The Antitumour Activity of Diorganotin(IV) Complexes with Adenine and Glycylglycine

R. BARBIERI, L. PELLERITO, G. RUISI, M. T. LO GIUDICE

Gruppo di Chimica dei Composti Organometallici, Università di Palermo, I-90123 Palermo, Italy

F. HUBER

Lehrstuhl fur Anorganische Chemie, Universität Dortmund, 4600 Dortmund, 50 F.R.G.

and G. ATASSI

Laboratory for Experimental Chemotherapy and Screening, Institut Jules Bordet, 1000 Brussels, Belgium

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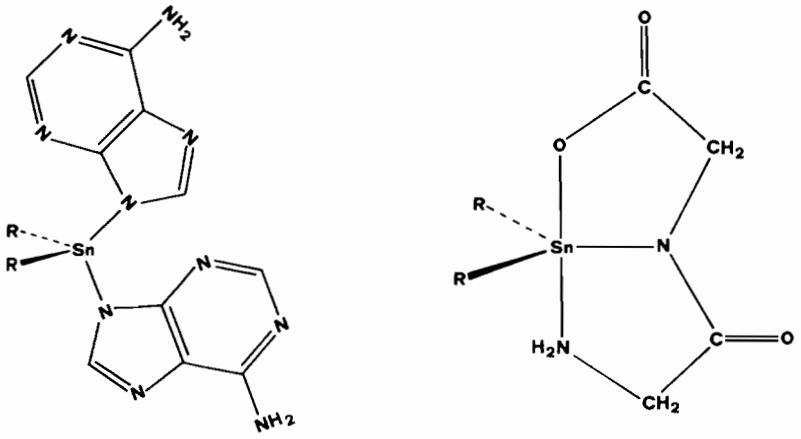
Recent studies have shown that organotin(IV) derivatives may exhibit anti-tumour activity: in particular, the compounds $Ph_2Sn(OH)Cl$, $(Et_2SnO)_n$ and $ClMe_2SnOSnMe_2Cl$, as well as the octahedral adducts $R_2SnX_2 \cdot L_2$ (where R is alkyl or aryl, X is halide or thiocyanate, and L_2 are nitrogen atoms of the bidentate ligands 1,10-phenanthroline, 2,2′-bipyridyl and 2-aminomethylpyridine), have been determined to be active against P-388 lymphocytic leukaemia in mice [1]. We report in the present note our results on the anti-leukaemia activity of some diorganotin(IV) complexes with the biological molecules adenine and glycylglycine, R_2SnAd_2 and $R_2SnGly\text{-}Gly$ (Fig. 1) [2–5]. Their synthesis has been effected as reported previously [2–4], and the antitumour bioassay has been carried out at the Institut J. Bordet, Brussels, according to U.S. National Cancer Institute standard protocols for primary screening [6]. Preliminary reproducible activity and toxicity data are reported in Table I, and are discussed in the following mainly in connection with the corresponding values of the adducts $R_2SnX_2JL_2$ [1], in view of the quality of the bioassay procedures, and in order to try to relate the respective biological properties and structural characteristics.

The complexes R_2SnAd_2 are definitely active against leukaemia (Table I). The T/C values (which reflect the percent increase in the survival of treated mice as compared to the controls) of Ph_2SnAd_2 correspond to those shown by the most effective terms of the $R_2SnX_2 \cdot L_2$ series [7], while toxicity is similar to that of the above mentioned adducts. Nevertheless, $Bu^n_2SnAd_2$ is consistently more toxic (Table I, and Ref. [1]). The structure of the solid complexes is very probably [1], Fig. 1, with Sn–N(9) covalent bonds. It is important to recall that N(9) is the primary binding site of coordinated adenine [7].

The action of water on the complexes (I) and on the adducts $R_2SnX_2 \cdot L_2$ could yield analogous species, due to the possible coordination of H_2O to the metal centre followed by hydrolysis, and to gradual dissociation of the Sn–N bonds (and Sn–X bonds in



(I) R_2SnAd_2 (II) $R_2SnGly\text{-}Gly$

Fig. 1. (I)· A possible structure of the complexes of R_2Sn^{IV} (R = Bu^n, Ph) with adenine, in the solid state, according to Mossbauer spectroscopic data [2]. A tin environment of octahedral type, C_2SnN_4 with *cis*-C_2 atoms, is also predictable [2]. (II): The structure of the complexes of R_2Sn^{IV} (R = Me, Bu^n, Oct^n, Ph) with glycylglycine, according to X-ray diffractometry and Mossbauer spectroscopy [3–5].

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TABLE I Evaluation of Treatment of P-388 Leukaemic Mice with Complexes of R_2Sn^{IV} with Adenine and Glycylglycine.

Compound[a]	Dose[b]	T/C[c]
$Bu^n_2SnAd_2$	12.50	131
(suspension or solution	6.25	123
	3 12	110
in Klucel)	1.56	98
Ph_2SnAd_2	100 0	169
(suspension in saline	50.0	135
or in Klucel)	25.0	145
	12.5	123
Me_2SnGly-Gly	25.0	139
(solution in Klucel or	12.5	126
saline with Tween-80)	6.25	118
	3.12	107
Bu^n_2SnGly-Gly	3.12	150
(suspension in saline	1.56	118
with Tween-80)	0.79	98
	0.39	100
Oct^n_2SnGly-Gly	1.56	132
(suspension in saline with Tween-80)		
Ph_2SnGly-Gly	3.12	141
(suspension in saline	1.56	128
or Klucel)	0.79	113
	0.39	100

[a]Ad = (adeninato)$^-$; Gly-Gly = (glycylglycinato)$^{2-}$; see Fig. 1. The vehicle of drug administration is given in parentheses. Klucel is an aqueous solution of 2-hydroxypropylcellulose and NaCl, and Tween-80 is oleylsorbitan polyethyleneglycol ether. [b]mg/Kg/injection (intraperitoneal). Doses larger than those reported have been determined to be toxic (according to Ref. [6]). The sex of host mice groups has been as follows in replicated trials. both male and female for Ph_2SnAd_2, Me_2Sn- and Ph_2Sn Gly-Gly; male for $Bu^n_2SnAd_2$, Bu^n_2Sn- and Oct^n_2Sn Gly-Gly. The latter complex was inactive when administered to a group of female mice (suspension in Klucel; dose 6.25, T/C 109, dose 3 12, T/C 111). [c]Median survival time of the treated mice group divided by that of the control group, per cent. Average values are reported Activity criteria are considered to be passed for T/C $\geq$ 125% [6]

the adducts) [1]. As a consequence, the same mechanism could be advanced for the anti-tumour action of these drugs, *i.e.*, preferred transportation of the complex species into the tumour cells, which would be attacked by hydrolyzed R_2Sn^{IV} moieties [1]. Alternatively, it may be assumed that the facile hydrolytic cleavage of the coordinated N → Sn bonds, presumably occurring in the adducts $R_2SnX_2 \cdot L_2$, does not take place at the same extent for the covalent N–Sn bonds in R_2SnAd_2, which would then act as anti-metabolites.

The trigonal bipyramidal R_2SnGly-Gly complexes (II) (Fig. 1) are generally active against leukaemia in very small doses (Table I). The derivatives of $Bu^n_2Sn^{IV}$, $Oct^n_2Sn^{IV}$ and Ph_2Sn^{IV}, practically insoluble in aqueous systems, are the most active. The toxicities of these compounds are of the same order, which contrasts, for example, with LD_{50} data referring to orally administered Alk_2SnCl_2 (a marked decrease of toxicity is detected for the latter by increasing the length of the alkyl chain, the $Oct^n_2Sn^{IV}$ derivatives being practically non-toxic [8]). These trends strongly suggest that the anti-leukaemic activity of R_2SnGly-Gly depends on the peculiar structure and bonding of the solids shown in (II), Fig. 1 (which presumably suffer gradual alteration when attacked by water). Consequently, it seems either probable that *i*) Gly-Gly^{2-}, as coordinated to R_2Sn^{IV} in (II) is quite effective in bringing the complexes (II) into the cells; *ii*) the complexes (II) behave as anti-metabolites.

Further work is in progress in our laboratories. The complexes Ph_2SnAd_2 and Bu^n_2Sn Gly-Gly are under testing for activity against a series of tumours at the Institut J. Bordet. Investigations are actually being carried out on the structure of the complexes in solution phase, as well as on the solutions of Me_2Sn Gly-Gly used in the bioassays, in order to understand better the structure activity relationship of these compounds.

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