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Organoelement Derivatives of Steroids: Synthesis and Structural Characterization of Diorganotin Chloride Adducts of Hormones

A. SAXENA, F. HUBER

University of Dortmund, Fachbereich Chemie, Postfach 500 500, D-4600 Dortmund 50, F.R.G.

L. PELLERITO, A. GIRASOLO

University of Palermo, Istituto di Chimica Generale, Via Archirafi 26, I-90123 Palermo, Italy

and G. C. STOCCO

University of Palermo, Istituto di Farmacologia e Farmacognosia, Via Forlanini 3, I-90123 Palermo, Italy

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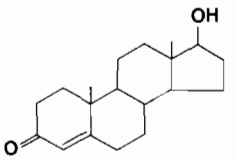
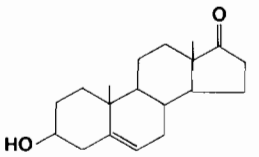
Abstract

Ten new diorganotin dichloride adducts of hormones of the type $R_2SnCl_2 \cdot 2L$ [where R = Me, Et, n-Bu, Oct and Ph; L = 4-androsten-17β-ol-3-one (**A**); 5-androsten-3β-ol-17-one (**B**); 4-androsten-17α-methyl-17β-ol-3-one (**C**) and 3,17-dihydroxy-5-pregnene-20-one (**D**)] have been prepared and characterized at 297 K and 223 K. Spectroscopic measurements (IR; Raman; ^1H, ^{13}C, ^{119}Sn NMR) suggest the dissociation or fast ligand exchange in solution at 297 K. Hexa-coordinated adducts with bonding through carbonyl oxygen and *trans*-R groups in octahedral geometry are formulated at 223 K.



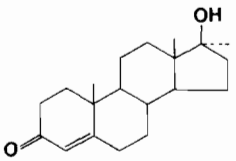
A

4-Androsten-17β-ol-3-one



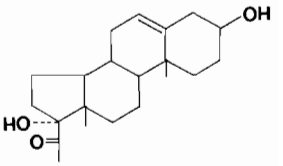
B

5-Androsten-3β-ol-17-one



C

4-Androsten-17α-methyl-17β-ol-3-one



D

3,17-Dihydroxy-5-pregnene-20-one

Introduction

Steroids are one of the most important biomolecules and by virtue of their intriguing roles in various metabolic processes have found applications in cancer chemotherapy [1]. The interaction of steroids with protein receptors is determined by the various substituents on the steroid nucleus. Organotin compounds have recently shown promise in cancer chemotherapy, and organotin steroids have been patented as potential antitumor agents [2, 3]. Despite the fact that most anticancer drugs are administered in solution phase, studies concerning the characterization of organotin species in potential antitumor agents, present in solution, are scarce [4, 5]. Our continuing interest in probing the nature of interaction of organotin moieties with biomolecules [6, 7] led us to synthesize diorganotin dichloride adducts with the following hormones:

and characterize the species formed with various spectroscopic techniques.

Experimental

All solvents were dried and purified by standard methods. Diorganotin dichlorides were prepared by literature methods [8]. Steroids were received as gifts from Schering A.G., Berlin, and **A** was purchased from Sigma. They were used without further purification.

Adducts were prepared by adding diorganotin dichloride with steroid in 1:2 molar ratio. In a typical preparation, a solution of diorganotin dichloride (2.5×10^{-3} mol) in 5 cm^3 $CHCl_3$ was dropped into a solution of the steroid (5×10^{-3} mol) in 150 cm^3

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TABLE I. Vibrational Spectral Data[a] and Melting Points for Organotin Chloride Adducts

Compound	Melting point (°C)	Assignments (solid state)		
		ν(C=O)	ν_{as}(Sn–C)	ν(Sn–Cl)
$Et_2SnCl_2 \cdot 2A$ (1)	62	1661	610	344
$Bu_2SnCl_2 \cdot 2A$ (2)	42	1658	598	349
$Oct_2SnCl_2 \cdot 2A$ (3)	32	1655	595	348
$Ph_2SnCl_2 \cdot 2A$ (4)[b]	40	1655	282	345
$Me_2SnCl_2 \cdot 2B$ (5)[b, c]	117	1725	585R	312R
$Ph_2SnCl_2 \cdot 2B$ (6)	62	1730		
$Me_2SnCl_2 \cdot 2C$ (7)[c]	134	1660	575	310
$Ph_2SnCl_2 \cdot 2C$ (8)[b]	114	1665	282	350
$Me_2SnCl_2 \cdot 2D$ (9)[c]	230[d]	1685	572	
$Ph_2SnCl_2 \cdot 2D$ (10)	228	1685	280	360

[a]Raman spectra of powders were measured in capillary tubes. IR spectra were recorded as Nujol mulls or in solution in $CDCl_3$ on a Perkin-Elmer 580 B Grating Spectrophotometer. Frequencies are in cm^{-1}. [b]ν(C=O) in solution at 1660, 1735 and 1670 cm^{-1} for compounds **4**, **5**, **8**, respectively. [c]ν_s(Sn–C) at 525R, 518 and 520 cm^{-1} for solid compounds 5, 7, 9, respectively. R = Raman spectra. [d]Decomposition.

$CHCl_3$ at −20 °C. It was stirred for 10 h at this temperature and left in a freezer overnight. It was filtered under N_2 while cold. The solvent was taken off and the resulting product was dried at 20 °C/0.01 mmHg for 10 h. These complexes have also been prepared in dry methanol under nitrogen atmosphere and recovered in a rotating evaporator. The adducts (see Table I) are white (**1**, **2**, **5**, **7**, **9**), yellow (**3**, **4**, **6**, **8**) and light brown (**10**). Attempts to crystallize or further purify the products were unsuccessful. Experimental details of spectroscopic measurements are given as footnotes in the appropriate Tables.

Results and Discussion

The solid 1:2 adducts **1** to **10** (see Table I) have been isolated at low temperatures in yields of 73 to 85% and analyzed for elemental composition*. The complexes are moisture sensitive and soluble in common organic solvents.

Infrared and Raman spectral data for the adducts are given in Table I. Only minor variations are observed in the IR spectra of adducts in comparison to the parent ligands and organotin chlorides. These variations totally disappear when the spectra are recorded in solution, suggesting the dissociation of adducts in solution.

The strong band at 1725 cm^{-1} in solid $R_2SnCl_2 \cdot 2B$ complexes is assigned to ν(CO) absorption which is observed at 1735 cm^{-1} in the spectra of pure **B** and of the solution of the complex. No change is observed in the frequency of ν(OH) vibration in the complexes. In the $Me_2SnCl_2 \cdot 2L$ complexes, two bands are observed at 585 and 525 cm^{-1} in IR and Raman spectra and may be assigned to ν_{as}(Sn–C) and ν_s(Sn–C), respectively; this suggests a linear C–Sn–C moiety with deviation from ideal linearity (due to differing intensity). ν(Sn–Cl) is observed at 312 cm^{-1} in Raman spectra as compared to 344 cm^{-1} in Me_2SnCl_2.

^1H NMR data at 223 K indicate that complex formation occurs as changes are observed in ligand and organotin proton chemical shifts. The separation between the two multiplets, arising from aromatic protons of diphenyltin compounds, increases by as much as 0.40 ppm, as compared to 0.20 ppm in the parent diphenyltin dichloride which supports the complexation. Similar trends have been observed by other workers investigating the complexation of organotin halides in solution [9–11]. However, single ^1H NMR signals for ligand and organotin protons are observed at 297 K; this suggests either total dissociation or fast exchange between free and complexed species.

^{13}C and ^{119}Sn NMR data for all complexes except **9** and **10** are given in Tables II and III. Upfield shifts are observed on increasing the coordination number of the tin atom, and the magnitudes of these shifts are dependent on the donor strengths of ligands [12]. On comparing the ^{119}Sn chemical shifts of parent organotin halides with the chemical shifts of compounds at 223 K, large differences are observed which suggest complex formation. Since ^{13}C NMR show only single peaks for ligand C-atoms, the possibility of the formation of 5-coordinate adducts with excess ligands can be safely ruled out. However, ^{119}Sn chemical shift values are considerably lower as would be expected from 6-coordinated complexes like $Me_2SnCl_2 \cdot 2DMSO$ [13], confirming the very weak coordinating ability of steroids.

*See 'Supplementary Material'.

TABLE II. ^{1}H and ^{119}Sn NMR Chemical Shifts (in δ ppm) for Organotin Chloride Adducts

Compound		T[a] (K)	^{1}H for *H* at C atom number						^{119}Sn
			(CH_2)[b]	(CH)[c]	$(CH_3)10$	$(CH_3)13$	(CH)[d]	R_2Sn[e]	
$Et_2SnCl_2 \cdot 2A$	(1)	297	2.35	5.70	1.16	0.75	3.61	1.40; 1.73	87.73
$Et_2SnCl_2 \cdot 2A$	(1)	223	2.25	5.70	1.07	0.65	3.58	1.31; 1.64	7.27
$Ph_2SnCl_2 \cdot 2A$	(4)	297	2.34	5.68	1.15	0.76	3.69	7.59[f] $\Delta = 0.20$	
$Ph_2SnCl_2 \cdot 2A$	(4)	223	2.22	5.66	1.09	0.69	3.52	7.69[f] $\Delta = 0.40$	−188.20
$Me_2SnCl_2 \cdot 2B$	(5)	297	2.30	5.35	1.17	0.83	3.47	0.98	
$Me_2SnCl_2 \cdot 2B$	(5)	223	2.28	5.34	1.19	0.83	3.48	0.94	−6.11
$Ph_2SnCl_2 \cdot 2B$	(6)	223		5.31	1.17	0.79	3.42	7.56[f] $\Delta = 0.37$	−169.06
$Me_2SnCl_2 \cdot 2C$	(7)	223	2.16	5.70	1.17	0.80		1.12	2.64
$Ph_2SnCl_2 \cdot 2C$	(8)	223	2.21	5.67	1.08	0.79		7.61[f] $\Delta = 0.34$	−123.22

^{1}H NMR spectra were recorded on a Bruker WP-80 FT Spectrometer as 5% *w/v* solutions in dry $CDCl_3$ with $(CH_3)_4Si$ as external standard at 297 K and 223 K. ^{119}Sn NMR spectra (reference: $(CH_3)_4Sn$) were recorded for 0.2 M solutions in $CDCl_3$ on a Bruker AM-300 Spectrometer at 297 K and 223 K. ^{119}Sn NMR spectra were measured at 111.9 MHz (digital resolution 6.7 Hz). ^{1}H gated decoupled FIDs were collected into 16 K data points with 55 000 Hz spectral width and 0.14 s acquisition time. [a]Temperature of NMR probe during measurement. [b, c, d]Carbon number 2^b, 4^c, 17^d in compounds 1, 4, 7, and 8; carbon number 16^b, 6^c, 3^d, in compounds 5 and 6. [e]R = CH_3, C_2H_5, C_6H_5. [f]Center of multiplet for aryl; Δ = separation of two multiplets in ppm.

TABLE III. ^{13}C NMR Data for Organotin Compounds at 223 K

Carbon atom	Compound[a]									
	1[b]	1	2[c]	3[d]	4	5	6	7	8[b, e]	8
Carbon chemical shifts δ in ppm										
C-1	35.52	34.90	34.91	35.01	34.87	36.60	36.54	35.07	35.33	34.92
C-2	33.80	33.51	33.55	33.57	33.37	30.83	30.41	33.63	33.73	33.52
C-3	199.90	201.30	201.21	200.92	201.83	72.36	71.20	200.97	200.36	201.61
C-4	123.59	123.09	123.12	123.19	123.12	41.30	41.02	123.23	123.51	123.27
C-5	172.02	174.00	173.88	173.45	174.31	140.15	140.15	173.53	172.37	174.00
C-6	32.75	32.60	32.61	32.61	32.60	120.97	120.65	32.72	32.73	32.69
C-7	31.42	30.90	30.90	31.00	29.34	30.83	30.41	31.17	31.38	31.08
C-8	35.52	34.90	34.91	35.01	34.87	30.74	30.74	35.07	35.33	34.92
C-9	53.78	53.17	53.17	53.31	53.13	50.98	50.85	53.16	53.42	53.04
C-10	38.60	38.36	38.36	38.37	38.36	36.18	36.05	38.45	38.45	38.39
C-11	20.53	20.06	20.06	20.13	20.04	19.93	19.82	20.19	20.39	20.12
C-12	36.30	35.73	35.74	35.85	35.65	30.36	30.24	35.87	36.12	35.78
C-13	42.69	42.31	42.32	42.37	42.29	47.56	47.44	44.93	45.07	44.85
C-14	50.33	49.60	49.61	49.75	49.55	49.35	49.27	49.48	49.75	49.37
C-15	23.22	22.90	22.91	22.95	22.92	21.65	21.53	22.93	23.03	22.90
C-16	30.23	29.39	29.46	29.58	30.88	35.84	35.60	30.90	31.11	30.81
C-17	81.40	81.08	81.06	81.07	81.11	223.64	223.45	81.52	81.38	81.49
C-18	10.99	10.95	10.96	10.95	10.96	13.31	13.15	13.84	13.83	13.86
C-19	17.31	16.95	16.96	16.98	16.93	19.26	19.10	17.04	17.16	16.95
C-20								25.49	25.61	25.41
α	9.30	9.70	29.31		140.91	10.70	140.54	10.58	138.10	140.10
β	19.81	22.65	26.82		135.05		134.77		134.93	134.99
γ			26.17		128.81		128.79		129.32	128.96
δ			13.72		130.55		130.55		131.31	130.77

(continued)

TABLE III. *(Continued)*

	Compound[a]									
	1[b]	1	2[c]	3[d]	4	5	6	7	8[b,e]	8
Coupling constants $^nJ(^{119}Sn^{13}C)$ (Hz)										
^1J	432	554.40	f		f	607.78	f	f	803.00	f
^2J	43.08	48.75	38.64		65.16		64.86		63.58	63.58
^3J					92.84		92.84		89.00	91.56
^4J					17.84		f		17.80	17.80

^{13}C NMR spectra (reference: $(CH_3)_4Si$) were recorded for 0.2 M solutions in $CDCl_3$ on a Bruker AM-300 Spectrometer at 297 K and 223 K at 75.4 MHz (digital resolution 1.2 Hz) with FIDs collecting in 32 K data points using 21 000 Hz spectral width. Steroid spectra have been taken from the literature [18] and C atoms have been numbered accordingly. Assignments for adducts are based on proton noise decoupling and DEPT spectral measurements. [a]For numbering of compounds see Table 1. [b]Chemical shift values at 297 K. [c] ^{119}Sn NMR chemical shift δ +28.60 ppm at 223 K. [d] ^{119}Sn NMR chemical shift δ +40.36 ppm at 223 K. [e] ^{119}Sn NMR chemical shift δ −63.44 ppm at 297 K. [f]Not resolved.

Depending upon the value of $\Delta(^{119}Sn$ chemical shift of adduct $- ^{119}Sn$ chemical shift of parent chloride), the coordinating ability of steroids may be formulated as: **A** > **B** > **C** (**D** is not included, since shift data are not available due to low solubility of appropriate adducts).

Similarly, the trends in the ^{119}Sn chemical shift variations in the series $R_2SnCl_2 \cdot 2\mathbf{A}$ can be explained on the basis of Lewis acidity of organotin halides: $Ph_2SnCl_2 > Et_2SnCl_2 > Bu_2SnCl_2 > Oct_2SnCl_2$ [14]. ^{119}Sn chemical shifts at 297 K for the two compounds $Et_2SnCl_2 \cdot 2\mathbf{A}$ (**1**) and $Ph_2SnCl_2 \cdot 2\mathbf{C}$ (**8**) are upfield from their parent halides by a value of approximately 32 ppm. An inspection of ^{13}C NMR of these two adducts at 297 K suggests a fast exchange between free and complexed species in solution at 297 K, rather than a dissociation of the adducts.

A comparison of the ^{13}C NMR chemical shifts of adducts at 223 K with parent steroids shows notable variations. A shift of approximately 2 ppm in the position of C-3 in (**A**) and (**C**) and C-17 in (**B**) points to the coordination of the ketonic oxygen to the Sn atom. This is strongly supported by the ^{13}C chemical shift displacement (approximately 2 ppm) of the C-5 signal upon complex formation with **A** and **C**, which reflects charge withdrawal at this site. Interaction of the carbonyl oxygen and the organometallic moiety would increase the contribution of the resonance form $\bar{O}$–(C-3)=(C-4)–($\dot{C}$-5) and thus deshield the C-5 carbon atom. A corresponding direction of chemical shift was reported for BF_3 complexes of steroidal hormones [15]. Competitive complexation between the hydroxyl group and the α,β-unsaturated keto group has been observed previously in **A**. Variations in the magnitude of coupling constants $J(^{119}Sn^{13}C)$ and in chemical shifts of carbons α to tin are also observed, suggesting the formation of coordinated species, in accordance with literature [16]. No appreciable change is observed for C-17 in **A** and **C** or C-3 in **B** in ^{13}C NMR spectra; this completely rules out the coordination by hydroxyl group to metal atom as reported for the complex $HgCl_2 \cdot 2\mathbf{A}$ [17].

Keeping in view the literature reports and on the basis of spectral data, an octahedral geometry with *trans* R and two steroid molecules coordinating through ketonic oxygen is postulated for these adducts in solution.

^{119}Sn Mössbauer spectral studies have been carried out on dialkyltin dichloride adducts with **A**. Preliminary results suggest that at 10 K the adducts maintained the octahedral configuration of the parent organotins. (Incidentally, the Mössbauer parameter nuclear quadrupole splittings are similar.) This behaviour can be explained in terms of breaking of some chlorine bridges which could be substituted by the donor atom of the hormone. Point charge calculations are under way and will be reported in a full paper.

Supplementary Material

Analytical data are available on request from the Editor-in-Chief.

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