Monotheophylline and Monotheophyllinato Complexes of Palladium(II) and their Interactions with Nucleosides

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Abstract

The interaction of potassium tetrachloropalladate-(II) with theophylline in a 1:1 molar ratio resulted in the formation of the monotheophylline ($K[Pd(ThH)Cl_3]$) or monotheophyllinato ($[Pd(Th)Cl]_2$) complexes, depending on the solvent and the acidity conditions. In the first complex, theophylline coordinates to Pd(II) as a neutral molecule through its N9 atom, while in the second as a monoanion through both its N7 and O6 atoms. Both complexes react with nucleosides, giving the complexes $[Pd(Nucl)(ThH)Cl_2]$ and [Pd(Nucl)(Th)Cl], respectively. Those complexes with one N(1)H ionizable imino-proton undergo deprotonation and two new series of mixed ligand complexes, $[Pd(Nucl - H^+)(ThH)Cl]$ and $[Pd(Nucl - H^+)(Th)]$ are formed. In the mixed ligand complexes, theophylline maintains its coordination modes. The nucleosides, on the other hand, exhibit their usual coordination sites; *i.e.* in the non-deprotonated complexes they coordinate only through their N7 atoms, while in the deprotonated they act as bidentate through both their N7 and O6 atoms. All complexes were characterized with elemental analyses, conductivity measurements and various spectroscopic techniques.

Introduction

The purine base 1,3-dimethylxanthine (theophylline (ThH)) has attracted considerable attention over the past years as a model for guanine–metal interactions [1, 2].

Investigations into the binding of metal ions and metal complexes to nucleic acids and their constituents is an active area of inorganic and structural chemistry. This interest has been stimulated by both the importance of such interactions in living systems, and also the success of certain platinum(II) compounds as potential cancer chemotherapeutics [1, 3–6]. It is generally conceded that platinum compounds function as chemotherapeutic agents by binding to guanine-rich portions of DNA and thereby inhibiting transcription, translation and replication [7].

It is widely accepted that N7 is the preferred coordination site in guanosine, inosine and other 6-oxopurines [8]. This site in guanosine is believed to be the primary target for platinum antitumour complexes in cellular DNA [8, 9]. To explain this specificity, several models have been proposed, one of which assumes that initial metal binding to N7 is followed by deprotonation of the N(1)H imino-proton and coordination of O6 with a second coordination site on the metal, leading to an N7/O6 chelate. Although studies on model compounds have conclusively shown that such chelates can be formed with 6-thiopurines [10], evidence for chelation in 6-oxo-ligands is much less convincing.

This problem was examined by Kistenmacher and coworkers by means of a series of copper complexes of theophylline [11, 12]. They confirmed N7 as the primary binding site and noticed that O6 is generally hydrogen bonded with other ligands in the metal coordination sphere. The same behaviour has also been observed with other metal ions [13–16]. When hydrogen bonding ligands were not available, O6 was found to occupy an apical coordination site around copper, but the Cu–O6 distance (292 pm) is much longer than the Cu–N7 distance (*ca.* 195 pm) [12]. Thus, even though this molecule can be described as a chelate, in the sense that a ring exists, the two bonding interactions are hardly comparable. However, a genuine N7/O6 chelate complex was found in the crystal structure of bis(η^5-cyclopentadienyl)-(theophyllinato)titanium(III), in which Ti–N7 and Ti–O6 distances (*ca.* 221 and 228 pm, respectively) are comparable and the angle O6–Ti–N7 is 79.6° [17].

In this paper we report the results of the interactions of Pd(II) with theophylline, in neutral and alkaline solution, and those of the interactions of the resulting monotheophylline- and monotheophyllinato-palladium(II) complexes with purine nucleosides.

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Results and Discussion

The neutral theophylline molecule is protonated at the N7 position and its pK_a has been reported to be 8.5 [18]. Protonation of the N9 atom can occur only under relatively acidic conditions, as the pK_a for the cationic species ThH_2^+ is only 0.7 [18]. These data have often been used as a guide in establishing the reaction conditions for the isolation of particular complexes. The majority of the complexes isolated to date have been prepared under basic reaction conditions and, not surprisingly, the N7 acts as the ligation site. Complex formation involving metal ion binding at N9 has been observed only in those instances in which the reaction solution was made sufficiently acidic so as to preclude ionization at N7 [2] or in those instances in which the N7 site was blocked by prior metal ion coordination [19, 20].

The direct interaction of the purine base theophylline (ThH) with potassium tetrachloropalladate(II) in a 1:1 molar ratio in DMF solution resulted in the formation of the monotheophylline complex $K[Pd(ThH)Cl_3]$:

$$K_2PdCl_4 + ThH \longrightarrow K[Pd(ThH)Cl_3] + KCl \quad (1)$$

Neutralization of the theophylline solution with the equivalent amount of triethylamine before the addition of K_2PdCl_4 resulted in the formation of the dimeric theophyllinato complex $[Pd(Th)Cl]_2$:

$$2K_2PdCl_4 + 2Th^- \longrightarrow [Pd(Th)Cl]_2 + 4KCl + 2Cl^- \quad (2)$$

The same dimeric complex was also obtained from aqueous solution, using KOH to neutralize theophylline.

The analytical and conductivity data of the complexes are given in Table I and fit well with the proposed formulation.

Metal–nitrogen binding in the pyrimidine ring of theophylline is precluded by the presence of methyl groups at the N(1) and N(3) positions. Thus, it is expected that 'soft' metal ions would be restricted in their coordination to the 'imidazole' sites N7, N9 and, possibly, C8.

A number of metal complexes with theophylline have been examined by X-ray crystal structure analysis [21]. The majority of these compounds exhibit bonding through the deprotonated N7 position, although the structure of a neutral, N7-bound metal complex has been elucidated [22]. More recently, coordination at the sterically hindered N9 position has been reported for complexes containing Pt(II) [19] and Rh(II) [23]. A novel mode of theophyllinate anion–metal bonding involving the bridging of two Pt(IV) residues via N7 and N9 has been proposed in order to rationalize the formation of a trimeric complex [19].

In the trichloro(monotheophylline)palladate(II) anion, $[Pd(ThH)Cl_3]^-$, theophylline acts as a monodentate ligand and, most probably, coordinates through its N9 atom. This is mainly deduced from the fact that N7 remains protonated, as is evidenced by the appearance of the N(7)–H resonance at 12.3 ppm in the ^1H NMR spectrum of the complex (see Table II). Also the H8 resonance remains essentially unchanged, and this may be attributed to the very low strength of the N9–Pd bond due to steric hindrance caused by the methyl group at N3. The exocyclic oxygens at positions 2 and 6 do not participate in coordination, as the band at 1690 cm^{-1}, which is attributed to ν(C=O), remains unchanged on complexation (see Table III). Another characteristic of the IR spectrum of this complex is the appearance of a strong band at 325 cm^{-1} attributed to ν(Pd–Cl).

In the theophyllinato complex $[Pd(Th)Cl]_2$, on the other hand, the stoichiometry suggests that the

TABLE 1. Analytical[a] and Conductivity Data of the Complexes

Compound	Pd (%)	Cl (%)	Λ_M (ohm^{-1} cm^2 mol^{-1})
$K[Pd(ThH)Cl_3]$	24.80(24.62)	24.30(24.65)	70(DMF)
$[Pd(Th)Cl]_2$	33.40(33.14)	11.40(11.06)	5(DMF)
$[Pd(ThH)(Ado)Cl_2]$	17.30(17.03)	11.50(11.36)	7(DMF)
[Pd(Th)(Ado)Cl]	17.80(18.09)	6.35(6.03)	6(DMF)
$[Pd(ThH)(Guo)Cl_2]$	16.80(16.60)	11.40(11.08)	8(DMF), 155(H_2O)
[Pd(Th)(Guo)Cl]	17.90(17.60)	6.10(5.87)	5(DMF), 60(H_2O)
$[Pd(ThH)(Guo - H^+)Cl]$	17.40(17.60)	5.70(5.87)	6(DMF)
$[Pd(Th)(Guo - H^+)]$	18.90(18.74)		5(DMF)
$[Pd(ThH)(Ino)Cl_2]$	16.80(17.00)	11.55(11.35)	7(DMF), 165(H_2O)
[Pd(Th)(Ino)Cl]	18.30(18.05)	6.35(6.02)	6(DMF), 65(H_2O)
$[Pd(ThH)(Ino - H^+)Cl]$	18.35(18.05)	5.85(6.02)	6(DMF)
$[Pd(Th)(Ino - H^+)]$	19.50(19.25)		4(DMF)

[a]The numbers in parentheses represent the calculated figures.

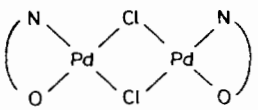
TABLE II. ^{1}H NMR Chemical Shifts of the Complexes in DMSO-d_6

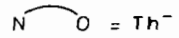
Compound	$H_{8(ThH)}$	$N_7H_{(ThH)}$	NH	NH_2	H_2	H_7
Theophylline (ThH)	8.06	12.30				
K[Pd(ThH)Cl_3]	8.15	12.05				
[Pd(Th)Cl]$_2$	7.65					
Adenosine (Ado)				7.37	8.15	8.36
[Pd(ThH)(Ado)Cl_2]	8.12	11.95		7.80	8.32	9.10
[Pd(Th)(Ado)Cl]	7.68			7.80	8.33	9.15
Guanosine (Guo)			10.60	6.40		7.85
[Pd(ThH)(Guo)Cl_2]	8.16	11.98	11.02	6.70		8.40
[Pd(Th)(Guo)Cl]	7.67		11.05	6.65		8.35
[Pd(ThH)(Guo – H^+)Cl]	8.14	12.05		6.60		8.38
[Pd(Th)(Guo – H^+)]	7.66			6.50		8.42
Inosine (Ino)			11.70		8.15	8.25
[Pd(ThH)(Ino)Cl_2]	8.17	12.10	11.50		8.22	8.78
[Pd(Th)(Ino)Cl]	7.65		11.10		8.44	8.83
[Pd(ThH)(Ino – H^+)Cl]	8.15	11.98			8.24	8.75
[Pd(Th)(Ino – H^+)]	7.64				8.40	8.80

TABLE III. Some Characteristic IR Frequencies of the Complexes (cm^{-1})

Compound	ν(C=O)	ν(Pd–Cl, Pd–Cl–Pd)
Theophylline (ThH)	1690	
K[Pd(ThH)Cl_3]	1692	325
[Pd(Th)Cl]$_2$	1690, 1650	290
Adenosine (Ado)		
[Pd(ThH)(Ado)Cl_2]	1692	320, 330
[Pd(Th)(Ado)Cl]	1690, 1650	325
Guanosine (Guo)	1695	
[Pd(ThH)(Guo)Cl_2]	1692	318, 328
[Pd(Th)(Guo)Cl]	1695, 1650	323
[Pd(ThH)(Guo – H^+)Cl]	1690, 1625	324
[Pd(Th)(Guo – H^+)]	1690, 1630	
Inosine (Ino)	1703	
[Pd(ThH)(Ino)Cl_2]	1695	322, 330
[Pd(Th)(Ino)Cl]	1695, 1650	323
[Pd(ThH)(Ino – H^+)Cl]	1690, 1625	325
[Pd(Th)(Ino – H^+)]	1690, 1632	

theophyllinate anion acts as a bidentate ligand through both its N7 and O6 atoms, in an O6/N7 chelate fashion, as in the case of the complex [η^5-Cp_2Ti(Th)] [17]. The participation of the deprotonated N7 atom in coordination was expected from the reaction conditions and is evidenced by the absence of the N(7)H resonance from the ^{1}H NMR spectrum of the complex and from the upfield shift of the H8 resonance by about 0.4 ppm (see Table II) [20]. The original ν(C=O) band at 1690 cm^{-1} is split on complexation, with one component remaining in the same position and a second being shifted to lower energy by about 40 cm^{-1}. This may be taken as an indication that one of the two carbonyl groups of the ligand (C2=O, C6=O) is coordinated to Pd(II) and the other remains free; the latter is probably the C6=O group, due to the very strong steric hindrance at C2=O caused by the two adjacent methyl groups. The complex shows one medium band at 290 cm^{-1} assigned to ν(Pd–Cl–Pd) and no bands attributable to terminal Pd–Cl groups. Therefore, we assign the dimeric structure [Pd(Th)Cl]$_2$ to the complex. The dimeric structure of the complex was also confirmed by molecular weight determinations (Calc. 662; Found 650).





The above two complexes were further reacted with nucleosides, and the mixed ligand complexes [Pd(ThH)(Nucl)Cl_2], [Pd(ThH)(Nucl – H^+)Cl], [Pd(Th)(Nucl)Cl] and [Pd(Th)(Nucl – H^+)] were prepared according to the reactions:

$$K[Pd(ThH)Cl_3] + Nucl \longrightarrow [Pd(ThH)(Nucl)Cl_2] + KCl \quad (3)$$

$$[Pd(ThH)(Nucl)Cl_2 + KOH \longrightarrow [Pd(ThH)(Nucl - H^+)Cl] + KCl \quad (4)$$

$$[Pd(Th)Cl]_2 + 2Nucl \longrightarrow 2[Pd(Th)(Nucl)Cl] \quad (5)$$

$$[Pd(Th)(Nucl)Cl] + KOH \longrightarrow [Pd(Th)(Nucl - H^+)] + KCl \quad (6)$$

The analytical and conductivity data are listed in Table I and correspond to the proposed formulae.

Reaction (3) is a straightforward replacement of one Cl^- with one nucleoside (Nucl = adenosine (Ado), guanosine (Guo) and inosine (Ino)), leading to monotheophylline mononucleoside neutral complexes. In reaction (5), on the other hand, the double chloride bridge of the dimer is broken and monomeric monotheophyllinato mononucleoside complexes are formed. Both series of mononucleosides complexes, and especially those with one ionizable N(1)H imino-proton (*i.e.* those with Nucl = Guo or Ino) undergo dissociation, and mononucleosidato complexes are formed according to reactions (4) and (6). This dissociation takes place even in neutral solution as is shown by the conductivities of the aqueous solutions of the respective complexes and the increase in their acidity, and it is the result of the lowering of the pK_a of the N(1)H imino-proton after coordination of the N7 atom of the nucleoside to a metal [24, 25]. Such a lowering of the pK_a value of guanosine and inosine, after N7 coordination, to the value of distilled water (*ca.* 7), should facilitate the ionization of the imino-protons and the formation of N7/O6 bound complexes [24–26]. Therefore the pH of the reactions (4) and (6) was kept to *ca.* 7 to 7.5, with addition of 1 N KOH, in order to facilitate these reactions.

The possible structures of the complexes were mainly deduced from their NMR (Table II) and IR (Table III) spectra. Thus the theophylline ^1H NMR chemical shifts and characteristic IR bands in the mixed ligand complexes are similar to those in the parent complexes. It was thus concluded that the coordination modes of theophylline do not change on going from the parent theophylline and theophyllinato complexes to the respective nucleoside and nucleosidato ones.

The ^1H NMR chemical shifts in the aromatic proton region are also very useful in assigning the coordination sites of the nucleosides and are listed in Table II.

The complexes $[Pd(ThH)(Ado)Cl_2]$ and [Pd(Th)-(Ado)Cl], besides the theophylline bands, show bands at 7.80, 8.32, 9.10 and 7.80, 8.33 and 9.15 ppm assigned to NH_2, H2 and H7, respectively. Since H8 shifts downfield by 0.74 and 0.79 ppm while H2 is shifted by only 0.17 and 0.18 ppm, in the respective complexes, it is concluded that N7 is the only binding site of adenosine in the above complexes [26 and refs. therein].

The H8 resonance of guanosine in the complexes $[Pd(ThH)(Guo)Cl_2]$, $[Pd(ThH)(GuO - H^+)Cl]$, [Pd-(Th)(Guo)Cl] and $[Pd(Th)(Guo - H^+)]$ is shifted downfield, relative to free guanosine, by 0.55, 0.50, 0.53 and 0.57 ppm, respectively, and this is strong evidence that the N7 atom participates in coordination in all these complexes [26–28 and refs. therein].

In the complexes $[Pd(ThH)(Ino)Cl_2]$, [Pd(ThH)-$(Ino - H^+)Cl]$, [Pd(Th)(Ino)Cl] and $[Pd(Th)(Ino - H^+)]$ the H8 resonance of inosine is shifted downfield, relative to free inosine, by 0.53, 0.58, 0.50 and 0.55 ppm respectively, while the H8 resonance is shifted by only 0.07, 0.29, 0.09 and 0.25 ppm. These results are comparable to those found in other similar cases [26–28 and refs. therein] and may be taken as a good indication for the N7 coordination of inosine to palladium in these complexes.

The IR spectra of the complexes are also helpful in drawing some concluding remarks on their structure. Thus, in all complexes derived from the dimeric complex $[Pd(Th)Cl]_2$, the band at 290 cm^{-1} assigned to ν(Pd–Cl–Pd) is absent, in accordance with the assumption that the double chloride bridge of this complex is broken during their preparation. The complexes $[Pd(ThH)(Nucl - H^+)Cl]$ and [Pd(Th)(Nucl)-Cl] show a weak band around 325 cm^{-1} assigned to ν(Pd–Cl), which is split and appears as a doublet in the IR spectra of the complexes $[Pd(ThH)(Nucl)Cl_2]$. This band is completely absent from the IR spectra of the complexes $[Pd(Th)(Nucl - H^+)]$, in accordance with their stoichiometry.

In the non-deprotonated complexes of guanosine and inosine, the ν(C6=O) frequencies of these nucleosides remain unchanged on complexation and this excludes participation of this group in the formation of the complexes. In the deprotonated complexes $[Pd(ThH)(Nucl - H^+)Cl]$ and $[Pd(Th)-(Nucl - H^+)]$, however, these bands are shifted to lower energies by about 65 cm^{-1} (see Table III), and this may be taken as an indication for the involvement in coordination of the C6=O of guanosine and inosine, after N(1)H imino-proton ionization [26, 29–31 and refs. therein]. The double bond character of the C(6)=O group is also lowered when the oxygen interacts covalently with a metal, without loss of the N(1)H imino-proton [32]. Oxygen involvement in bonding, following deprotonation of the imino-proton, has also been found in the crystal structure of *cis*-diammineplatinum-a-pyridone blue, where both O^- and N atoms bridge two platinum atoms [33]. Oxygen–Ag(I) bonding was also found in the crystal structure of (nitrato)(1-methylcytosine)silver(I) by Kistenmacher *et al.* [34].

These observations, together with the ^1H NMR data, suggest that guanosine and inosine act as bidentate ligands in the deprotonated complexes through both their O6 and N7 atoms, while in the non-deprotonated nucleoside complexes the nucleosides act as monodentate ligands through their N7 atoms.

Experimental

Materials and Methods

Theophylline, nucleosides and potassium tetrachloropalladate were purchased from Fluka A.G. and used without further purification.

The IR spectra were recorded on a Jasko spectrophotometer as KBr pellets and Nujol mulls. ^{1}H NMR spectra were obtained on a Varian-T60 high resolution spectrometer, with tetramethylsilane as internal standard. The Metrohm E365 conductoscop was used for the conductivity measurements.

Preparation of the Complexes

(1) Potassium Trichloro(theophylline)palladate(II), [K[Pd(ThH)Cl$_3$]

Potassium tetrachloropalladate(II), K_2PdCl_4 (0.327 g, 1 mmol) and theophylline (0.180 g, 1 mmol) were suspended into 10 ml DMF and heated at 65 °C for 6 h. The refrigerated solution was filtered and the compound precipitated with excess isopropanol:ether (1:2). Yield *ca.* 90%.

(2) Bis[μ-Chlorotheophyllinatopalladium(II)], [Pd(Th)Cl]$_2$

Theophylline (0.180 g, 1 mmol) was suspended into 5 ml DMF and neutralized with triethylamine (1 mmol). Potassium tetrachloropalladate(II) (0.327 g, 1 mmol) was then added and stirred for 1 h at room temperature. The refrigerated mixture was then filtered and the compound precipitated with excess isopropanol:ether (1:2). Yield *ca.* 65%.

Alternatively, the title compound could be prepared from aqueous solutions with the following procedure. Theophylline (0.180 g, 1 mmol) was suspended in 10 ml distilled water and neutralized with 1 ml 1 N KOH. Potassium tetrachloropalladate-(II) (0.327 g, 1 mmol) was dissolved into 10 ml water. The two solutions were mixed and stirred for 1 h at room temperature. The resulting red–brown solution was roto-evaporated at 60 °C to dryness. The residue was taken up with 5 ml DMF, filtered and the compound was precipitated with excess isopropanol: ether (1:2). Yield *ca.* 60%.

(3) Dichloro(adenosine)(theophylline)palladium-(II), [Pd(ThH)(Ado)Cl$_2$

K[Pd(ThH)Cl$_3$] (1 mmol, 0.432 g) was dissolved in 3 ml DMSO and adenosine (1 mmol, 0.267 g) was added and stirred to complete dissolution. Water (20 ml) was then added to the mixture and stirred for 1 h at room temperature. The yellow precipitate which formed was filtered, washed with water, ethanol and ether, and dried at 60° under vacuum. Yield *ca.* 85%.

(4) Dichloro(nucleoside)(theophylline)palladium-(II), [Pd(ThH)(Nucl)Cl$_2$], (Nucl = Guo, Ino)

(a) K[Pd(ThH)Cl$_3$] (1 mmol, 0.432 g) and 1 mmol of each of the nucleosides guanosine or inosine were suspended into 150 ml methanol and heated under reflux for 2 h. The yellow solution was filtered and roto-evaporated to dryness at 50 °C. The residue was taken up with 5 ml DMF, filtered, and the compound precipitated with excess isopropanol:ether (1:2). Yield *ca.* 65%.

(b) Alternatively, the title compounds could be prepared from the respective nucleosidato complexes with the following procedure: 1 mmol of each of the complexes [Pd(ThH)(Nucl – H$^+$)Cl] was dissolved into 2 ml DMSO and diluted with 2 ml 0.5 N HCl. After stirring for 1 h at room temperature the compound was precipitated with excess isopropanol. Yield *ca.* 70%.

(5) Chloro(nucleosidato)(theophylline)palladium-(II), [Pd(ThH)(Nucl – H$^+$)Cl], (Nucl = Guo, Ino)

K[Pd(ThH)Cl$_3$] (1 mmol, 0.432 g) was dissolved into 3 ml DMSO and 1 mmol of each of the nucleosides guanosine or inosine was then added. After complete dissolution the mixture was diluted with 10 ml water and the resulting yellow solution neutralized to pH ~ 6.5 with 1 N KOH. The precipitate formed was filtered, washed with water, ethanol and ether, and dried at 60 °C under vacuum. Yield *ca.* 85%.

(6) Chloro(adenosine)(theophyllinato)palladium-(II), [Pd(Th)(Ado)Cl]

Procedure (3) was followed starting with 0.5 mmol of the dimeric complex [Pd(Th)Cl]$_2$ and 1 mmol adenosine.

(7) Chloro(nucleoside)(theophyllinato)palladium-(II), [Pd(Th)(Nucl)Cl], (Nucl = Guo, Ino)

Procedure (4a) was followed starting with 0.5 mmol of the dimeric complex [Pd(Th)Cl]$_2$ and 1 mmol of the respective nucleoside.

(8) Chloro(nucleosidato)(theophyllinato)-palladium(II), [Pd(Th)(Nucl)Cl], (Nucl = Guo, Ino)

Procedure (5) was followed starting with 0.5 mmol of the dimeric complex [Pd(Th)Cl]$_2$ and 1 mmol of the respective nucleoside.

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