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Synthesis and Characterization of Dibutyltin Compounds with α-Amino Acids

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Abstract: This paper describes the preparation and description of four new complexes [$Bu_2Sn(AA)Cl$] (AA = glycine, DL-valine and L-leucine) and [$Bu_2SnPhen_2$] (Phen = DL-phenylalanine) They were characterized by elemental analyses of carbon, hydrogen, nitrogen, chlorine and tin; and by infrared, ^{119m}Sn-Mössbauer and ^{119m}Sn-RMN spectroscopies, and by the applications of TG and DSC techniques in dynamic helium atmosphere. For the [$Bu_2Sn(AA)Cl$], trigonal bipyramidal tin species, AA were coordinated bidentatedly by the carboxylic oxygen and by the NH_2 group. The [$Bu_2SnPhen_2$)], with tin atoms in *trans*-octahedral sites, had the Phen-coordinated by both carboxylic oxygen atoms.

Keywords: organotin compounds; dibutyltin compounds; tin α-amino acids compounds; thermal decomposition

1. Introduction

Amino acids are ligands potentially polidentated, that can bond to metals, enabling the synthesis of compounds with varied structures, for which the geometry and the coordination number are governed by the size and for the ramification degree of the ligand [1]. The existence of *cis*-platinum complexes, [$Pt(NH_3)_2Cl_2$], and related bis(amine) complexes in the treatment of cancer, is motivating the investigation of compounds with the same molecular modeling with other metals, among which organotin derivatives with nitrogenated group stand out, which present a promising activity [2-8]. The first reports on diorganotin compounds with antitumoral activities were published in 1980. Ever since, diorganotin compounds were tested as for their effects on biological systems, being verified that the effects are related with the stability of the compounds and with the length of the bond Sn-N. It was verified that stable compounds and whose length of the connection Sn-N is inferior to 239 nm are inactive, suggesting that the effects on biological systems are related with the dissociation of the nitrogenated ligand, as part of the mechanism of action [9-12]. A relatively high number of diorganotin compounds with N-protected amino acids is known and studied, which is verified in the pertinent literature. The first studies in solid state about diorganotin compounds of the same nature derived of simple essential α-amino acids, containing one amino group and one carboxyl group, except for a dimethyl diglycinate compound [13]; for some dibutyltin (IV) Schiff base complexes derived from phenylalanine, isoleucine, and glycine [14] and by the dimethyltin dimeric compounds with glycine or *dl*-valine, prepared in this work [15, 16]. The present investigation relates to the preparation and characterization of four new complexes [$Bu_2Sn(AA)Cl$] (AA = glycine, DL-valine and L-leucine) and [$Bu_2SnPhen_2$] (Phen = DL-phenylalanine), characterized by elemental analyses of carbon, hydrogen, nitrogen, chlorine and tin, by infrared, ^{119m}Sn-Mössbauer and ^{119m}Sn-RMN spectroscopies, and the applications of TG and DSC techniques in dynamic helium atmosphere.

2. Material and Methods

The TG curve was recorded using Shimadzu TGA-50 model at the range of 25-700 ^{o}C, the heating rate of 20 K min^{-1} and a dynamic atmosphere of helium with rate flow of 20 mL min^{-1}. The initial sample masses used were 8-10 mg.

Shimadzu DSC-50 equipment was used to record the DSC curves. The experimental conditions were: 25-200 ^{o}C temperature range, β = 10 K min^{-1} heating rate, helium purging with a flow of 50.0 mL min^{-1}. The initial sample masses were 6-8 mg.

The melting points were determined on a FP-2 Mettler system.

The infrared spectra of the complexes were recorded between 5000-275 cm^{-1}, using a Perkin Elmer Paragon 1000 spectrophotometer, in CsI pellets.

The X-ray fluorescence characterization of the TG analyses was performed by means of a Rigaku-Geigerflex spectrophotometer.

The elemental analysis of carbon, hydrogen and nitrogen was carried out using Perkin Elmer 2400CHN Elemental Analyzer.

Chlorine determination was made by neutron activation analysis. The samples were irradiated in the central tube of the Triga-3 reactor and the measurement was performed applying a Low Lewel α/β Counting System Model 2200 Canberra Proportional Detector, on the Nuclear Development Technology Center of Nuclebrás, in Belo Horizonte-MG, Brazil.

The tin determination were performed by atomic absorption by means of a Hitachi Z-8200 spectrometer.

The ^{119m}Sn-Mössbauer spectra were provided by a constant acceleration spectrometer equipped at $BaSnO_3$ source, at 85 K.

The ^{119m}Sn-NMR spectrum was obtained with a Bruker DRX 400 MHz Avance spectrophotometer, using D_2O.

The complex [$Bu_2SnGlyCl$] (compound **I**) was synthesized reacting glycine, $CH_2(NH_2)COOH$, and dibutyltin dichloride with 1:1 molar ratio. The α-amino acid was added to stirred methanol solutions for 2 h. After adding the tin compound, the system was further stirred and refluxed over night. After reduction of 50% in the volume of the solvent, the solution was maintained at -18 ^{o}C for 24-48 h. The mixture was then filtered at room temperature and the obtained solid was washed with methanol (3 x 2 mL) and dried at 100 ^{o}C in an Abderhalden pistol for 1 h with all manipulations performed in air.

The complexes [$Bu_2SnValCl$] (compound **II**) were synthesized from DL-valine, $(CH_3)_2CHCH(NH_2)COOH$; [$Bu_2SnLeuCl$] (compound **III**) from L-leucine, $(CH_3)_2CHCH_2CH(NH_2)COOH$; and [$Bu_2SnPhen_2$] (compound **IV**) from DL-phenylalanine, $C_6H_5CH_2CH(NH_2)COOH$, using similar procedures which were written for compound **I**.

Complexes **I** to **IV** were characterized by their IR spectra, by elementary analysis of carbon, hydrogen, nitrogen, chlorine and tin and by ^{119m}Sn-Mössbauer and ^{119m}Sn-NMR spectroscopic studies.

3. Results and discussion

The new complexes [$Bu_2SnGlyCl$] (compound **I**), [$Bu_2SnValCl$] (compound **II**), [$Bu_2SnLeuCl$] (compound **III**) and [$Bu_2SnPhen_2$] (compound **IV**), were observed using optical microscope. They exhibited microcrystalline constitution. As it was observed for the glycine and DL-valine dimethyltin derivatives previously prepared in this work [15, 16], it - was not possible to obtain suitable single crystals to determine their structures by X-ray crystallography. Similarly during several attempts to recrystallize the complexes which underwent decomposition, even under inert atmosphere, producing crystals of dibutyltin oxide, Bu_2SnO.

The melting points and the results of elementary analysis of carbon, hydrogen, nitrogen, chlorine and tin for **I** to **IV** are shown in Table 1.

Table 1. Melting points and elementary analysis data for the dibutyltin complexes

Compo-und	Molecular mass/ g mol^{-1}	Yield/ %	*m.p.*^{1}/ ^oC	C/% found (calc.)	H/% found (calc.)	N/% found (calc.)	Cl/% found (calc.)	Sn/% found^2 (calc.)	Sn/% found^3 (calc.)
I	342.45	65	150-153	34.4 (35.1)	5.8 (6.5)	4.1 (4.1)	12 ± 2 (10.4)	33.6 (34.6)	34.1 (34.7)
II	384.53	70	138-141	41.0 (40.6)	8.4 (7.3)	3.7 (3.6)	9 ± 1 (9.2)	30.2 (30.9)	30.1 (30.9)
III	398.56	60	107-110	40.9 (42.2)	7.7 (7.6)	3.3 (3.5)	11 ± 3 (8.9)	28.9 (29.9)	29.2 (29.8)
IV	561.31	50	191-194	55.7 (55.6)	7.2 (6.8)	5.6 (5.0)	---	20.8 (21.1)	20.8 (21.1)

[1]Determined on a FP-2 Mettler system; [2]by atomic absorption; [3]by TG analysis

In the experiments for the synthesis of the dibutyltin compounds described in this work, it was verified that the relative reactivity of the α-amino acids ligands was sensibly lower than the one of α-hydroxycarboxylic acids used in the synthesis of the organotin compounds also previously described by the authors[17-20].

The most representative stretching vibrations from the infrared spectra of **I** to **IV** are presented in Table 2. The evaluation of the infrared spectra of glycine, DL-valine, L-leucine and DL-phenylalanine allowed to assign the ν_{COOass} values which were in good agreement with the literature data [20]. In the infrared spectra of **I** to **IV** relatively small shifts for the ν_{COOass} values were verified for the highest region in the spectra of the complexes, in relation to the free α-amino acids. The observed alterations are from 1600 to 1620 cm^{-1} for glycine in **I**, from 1595 to 1605 cm^{-1} for DL-valine in **II**; from 1580 to 1590 cm^{-1} for DL-leucine in **III** and from 1620-1585 to 1640 cm^{-1} for DL-phenylalanine in **IV**, indicating the participation of the carboxyl of the α-amino acids in the coordination to the tin [21-23]. Similar results were obtained for the other compounds [$(CH_3)_2Sn(AA)_2$ (AA = glycine, alanine) [1, 13] and for the compounds [$(CH_3)_2Sn(AA)Cl$] (AA = glycine, DL-valine [15, 16]. In the first case, in the infrared spectra of both complexes the ν_{COOass} values were shifted to 1605 cm^{-1} for free amino acids and to 1629 cm^{-1} for the derivatives [1, 11, 20-24], whereas in the second case, in the infrared spectra of both complexes the ν_{COOass} values were shifted to 1600 and 1595 cm^{-1} for free amino acids and to 1610 and 1640 cm^{-1} for the derivatives, respectively [16].

Table 2. Representative stretching data (cm^{-1}) for the dibutyltin complexes

Compounds	Free ligands		Complexes								
	ν_{NH}	ν_{COOass}	ν_{COOass}	ν_{COOsym}	$\Delta\nu$	ν_{NH}	ν_{CH}	ν_{SnO}	ν_{SnC}	ν_{SnN}	ν_{SnCl}
I	3170	1600	1620	1440	180	3190	2960 2900 2850	450	560 550	410	310
II	3140	1595	1605	1410	195	3120	2940 3920 2840	445	570 555	395	255
III	3100	1580	1590	1405	185	3150	2940 2900 2840	455	565 555	380	325
IV	3100	1620 1585	1640	1410	230	3410	2960 2900	445	570 550	---	---

The $\Delta\nu = \nu_{COO\ (ass)} - \nu_{COO\ (sym)}$ values have also been used as criterion for the evaluation of the forms of coordination of amino acids to the metals, helping in the molecular structures inferences [1, 24, 28]. The magnitude of Δν can be indicated in carboxylate groups linked by one or both atoms of oxygen; simultaneous coordination by both carboxylic and amine groups or with the formation of intermolecular hydrogen bonds, as in liquid carboxylic acids free [24, 28-34]. However, conflicting values have been mentioned in the literature. Ho and Zuckerman studying trialkyltin amino acids and dipeptides derivatives set up that Δν = 205-264 cm^{-1} indicates coordination by the desprotonated alcoholic oxygen of the carboxylate and by the NH groups [1]. For organotin compounds with EDTA, Sandhu and Hundal established that Δν = 400-435 cm^{-1} indicates carboxylate groups intermolecularly bonded, and that for Δν = 205-264 cm^{-1}, carboxylates bonded bidentatedly [34]. In the studied complexes a Δν = 180 cm^{-1} for glycine in **I**, a Δν = 195 cm^{-1} for DL-valine in **II** and a Δν = 185 cm^{-1} for L-leucine in **III** were verified, suggesting the participation only of the oxygen atoms of the carboxylic group in the coordination of the amino acids to the tin. In case of DL-phenylalanine in **IV** an $\Delta\nu = 230$ cm^{-1}, it was observed suggesting the participation of both oxygen atoms of the carboxylic group in the coordination of the amino acids to the tin [24, 28-34].

The stretching of N-H may also help to explain the coordination form of amino acid. Free NH_2 groups were found in the amino acid salts, like in sodium glycinate, where ν_{NH} appeared at 3380 cm^{-1}. Compared to the free glycine, where the band of the zwitterions form H_3N^+-CH_2-COO^-, appears at $\nu_{NH} = 3170$ cm^{-1} [35]. Glycine, in the H_2N-CH_2-COOH isolated form of glycine, with the experimental value of the N-H stretching is 3411 cm^{-1} [35]. Thus, for the complexes with amino acids which present ν_{NH} appear at about 3400 cm^{-1}, the amino group must be free. If the band is located at 3100-3300 cm^{-1}, the amino group must be coordinated to the metal [1, 13, 23-27]. For the compounds studied in ν_{COOass} from 3170 to 3190 cm^{-1} for glycine in **I**, from 3140 to 3120 cm^{-1} for DL-valine in **II** and from 3100 to 3150 cm^{-1} for DL-leucine in **III**, an alteration was verified suggesting the participation of the NH_2 group in the coordination of the amino acids to the tin [1, 13, 23-27]. For the DL-phenylalanine in **IV** a shift from 3100 to 3410 cm^{-1} was observed indicating that the amino group must be free in this complex [1, 13, 23-27].

It was also observed in the spectra of the compounds **I** to **IV** studied the presence of two absorption bands at 550-570 cm^{-1} region, attributed to stretchings of the Sn-C bonds, which indicate a *trans* non-linear configuration of the skeleton C-Sn-C [36], as well as those at 395-480 cm^{-1}, which could be attributed to the stretchings of the Sn-N bonds [1, 24-26, 28].

In the ^{119m}Sn Mössbauer spectroscopy, a single quadrupole splitting doublets was indicated, making evident that **I** to **IV** present only one site around the tin atoms, where Δ quadrupole splitting doublets and δ isomer shift values, in mm s^{-1}, are consistent with the tin atoms located in sites with coordination numbers higher than four, what is highlighted by the relation among the values $\varrho = \Delta/\delta > 2.1$ [29-33,

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37-40]. The values of the Mössbauer parameters and Mössbauer spectrum for the compound [$Bu_2SnPhen_2$] are presented in Table 3 and in Fig. 1, respectively.

Table 3. Values of the Mössbauer parameters (mm s^{-1}) for the dibutyltin complexes

Compounds		Mössbauer parameters (mm s^{-1})			
		δ	Δ	Γ[1]	ϱ = Δ/δ
I	[$Bu_2SnGlyCl$]	1.44	3.33	0.95	2.31
II	[$Bu_2SnValCl$]	1.40	3.25	0.88	2.32
III	[$Bu_2SnLeuCl$]	1.40	3.26	0.81	2.33
IV	[$Bu_2SnPhen_2$]	1.41	3.29	0.84	2.33

[1] Fullwidth at half maximum

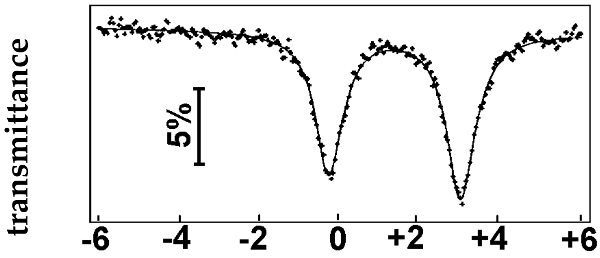

Fig. 1. Mössbauer spectra of compound **IV** - [$Bu_2SnPhen_2$] (obtained at T = 85 K, using a $CaSnO_3$ source at room temperature)

The presented data allowed the settlement of the proposed formulations and the structures of **I**, **II** and **III**, a trigonal bipyramidal tin species, as they are shown in Fig. 2, whereas for the **IV** structure, a slightly distorted *trans*-octahedral tin specie, is shown in Fig. 3 [24, 28-33, 41].

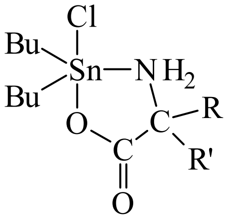

Fig. 2. Proposed structures for dibutyltin complexes.

I - [$Bu_2SnGlyCl$] (Gly = glycine, R = R′ = H);

II - [$Bu_2SnValCl$] {Val = DL-valine, R = H, R′ = $-CH(CH_3)_2$}; and

III - [$Bu_2SnLeuCl$] {Leu = L-leucine, R = H, R′ = -$CH_2CH(CH_3)_2$}

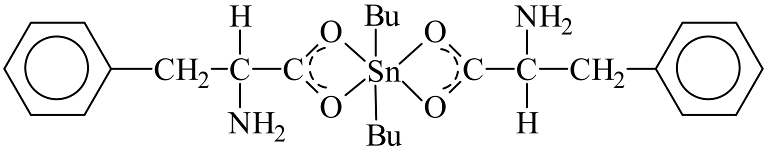

Fig. 3. Proposed structure for [$Bu_2SnPhen_2$], **IV** - Phen = DL-phenylalanine

For the compounds **I** and **III** it was possible to obtain the ^{119m}Sn-NMR spectra, in D_2O. The spectrum of **I** is shown in Fig. 4. The absorption signals δ(^{119m}Sn) (**I** = -143.6 ppm and **III** = -146.1 ppm) indicates that in solution the compounds **I** and **II** are present in dissociated forms, assuming trigonal bipyramidal geometry [23-26, 29-35, 41]. The proximity of absorption signals δ(^{119m}Sn) values of **I** and **III** is an evidence that the structural differences of these compounds are distant of the tin sites and do not affect the degree of protection or disprotection of the tin nucleus. A second signal, of lower intensity, was also observed in the ^{119m}Sn-NMR spectra of the two compounds (δ = 96.2 ppm, for both cases), which were attributed to the probable products of reactions of the complexes with D_2O.

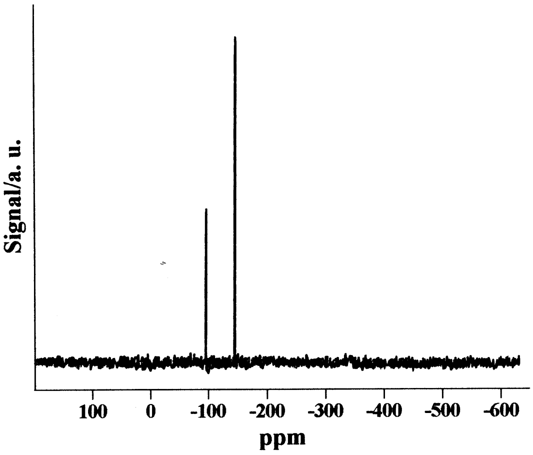

Fig. 4. ^{119m}Sn-NMR spectrum of the compound **I** - [$Bu_2SnGlyCl$] (400 MHz, D_2O)

Due to its insolubility for compounds **II** and **IV** it was not possible to record the NMR spectra. The insolubility of **II** and **IV** may be attributed to certain

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polymerization degree, as observed for diorganotin compounds with α-hydroxycarboxylic acid [17, 20].

TG curves of the compounds obtained in dynamic helium atmosphere are presented in Fig. 5. The initial and final temperatures of thermal decomposition process and the thermogravimetric data for the dibutyltin complexes are shown in Table 4. One can notice that the relative thermal stability of the compounds is significantly different. While the thermal degradation of the glycinate derivative (**I**) starts at 183°C, the DL-valinate complex (**II**) starts to decompose at 130 °C and the L-leucinate derivative (**III**) starts to decompose at 125 °C, all pentacoordinated species, in inverse correlation to the increase of their respective mass weights. For the dimethyltin compounds $[(CH_3)_2SnAACl]_2$ (AA = glycine, DL-valine), previously described by the authors [15], an increase was related in its thermal stability in agreement with the increase of their respective mass weights indicate that even the higher hindrance effects in the case of the dimethyltin DL-valinate derivative, this effect does not cause the decrease in its thermal stability.

For the DL-phenylalaninate derivative (**IV**), a hexacoordinated specie, the thermal degradation starts at 165 °C.

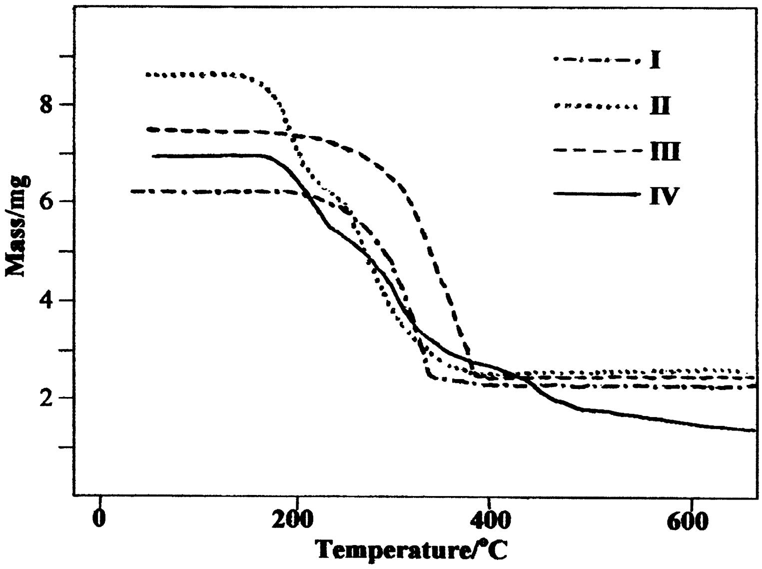

Fig. 5. TG curves of dibutyltin complexes. **I** - $[Bu_2SnGlyCl]$, **II** - $[Bu_2SnValCl]$, **III** - $[Bu_2SnLeuCl]$, and **IV** - $[Bu_2SnPhen_2]$

Table 4. Initial and final temperatures of thermal decomposition and the thermogravimetric data for the dibutyltin complexes

Compounds		Temperature/°C		Thermogravimetric data			
		Initial	Final	m_{initial}/mg	m_{final}/mg	Sn theor./%	Sn found/%
I	[Bu_2SnGlyCl]	183	375	6.280	2.140	34.66	34.08
II	[Bu_2SnValCl]	130	370	8.640	2.601	30.87	30.12
III	[Bu_2SnLeuCl]	125	372	7.490	2.187	29.78	29.20
IV	[Bu_2SnPhen$_2$]	165	700	6.914	1.438	21.15	20.80

For the compounds **I** and **III**, the thermal decomposition processes occur in one step, with final decomposition temperatures at 375 and 372 °C, with loss mass corresponding to 65.92 and 70.80%, respectively. For the compound **II**, the TG curve suggests that the thermal decomposition proceeds in two steps consecutively. In the first step there is a loss of mass of 30.21% up to 130-162 °C and in the second step, a loss of mass of 39.67% with final temperature of 370 °C, in agreement with the loss of one DL-valine ligand in the first step and by loss of others ligands in the second step. The TG curve of the compound **IV** suggests that the thermal decomposition proceeds in four steps consecutively, ended at 700 °C, with total loss mass corresponding at 79.20%. In the first step there is a loss of mass of 20.15% in the 162-250 °C intervals; in the second step, a loss of mass of 29.73% in the 263-344 °C intervals and in the third and fourth steps, a loss of 29.32% with final temperature at 700 °C, in agreement with the simultaneous loss of the two butyl groups in the first step; the loss of a DL-phenylalanine ligand in the second step and the loss of a second DL-phenylalanine in the third and fourth consecutives steps. In all the processes there was the production of tin metal as final product proved by X-ray fluorescence.

Based in the mass losses observed in the TG curves it is possible to establish tentative mechanisms of thermal decompositions for the dibutyltin complexes:

$$\text{I - [Bu}_2\text{SnGlyCl]} \xrightarrow{183\text{-}375\,^{o}\text{C}} \text{Sn}$$

$$\text{II - [Bu}_2\text{SnValCl]} \xrightarrow{130\text{-}250\,^{o}\text{C}} \lvert \text{Bu}_2\text{SnCl} \rvert \xrightarrow{263\text{-}370\,^{o}\text{C}} \text{Sn}$$

$$\text{III - [Bu}_2\text{SnLeuCl]} \xrightarrow{125\text{-}372^{o}\text{C}} \text{Sn}$$

$$\text{IV - [Bu}_2\text{SnFal}_2\text{]]} \xrightarrow{165\text{-}250^{o}\text{C}} \lvert \text{SnFal}_2 \rvert \xrightarrow{260\text{-}350^{o}\text{C}} \lvert \text{SnFal} \rvert \xrightarrow{360\text{-}700^{o}\text{C}} \text{Sn}$$

The DSC curves of the compounds are presented in Fig. 6 and the corresponding melting points, temperature values at the peaks observed and the calculated heat of fusion values (kJ mol^{-1}) for the dibutyltin compounds are shown in Table 5.

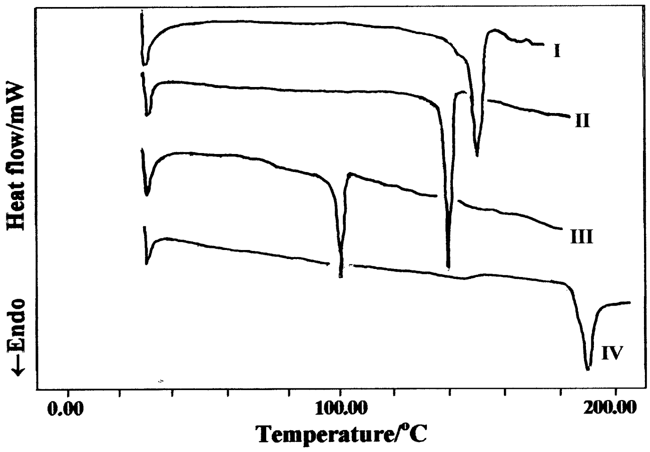

Fig. 6 DSC curves of dibutyltin complexes. **I** - [Bu_2SnGlyCl], **II** - [Bu_2SnValCl], **III** - [Bu_2SnLeuCl] and **IV** - [Bu_2SnPhen$_2$]

Table 5 The melting points (°C), the onset points (°C) and the heat of fusion (kJ mol^{-1}) for the dibutyltin complexes

Compounds		*m.p.*/ °C	T_{onset}/ °C	ΔH_{fusion} kJ mol^{-1}
I	[Bu_2SnGlyCl]	150-153	149.5	-4.24
II	[Bu_2SnValCl]	138-141	239.8	-8.30

III	[$Bu_2SnLeuCl$]	107-110	103.6	-3.27
IV	[$Bu_2SnPhen_2$]	191-194	191.2	-6.93

In these curves DSC the temperature values at the peaks are in accordance with the determined fusion intervals. Considering the heat of fusion values for the compounds **I** and **III** (ΔH_{fusion} = -4.24 and -3.27 kJ mol^{-1}, respectively) in comparison with the values for the compounds **II** and **IV** (ΔH_{fusion} = -8.30 and -6.93 kJ mol^{-1}, respectively) it can be concluded that the compound **I** and **III** can exist as monomeric species in solid-state while for the compounds **II** e **IV**, may be a sign of a certain polymerization degree [15-17, 20]. This observation is reinforced by minor solubility of the compounds **II** and **IV** in relation to the solubility of the compounds **I** and **III**, described to get their respective ^{119m}Sn-NMR spectra.

4. Conclusions

The studied compounds **I**, **II** and **III** exist as trigonal bipyramidal tin species while the compound **IV** exists as slightly distorted *trans*-octahedral tin specie in solid-state, probably as monomeric or certain polymerization degree structures, as observed for diorganotin compounds with α-hydroxycarboxylic acid [17,20] or α-amino acids [15]. These results are distinct from the ones described for diglycinatotin (II) [1], trimethyltin (IV) glycinate and alaninate [21] and dimethyltin (IV) glycinate and β-alaninate compounds [1] which show polymeric species with bridging α-amino acids, which should link the carboxylic oxygen to the tin and the amino group to the other tin atom [1,21]. Among these compounds dibutyltin derivatives have displayed both higher activity anti-tumor and relatively low toxicity [42].

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Conflicts of Interest: The authors declare no conflict of interest.

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