

Biologically Potent New Organotin(IV) Complexes of *N*-Maleoyltranexamic Acid

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Five new diorganotin(IV) complexes of the general composition $[R'_2SnR_2]$ (where R′: Me, Et, Bu, Ph, Bn and R: *N*-maleoyltranexamic acid) have been prepared and structurally characterized by means of FT IR and ^{119m}Sn Mössbauer spectroscopy in the solid state. The solution-state structures were determined by means of multinuclear NMR (^{1}H, ^{13}C, and ^{119}Sn) spectroscopies. The spectroscopic data explained the 1:2 metal to ligand stoichiometry and hypervalency of Sn^{IV} in a *trans*-octahedral arrangement. Inveterate mass spectrometric and elemental analysis data has supported the solid and solution spectroscopic results. The complexes and the ligand have been evaluated in vitro against seven human tumoural cell lines. Interesting results were noticed during the bio-activity screenings, which proved their in vitro biological potential. The nature of covalent attachments (methyl, ethyl, butyl, phenyl, and benzyl) of Sn^{IV} has played a decisive role from the bioactivity stand-point.

Organotin(IV) compounds have wide-ranging practical applications, although their usage has considerably decreased in the last decade or so due to environmental concerns.[1,2] However, organotin(IV) derivatives, and particularly those of dialkyltin(IV) have been found to possess anti-cancer effects on different tumour cells.[3] The moieties like $[R_nSn^{IV}]^{(4-n)+}$ ($n = 2$ or 3) can bond to proteins and glycoproteins of the cell membranes and also to cellular proteins and DNA.[4] Carboxylate oxygens are frequent donor atoms for organotin(IV) cations in both proteins and biologically relevant low molecular weight compounds, such as amino acids and glutathione.[5] These facts have led to considerable efforts to synthesize and characterize ligands containing oxygen donor atoms.[5,6] The interaction of carboxylate ligands with organotin(IV) cations is interesting from the practical point of view, since such complexes are widely used as PVC stabilizers.[1,5–7] The present paper describes the solution- and solid-state spectral analysis of new diorganotin(IV) complexes of *N*-maleoyltranexamic acid. These complexes were also tested in vitro for their toxicity against tumour cell lines of human origin.

Results and Discussion

The reported complexes **1**–**5** are non-hygroscopic, quite stable at room temperature, non-crystalline afforded in with good yields (77–86%), and are soluble in most organic solvents. The elemental analysis data were in good agreement with the calculated percentages of C, H, N, and Sn for all the synthesized complexes.

Characteristic vibrational frequencies have been identified by comparing the spectra of all the complexes with their precursors; the bands associated with the *N*-maleoyl ring are in positions similar to those they occupy as a free ligand, which rules out any coordination to Sn^{IV} via maleimido C=O.[8] The data are consistent with the formation of well-defined complexes with the composition R'_2SnR_2, which was confirmed by the presence of Sn–O and Sn–C bonds in the range 515–560 and 525–540 cm^{-1}, respectively; the broad band of the OH group disappeared in the spectra of all the complexes.[9] The difference of $\Delta\nu$ between the carboxylic group's $\nu(COO)_{sym}$ and $\nu(COO)_{asym}$ give interesting information about the molecular arrangement in such complexes; the literature reveals that the complexes where difference of $\Delta\nu < 200\,cm^{-1}$, the carboxylate group of such complexes can be considered to be practically bidentate (Fig. 1) in a *trans*-octahedral arrangement.[10]

^{119m}Sn Mössbauer spectroscopy provides useful information on the geometry around a tin nucleus in the solid state.[11] All the complexes present one hexa-coordinated Sn(IV) site. Iso-

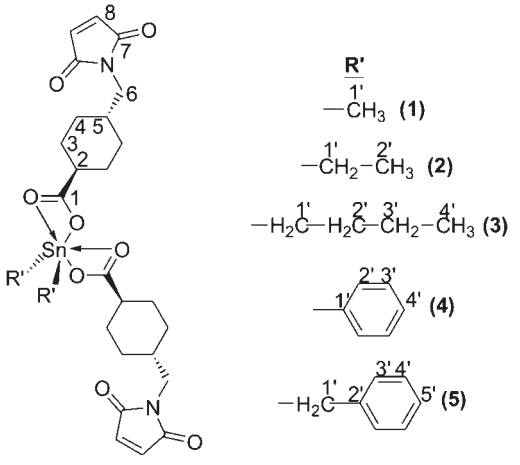

Fig. 1. *trans*-Octahedral geometry and numbering scheme for NMR.

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mer shifts of **1–5** fell in the range 1–1.28 mm s^{-1} lower than that of the parent organotin moieties; this decrease in IS values is a consequence of rehybridization to higher coordination for Sn^{IV} atoms in the complexes, indicating lower s-electron density at the Sn^{IV} nucleus in the complexes as compared to the precursor tins.[12] This can be attributed to the great involvement of d-orbitals, which take part in the Sn^{IV} hybridization, thus reducing the weight of s-orbitals in the overall hybridization of the metal; similar results have been reported for a great variety of other organotin(IV) compounds.[7,12,13] Quadrupole splitting (QS) values; are not sufficient to characterize a Sn^{IV} complex as tetra-, penta-, or hexa-coordinated,[14] but a comparison with the reported QS data for analogous compounds[7,10–16] leads to a conclusion that in the solid state the complexes **1–5** are six-coordinated in *trans*-octahedral geometry. These results are in full agreement with the structural hypothesis based upon the FT IR study. Such combination of spectroscopic methods in the solid state is important for the detection of coordination modes of hypervalent organotin(IV) compounds.

^{1}H and ^{13}C signals in the NMR spectra of **1–6**, were successfully assigned with the help of data on *N*-protected amino acids.[7] The integrated intensities in the ^{1}H NMR spectra clearly indicate a 1:1 metal-to-ligand stoichiometry in solution in agreement with the analytical data on the solids. Characteristic values of $J[^{119}Sn–^{1}H]$ are extremely helpful in determining the C–Sn–C angle (θ), with the help of Lockhart's equation.[17]

In ^{13}C NMR spectroscopy of organotin(IV) complexes, $J[^{119}Sn–^{13}C]$ values of R′ provide a simple way for the determination of the C–Sn–C bond angle in the coordination polyhedra of such complexes.[18] Two R′ groups attached to Sn^{IV} are bonded through an sp^2 hybrid orbital of the Sn atom and sp^3 hybrid orbital of the carbon atoms resulting in increase in the $J[^{119}Sn–^{13}C]$ values, thereby indicating a *trans*-octahedral geometry (Fig. 1).[7,16] In ^{13}C NMR the $^{1'}J[^{119}Sn–^{13}C]$ values provide vital information for determining θ(C–Sn–C): substituting $^{1'}J$ values in Eq. 1, θ can be calculated; θ(C–Sn–C) for **1–5** obtained from Eq. 1 were $> 126^\circ$, in agreement with the other experimental results, suggesting an octahedron.

$$^{1'}J = 11.4\theta - 875. \quad (1)$$

Moreover, it is also reported in the literature that for such type of diorganotin(IV) dicarboxylates, the $^{n'}J[^{119}Sn–^{13}C]$ follow the trend $[^{1'}J] \gg [^{2'}J] < [^{3'}J]$, which is characteristic of the *trans*-octahedral geometry.[18,19]

The ^{119}Sn nucleus is influenced by several factors, including the aromatic or aliphatic nature of R′ group bound to the tin atom (and possibly the type of donor atoms of the ligand); it may be used with caution to infer the coordination number of the tin atom.[20] The solution ^{119}Sn NMR spectra of all the complexes show just one signal at −152.5, −140.7, −121.6, −90.7, and −42.4 ppm for complexes **1–5**, respectively, which kowtow previous data for analogous hexa-coordinated diorganotin(IV) carboxylates in a *trans*-octahedral arrangement.[7,19,20]

The CI mass spectral data for **1–5** are given in Table 7. A molecular ion peak of very low intensity is observed in complexes **2**, **3**, and **5**, while **1** and **4** it was absent. The base peaks are due to a $[C_5H_4NO_2]^+$ fragment at m/z 110 in **1**, **3**, and **5**, while in **2** and **4** the $[C_{11}H_{14}NO_2Sn]^+$ fragment is at m/z 408. Primary fragmentation is due to the consecutive loss of R′ groups, however, secondary and tertiary fragmentation occurs by the loss of an R group.[21] Secondary fragmentation is achieved due to a loss of either an R′ group or CO_2 molecule. The general fragmentation pattern is given in Fig. 2. Two modes of fragmentation are depicted in Fig. 2 and it was observed that all the complexes obey these modes ably supported by literature.

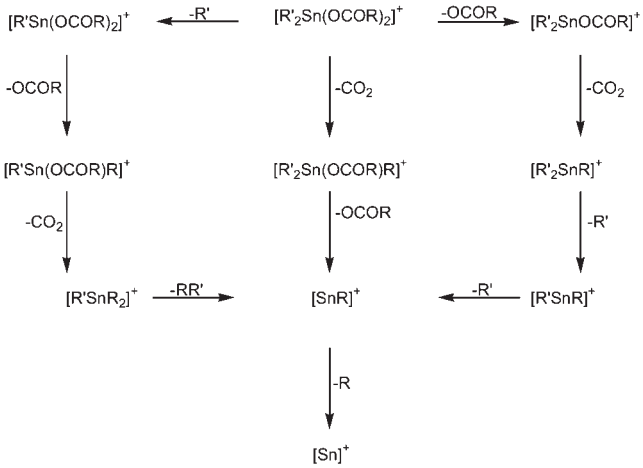


Fig. 2. General fragmentation pattern for complexes **1–5**.

All the complexes (**1–5**) exhibited interesting results during the in vitro anti-tumour activity against seven human cell lines. The literature reveals that some workers suggested that organotin(IV) compounds wield anti-tumour effects through binding to thiol groups of proteins, in contrary, but in analogy with the behavior of several cytotoxic organotin(IV) complexes may interact with DNA.[22,23] However, the cause of enhancement in cytotoxicity and the exact mechanism of action of such organotin(IV) complexes is still a question to be answered.

It has been observed in our complexes that the in vitro cytotoxicity against the tumoural cell lines increases with the bulkiness of the R′ groups attached to Sn^{IV}. To highlight this statement, the average IC_{50} data have been plotted versus the percent CH. The percent CH has been defined as:

$$\text{Percent CH (R}') = \frac{(C_n \times 12.011) + (H_n \times 1.0079)}{\text{Molecular mass of the complex}} \times 100, \quad (2)$$

where n is the number of carbon or hydrogen atoms in R′ groups. The above mentioned plot showed that IC_{50} decreases with the increase in percent CH almost linearly. However, some deviations in the case of alkyl R′ groups have been observed, which may be attributed to variation in conformational behavior and the distribution of complexes between different phases.

Since it is difficult to judge the bioactivity of any compound by a single factor, hence we have tried another important parameter, i.e., partition coefficient; the average IC_{50} values have been plotted versus it (see Fig. 3). It is interesting to note that the data of complexes **1–5** show that average IC_{50} values decrease linearly with the increase in partition coefficient. This is certainly encouraging for us that the major controlling parameter seems to be P_{ow} (partition coefficient in an octanol/water system) or, in other words the polarizibility of the R′–Sn

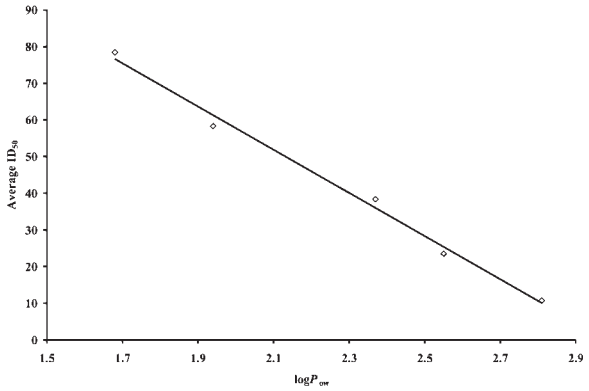


Fig. 3. Dependence of average IC_{50} over Partition coefficients of complexes **1–5**.

bond induced by R′ groups. It can therefore be concluded that in complexes **1–5**, hydrophilicity increases with the bulkiness of R′ groups, which enhances the partition coefficient, thereby boosting up the bioactivity. We can say that the increase in hydrophilicity of these complexes might be responsible for such significant results, as observed by others.[14,19] For reference Sn–C polarity (Bn > Ph > Bu > Et > Me) is in the same order. Conclusively, we can say that the bulkiness of the attached R′ group/percent CH values are interlinked with each other, which enhances the polarity and partition function of the complexes. The increase in partition coefficient provides the complexes an opportunity to interact with the target sight resulting in enhancement in activity. At higher concentrations, these complexes showed notable anti-fungal and anti-leishmanial activity, but due to endocrine disruption/environmental concerns is of no significance.

Experimental

Maleic anhydride, dimethyltin(IV) dichloride, dibutyltin(IV) dichloride, diphenyltin(IV) dichloride, and diethylamine were procured from commercial sources (AR Grade, Aldrich Chemicals). Diethyltin(IV) dichloride was an Alfa Aeser product and used as such, while dibenzyltin(IV) dichloride was prepared as reported.[24] Tranexamic acid was a gift from Tabros Parma., Pakistan. Solvents used during this work were dried according to reported methods.[25]

The ligand was synthesized as described elsewhere (Eq. 3)[26] while the complexes were synthesized as given in Eq. 4.[7] Partition coefficient measurements were made in a 1-octanol/water system.[25]

$$(CHO)_2O + H_2NC_7H_{12}COOH \rightarrow (CHO)_2NC_7H_{12}COOH + H_2O, \quad (3)$$

$$2(CHO)_2NC_7H_{12}COOH\cdots NEt_3 + R'_2SnX_2 \rightarrow [(CHO)_2NC_7H_{12}COO]_2SnR'_2 + 2Et_3NHX. \quad (4)$$

Table 1. Physical and Analytical Data for **1–6**

Compound	Mol. Formula	M.W.	mp/°C	Yield/%	Solubility
1	$C_{26}H_{34}N_2O_8Sn$	621.27	109	81	C_6H_6
2	$C_{28}H_{38}N_2O_8Sn$	649.32	154	80	C_6H_6
3	$C_{32}H_{46}N_2O_8Sn$	705.43	117	82	CH_2Cl_2
4	$C_{36}H_{38}N_2O_8Sn$	745.41	Gel	87	$CHCl_3$
5	$C_{38}H_{42}N_2O_8Sn$	773.46	143	83	$CHCl_3$
6	$C_{12}H_{15}NO_4$	237.25	89–91	80	C_2H_5OH

Table 2. Analytical Data for **1–6**

Compound	Found (Calculated)			
	%C	%H	%N	%Sn
1	50.24 (50.26)	5.50 (5.52)	4.49 (4.51)	19.08 (19.11)
2	51.77 (51.79)	5.87 (5.90)	4.29 (4.31)	18.24 (18.28)
3	54.46 (54.48)	6.55 (6.57)	3.95 (3.97)	16.80 (16.83)
4	57.98 (58.01)	5.12 (5.14)	3.74 (3.76)	15.89 (15.93)
5	59.00 (59.01)	5.45 (5.47)	3.60 (3.62)	15.30 (15.35)
6	60.73 (60.75)	6.35 (6.37)	5.88 (5.90)	—

Table 3. FT IR Spectral Data for **1–6** (cm^{-1})

Compound	ν(NCO)	$\nu(COO)_{sym}$	$\nu(COO)_{asym}$	$\Delta\nu$	ν(Sn–C)	ν(Sn–O)
1	1781	1460	1630	170	521	531
2	1772	1444	1602	158	540	515
3	1750	1432	1605	173	535	523
4	1765	1458	1651	192	550	530
5	1778	1463	1634	171	545	522
6	1750	1690	1724	34	—	—

Elemental analyses (C, H, and N) were performed on a Yanaco high-speed CHN analyzer; antipyrene was used as a reference, while tin content was estimated according to reported procedures.[27] Uncorrected melting points were taken on a Reichert Thermovar of F. G. Bode Co., Austria (Tables 1 and 2).

The FT IR spectra of the ligand and the complexes were measured on a Bruker FT IR spectrophotometer TENSOR27 using OPUS software in the range of 5000–500 cm^{-1} (Table 3).

For Mössbauer measurements, the solid samples were maintained at liquid nitrogen temperature (77.3 K) using a V. G. Micromass 7070 F Cryolid liquid nitrogen cryostat. The multichannel calibration was performed with an enriched iron foil using ^{57}Co–Pd source, while the zero point of the Doppler velocity scale was determined through the absorption spectra of $CaSnO_3$ (^{119}Sn = 0.5 mg cm^{-2}). The resulting 5 × 105-count spectra were refined to obtain the isomeric shift IS (mm s^{-1}), the nuclear quadrupole splitting QS (mm s^{-1}), ρ, and the width at half-height of the resonant peaks, Γ (mm s^{-1}), shown in Table 4.

^{1}H and ^{13}C NMR spectra in deuterated chloroform ($CDCl_3$) were recorded on a multinuclear Bruker *Biospin* AMX 300 MHz

Table 4. ^{119m}Sn Mössbauer Spectroscopic Data for **1–5**

Compound	QS /mm s^{-1}	IS /mm s^{-1}	Γ_1 /mm s^{-1}	Γ_2 /mm s^{-1}	ρ = QS/IS	^{119}Sn /ppm
Me_2SnR_2	3.11	1.41	1.21	1.03	2.21	−152.5
Et_2SnR_2	3.22	1.47	1.13	1.20	2.21	−140.7
Bu_2SnR_2	3.41	1.63	1.17	1.10	2.12	−121.6
Ph_2SnR_2	3.15	1.48	1.22	1.15	2.13	−90.7
Bn_2SnR_2	3.01	1.43	1.30	1.22	2.10	−42.4

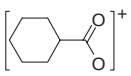
Table 5. ^{1}H NMR Data in ppm for **1–6** (^{n}J in Hz)

Proton No.	Compound					
	1 (Me)	**2** (Et)	**3** (Bu)	**4** (Ph)	**5** (Bn)	**6**
2	2.35 d	2.33 d	2.27 d	2.29 d	2.41 d	2.36 d
3	2.31 m	2.30 m	2.43 m	2.44 m	2.51 m	2.40 m
5	1.55 m	1.40 m	1.50 m	1.55 m	1.48 m	1.52 m
6	1.73 t	1.82 t	1.74 t	1.70 t	1.81 t	1.69 t
8	7.14 s	7.18 s	7.31 s	7.24 s	7.34 s	7.53 s
1′	0.34 s (38.1)	0.97 q	1.13 m	—	2.92 s (58.9)	—
2′	—	0.83 t (60.6)	1.61 m (68.4)	7.72 m (65.2)	—	—
3′	—	—	1.28 m	7.49 m	7.41 m	—
4′	—	—	0.91 m	7.31 m	7.47 m	—
5′	—	—	—	—	7.11 m	—

Table 6. ^{13}C NMR Data for Compounds **1–6** (ppm) with Coupling Constants Given in Parentheses

Carbon No.	Compound					
	1 (Me)	**2** (Et)	**3** (Bu)	**4** (Ph)	**5** (Bn)	**6**
1	190.23	191.41	190.22	189.33	188.41	196.3
2	47.43	47.41	46.63	46.98	45.33	50.32
3	29.72	29.71	29.61	28.64	28.42	29.87
4	31.44	31.40	30.94	29.81	28.97	32.14
5	34.67	33.47	34.66	34.16	33.94	35.62
6	47.53	48.41	47.22	46.66	45.64	47.00
7	170.43	171.44	170.22	171.03	170.67	179.3
8	135.26	135.43	136.42	137.71	135.94	134.6
1′	0.01 (536)	5.94 (582)	25.73 (580)	122.31 (573)	19.36 (596)	—
2′	—	5.39 (97)	26.71 (60)	134.24 (84)	142.81	—
3′	—	—	24.43 (36)	130.12	130.21 (242)	—
4′	—	—	11.86	128.81	130.02 (50)	—
5′	—	—	—	—	123.74 (100)	—

Table 7. MS Data for Compounds **1–5** (% Relative Abundance Given in Parentheses)

Fragment ion	Complex				
	1	**2**	**3**	**4**	**5**
$[R'_2Sn(OCOR)_2]^+$	621 (21)	649 (28)	705 (27)	745 (60)	773 (3)
$[R'SnOCOR]^+$	370 (36)	384 (41)	412 (26)	432 (71)	446 (61)
$[SnOCOR]^+$	355 (10)	355 (63)	355 (22)	355 (8)	355 (44)
	127 (12)	127 (23)	127 (63)	127 (20)	127 (30)
$[C_5H_4NO_2]^+$	110 (100)	110 (36)	110 (100)	110 (10)	110 (100)
$[C_{11}H_4NO_2Sn]^+$	192 (28)	455 (100)	514 (11)	554 (100)	581 (30)
$[Sn]^+$	119 (7)	119 (28)	119 (30)	119 (26)	119 (32)

FT NMR spectrometer operating at room temperature (300 MHz for ^{1}H and 75 MHz for ^{13}C); the proton and carbon chemical shifts were measured with respect to $SiMe_4$. ^{119}Sn NMR spectra in $CDCl_3$ were recorded at 186.50 MHz on a Bruker AMX-500 spectrophotometer using 5 mm o.d. tubes and are reported relative to external neat $SnMe_4$ ($\delta^{119}Sn = 0$ ppm). Detailed NMR data is given in Tables 5 and 6.

Mass spectra were recorded using EI ionization on models MAT 112 and 113 Double-Focusing Mass Spectrometer (Finnigan) connected to an IBM compatible PC based system (Table 7).

The in vitro inhibition concentrations (IC_{50} ng mL^{-1}) are presented in Table 8. The complexes **1–5** and the ligand **6** were screened in vitro against seven human cancer cell lines, i.e., MCF-7 mammary cancer, EVSA-T mammary cancer, WiDr colon cancer, IGROV ovarian cancer, M19 melanoma, MEL A498 renal cancer, and H226 lung cancer; the reference drugs used were doxorubicin (Do), cisplatin (Cp), 5-fluorouracil (5-Fu), and methotrexate (Mt) using MTT assay protocol that measures the metabolic activity of living cells.[28] In brief, the cells were seeded onto 96-well microtiter plates at a concentration of 5×10^4–10^5 cells mL^{-1}, volume 200 µL well^{-1}. The medium used was RPMI-1640 buffered with 2.2 g L^{-1} $NaHCO_3$ supplemented with

Table 8. In Vitro IC_{50} ($ng\,mL^{-1}$) of Compounds **1–6** against Seven Human Tumoural Cell Lines[a)]

Compound	Cell Line						
	A498	EVSA-T	H226	IGROV	M19	MCF-7	WiDr
1	119	77	102	55	100	66	96
2	84	70	51	42	85	40	36
3	79	38	40	10	41	18	58
4	55	31	22	7	10	11	36
5	24	22	11	>3	6	8	28
6	301	93	200	201	122	74	203
Do	28	44	68	112	201	35	66
Cp	142	68	125	325	287	214	116
5-Fu	214	325	200	225	100	54	83
Mt	3094	210	104	39	200	98	66
Et	114	301	369	329	168	104	103

a) Cell Lines: A498 (renal cancer), EVSA-T (mammary cancer), H226 (lung cancer), IGROV (ovarian cancer), M19 (melanoma), MCF-7 (mammary cancer), and WiDr (colon cancer). Reference Drugs: Do (doxorubicin), Cp (cisplatin), 5-Fu (5-fluorouracil), Mt (methotrexate), and Et (Etopside).

10% heat-inactivated foetal bovineserum (HIFBS), pH 7.4. The plates were incubated at 36.5 °C in a humidified CO_2 (10%) incubator for 24 h. Fresh medium was added to remove the old medium. Different concentrations of test compounds were added using reference drugs and solvent as controls. These plates were incubated for next the 48–72 h at 36.5 °C in a humidified CO_2 (10%) incubator. After incubation, the medium was removed from the wells, 150 µL of fresh medium + 50 µL MTT was added, and then the plates were again incubated for 4 h at 36.5 °C in the humidified CO_2 (10%) incubator. MTT was removed and the insoluble formazan product was dissolved in 50 µL of DMSO. The absorbance was measured at 540 nm. IC_{50} for compounds **1–6** was determined using the statistical analysis program Finny.

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