Anticancer Activity of Organometallic Compounds. 2. Synthesis and Spectroscopic Characterisation of L-ascorbic Acid Complexes of Cyclopentadienyltitanium and Dialkyltins

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L-ascorbic acid has been known for years as an important biological molecule. The recent discovery [1] that a compound prepared from a diamineplatinum(II) and ascorbic acid displays an antitumour activity at least as great as that shown by *cis*-platin, opens up a new and very useful chemistry for ascorbic acid. To the best of our knowledge to date, surprisingly nothing concerning the organometallic derivatives of ascorbic acid has appeared in the literature. Our continuing interest in tin and early transition metal anticancer compounds leads us to study the interactions of organotin and titanium derivatives with ascorbic acid. As a result of our preliminary studies, we now report the first syntheses and characterisation of organotin and -titanium complexes of ascorbic acid. Simultaneously, experiments on X-ray crystallographic characterisation and their antitumour activites of these compounds are ongoing, the results of which will be published elsewhere.

Experimental

Reagents and solvents were purchased from commercial sources and were purified (where necessary) and dried before use by standard procedures. Reactions were carried out under a N_2 atmosphere and precautions were taken to avoid the presence of oxygen at every stage.

Preparations

$(\eta\text{-}C_5H_5)_2Ti(C_6H_7O_6)_2$, (I)

To a solution of Cp_2TiCl_2 (0.40 gm, 1.60 mmol) in 20 ml water was added dropwise a solution of sodium ascorbate (0.63 gm, 3.20 mmol) in 10 ml water with stirring at 10 °C. This produced a deep red solution with a formation of red precipitate. The mixture was stirred for 2 h allowing it to warm slowly up to room temperature. The red precipitate was then collected by filtration, washed with cooled water and redissolved in 50 ml THF. The brownish red compound **(I)** was obtained from THF solution by the addition of hexane.

$(CH_3)_2Sn(C_6H_6O_6)\cdot H_2O$, (II)

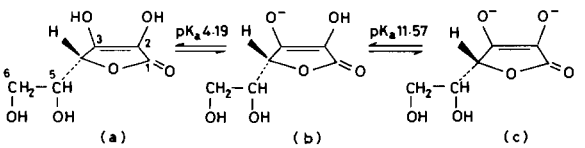
To a suspension of sodium ascorbate (0.87 gm, 4.38 mmol) in methanol (100 ml) was added dropwise a methanolic (25 ml) solution of $(CH_3)_2SnCl_2$ (0.48 g, 2.19 mmol) at 0 °C with stirring. After allowing it to warm up to room temperature, the mixture was heated under reflux for 3.50 h. The volatiles were removed *in vacuo* and the white solid was then successively washed with 30 ml portions of CH_2Cl_2 and THF. The white solid thus left, on recrystallisation from methanol afforded the compound **(II)**.

$(C_2H_5)_2Sn(C_6H_6O_6)\cdot H_2O$, (III)

To a suspension of sodium ascorbate (0.98 g, 4.94 mmol) in methanol (100 ml) was added dropwise a solution of $(C_2H_5)_2SnCl_2$ (0.61 g; 2.47 mmol) in 10 ml methanol at 0 °C with stirring. After allowing it to warm up to room temperature, the mixture was heated under reflux for 3 h. The volatiles were removed *in vacuo* leaving a white solid. This was then successively washed with 50 ml portions of CH_2Cl_2, THF and water and finally recrystallised from methanol which afforded the compound **(III)**.

Results and Discussion

L-ascorbic acid (Scheme 1(a)) is known to form both a mono and a dianion depending on the pH [2]



Scheme 1.

of the aqueous solution. In the monosodium salt (which exists in neutral solution) the deprotonation takes place at the hydroxyl group of C(3) (Scheme 1(b)). However, at higher pH, further deprotonation of the hydroxyl group at C(2) leads to the formation of the dianion (Scheme 1(c)). Thus, under suitable conditions, L-ascorbic acid may behave either as a mono or a bidentate ligand, and on the basis of IR and NMR evidence here represented we suggest that the ligand coordinates as the monoanion to titanium but as the dianion to tin.

Products **(I)**, **(II)** and **(III)** are produced by the nucleophilic substitution at the metal centre [3] by either C(3) (in **I**) or both C(3) and C(2) (in **II** and **III**)

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TABLE I. Analytical and some Physical Data for the new Compounds.

Compound	m.p. (°C)	yield (%)	λ_{max}[a] (nm)	Analytical data[b]					
				Found (%)			Calcd. (%)		
				C	H	M	C	H	M
I	190–210(d)	45	252	50.10	4.81	8.75	50.00	4.54	9.07
II	190–215(d)	73	272	28.36	3.71	34.62	28.17	4.10	34.84
III	190–210(d)	85	270	33.30	4.87	31.92	32.54	4.88	32.19

[a]Spectra were recorded in water by using quartz cells of 1 cm path length with a Perkin-Elmer 402 UV–Vis spectrophotometer; [b]C, H analyses were done by microanalytical laboratory, U.C.D., Dublin, M were estimated as MO_2 gravimetrically. M = Ti or Sn.

TABLE II. Relevant IR Data.[a]

Compound	ν(OH/H_2O)	ν(C=O)	ν(C=C)	ν(C–O···M/ C–O)	ν(M–O)	ν(M–C)
L-Ascorbic acid[b]	3535s	1753s	1670vs	1138s		
	3420s		1659vs	1118s		
	3330s					
	3230s					
Sodium ascorbate[b]	3320s	1702vs	1595vs	1156s		
	3260s			1124vs		
	3170w,b					
I	3435s,vb	1725m	1603vs	1060s, 1040s	502w,b	412w,b[c]
II	3422s,vb	1730m	1640vs,b	1062s,b	635m	580m
III	3490sh	1730m	1640vs	1082s,b	652w	500m
	3375s,vb					

[a]Spectra were recorded on Perkin-Elmer 599 IR spectrophotometer as KBr pellet. vs = very strong, s = strong, m = medium, w = weak, sh = shoulder, vb = very broad, b = broad, M = Ti or Sn; [b]Ref. 5; [c]Ref. 16, $TiCp_2$ str.

alcoholic groups (or its sodium derivative) of ascorbic acid. The attack by both C(3) and C(2) hydroxyl groups in the case of **(II)** and **(III)** are presumably due to the greater acceptor properties of the tin atom in diorganotin dichloride [3].

Relevant IR data are presented in Table II. The sharp ν(OH) absorptions in the free neutral ligand are replaced by a strong but broad absorption band around 3400 cm^{-1}. This implies involvement of hydroxyl groups in the complex formation. Association of a water molecule in the complexes might also be indicated by this broad absorption [4]. However, the analytical data (Table I) strongly suggests the absence of such coordinated H_2O in **(I)**. Both ν(C=O) and ν(C=O) in the complexes appear at lower frequencies than in the corresponding free ligand. The lowering of ν(C=C) in **(I)** (1603 cm^{-1}) is much larger than in **(II)** and **(III)** (1640 cm^{-1}). In fact, the ν(C=C) value in **(I)** closely corresponds to that for monosodium ascorbate (1595 cm^{-1}) where a monodentate anionic ligand is present. The lowering of ν(C=O) (by about 30 cm^{-1}) in these complexes is very likely due to the presence of inter- or intramolecular coordination in the solid state involving the carboxyl oxygen and the metal atom. The absorptions between 1040–1082 cm^{-1} are attributed to the C–O···M stretching vibration in the complexes which are in reasonable agreement with the literature values for cyclopentadienyltitanium [6] and alkyltin compounds [7, 9]. Tentative assignments are made (see Table II) for ν(Ti–O) [6, 10], ν(Sn–O) [7, 9, 12] and ν(Sn–C_2) [7, 11–14] and are in good agreement with the literature data. We could not identify ν_{sym}(SnC_2) frequencies for **(II)** and **(III)** with reasonable certainty. Dialkyltin complexes usually prefer octahedral geometry [3]. On the assumption that the complexes **(II)** and **(III)** are examples of tin with coordination number six (including H_2O and inter-/intramolecular C(1)=O coordination), the lack of ν_{sym}(Sn–C_2) IR active stretching vibrations may be accounted for in terms of a *trans*-alignment of the alkyl groups [12–15].

The data on 270 MHz ^1H NMR are presented in Table III. The ascorbic acid spectrum consists essentially of three groups of resonances assigned to the protons on C(4), C(5) and C(6) respectively, in order of increasing field [17]. Greater change is expected

TABLE III. ^{1}H NMR Data for New Compounds.[a]

Compound	δCp	δC(4)H	δC(5)H	δC(6)H_2	δMe/Et
L-Ascorbic Acid		4.80d	3.90m	3.69m	
I	6.67s	4.79d	3.90m	3.70m	
II		4.63d	3.85m	3.70m	0.81s
III		4.62d	3.87m	3.70m	1.58m
					1.35m

[a]Spectra recorded in CD_3OD solutions using internal TMS reference with a JEOL GX-270 MHz NMR spectrometer. All shifts are in p.p.m. downfield from TMS; s = singlet, d = doublet, m = complex multiplet, Me = CH_3, Et = CH_2CH_3.

in C(4)–H signals when complex formation is achieved either through C(3)–O– or both C(3)–O– and C(2)–O–. This is reflected by the fact that the C(5)–H and C(6)–H_2 signals remain practically unchanged whereas C(4)–H signals for all the complexes have a significant shift. Signals for methyl protons in (**II**) appear as a sharp singlet at 0.81 p.p.m. whereas the ethyl protons for (**III**) give complex multiplets centered at 1.28 and 1.49 p.p.m. The cyclopentadienyl proton peak for (**I**) appears as a sharp singlet at 6.67 p.p.m. indicating the presence of η-C_5H_5 groups in the complex. However, it should be pointed out that in the spectrum of (**I**), apart from the sharp cyclopentadienyl resonance, very low intensity (~20 times weaker than the cyclopentadienyl peak intensity) signals are present as a complex multiplet between 6.40–6.58 p.p.m. This may be due to the presence of low amounts of other isomers; the actual reason for the appearance of such signals are, however, still uncertain.

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