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Synthesis and spectroscopic characterization of dicyclohexyltin derivatives of dipeptides, and *in vitro* effects against MDA-MB 231 breast cancer cells: Crystal structures of dicyclohexyltin glycylglycinate and glycylalaninate

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Dicyclohexyltin derivatives Cy_2SnL (Cy = cyclohexyl) of the dipeptides H_2L, glycylglycine, glycylalanine, alanylglycine, glycylvaline, glycylmethionine, glycylphenylalanine and glycyltyrosine, have been obtained by neutralization of Cy_2SnO and H_2L.

The crystal structures of Cy_2SnL (L = glycylglycinate, glycylalaninate) have been determined by single X-ray diffraction. Tin in each case has a distorted trigonal bipyramidal environment with the dipeptide acting as a tridentate *NNO*-ligand. From IR-data, and in some cases from ^{119}Sn Mössbauer and ^{119}Sn NMR data, analogous molecular structures are inferred for the other compounds Cy_2SnL. Spectroscopic data indicate that the solid-state structures are retained in organic solvents.

***In vitro* tests showed Cy_2SnL (H_2L = glycylglycine, glycylalanine, alanylglycine, glycylphenylalanine, glycyltyrosine) to exhibit high cytotoxicity against MDA/MB 231 breast cancer cells, while Me_2SnL (L = glycylalaninate, glycyltyrosinate, glycyltryptophanate), and R_2Snglycylglycinate (R = n-Bu, Ph) proved to be much less active.**

Keywords: Dicyclohexyltin dipeptides, dicyclohexyltin glycylglycinate, dicyclohexyltin glycylalaninate, crystal structures

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INTRODUCTION

The antileukemia activity demonstrated by organotin compounds has been suggested to be ultimately due to $R_2Sn(IV)$ moieties, possibly intermediates produced during hydrolysis.[1,2] Considering that the activity of such compounds follows the trend that ethyl and phenyl groups bound to tin appear to induce antileukemia activity,[1,3] it seemed worthwhile to extend activity studies to new compounds with $R_2Sn(IV)$ central units which had not yet been subjected to screening tests. With this in mind we synthesized, following earlier studies,[4–9] dicyclohexyltin(IV) derivatives of dipeptides for the first time; we report here on their preparation and characterization and on *in vitro* effects on breast cancer cells.

EXPERIMENTAL

Cy_2SnO (Cy = cyclohexyl) was prepared according to Ref. 10. The dipeptides were a gift from Degussa, Frankfurt, Federal Republic of Germany.

The new compounds Cy_2SnL listed in Table 1 (H_2L = dipeptide; H_2GlyGly = glycylglycine; H_2GlyAla = glycylalanine; H_2AlaGly = alanylglycine; H_2GlyVal = glycylvaline;

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Table 1 Analytical data for dicyclohexyltin derivatives of dipeptides Cy_2SnL

Compound		Method of synthesis	Yield (%)	M.p. (°C)	Analysis (%): Found (Calcd) C	H	N
$Cy_2SnGlyGly$	**1**	A	90.3	262–263	46.3 (46.3)	6.8 (6.8)	6.7 (6.8)
		B	72.6	262–263	45.8 (46.3)	6.9 (6.8)	6.8 (6.8)
$Cy_2SnGlyAla$	**2**	A	67.6	266–269	45.7 (47.6)	6.9 (7.1)	6.4 (6.5)
		B	71.5	266–269	47.3 (47.6)	7.0 (7.1)	6.5 (6.5)
$Cy_2SnAlaGly$	**3**	A	83.9	239[a]	46.9 (47.6)	7.1 (7.1)	6.5 (6.5)
		B	93.2	239[a]	47.2 (47.6)	7.1 (7.1)	6.4 (6.5)
$Cy_2SnGlyVal$	**4**	A	67.8	182–183	48.3 (49.9)	7.4 (7.4)	5.9 (6.1)
$Cy_2SnGlyMet$	**5**	A	72.4	192–194	46.0 (46.7)	7.1 (7.0)	5.7 (5.7)
$Cy_2SnGlyPhe$	**6**	A	75.3	228–230	54.5 (54.7)	6.5 (6.8)	5.2 (5.5)
$Cy_2SnGlyTyr$	**7**	A	85.8	286[a]	52.7 (53.0)	6.4 (6.6)	5.2 (5.4)

[a] With decomposition.

$H_2GlyMet$ = glycylmethionine; $H_2GlyPhe$ = glycylphenylalanine; $H_2GlyTyr$ = glycyltyrosine) were synthesized by refluxing a mixture of 2 mmol each of Cy_2SnO and H_2L (Method A) or of Cy_2SnBr_2 and Na_2L (Method B) in 50 cm^3 of anhydrous methanol. In the case of Method A, 2,2-dimethoxypropane was added to remove the water of reaction. After reducing the volume of the solution to about 5–10 cm^3, petroleum ether/ether (1:1, v/v) was added to precipitate the product. The analytical data of the new compounds are compiled in Table 1.

Elemental analyses were carried out with an Elemental Analyzer (1106 Carlo Erba, Milano, Italy). Melting points were measured in open capillaries and are uncorrected. Molecular weights were determined osmometrically in anhydrous methanol; values for **1**, **2** and **3** were determined to be 417 (415), 441 (429), and 437 (429), respectively (calculated values in parentheses). The IR spectra were recorded on a Perkin–Elmer grating spectrometer (PE 580B) in KBr, CD_3OD and DMSO. ^{119}Sn NMR spectra were recorded in CD_3OD on a Bruker AM300 and chemical shifts were measured in ppm downfield from an external Me_4Sn reference.

The ^{119}Sn Mössbauer spectral data were obtained with the apparatus and data reduction techniques described in a preceding paper.[9]

Single crystals of $Cy_2SnGlyGly$ and $Cy_2SnGlyAla$ have been obtained from methanol solutions by adding a mixture of petroleum ether and diethyl ether. A Nonius CAD-4 diffractometer served to measure the intensities of reflexions of single crystals of **1** and **2** for X-ray structure determination. Graphite-monochromated Ag Kα radiation, $\lambda = 0.5608$ Å ($T = 291(1)$ K) was used. Crystallographic data are given in Table 2. Lattice parameters were taken from the least-squares fit with 25 reflexions up to $2\theta = 23.7°$ (**1**) or 25.8° (**2**), respectively, after Lorentz-polarization correction and absorption correction via ψ scans. Structure determination was performed via the Patterson function, ΔF synthesis, and full-matrix least-squares refinements with anisotropic temperature factors for all non-H atoms and a common isotropic temperature factor for H atoms, which were placed in geometrically calculated positions (C–H 1.08 Å). Complex neutral atom scattering factors were taken from Refs 11 and 12. The absolute configuration was not determined. The following programs were used: Enraf–Nonius Structure Determination Package,[13] SHELX76[14] and

SCHAKAL.[15] Atomic coordinates and equivalent isotropic thermal parameters for the non-H atoms are given in Table 3, and bond lengths and bond angles in Table 4. (Other crystallographic details are available from the authors upon request.)

The tumor-inhibiting effect of the compounds **1**, **2**, **3**, **6** and **7** and of some other diorganotin derivatives of dipeptides [Me_2SnGlyAla[8] (**8**), Me_2SnGlyTyr[8] (**9**), Me_2SnGlyTry[8] (**10**), n-Bu_2SnGlyGly[4,8] (**11**) and Ph_2SnGlyGly[5,8] (**12**)] was tested *in vitro* using the hormone-independent human mammary carcinoma cell line MDA-MB 231. Inhibition of cell growth and [^{3}H] thymidine incorporation was measured as described previously.[16]

RESULTS AND DISCUSSION

The diorganotin derivatives of dipeptides Cy_2SnL, Nos **1** to **7**, listed in Table 1, were prepared by reaction of Cy_2SnO with the appropriate dipeptide H_2L, or of Cy_2SnBr_2 with Na_2L in methanol, in a 1:1 mole ratio. Compounds **1–6** are soluble in methanol, **7** is soluble in warm DMSO and slightly soluble in boiling water. According to molecular weight measurements, compounds **1**, **2** and **3** for which values could be obtained (*vide supra*) are monomeric in methanol.

In the IR spectra of the compounds (Table 5) the rather sharp bands associated with $\nu(NH_3^+)$ of H_2L between 3060 to 3080 cm^{-1} are missing, so bonding of the Cy_2Sn(IV) moiety to the carboxylate group is inferred. The values of $\Delta\nu$ [$=\nu_{as}(COO)-\nu_s$ (COO)] are higher than 200 cm^{-1} in **1–6**, and this would suggest the presence of monodentate carboxylate groups.[17,18] The 'borderline' value of 200 cm^{-1} in **7** might be indicative of an unsymmetrically bridging carboxylate group. The comparison of $\nu(NH_{amino})$ of the appropriate sodium salts (3350–3380 cm^{-1}; mean value of $\nu(NH_{amino})$ bands of Na_2GlyVal: 3360 cm^{-1}) with those of the solid compounds **1–7**

Table 2 Crystallographic data

	Cy_2SnGlyGly (**1**) $(C_6H_{11})_2SnC_4H_6N_2O_3$	Cy_2SnGlyAla (**2**) $(C_6H_{11})_2SnC_5H_8N_2O_3$
Molar mass (g mol^{-1})	415.10	429.13
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	10.255(5)	10.040(3)
b (Å)	13.007(9)	13.453(5)
c (Å)	13.638(9)	14.077(9)
Volume (Å^3)	1819.1	1901.4
Z	4	4
density D_{calc}(Mg m^{-3})	1.516	1.499
μ, Ag Kα (mm^{-1})	0.75	0.72
F(000)	848	880
Crystal dimensions (mm)	0.30 × 0.35 × 0.29	0.29 × 0.35 × 0.29
Method	Ag Kα, $\omega/2\theta$ scan 3.3–6.6° min^{-1} in θ	Ag Kα, $\omega/2\theta$ scan 2.0–10.0° min^{-1} in θ
Range	$0\le h\le 12$, $0\le k\le 15$, $-16\le l\le 16$	$-12\le h\le 12$ $0\le k\le 16$ $0\le l\le 17$
θ	$1°\le\theta\le 20°$	$1°\le\theta\le 20°$
No. of reflexions measured	3870	4015
No. of reflexions used for structure determination	3110 ($F\ge 4.0\sigma(F)$)	3126 ($F\ge 4.0\sigma(F)$)
R (unweighted)	0.028	0.026
Max./min. transmission	1.00/0.85	1.00/0.95
Largest peak in final ΔF map (eA^{-3})	±0.7(3)	±0.4(2)
No. of reflexions for refinements on F	3110	3126
No. of refined parameters	200	209
$w=k/(\sigma^2(F)+0.005F^2)$	$k=0.91$	$k=0.24$
S	1.1	1.1
wR	0.034	0.030
$(\Delta/\sigma)_{max}$	0.08	0.03

Table 3 Atomic coordinates and equivalent isotropic thermal parameters ($Å^2 \times 10^3$)

	Cy_2SnGlyGly (**1**)				Cy_2SnGlyAla (**2**)			
	x	y	z	U_{eq}[a]	x	y	z	U_{eq}[a]
Sn	0.59423(3)	0.36862(2)	0.72356(2)	32	0.57149(2)	0.33196(2)	0.71592(2)	28
O(1)	0.4861(4)	0.5113(2)	0.7367(3)	44	0.4879(3)	0.4791(2)	0.7310(2)	39
O(2)	0.3026(4)	0.5892(3)	0.6936(3)	52	0.3141(3)	0.5731(3)	0.6963(3)	53
O(3)	0.3527(5)	0.2623(4)	0.4982(4)	72	0.2852(3)	0.2499(3)	0.5135(3)	47
N(1)	0.4637(4)	0.3643(3)	0.6051(2)	37	0.4254(3)	0.3375(2)	0.6107(2)	31
N(2)	0.6465(4)	0.2216(3)	0.6413(3)	39	0.5929(3)	0.1854(2)	0.6338(2)	35
C(1)	0.3840(5)	0.5222(3)	0.6828(4)	38	0.3838(4)	0.4993(3)	0.6821(3)	36
C(2)	0.3673(5)	0.4457(4)	0.5992(4)	47	0.3477(4)	0.4278(3)	0.6010(3)	34
C(3)	0.4434(5)	0.2780(4)	0.5561(3)	40	0.3844(4)	0.2563(3)	0.5655(3)	33
C(4)	0.5395(5)	0.1928(4)	0.5744(4)	47	0.4689(5)	0.1632(3)	0.5815(3)	40
C(5)	—	—	—	—	0.3743(7)	0.4783(4)	0.5054(4)	58
C(11)	0.7834(5)	0.4390(4)	0.7250(4)	46	0.4920(4)	0.2742(3)	0.8466(3)	29
C(12)	0.8912(5)	0.3590(5)	0.7298(5)	63	0.4711(5)	0.3551(3)	0.9221(3)	39
C(13)	1.0254(6)	0.4098(7)	0.7389(7)	83	0.4191(5)	0.3097(4)	1.0136(3)	48
C(14)	1.0327(7)	0.4800(7)	0.8247(7)	86	0.2919(5)	0.2493(4)	0.9963(4)	47
C(15)	0.9289(7)	0.5616(6)	0.8178(7)	87	0.3114(5)	0.1709(4)	0.9212(4)	50
C(16)	0.7927(6)	0.5129(5)	0.8118(6)	63	0.3655(5)	0.2165(4)	0.8290(3)	39
C(21)	0.5056(4)	0.3002(4)	0.8500(3)	35	0.7747(4)	0.3775(3)	0.7004(3)	38
C(22)	0.3731(5)	0.2558(4)	0.8227(4)	47	0.8051(5)	0.4641(4)	0.7659(5)	53
C(23)	0.3118(6)	0.2010(5)	0.9100(5)	61	0.9543(6)	0.4949(5)	0.7577(5)	73
C(24)	0.2984(6)	0.2731(6)	0.9968(5)	62	1.0422(5)	0.4088(5)	0.7797(5)	61
C(25)	0.4303(6)	0.3205(5)	1.0243(4)	57	1.0147(5)	0.3206(6)	0.7148(5)	72
C(26)	0.4918(5)	0.3738(4)	0.9366(3)	46	0.8686(4)	0.2900(4)	0.7204(4)	47

[a] $U_{eq} = (1/6\pi^2)\Sigma_i\Sigma_j\beta_{ij}a_ia_j$

(3310–3230 cm^{-1}, Table 5) shows a distinct shift to lower frequencies for the latter, and therefore coordination of the amino group to tin is inferred.[19]

The strong band $\nu(NH_{pept})$ present in the IR spectra of H_2L (3230–3320 cm^{-1}) is missing in the spectra of **1** to **7**, suggesting that the $Cy_2Sn(IV)$ moiety is bonded to the peptide nitrogen. This correlates with shifts of $\nu(CO_{pept})$ observed in **2**, **4** and **5**, with respect to the corresponding sodium salts (1665–1670 cm^{-1}) to lower frequencies in the range 1635–1650 cm^{-1} (Table 2). Considering the values of $\nu(CO_{pept})$ in **1**, **3**, **6** and **7** it seems justified to assume similar $N_{pept}\rightarrow$tin bonding. The rather low values of $\nu(CO_{pept})$ of 1635 cm^{-1} in **3** and **4** might indicate weak additional $CO_{pept}\rightarrow$ Sn coordination in the solid state. The shifting of both these vibrations to appreciably higher values on solution of **3** in DMSO, and of **4** in methanol, might be correlated with breaking of such bonds (possibly also of Sn—N bonds in **3**).

A molecule of **1** and a molecule of **2** are shown in Figs 1 and 3, respectively, and stereoviews of the appropriate unit cells in Figs 2 and 4. Both compounds, like most other diorganotin derivatives of dipeptides hitherto studied, crystallize in the space group $P2_12_12_1$.

In the molecules of **1** and of **2**, the atoms bound to tin form a distorted trigonal bipyramid with peptide-N and the cyclohexyl-C atoms occupying the equatorial positions whereas carboxylate-O and amino-N are in axial positions. The bond distances and angles within the two chelate rings of **1** and of **2** correspond essentially to those found in other comparable R_2SnL compounds. Thus, the equatorial angles C(11)–Sn–C(21) [123.6(2)° in **1**, 122.9(2)° in **2**] are in the same range as in Me_2SnGlyMet [123.8(3)°],[20] n-Bu_2SnGlyVal [125.3(3)°],[8] or tert-Bu_2SnGlyGly·H_2O [121.7(4)°].[21] A smaller angle is observed in Ph_2SnGlyGly [117.5(3)°][5] and a larger one in Et_2SnGlyTyr [131.4(2)°],[9] but no obvious reasons are perceivable for such deviations. From the short N . . . O distances the presence of hydrogen bonds between N(2) and O(2) [2.882(6) Å (**1**), 2.979(5) Å (**2**)] is inferred. The molecular structure therefore is in principle identical with that of the other diorganotin derivatives of H_2GlyGly which have been characterized hitherto by X-ray diffraction: Ph_2SnGlyGly[5] and tert-$Bu_2SnGlyGly \cdot H_2O$.[21] The present examples, like tert-$Bu_2SnGlyGly \cdot H_2O$,[21] demonstrate that the dichelate type of structure is apparently independent of the steric requirements of the organo groups at Sn. Similarly, substituents at the α-positions of the dipeptide ligand, such as Me in **2** or larger groups in $Me_2SnGlyMet$[20] or $Et_2SnGlyTyr$,[9] also seem to have no serious steric effect on the molecular structure of R_2SnL. Intermolecular interactions are usually restricted to hydrogen bonds. $(Et_2SnGlyHis)_2 \cdot CH_3OH$ is the only example we know which does not follow fully these rules, since one molecule coordinates via the imide-N of His to the central atom of the second $Et_2SnGlyHis$ molecule, increasing its coordination number to six.[22]

Chemical shifts $\delta(^{119}Sn)$ of **1** and **2** are observed at −175.9 ppm (**1**), and at −183.4 ppm (**2**) [coupling constants $^1J(^{119}Sn,^{13}C)$: 553 Hz(**1**), 546 Hz(**2**)]. The $\delta(^{119}Sn)$ values are in the upper part of the range that appears to be characteristic for pentacoordination; for example, for dibutyltin compounds, a range of −90 to −190 ppm was given.[23] Values of $\delta(^{119}Sn)$ for Me_2SnL compounds lie in the lower range: $Me_2SnGlyGly$, −92.0 ppm;[7] $Me_2SnGlyMet$, −93.8 ppm;[8] $Me_2SnGlyVal$, −89.4 ppm[8]). A high-field shift of cyclohexyltin compounds with respect to analogous methyltin compounds was also observed with R_3Sn derivatives of *N*-acetyl-β-alanylglycine = HL′, and of

Table 4 Bond distances (Å) and angles (degrees) of $Cy_2SnGlyGly$ (**1**) and $Cy_2SnGlyAla$ (**2**)

	$Cy_2SnGlyGly$ (**1**)	$Cy_2SnGlyAla$ (**2**)
Sn–O(1)	2.170(3)	2.160(3)
Sn–N(1)	2.098(3)	2.086(3)
Sn–N(2)	2.281(4)	2.296(3)
Sn–C(11)	2.145(5)	2.151(4)
Sn–C(21)	2.143(4)	2.142(4)
O(1)–C(1)	1.287(6)	1.281(5)
O(2)–C(1)	1.216(6)	1.230(6)
O(3)–C(3)	1.237(7)	1.239(6)
N(1)–C(2)	1.451(6)	1.450(5)
N(1)–C(3)	1.323(7)	1.330(5)
N(2)–C(4)	1.476(7)	1.477(6)
C(1)–C(2)	1.522(7)	1.536(6)
C(3)–C(4)	1.504(7)	1.529(6)
C(2)–C(5)	—	1.531(7)
C(11)–C(12)	1.519(8)	1.535(6)
C(11)–C(16)	1.529(9)	1.509(6)
C(12)–C(13)	1.532(9)	1.518(7)
(C13)–C(14)	1.486(13)	1.534(7)
C(14)–C(15)	1.507(12)	1.507(8)
C(15)–C(16)	1.536(9)	1.534(7)
C(21)–C(22)	1.522(6)	1.515(7)
C(21)–C(26)	1.527(7)	1.534(7)
C(22)–C(23)	1.524(8)	1.558(8)
C(23)–C(24)	1.517(9)	1.489(9)
C(24)–C(25)	1.533(8)	1.523(10)
C(25)–C(26)	1.521(7)	1.525(7)
N(1)–Sn–O(1)	76.1(1)	76.3(1)
N(1)–Sn–N(2)	75.5(2)	74.9(1)
N(1)–Sn–C(11)	126.5(2)	111.1(1)
N(1)–Sn–C(21)	109.7(2)	126.0(1)
N(2)–Sn–O(1)	151.4(1)	150.8(1)
N(2)–Sn–C(11)	98.6(2)	98.9(1)
N(2)–Sn–C(21)	98.5(2)	96.1(2)
O(1)–Sn–C(11)	98.5(2)	95.9(1)
O(1)–Sn–C(21)	94.1(2)	96.8(2)
C(11)–Sn–C(21)	123.6(2)	122.9(2)
C(1)–O(1)–Sn	117.5(3)	117.4(3)
C(2)–N(1)–Sn	117.3(3)	118.4(3)
C(3)–N(1)–Sn	120.8(3)	121.9(3)
C(4)–N(2)–Sn	110.0(3)	110.2(3)
C(3)–N(1)–C(2)	118.9(4)	118.5(3)
O(1)–C(1)–O(2)	124.5(5)	123.3(4)
O(1)–C(1)–C(2)	116.6(4)	117.3(4)
O(2)–C(1)–C(2)	118.9(4)	119.5(4)
C(1)–C(2)–N(1)	111.0(4)	109.1(4)
N(1)–C(3)–O(3)	125.6(5)	126.0(4)
C(4)–C(3)–O(3)	118.4(5)	118.4(4)
C(4)–C(3)–N(1)	116.0(4)	115.5(4)
C(3)–C(4)–N(2)	113.8(4)	112.1(4)
C(12)–C(11)–Sn	111.5(4)	112.7(3)
C(16)–C(11)–Sn	109.4(4)	111.0(3)
C(12)–C(11)–C(16)	110.6(5)	111.3(3)
C(11)–C(12)–C(13)	111.2(6)	110.5(4)
C(12)–C(13)–C(14)	112.0(6)	111.4(4)
C(13)–C(14)–C(15)	110.4(7)	112.0(4)
C(14)–C(15)–C(16)	110.8(6)	111.1(5)
C(11)–C(16)–C(15)	110.9(6)	111.4(4)
C(22)–C(21)–Sn	109.8(3)	110.5(3)
C(26)–C(21)–Sn	113.6(3)	110.3(3)
C(22)–C(21)–C(26)	110.2(4)	110.8(4)
C(21)–C(22)–C(23)	110.7(4)	110.7(5)
C(22)–C(23)–C(24)	110.9(5)	110.3(5)
C(23)–C(24)–C(25)	111.1(5)	111.9(5)
C(24)–C(25)–C(26)	110.9(4)	110.7(5)
C(21)–C(26)–C(25)	111.1(5)	112.0(5)
N(1)–C(2)–C(5)		111.2(4)
C(1)–C(2)–C(5)		109.5(4)

Intermolecular hydrogen bond distances
N(2) . . . O(2) (1 − *x*, 0.5 + *y*, 1.5 − *z*)
(**1**) 2.882(6)
(**2**) 2.979(5)

N-acetylglycyl-β-alanine = HL″. The following $\delta(^{119}Sn)$ values have been measured for Cy_3SnL': −23.6 and 32.1: for Me_3SnL', 25.6 and 142.1 (in CD_3OH and $CDCl_3$, respectively); for Cy_3SnL'', 10.2; for Me_3SnL'', 25.8 (in CD_3OD) (Huber, F and Schmiedgen R, unpublished results).

The ^{119}Sn Mössbauer parameters of Cy_2SnL compounds, Table 6, confirm the assignments based on both X-ray and IR spectral data. The quadrupole splitting values, ΔE, are in fact comparable with those obtained for other dialkyltin derivatives of dipeptides,[4,8,9] for which an identical arrangement of donor atoms around tin was established by X-ray analysis or was proposed on the basis of spectral data. Literature ΔE data (solid-state) range from 2.53 mm s^{-1} ($Me_2SnGlyMet$[8]) to 3.27 mm s^{-1} (n-$Bu_2SnGlyAla$[8]), these differences accounting, essentially, for different values of C–Sn–C angles, the electric field gradient being dominated by the highly covalent Sn–C bonds.[24] On the other hand, calculations based on the point-charge model,[25] assuming a regular trigonal bipyramidal configuration around tin and using the pqs values

Table 5 Characteristic IR vibrations of Cy_2SnL and of H_2L and Na_2L (in cm^{-1})

Compound		ν(NH)	$\nu(NH_3^+)$	$\nu(NH_2)$	$\nu(CO_{pept})$	$\nu_{as}(COO^-)$	$\nu_s(COO^-)$	$\Delta\nu$[a]
H_2GlyGly		3295 vs	3080 vs		1678 vs	1608 s	1410 vs	198
Na_2GlyGly				3380 s, br		1588 s	1413 vs	175
H_2GlyAla		3320 vs	3060 vs		1690 vs	1640 s	1410 s	230
Na_2GlyAla				3380 s, br	1665 s	1600 br	1415 br	185
H_2GlyVal		3260 s	3080 s		1690 vs	1625 vs	1410 vs	215
Na_2GlyVal				3315 s 3410 s	1670 vs	1590 vs	1420 vs	170
H_2GlyMet		3240 vs 3260 vs	3080 s		1690 vs	1630 vs	1410 vs	220
Na_2GlyMet				3350 vs, br	1665 vs	1600 vs	1405 s	195
H_2GlyTyr		3230 vs	3080 s		1685 vs	1615 vs	1405 vs	210
H_2AlaGly		3270 vs	3075 s		1690/1680 vs	1635 vs	1415 vs	220
Cy_2SnGlyGly	**1**	3060 s, br 3120 s, br 3210 vs			1650 vs	1622 s	1400 vs	222
In CD_3OD		—[b]			1675 vs	1630 vs	—[b]	—
Cy_2SnGlyAla	**2**	3120 s 3220 vs			1650 s	1620 s, br	1392 vs	228
Cy_2SnAlaGly	**3**	3110 s, br 3190 s, br 3140 s, br 3280 s, br 3360 s, br			1635 sh	1615 s, br	1408 vs	207
In CD_3OD		—[b]			1645 sh	1620 s, br	—[b]	—
In DMSO		—[b]			1680 s	1625 vs	—[b]	—
Cy_2SnGlyVal	**4**	3120 s 3220 vs, br			1635 s, br	1619 s	1395 sh	224
In CD_3OD		—[b]			1680 vs	1625 vs	—[b]	—
Cy_2SnGlyMet	**5**	3120 s, br 3200 s, br 3230 s, br			1650 sh	1625 br	1395 vs	230
Cy_2SnGlyPhe	**6**	3120 s, br 3220 s			1645 s, br	1620 s, br	1398 vs	222
Cy_2SnGlyTyr[c]	**7**	3210 vs 3295 vs			1660 vs	1580 s	1380 sh	200
In DMSO		—[b]			1665 s, br	1625 s	—[b]	—

[a] $\Delta\nu = \nu_{as}(COO^-) - \nu_s(COO^-)$.
[b] Solvent bands overlap.
[c] $\nu(OH) = 3590\ cm^{-1}$.

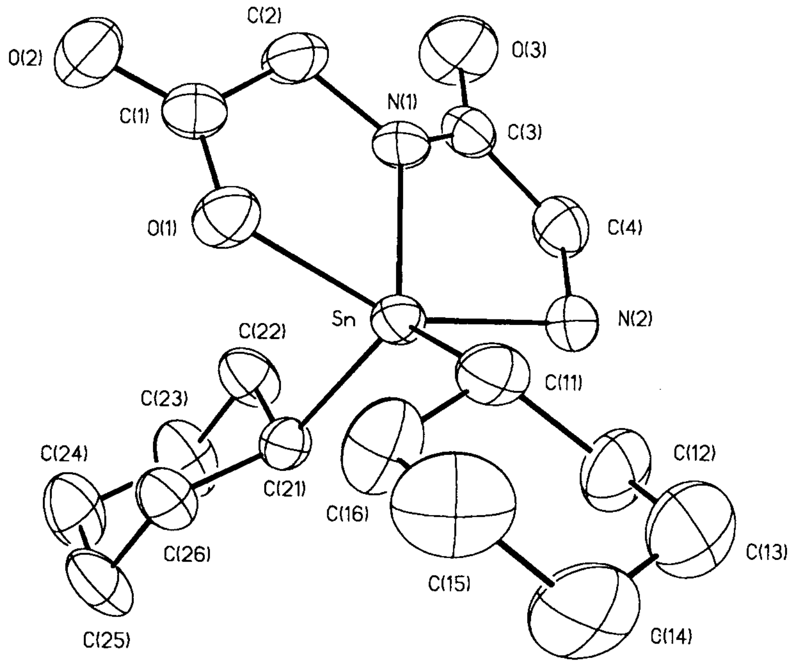

Figure 1 Structure of $Cy_2SnGlyGly$ (**1**): view of molecule showing atom numbering scheme.

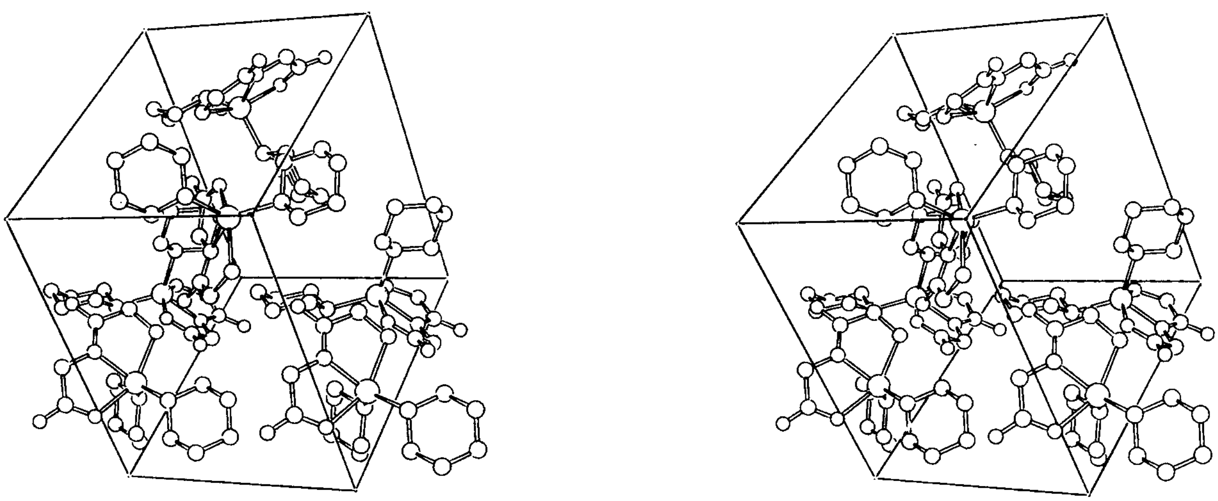

Figure 2 Structure of $Cy_2SnGlyGly$ (**1**): stereoscopic view of the unit cell (*a* vertical; *c* horizontal).

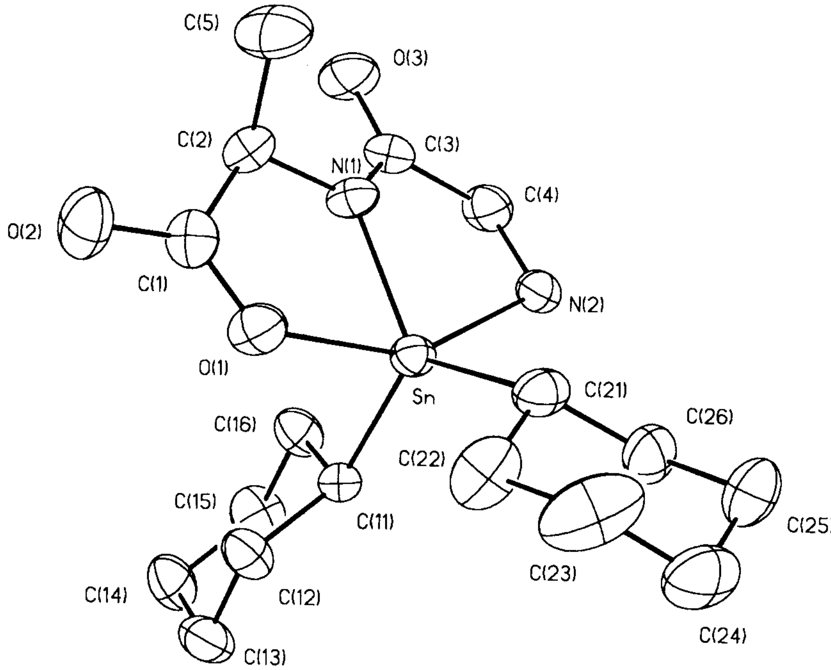

Figure 3 Structure of Cy_2SnGlyAla (**2**): view of molecule showing atom numbering scheme.

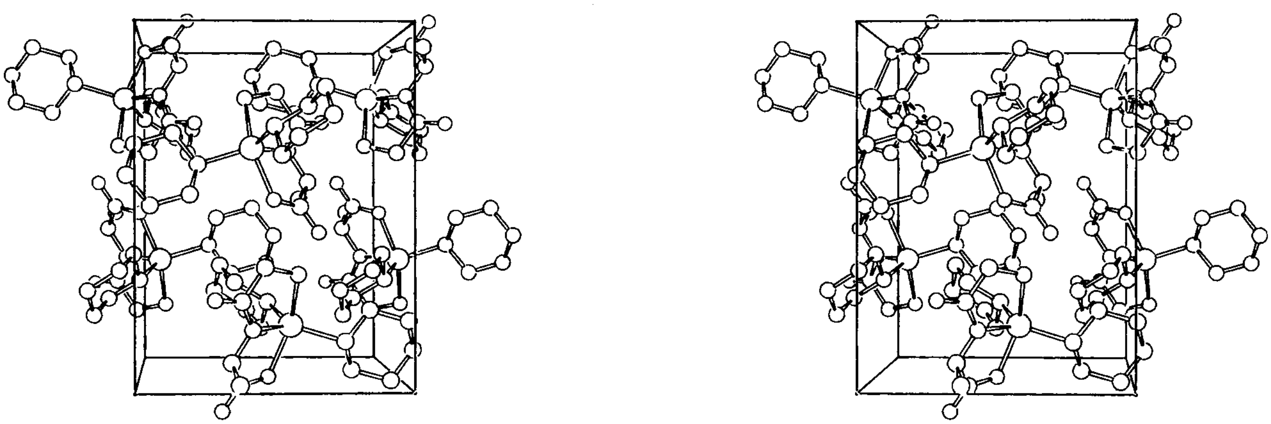

Figure 4 Structure of Cy_2SnGlyAla (**2**): stereoscopic view of the unit cell (*a* vertical; *c* horizontal).

Table 6 ^{119}Sn Mössbauer parameters of dicyclohexyltin derivatives of dipeptides Cy_2SnL^a

Compound	δ^b (mm s^{-1})	ΔE^c (mm s^{-1})	Γ_1^d (mm s^{-1})	Γ_2^d (mm s^{-1})
Cy_2SnGlyGly **1**	1.42	3.11	0.88	0.84
Cy_2SnGlyAla **2**	1.41	3.09	0.90	0.84
Cy_2SnAlaGly **3**	1.41	3.08	0.92	0.82
Cy_2SnGlyPhe **6**	1.32	2.72	0.83	0.81
Cy_2SnGlyTyr **7**	1.35	2.83	0.85	0.84

^{a} In the solid state. $T = 77$ K. Absorber thickness $\simeq$ 0.50 mg ^{119}Sn cm^{-2}.
^{b} Isomer shift with respect to RT Ca $^{119}SnO_3$.
^{c} Nuclear quadrupole splitting.
^{d} Full width at half height of the resonant peaks, at lower and higher velocity than the spectrum centroid, respectively.

reported in the literature, ($[\text{Alk}]^{\text{tbe}} = -1.13$ mm s^{-1};[26] $[\text{N}_{\text{pept}}]^{\text{tbe}} = -0.30$ mm s^{-1};[27] $[\text{N}_{\text{amino}}]^{\text{tba}} = 0.01$ mm s^{-1};[26] and $[\text{COO}_{\text{unidentate}}]^{\text{tba}} = -0.10$ mm s^{-1}[28]) give a ΔE_{calcd} of 2.78 mm s^{-1} which is consistent with all the quadrupole splitting values so far encountered for dialkyltin derivatives of dipeptides.

In vitro tests for tumor-inhibiting activity using the human mammary carcinoma cell line MDA-MB 231 (Table 7) showed the dicyclohexyltin compounds with the exception of **6** to possess rather high cytotoxicity, while the cytotoxic effects of the other compounds are considerably lower. Corresponding with results on the effect against murine 1210 cell cultures is demonstrated by the value of EC_{90} (0.028 μg cm^{-3}). *In vivo* tests against leukemia P388 in mice,[1,3] the dibutyltin and diphenyltin derivatives are at least gradually more active than the dimethyltin compounds.

Compounds **1** and **2** proved to be rather toxic on i.p. administration to mice (DL_{50}: **1**, 16 mg kg^{-1}, **2**, 73 mg kg^{-1}). The toxicity of **1** of the antitumor activity of **1** against the murine leukemia P388 showed the compound not to effect a significant increase of lifetime.

Table 7 Inhibition of cell growth and [^{3}H]-thymidine incorporation in human mammary carcinoma cell line MDA-MB 231 by some diorganotin derivatives of dipeptides (for numbers see Table 1 and Experimental section)

Concentration of compounds (mol dm^{-3})	**1**	**2**	**3**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
(1) Inhibition of cell growth^a										
1×10^{-5}	7	5	1	1	2	83	111(88)	61(38)	7	3
5×10^{-6}	7	5	—	2	—	—	—	77(93)	7	3
2×10^{-6}	—	—	—	18	—	—	—	—	—	85^b
1×10^{-6}	5	5	1	82	3	93	111	99	35(20)	85
5×10^{-7}	26^c	13	1	—	5	—	—	—	90	90
2×10^{-7}	70	27	11	—	34	—	—	—	—	—
1×10^{-7}	97	76^d	70	100	96	90	107	103	99	—
(2) Inhibition of [^{3}H]thymidine incorporation^e										
1×10^{-5}	0	0	1	1	1	98	93(74)	18(3)	0	0
5×10^{-6}	0	0	—	1	—	—	—	58(68)	0	0
2×10^{-6}	—	—	—	1	—	—	—	—	—	90^b
1×10^{-6}	0	0	1	82	1	140	88	113	0(3)	110
5×10^{-7}	1^c	1	1	—	1	—	—	—	34	118
2×10^{-7}	23	2	2	—	52	—	—	—	—	—
1×10^{-7}	107	59^d	110	94	83	106	94	99	78	—

^{a} T/C (%), number of cells compared with control. Values in parentheses are from repeat measurements.
^{b} At 3×10^{-6} mol dm^{-3}: (1) 19; (2) 21.
^{c} At 3×10^{-7} mol dm^{-3}: (1) 32; (2) 1.
^{d} At 5×10^{-8} mol dm^{-3}: (1) 94; (2) 97; at 2×10^{-8} mol dm^{-3}: (1) 98; (2) 121.
^{e} T/C (%), inhibition in percentage uptake compared with control.

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