Antitumor Activity of Organotin Compounds. Reaction, Synthesis and Structure of Et_2SnCl_2(phen) with 5-Fluorouracil

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Abstract

The antitumor agent Et_2SnCl_2(phen) (phen = phenanthroline) reacts with 5-fluorouracil (UF) to form Et_2Sn(phen)UF)Cl by a basic catalytic process. The reaction may be characterized as nucleophilic attack on $H^+N(3)$ in the 5-fluorouracil ring by the *cis*-chloro in Et_2SnCl_2(phen). The product has been identified by microanalysis, IR, UV and NMR spectra and these results are consistent with the expected complex. The binding of the 5-fluorouracil ligand to the *cis*-chloro in Et_2SnCl_2(phen) not only enhances the antitumor activity of the complex, but also promotes studies aimed at understanding the mechanism of drug action.

Introduction

Since *cis*-dichlorodiammineplatinum(II) (cisplatin) was first reported to exhibit a wide spectrum of anticancer activity [1], metal complexes have attracted much attention as a new type of potential antitumor drug. Among others, some organotin compounds of the type $R_2SnCl_2(L)$ (where L is a $\widehat{NN}$ chelating ligand) were investigated extensively [2–4]. It was found that some $R_2SnCl_2(L)$ complexes are potent antitumor agents, being effective against P388 cells in mice. It is well known that *cis*-[Pt-$(NH_3)_2Cl_2$] has been widely used as a cancer chemotherapeutic drug. In order to investigate the mechanism of antitumor activity, Pt(II) complexes with nucleosides and with their bases have been studied most extensively [5–7]. The complexes are all neutral and contain exclusively at least two adjacent reactive ligands, such as *cis*-chloro, but the *trans*-isomers (e.g. of the *cis*-ammine complex) are completely inactive. It is accepted that the antitumor activity is due to the inhibition of DNA synthesis in the cancer cells and the mode of action is thought to be the release of the chloro ions to form *cis*-$[Pt(NH_3)_2(H_2O)_2]$ or *cis*-$[Pt(NH_3)_2(OH)]^+$, thus allowing the Pt(II) to form a cross-link between the N(7) of the guanines on the DNA chain.

Compared with Pt(II) antitumor complexes, R_2SnCl_2L-type compounds also have been shown to have potent antitumor activity, although they have not yet been used as anticancer drugs. Secondly, almost nothing is known about the interaction between $R_2SnCl_2(L)$-type compounds with nucleic acid bases and nucleotides. Since 5-fluorouracil is a good anticancer drug on the one hand, and it is similar to nucleic acid bases on the other hand, the reaction between Et_2SnCl_2(phen) (where phen = phenanthroline) with 5-fluorouracil to synthesis Et_2SnCl(UF)(phen) (where UF = 5-fluorouracil) by a basic catalytic process was carried out. The product has been identified by microanalysis, IR, UV and NMR spectra and the results are reported here.

Experimental

All reagents, solvents and biochemical reagents were AR, CP and were used without further purification. Et_2SnCl_2(phen) was prepared by the literature method [8] and was recrystallized and identified before use by melting point and IR spectra, in accordance with the literature. Microanalyses were carried out on a Perkin-Elmer 240c instrument. UV spectra were recorded on a Specord UV–Vis spectrometer. IR spectra were recorded on a Perkin-Elmer model 983 IR spectrophotometer with CsI plates. ^1H NMR spectra were recorded on an FT-80 spectrometer in DMSO-d_6 with TMS as an internal standard.

Et_2SnCl_2(phen) (4 mmol) was dissolved in 10 ml water and 4 mmol 5-fluorouracil was dissolved in 15 ml water. The two solutions were mixed and stirred at 50–60 °C for several hours until the pH of the solution went down to 3, and a dilute base was

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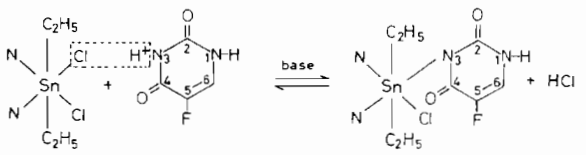
added slowly and carefully with stirring. A white precipitate separated slowly in solution as the pH value rose gradually. The reaction went on until the solution appeared to be neutral. The precipitate was washed with cool water, recrystallized with water/ethanol mixed solvents and finally dried under vacuum. *Anal.* Found: C, 41.47; H,3.98; N, 9.20. Calc. for $SnC_{20}H_{26}N_4O_5FCl$: C, 41.72; H, 4.35; N, 9.73%.

Results and Discussion

The reaction did not form any adduct until the pH was low. When the dilute base was added, a white solid separated slowly from the solution, but the pH value of the solution remained almost constant. The composition of the white solid obtained by the reaction is consistent with that suggested by microanalysis. It is obvious that the reaction of Et_2SnCl_2-(phen) with 5-fluorouracil carried out in a 1:1 stoichiometry gives the expected formation of Et_2SnCl-(UF)(phen). The reaction may be characterized as nucleophilic attack on $H^+N(3)$ in the 5-fluorouracil ring by the *cis*-chloro in Et_2SnCl_2(phen) in a basic catalytic process. It can be shown by UV, IR and ^1H NMR spectra that the reaction proceeds as follows:



The UV spectrum of the obtained complex gives λ_{max} = 271.9 nm under certain pH conditions, while under the same conditions, a value of λ_{max} = 269.1 nm was found for a solution of 5-fluorouracil; this indicates that the obtained complex contains the 5-fluorouracil ligand.

Relevant IR spectral data and assignments for the obtained compound as well as for Et_2SnCl_2(phen) (from ref. 9) are listed in Table I.

Table I shows that ν(SnC) in the IR spectra has two bands in the product but their stretching vibrations are increased with respect to Et_2SnCl_2(phen). ν(SnN) of the product also shows two bands; that at 433 cm^{-1} is assigned to Sn binding with N in phenanthroline, whilst the band at 244m is assigned to Sn binding with N in the 5-fluorouracil ring [9]. The value for ν(SnCl) is reasonable when compared with the related reference. The characteristic frequencies of 5-fluorouracil in the range 700–1700 cm^{-1} are also found in the product, but reveal a displacement of one order of magnitude. Since six-coordination is the general case for organotin(IV) compounds, the 5-fluorouracil is coordinated unidentately with Sn(IV).

In addition, the ^1H NMR spectral data give further support for the expected compound. The characteristic δ (ppm) of the ^1H NMR spectra for the suggested composition of the product should theoretically have eight peaks namely: one for the six hydrogens of the $2CH_3$–; another one for the four hydrogens of the $2CH_2$–; two for the 5-fluorouracil ring; and four for phenanthroline. Indeed, the observed spectra agree with these predictions, as shown in Table II.

In Table II, in the spectra of UF, there are two peaks for the two hydrogens of N(1)–H and the UF ring, but no peak for the hydrogen of N(3)–H. This is in agreement with reaction A as described. No crystal suitable for X-ray diffraction has yet been obtained. Tentative IR assignments of both symmetric and antisymmetric stretching vibrations for SnC are consistent with non-linear C–Sn–C, which indicate that the diethyltin coordination is probably at the *trans*-positions of a distorted octahedron. As for the stretching vibration of Sn–Cl, bands at 242s and 220 are consistent with non-linear Cl–Sn–Cl groupings in Et_2SnCl_2(phen) which disappear after reaction, giving instead a single stretching vibration for Sn–Cl in the obtained compound. This also indicates that one of the *cis*-chloro atoms has been substituted by 5-fluorouracil. However, ^1H NMR spectra for the product confirm that the phenanthroline in Et_2SnCl_2(phen) has not been displaced.

Because 5-fluorouracil is an analogue of nucleic acid bases, this is the first report to our knowledge of antitumor activity of a typical organotin compound such as Et_2SnCl_2(phen) with coordination substitution of the nucleic bases. Furthermore, this paper suggests that the mode of action would be similar to that of *cis*-$[Pt(NH_3)_2Cl_2]$. Crowe *et al.* [4, 10] have suggested that activity for the organotins occurs via a different route compared to that of cisplatin, e.g. a predissociation of the N-containing bidentate ligand may be a crucial step in the forma-

TABLE I. Relevant IR Spectral Data[a] (cm^{-1}) for the Obtained Product and Et_2SnCl_2(phen) [9]

Compound	ν(SnC)	ν(SnCl)	ν(SnN)	ν(C=O)	ν(NH)	ν(OH)
Et_2SnCl_2(phen)	525m, 470w	242s, 220	415			
$SnEt_2$(phen)(UF)Cl($3H_2$)	457m, 532w	223s	433, 244m	1619sh	3082–3200br	3463br

[a]s = strong, m = medium, w = weak, sh = shoulder, br = broad.

TABLE II. ^{1}H NMR, δ (ppm), DMSO-d_6 for Product

Band assignments	Compounds	
	Product	Ligands (control)[a]
$2(CH_2CH_3)$	2.12 (6H, $2CH_3-$) 2.91 (4H, $2CH_2-$)	
Phenanthioline	3.44 (2, 9H) 7.41 (3, 8H) 8.14 (5, 6H) 8.72 (4, 7H)	3.34 (2, 9H) 7.72 (3, 8H) 7.91 (5, 6H) 8.14 (4, 7H)
5-Fluorouracil ring	7.62 (S, 1H, UF) 10.82 (m, 1H N(1)–H UF)	7.50, 1H 10.60 N(1)–H 11.36 N(3)–H

[a] ^{1}H NMR, ppm for ligands have been carefully checked and compared with ^{1}H NMR Sadter spectra.

tion of a tin–DNA complex. As to the antitumor activity, the compound reported here shows that the binding of the 5-fluorouracil ligand to the *cis*-chloro in Et_2SnCl_2(phen) not only enhances the antitumor activity, but also promotes studies aimed at understanding the mechanism of drug action. Determination of the crystal structure and an investigation into the relationship between the structure and its antitumor activity are in progress.

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