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Anticancer Activity of Organometallic Compounds. 1. Synthesis and Spectroscopic Characterisation of Cyclopentadienyltitanium Amino/Amido Acid Complexes

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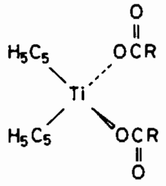
We wish to report in this communication the synthesis and characterisation of carboxylate complexes of titanocene dichloride with amino and amido acids. This, we believe, is the first report of cyclopentadienyltitanium complexes of amino and related acids. The recent discovery by Köpf and Köpf-Maier [1] that titanocene dichloride exhibits adequate cytostatic properties without significant heavy metal toxicity demands a thorough study of the interactions of titanocene dichloride with biologically important molecules, such as amino acids or purine and pyrimidine bases. Very recently, as a result of one such study, a crystallographic description of η-$(C_5H_5)_2Ti(L)_2$ [where L = purine anion] has appeared in the literature [2].

Interactions of Cp_2TiCl_2 (Cp = cyclopentadienyl anion) with anthranilic acid, L-cysteine and hippuric acid are being studied in our laboratories which produce $Cp_2Ti(OCOC_6H_4NH_2)_2$(I), $CpTi(Cl)(SCH_2CHNH_2OCO)\cdot 2H_2O$(III), and $Cp_2Ti(OCOCH_2NHCOC_6H_5)_2$(II) respectively.



I = o-$NH_2C_6H_4$ -

II = $C_6H_5CONHCH_2$ -

Compounds (I) and (II) are synthesised by stirring (3 h) at room temperature, titanocene dichloride and the appropriate acid room temperature, titanocene dichloride and the appropriate acid in 1:2 molar proportions in THF under nitrogen atmosphere in presence of two equivalents of triethylamine. Yellow (**I**, m.p. 160–165 °C(d), 70%) and orange (**II**, m.p. 60–65 °C(d), 65%) crystals are obtained from the filtrate after removing the triethylamine hydrochloride formed. The compounds are soluble in

TABLE I. Relevant IR Absorption Bands (cm^{-1}).[a]

Compound	ν(HOH)	$\nu(NH_2)$	$\nu(NH_3^+)$	ν(NH)	ν(SH)	ν_{asym}(OCO)	ν_{sym}(OCO)	$\Delta\nu$	ν(TiCl)
o-$NH_2C_6H_4COOH$[b]		3484m 3378m				1669s			
o-$NH_2C_6H_4COONa$[c]		3441m 3331m				1515s,b	1390s,b	125	
$(C_5H_5)_2Ti(OCOC_6H_4NH_2$-o$)_2$(I)[c]		3440m 3330m				1620s	1352w	268	
$C_6H_5CONHCH_2COOH$[d]				3367m		1748s			
$C_6H_5CONHCH_2COONa$[c]				3367m		1602s	1402s	200	
$(C_5H_5)_2Ti(OCOCH_2NHCOC_6H_5)_2$(II)[c]				3310m,b		1655,sb	1375s	280	
$HSCH_2CHN^+H_3COO^-$[e]			3012s,b		2568s	1590s	1400s	190	
$C_5H_5Ti(Cl)(SCH_2CHNH_2OCO)\cdot 2H_2O$(III)[c]	3420m,b	3160m,sh				1660s	1380s	280	390w,b[f]

[a] IR spectra are recorded on a Perkin-Elmer 599 instrument as KBr disks; [b] ref. 8. [c] this work; [d] ref. 9; [e] ref. 10; [f] nujol mull on CsI plates, m = medium, b = broad, w = weak, s = sharp, sh = shoulder, $\Delta\nu = \nu_{asym}(OCO) - \nu_{sym}(OCO)$.

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TABLE II. Relevant ^1H NMR Data for the New Compounds.[a]

Compound	δ(Ph)	δ(Cp)	δ(NH)	δ(NH_2)	δ(H_2O)	δ(CH)	δ(CH_2)
$Cp_2Ti(OCOC_6H_4NH_2$-o$)_2$ (I)	7.87m	6.61s					
$Cp_2Ti(OCOCH_2NHCOC_6H_5)_2$ (II)	7.80m 7.50m	6.54s	6.98b				4.05s
$CpTi(Cl)(SCH_2CHNH_2OCO)\cdot 2H_2O$[b] (III)		6.74s		6.62b	4.11s	3.35b,m	3.06b,m

[a] Spectra were recorded on Bruker WP80 NMR in saturated solutions of $CDCl_3$ or d_6-DMSO using internal TMS reference. All shifts are in p.p.m. downfield TMS; [b] spectra recorded in d_6-DMSO solution; b = broad; s = singlet; m = complex multiplets.

common organic solvents but have limited moisture stability. Compound (III), on the other hand, is obtained by the cyclopentadienyl group cleavage of Cp_2TiCl_2. When Cp_2TiCl_2 is stirred (3 h) with L-cysteine (1:1) in the presence of pyridine (two equivalents) in DMSO under N_2 at room temperature, compound (III) is formed as a pale yellow powder (m.p. 165–170 °C(d), 45%). (III) is stable hydrolytically but poorly soluble in common organic solvents.

All the new compounds gave satisfactory elemental analyses; relevant IR and ^1H NMR spectral data are presented in Tables I and II.

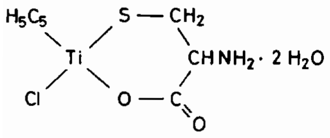
Results and Discussion

IR Data

In complex (I) both ν_{asym} and ν_{sym} stretching frequencies due to NH_2 are shifted to a lower frequency. This lowering of NH_2 stretching frequencies may be due to NH_2 coordination to metal atom or inter- or intramolecular hydrogen bonding. In the ionic sodium anthranilate similar shifts of NH_2 to lower frequency are observed which may be explained in terms of hydrogen bonding. Coordination of the NH_2 group to the metal atom in the sodium salt is unlikely. Evidence of intramolecular hydrogen bonding is available in the crystal structure of the triphenyltin anthranilate complex (ν(CO) 1625 cm^{-1}) [7]. Lowering of $\nu(NH_2)$ in compound (I) may therefore be attributed to hydrogen bonding interactions. The ν_{asym} and ν_{sym}(OCO) frequencies for (I) are identified at 1620 cm^{-1} and 1352 cm^{-1} respectively. The magnitude of the $\nu_{asym} - \nu_{sym}$ (= $\Delta\nu$) has been used successfully to interpret the nature of carboxylate binding to the metal atom [3–6]. The value $\Delta\nu$ = 268 cm^{-1} compared to 125 cm^{-1} for the ionic sodium salt of the parent acid strongly suggests the presence of unidentate carboxylate groups. It may be pointed out that the ν_{asym}(OCO) (1620 cm^{-1}) in the complex is lower than the parent acid (1669 cm^{-1}) is an indication of C=O involvement in bridging or bidentate chelation. However, we notice this type of ν_{asym}(OCO) frequency lowering in $Cp_2Ti(OCOC_6H_5)_2$ (1642 cm^{-1}) [4] from free benzoic acid (1689 cm^{-1}) [8] for which unidentate binding of the benzoate group is demonstrated by X-ray crystal structure determinations. Although in triphenyltin anthranilate the presence of a bidentate carboxylate group is reported by Holmes *et al.* [7], by analogy with $Cp_2Ti(OCOC_6H_5)_2$ we believe a unidentate binding of anthranilate group is present in the compound. However, in the absence of X-ray data, other weak interactions involving carboxyl oxygen cannot be completely ruled out.

In compound (II) lower values of νNH are observed than those present in the parent hippuric acid or its sodium salt. This indicates the presence of a probable hydrogen bonding interaction. A unidentate carboxylate binding may be predicted from the magnitude of $\Delta\nu$ which is 280 cm^{-1} in this case. However like compound (I), the ν_{asym}(OCO) lowering from 1748 cm^{-1} in parent acid to 1655 cm^{-1} in the complex is observed. But, on the other hand, ν_{asym}(OCO) in (II) is substantially higher than the ionic sodium salt (see Table I). Therefore, although we propose the presence of unidentate carboxylate group in the complex other weak interactions of the carboxyl C=O cannot be totally ruled out. There is no change in the stretching frequency of CO in the CONH group for complex (II) from sodium hippurate indicating lack of interaction of the CONH group in the complex.

Compound (III), on the other hand, shows a strong broad absorption around 3420 cm^{-1} which we attribute to the stretching frequency of a coordinated H_2O molecule [10–12]. The $\nu(NH_2)$ frequency appears as a medium broad shoulder at 3160 cm^{-1} of a very strong broad band having absorptions between 3200 cm^{-1} to 2500 cm^{-1} (νNH_2, νCH) [10–12]. Presence of a coordinated water molecule minimises the probability of NH_2 coordination in the molecule. Hydrogen bonding interactions, however, may be present. The IR spectrum shows no band due to SH absorptions indicating the deprotonation of the sulphydryl group leading to the formation of a Ti–S bond. ν_{asym} and ν_{sym}(OCO) frequencies have been assigned to strong bands at 1660 cm^{-1} and 1380 cm^{-1} respectively. The value is 280 cm^{-1} which again indicates a unidentate carboxylate group binding to the metal atom. A weak



III

broad band at 395 cm^{-1} may be tentatively assigned to a Ti–Cl stretching vibration in the complex.

^{1}H NMR Data

Relevant spectral data for (**I–III**) are presented in Table II.

In compound (**I**), the NH_2 proton signals appear as a broad band centered at 5.86 ppm. A similar downfield shift of the NH_2 proton peak in triphenyltin anthranilate has been attributed to the presence of an intramolecular hydrogen bond between the carbonyl group and the ortho amino protons observed by X-ray difrraction in the solid state [7]. Considering our IR and ^{1}H NMR evidence, we believe a similar hydrogen bonding interaction is present in compound (**I**) and hope to confirm this by X-ray diffraction. In compound (**II**), CH_2 proton signals appear as a characteristic doublet of equal intensity at 4.05 and 3.99 p.p.m. The low field appearance of NH proton signal of the amide group at 6.98 p.p.m probably suggests the presence of hydrogen bonding interactions in this compound as in (**I**). An X-ray diffraction analysis of this compound is in progress. For compound (**III**), the CH_2, CH, H_2O and NH_2 protons appear at 3.06, 3.35, 4.11 and 6.62 p.p.m., respectively which are consistent with the literature data [13] for free ligand in trifluoroacetic acid solutions. Compounds (**I**), (**II**) and (**III**) show a sharp singlet due to cyclopentadienyl protons as expected for the η^5-cyclopentadienyl group. Appropriate proton integrations are achieved for all the compounds (**I–III**).

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