]				1.42	3.20	0.90	0.94

[a]*IS*: isomer shift; *QS*: quadrupole splitting; Γ_1 and Γ_2: linewidths.

^{1}H NMR data

The ^{1}H NMR parameters of compounds **1–4** are presented in Tables 2 and 3. The ethyl groups of the tetraethylammonium moiety give a homonuclear A_2X_3 spin system, the methyl groups appearing as a triplet ($^3J(^1H, ^1H)$, 1:2:1) of triplets ($^3J(^1H, ^{14}N)$, 1:1:1) due to the coupling constant with the spin 1 ^{14}N nucleus. The $^nJ(^1H, ^{117/119}Sn)$ coupling constants of the salts $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)X]^{(-)}$ $NEt_4^{(+)}$ are insensitive to the nucleophilicity of the solvent and are comparable with the values of the parent $R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)$ compounds observed in DMSO. It should be outlined that the $^3J(^1H, ^{117/119}Sn)$ coupling constant increases when the electronegativity of the halogen decreases. This implies that the s-character in the tin hybrid orbitals associated with the phenyl–tin bond increases with decreasing halogen electronegativity, i.e. with increasing halogen atomic radius and softness. This in turn means that the ionic character of the tin–halogen bond increases in the order F < Cl ≪ Br.

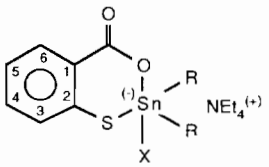

TABLE 2. ^{1}H NMR data for compounds $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}[NEt_4]^{(+)}$, **1** and **4** ($CDCl_3$ solutions): chemical shifts in ppm (multiplicities and coupling constants $^nJ(^1H, ^1H)$ in Hz); the coupling constants $^nJ(^1H, ^{117/119}Sn)$ are given between brackets

Protons	**1**, R = Ph	**4**, R = Et
H_3C	0.77 (t, 7)	1.24 (tt, 7, 2)[a]
CH_2-N	2.62 (q, 7)	3.18 (q, 7)
H_3C		1.23 (t, 8) [^3J = 122/128]
CH_2Sn		1.28 (qd[b], 8, 3) [^2J = 81]
o-C_6H_5	7.92–7.96 (m) [^3J = 75]	
m and *p*-C_6H_5	7.23–7.35 (m)	
3-H	7.37 (dd, 8, 1)	7.48 (dd, 7, 1)
4-H	7.08 (ddd, 8, 8, 2)	7.12 (ddd, 7, 7, 2)
5-H	7.03 (ddd, 8, 8, 1)	7.05 (ddd, 7, 7, 1)
6-H	8.01 (dd, 8, 2)	7.87 (dd, 7, 2)

d: doublet; t: triplet; q: quartet; m: complex pattern. [a]tt = triplet $^3J(^1H, ^1H)$ of 1:1:1 triplets $^3J(^1H, ^{14}N)$. [b]Coupling $^3J(^1H, ^{19}F)$.

^{13}C NMR data

The ^{13}C NMR data of compounds **1–4** are reported in Tables 4 and 5. The assignment of the ^{13}C resonances of the aromatic carbons of the thiosalicylato ligand, achieved by the DEPT spectra and the aromatic chemical shift increments [8], was completed with the 2D HETEROCOSY spectrum of compound **1**. The *ipso* and *ortho* carbon resonances of the phenyl groups are doublets in $CDCl_3$ solutions because of the coupling with the ^{19}F nucleus. Such a coupling is not observed for the carbon atoms of the ethyl groups in compound **4**. Though yet unexplained, this observation might be related to a stronger ionic character of the Sn–F bond in the ethyl compound than in the phenyl one.

This assumption is reasonable in view of the inductive electron releasing effect of the ethyl group as opposed to the inductive electron withdrawing effect of the phenyl group. Therefore, the Sn–F bond should have a higher covalent character in the phenyl compound than in the ethyl one.

^{19}F NMR data

The ^{19}F resonance of compound **1** was found at 149.8 ppm [$^1J(^{19}F, ^{117/119}Sn)$ = 2261/2366 Hz].

^{119}Sn NMR data

Usually the ^{119}Sn chemical shifts are strongly solvent- and concentration-dependent. In a nucleophilic medium, upfield shifts of 100 ppm are not uncommon. The results in Table 6 indicate that the salts $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)X]^{(-)}$ $NEt_4^{(+)}$ do not follow this trend. The

TABLE 3. ^{1}H NMR data for compounds $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)X]^{(-)}[NEt_4]^{(+)}$, **1–4** (DMSO-$d_6$ solutions): chemical shifts in ppm (multiplicities and coupling constants $^nJ(^1H, ^1H)$ in Hz); the coupling constants $^nJ(^1H, ^{117/119}Sn)$ are given between brackets

Protons	**1**: Ph; F	**2**: Ph; Cl	**3**: Ph; Br	**4**: Et; F
H_3C	1.12 (tt, 7, 2)[a]	1.12 (tt, 7, 2)[a]	1.13 (tt, 7, 2)[a]	1.14 (tt, 7, 2)[a]
CH_2-N	3.14 (q, 7)	3.17 (q, 7)	3.17 (q, 7)	3.19 (q, 7)
H_3C				1.12 (t, 8) [^3J=119]
CH_2Sn				1.08–1.10 (m) [^2J:(nv)]
o-C_6H_5	7.82–7.86 (m) [^3J=77]	7.97 (dd, 7, 2) [^3J=79]	7.73–8.01 (m) [^3J=86]	
m and *p*-C_6H_5	7.32–7.39 (m)	7.34–7.43 (m)	7.35–7.41 (m)	
3-H	[b]	[b]	[b]	7.34 (dd, 7, 1)
4-H	7.13 (ddd, 7, 7, 2)	7.17 (ddd, 8, 8, 1)	7.21 (dd, 7, 7)	7.10 (ddd, 7, 7, 2)
5-H	7.04 (ddd, 7, 7, 1)	7.06 (ddd, 8, 8, 1)	7.10 (dd, 7, 7)	6.99 (ddd, 7, 7, 1)
6-H	[c]	7.86 (dd, 8, 1)	[c]	7.69 (dd, 7, 2)

d: doublet; t: triplet; q: quartet; m: complex pattern; nv: non-visible. [a]tt = triplet $^3J(^1H, ^1H)$ of 1:1:1 triplets $^3J(^1H, ^{14}N)$. [b]Overlapping with the signals of the *m* and *p*-C_6H_5 protons. [c]Overlapping with the *o*-C_6H_5 protons.

TABLE 4. ^{13}C NMR data of compounds $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}[NEt_4]^{(+)}$, **1** and **4** ($CDCl_3$ solutions): chemical shifts in ppm; the calculated values using chemical shift increments of aromatic substituents [8] are given between accolades; the coupling constants ($^nJ(^{13}C, ^{19}F)$) are given between parentheses; the coupling constants [$^nJ(^{13}C, ^{117/119}Sn)$] are given between brackets

Carbon	**1**: R = Ph; X = F	**4**: R = Et; X = F
H_3C	6.7	7.2
CH_2-N	51.6	52.4
H_3C		7.8 [^2J=37]
CH_2-Sn		14.3 [^1J=622/651]
i-C_6H_5	143.8 (^2J=20) [^1J=957/1000]	
o-C_6H_5	136.4 (^3J=2) [^2J=54]	
m-C_6H_5	127.6 [^3J=82]	
p-C_6H_5	128.7 [^4J=20]	
C(1) {130.9}	136.1	137.1
C(2) {132.5}	135.2 [^2J=20]	136.8
C(3) {128.9}	133.0 [^3J=45]	134.1 [^3J=27]
C(4) {133.3}	129.1	128.9
C(5) {125.0}	123.9	124.1
C(6) {130.7}	131.7	131.3
COO	171.3	171.8

fluorides **1** and **4** exhibit a ^{119}Sn shielding only slightly larger in DMSO than in $CDCl_3$. Furthermore, the ^{119}Sn chemical shift of the fluoride adduct **1** in $CDCl_3$ is more negative than that of the parent compound **5** in DMSO. This points to a higher coordination ability of the fluoride ligand of **1** in $CDCl_3$ than of the DMSO ligand of **5** in the DMSO solution. The coordination sphere around tin in the fluoride appears to be almost unaltered when DMSO is the solvent rather than $CDCl_3$. The ^{119}Sn chemical shift of the chloride and bromide adducts of the diphenyltin compound, **2** and **3**, only soluble in DMSO, is close to that of the parent compound **5** in the same solvent. This suggests that the hexacoordination proposed for the parent compound **5** [1] in DMSO is preserved for the two halide adducts **2** and **3**. In this view, the hexacoordination is achieved through the coordination of two DMSO molecules to the tin atom in the parent compound **5**, whereas it is achieved by the halide ion and one DMSO ligand in compounds **2** and **3**.

The ^{119}Sn NMR spectra of the fluoride adducts **1** and **4** in $CDCl_3$ exhibit $^1J(^{119}Sn, ^{19}F)$ coupling constants of 2335 and 2223 Hz, respectively (Table 6). These values are comparable to those found for triorganotin fluorides [9] and for complexes of the type $[Sn\text{-}F_{6-n}(OH)_n]^{2-}$ [10]. In $CDCl_3$, the substitution of the ethyl groups by the phenyl ones causes a small increase of the $^1J(^{119}Sn, ^{19}F)$ coupling constant.

The ^{119}Sn NMR spectra of the diphenyltin halide adducts **1** to **3** in DMSO are remarkable. Instead of the single doublet of compound **1** in $CDCl_3$, five doublets with $^1J(^{119}Sn, ^{19}F)$ values of 2386 ± 6 Hz are now observed in the integrated intensity ratio 1:5.8:15.1:5.6:1.1. At 186.5 MHz and 30 °C, these resonances are separated from one another by 46–60 Hz. At 93.2 MHz and 30 °C, only a single broad doublet is observed. At 186.5 MHz and 80 °C, such a broad doublet is likewise observed. These results suggest an exchange coalescence becoming observable on the ^{119}Sn NMR time scale at 93.2 MHz and 30 °C and at 186.5 MHz and 80 °C. Five resonances are also observed for the chloride adduct **2**. For the bromide adduct **3**, only a very broad signal is observed.

We interpret these observations as being due to the presence of diastereomeric species in DMSO solution. Assuming six-coordination in DMSO, these halides can exist as several isomers shown in Fig. 1. It is possible to predict qualitatively the relative stability of these isomers according to the basic principle that ligands of comparable electronegativities should occupy as much as possible *trans* positions in order to redistribute

TABLE 5. ^{13}C NMR data of compounds $[R_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)X]^{(-)}[NEt_4]^{(+)}$, **1–4** (DMSO-$d_6$ solutions): chemical shifts in ppm; the calculated values using chemical shift increments of aromatic substituents [8] are given between accolades; the coupling constants $^nJ(^{13}C, ^{19}F)$ are given between parentheses; the coupling constants $^nJ(^{13}C, ^{117/119}Sn)$ are given between brackets

Carbon	**1**: R = Ph; X = F	**2**: R = Ph; X = Cl	**3**: R = Ph; X = Br	**4**: R = Et; X = F
H_3C	7.1	7.1	7.1	7.1
CH_2-N	51.5	51.6	51.5	51.5
H_3C				9.7 [^2J = 38]
CH_2Sn				13.9 [^1J = 642/670]
i-C_6H_5	144.3 (^2J = 21)	144.7 [^1J = 908/951]	143.5 [^1J = 899/940]	
o-C_6H_5	136.5 [^2J = 54]	136.1 [^2J = 58]	135.9 [^2J = 57]	
m-C_6H_5	128.0 [^3J = 80]	128.1 [^3J = 83]	128.3 [^3J = 82]	
p-C_6H_5	129.1	129.1	129.5	
C(1) {130.9}	136.7	137.3	[a]	137.3
C(2) {132.5}	135.8 [^2J = 20]	135.0	134.8	137.0
C(3) {128.9}	133.1 [^3J = 47]	132.5 [^3J = 54]	134.1 [^3J = 68]	133.5 [^3J = 31]
C(4) {133.3}	129.4	129.7	130.0	128.7
C(5) {125.0}	124.0	124.2	124.7	123.6
C(6) {130.7}	131.6	134.7	132.7	131.1
COO	171.3	169.5	169.2	169.7

[a]Overlapping with the signal of the *o*-C_6H_5 carbon.

TABLE 6. ^{119}Sn NMR parameters for compounds **1–5**; the values of the $^1J(^{119}Sn, ^{19}F)$ coupling constant (in Hz) are given between brackets; the relative intensities of the resonances is given between parentheses

Compound	$\delta(^{119}Sn)$ in $CDCl_3$	$\delta(^{119}Sn)$ in DMSO-d_6
1, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}NEt_4^{(+)}$	−311.5 [2335]	−323.8 [2380] (1) −324.1 [2393] (5.8) −324.4 [2393] (15.1) −324.6 [2392] (5.6) −324.9 [2384] (1.1)
2, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)Cl]^{(-)}NEt_4^{(+)}$		~ −285.3[a] (~0.3) −285.6 (1.0) −285.8 (2.0) −286.0 (1) ~ −286.3[a] (~0.3)
3, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)Br]^{(-)}NEt_4^{(+)}$		−283.4 (broad signal)
4, $[Et_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}NEt_4^{(+)}$	−160.0 [2223]	−174.2 [~2400] (broad doublet)
5, $Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)^{(6)}$		−276.4

[a]The two lateral peaks appear as shoulders.

optimally the six sp^3d^2 hybrids of the central atom in the ideal MX_6 octahedron into one pair of sp and two different pairs of pd hybrids in the present MABCDEF case. Applying this principle, the diastereomer **a** is expected to be the most stable one because it has two *trans* phenyl groups and the fluoride ligand *trans* to the oxygen of the thiosalicylate moiety. The diastereomer **b** is expected to be less stable because the fluoride is *trans* to the sulfur of the thiosalicylate. In all other possible isomers, the phenyl groups span *cis* positions. Isomer **c** has one phenyl *trans* to DMSO, which is probably less unfavourable than the fluoride *trans* to sulfur of isomer **b**. However, since the phenyl groups are *cis* to one another in isomer **c**, it might have a stability analogous to that of isomer **b**. In isomer **d**, the fluoride *trans* to the phenyl group, and the *cis* phenyl groups lead to a stereoisomer less stable than **b** or **c**. Isomer **d** is probably of comparable stability as isomer **e**, where a phenyl group is *trans* to the oxygen atom rather than to the fluoride. Isomers **f** and **g** should be much less stable because of the three unfavourable pairs of *trans* ligands. We propose that the resonances of the ^{119}Sn NMR spectra of compounds **1** and **2** in DMSO arise from the five diastereoisomers **a–e**.

An analogous phenomenon was mentioned in the literature. When $X^{(-)}$ ($OH^{(-)}$, $Cl^{(-)}$ or $Br^{(-)}$) is added to an aqueous solution of $SnF_6^{(2-)}$, all the possible mixed octahedral species $SnF_{6-n}X_n^{(2-)}$ with n = 0–6 are obtained, geometrical isomers included, in statistical ratios reflecting their respective symmetry numbers [11,

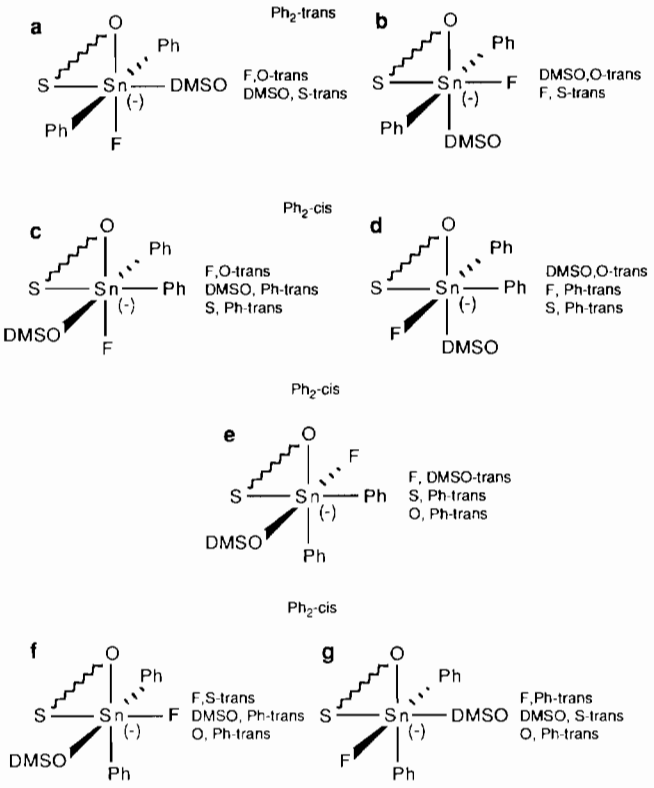

Fig. 1. All the possible diastereoisomers for the six-coordinate fluoride adduct **1** solvated by a DMSO molecule. Isomers **a** and **b** are achiral; isomers **c**–**e** are chiral as are the two unlikely ones, **f** and **g**.

TABLE 7. ID_{50} inhibition doses (in ng/ml) measured for compounds **1** to **4** and for some parent compounds, and cis-platin as reference compounds against MCF-7 and WiDr

Compound	Cell lines	
	MCF-7	WiDr
1, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}NEt_4^{(+)}$	360	831
2, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)Cl]^{(-)}NEt_4^{(+)}$	349	1319
3, $[Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)Br]^{(-)}NEt_4^{(+)}$	256	831
4, $[Et_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)F]^{(-)}NEt_4^{(+)}$	1106	2974
5, $Ph_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)$	585	15800
$n\text{-}Bu_2Sn(O_2C\text{-}C_6H_4\text{-}2\text{-}S)$	92	334
cis-platin [15]	850	624

12]. Furthermore the exchange between these different species appeared to be slow within the ^{19}F NMR time scale [11].

In the case of compound **1**, the statistical distribution would be 1:1:2:2:2 for the two achiral isomers **a** and **b** and for the three pairs of enantiomers **c**–**e**, respectively, because they have all a symmetry number one. The actual distribution reflects the relative stabilities of the different stereoisomers according to the above-mentioned argumentation. The existence of an exchange between these different species is undisputable from the line broadening observed in the doublet at 30 °C and 93.2 MHz on the one hand, and at 80 °C and 186.5 MHz on the other hand. Moreover these diastereomer conversions are rapid on the proton and ^{13}C NMR time scales, since single ^{1}H and ^{13}C resonances are observed for all types of atoms. An attempt to obtain exchange cross-peaks from a ^{119}Sn 2D EXSY (EXchange SpectroscopyY) NMR spectrum failed so that no data could be gained to propose a specific exchange mechanism for compound **1**. However there is only little doubt that the exchange occurs through intermolecular transfer of DMSO via a five-coordinate intermediate since the fluorine–tin coupling is preserved on the observational time scale. In the case of the bromide adduct **2** and the fluoride adduct **4**, the existence of an exchange phenomenon can be deduced from the broad line observed. Because the doublet coalesces in the case of the fluoride adduct **4**, the $^{1}J(^{119}Sn, ^{19}F)$ coupling gets lost on the NMR time scale, indicating that the diethyltin fluoride adduct undergoes an intermolecular fluoride exchange becoming rapid on the ^{119}Sn NMR time scale. This is in obvious contrast with the diphenyltin fluoride adduct **1** in which this intermolecular fluoride exchange is slow on the ^{119}Sn NMR time scale.

Analogous exchanges were proposed in the literature for halogenophosphates and -silanes [13, 14].

In vitro antitumor activities

Table 7 reveals the activities of compounds **1** to **3** to be comparable or better than that of the parent compound **5**. This improved activity, that might be due to the higher water solubility of the ionic compounds **1**–**3**, is however of little significance with regards to the activity of di-n-butyltin thiosalicylate, which is significantly higher than that of all the compounds mentioned in Table 7.

Experimental

Syntheses

The tetraethylammonium adducts were prepared following the procedure described by Holmes and coworkers [3].

Instruments

The ^{119m}Sn Mössbauer spectra were recorded at liquid nitrogen temperature with $Ca^{119m}SnO_3$ as the source using a home-made microprocessor-based device operating in constant acceleration mode.

The ^{1}H NMR spectra were recorded at 270.13 MHz on a Bruker AM 270 instrument (TMS as internal reference); the ^{13}C NMR spectra were obtained at 62.9

MHz from a Bruker SF 250 instrument (solvent peak as internal reference); the ^{19}F NMR spectra were recorded at 235.19 MHz on a Bruker AC250 instrument ($CFCl_3$ as external reference); the ^{119}Sn NMR spectra were obtained at 186.5 MHz from a Bruker WM 500 instrument and at 93.2 MHz from a Bruker AC250 instrument (tetramethyltin as external reference).

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