Complexes of palladium(II) with theophylline-7-acetic acid

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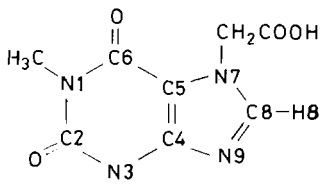
Abstract

The complexes *trans*-$[Pd(tpH)_2Cl_2]$, tpH = theophylline-7-acetic acid; *cis*- and *trans*-$[Pd(tpH)(BH)Cl_2]$, BH = adenine (adH), guanine (guaH) or cytosine (cytH); and *trans*-$[Pd(tpH)(B'H)Cl_2]$ and [Pd(tp)(B'H)Cl], B'H = inosine (inoH) or guanosine (guoH) have been prepared and characterised by elemental and thermal analyses, electronic, infrared, ^1H and ^{13}C NMR spectroscopic studies. Coordination through the imidazole nitrogen, N9 and in some cases additional coordination through the acetate oxygen are demonstrated. The complexes with the theophylline-7-acetate anion are dimeric involving the bridging of theophylline-7-acetate anion. Extended Hückel molecular orbital (EHMO) calculations on tpH and structurally related xanthines indicate N9 of tpH is the most probable binding site which also agrees with the experimental results. The anticancer activity studies on the complex *cis*-$[Pd(tpH)(cytH)Cl_2]$ against Dalton's lymphoma in Swiss mice indicate that the complex possesses marginal activity.

Introduction

Xanthine is a purine base which occurs as a minor constituent of t-RNA. It undergoes facile N-alkylation giving rise to a number of substituted xanthines [1, 2]. Alkylation, in this way, limits the number of nitrogen sites available for metal binding in addition to increasing the solubility. The xanthines, therefore, form an interesting class of ligands. The complex species pentammineaquoruthenium(II) exhibits a high degree of selectivity for binding to unsaturated nitrogens [3]. This behaviour coupled with the use of methylated xanthines has led to the synthesis of a number of pentammineruthenium xanthine complexes with the metal bound at N7. The xanthines also coordinate to metals through the carbon adjacent to the imidazole nitrogens when the nitrogen sites are blocked with substituents [4]. Also, the presence of an alkyl group at N3 is reported to sterically hinder coordination at N9 by large metal ions [5]. Thus, in a ruthenium complex of caffeine (1,3,7-trimethylxanthine), coordination of the ligand is reported [6] through C8. We report here the syntheses and studies on N9 coordinated theophylline-7-acetic acid (tpH) complexes of palladium(II).



tph

Experimental

Palladium chloride was purchased from Arora Matthey (India) and the biochemicals, namely, the nucleosides, the nucleobases and theophylline-7-acetic acid from Sigma Chemical Co. The infrared spectra in KBr (4000–600 cm^{-1}), in polythene (600–200 cm^{-1}) and electronic spectra were recorded on Perkin-Elmer 983 and Cary 2300 model spectrophotometers, respectively. The ^1H NMR data were obtained on a 90 mHz Varian EM-390 spectrometer and ^{13}C NMR data on a JEOL FX 90 Q spectrometer in d_6-DMSO with TMS as an internal reference. Thermoanalytical studies were made on a Stanton Redcroft simultaneous thermal analyser model 781 in static air, at a heating rate of 10 °C/min. Antitumor activity was studied using the Dalton's lymphoma

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model in Swiss mice. The ascites tumor cells were obtained from the Chittaranjan National Cancer Institute, Calcutta and were maintained by sevial passage intraperitoneally, every two weeks. Fresh ascitic fluid was drawn from the peritoneal cavity of ascitic tumor bearing mice and diluted with sterile isotonic saline to a concentration of 1×10^6 cells/ml and solid tumors were produced by injecting 1 ml of the cell suspension subcutaneously into the right thigh region of Swiss mice (male, 1½ months old, weighing about 25 g). The mean tumor diameter was determined by measuring the tumor in two mutually perpendicular directions. The statistical analysis was performed using the 't' test [7].

Synthesis of the complexes

(a) trans-Dichlorobis(theophylline-7-acetic acid)-palladium(II), trans-[Pd(tpH)$_2$Cl$_2$]

Palladium chloride (1.0 mmol) is dissolved in an aqueous solution of KCl (2.0 mmol in 10 ml of water). This is added to an acidic solution of theophylline-7-acetic acid (2.0 mmol of tpH in 2.0 milliequivalents of HCl). From the resultant solution, a yellow crystalline complex is precipitated in 3–5 min which is filtered, washed with water, acetone and air dried. Yield is 80%.

(b) trans-Dichloro(nucleobase/nucleoside)-(theophylline-7-acetic acid)palladium(II), trans-[Pd(tpH)(BH)Cl$_2$] and trans-[Pd(tpH)(B'H)Cl$_2$]

Palladium chloride (1.0 mmol) is dissolved in an aqueous solution of KCl (2.0 mmol in 10 ml of water). To this is added an alkaline solution of theophylline-7-acetic acid (1.0 mmol of tpH in 1.0 milliequivalents of KOH) and the mixture is stirred well. The resultant clear solution is added to an acidic solution of the nucleobase or nucleoside (1.0 mmol of BH in 1.0 milliequivalents of HCl). The yellow solid that precipitates is filtered, washed with water, acetone and air dried. Yields are 60–65%.

(c) cis-Dichloro(nucleobase)(theophylline-7-acetic acid)palladium(II), cis-[(Pd(tpH)(BH)Cl$_2$]

Palladium chloride (1.0 mmol) is dissolved in an aqueous solution of KCl (2.0 mmol in 10 ml of water). To this is added an acidic solution of the nucleobase (1.0 mmol of BH in 1.0 milliequivalent of HCl) and the mixture is stirred well for 2–3 min. Theophylline-7-acetic acid (1.0 mmol) is then added as such to the above solution which is stirred continuously for 45 min till a homogenous yellow precipitate is obtained. It is filtered, washed with water, acetone and dried. Yields range from 60–70%.

(d) μ-(Theophylline-7-acetato)chloro(guanosine/inosine)palladium(II), [Pd(tp)(B'H)Cl]

Palladium chloride (1.0 mmol) is dissolved in an aqueous solution of KCl (2.0 mmol in 10 ml of water). To this is added an alkaline solution of theophylline-7-acetic acid (1.0 mmol of tpH in 1.0 milliequivalent of KOH) and the mixture is stirred well. The resultant red solution is added to an aqueous solution of nucleoside (1.0 mmol in 10 ml of water) which is stirred well for 30 min. The yellow complex that precipitates is filtered, washed with water, acetone and air dried. Yields are 60–70%.

Results and discussion

The elemental analysis data which suggest the proposed composition are presented in Table 1. The complexes are fairly soluble in DMSO and DMF and the molar conductances of the complexes in these solvents range from 3–5 ohm^{-1} cm^2 indicating their non-electrolytic nature. The complexes are diamagnetic as expected for the +2 oxidation state of the metal.

The electronic transitions exhibited by the complexes are assigned (Table 2) based on position and molar absorptivity of the transitions and by comparison of the spectra of the complexes with those of metal complexes of related xanthines [8]. The presence of either d → d transition or ligand → Pd charge transfer in the region 320–395 nm in the complexes suggests a four coordinate planar geometry around palladium(II) [9, 10]. The principal infrared frequencies and their assignments are presented in Table 3. Strong bands at 1710 and 1665 cm^{-1} in the infrared spectrum of tpH are assigned to νC(6)=O and νC(2)=O, respectively, similar to the assignments made for other xanthines [11]. Another strong absorption at 1735 cm^{-1} in tpH is found to disappear in the spectrum of its potassium salt and therefore, is assigned to the ν_{as}COO of the carboxylic group. Three strong and sharp vibrational frequencies at 1625, 1545 and 1480 cm^{-1} in tpH are assigned [11] to combinations of νC=N and νC=C of tpH. In the infrared spectra of the complexes [Pd(tpH)$_2$Cl$_2$], [Pd(tpH)(BH)Cl$_2$] and [Pd(tpH)-(B'H)Cl$_2$], the ν_{as}COO, νC(6)=O and C(2)=O of tpH are not considerably shifted to lower wave numbers indicating the non-involvement of both carboxylic and carbonyl groups of tpH in bonding to the metal [12]. A positive shift of ν_{as}COO in a few complexes may be due to the stacking of the complex molecules. However, the ν_{as}COO of tpH shifts to 1640 and 1635 cm^{-1} in [Pd(tp)(guoH)Cl] and [Pd(tp)(inoH)Cl], respectively, suggesting deprotonation and coordination [13] of the COOH group

TABLE 1. Elemental analysis data

Complexes	Elements[a] (%)				
	C	H	N	Cl	Pd
trans-[Pd(tpH)$_2$Cl$_2$]	33.71 (33.05)	3.52 (3.00)	17.03 (17.14)	10.76 (10.85)	16.13 (16.27)
trans-[Pd(tpH)(cytH)Cl$_2$]	29.72 (29.62)	2.65 (2.85)	18.43 (18.61)	13.73 (13.47)	20.18 (20.19)
cis-[Pd(tpH)(cytH)Cl$_2$]	29.50 (29.62)	2.75 (2.85)	18.32 (18.61)	13.57 (13.47)	20.17 (20.19)
trans-[Pd(tpH)(guaH)Cl$_2$]	29.21 (29.65)	2.53 (2.65)	22.12 (22.24)	12.37 (12.51)	18.90 (18.77)
cis-[Pd(tpH)(guaH)Cl$_2$]	29.32 (29.65)	2.42 (2.65)	22.31 (22.24)	12.38 (12.51)	18.30 (18.77)
trans-[Pd(tpH)(adH)Cl$_2$]	30.01 (30.52)	2.43 (2.72)	22.47 (22.89)	12.56 (12.88)	19.47 (19.31)
cis-[Pd(tpH)(adH)Cl$_2$]	30.12 (30.52)	2.69 (2.72)	22.63 (22.89)	12.52 (12.88)	19.23 (19.31)
trans-[Pd(tpH)(inoH)Cl$_2$]	32.98 (33.46)	3.14 (3.23)	16.23 (16.39)	10.12 (10.37)	15.47 (15.56)
trans-[Pd(tpH)(guoH)Cl$_2$]	31.95 (32.64)	3.02 (3.29)	18.57 (18.04)	10.01 (10.15)	15.11 (15.22)
[Pd(tp)(inoH)Cl]	35.45 (35.35)	3.42 (3.26)	17.23 (17.31)	5.33 (5.48)	16.57 (16.43)
[Pd(tp)(guoH)Cl[	34.01 (34.44)	3.12 (3.32)	19.46 (19.03)	5.78 (5.35)	16.03 (16.06)

[a]Values in parentheses are calculated values.

TABLE 2. Electronic spectral data[a]

Complexes	λ_{max} (nm) (ϵ (l mol^{-1} cm^{-1}))			
	$\pi \rightarrow \pi^*$ [b] (adH)/(guaH)	$\pi \rightarrow \pi^*$ [b] tpH	Ligand $\rightarrow$ Pd charge transfer	d $\rightarrow$ d
trans-[Pd(tpH)$_2$Cl$_2$]		277 (14932)	324 (8013) 384 (724)	
trans-[Pd(tpH)(cytH)Cl$_2$]		256 (24920)	345 (716)	
cis-[Pd(tpH)(cytH)Cl$_2$]		275 (15872)	362 (7897)	
trans-[Pd(tpH)(guaH)Cl$_2$][b]	208	260	324sh	
cis-[Pd(tpH)(guaH)Cl$_2$][b]	200	260	320sh	
trans-[Pd(tpH)(adH)Cl$_2$][b]	240	304	380sh	
cis-[Pd(tpH)(adH)Cl$_2$][b]	230	274	356sh	
trans-[Pd(tpH)(inoH)Cl$_2$]		272 (14815)		368 (369)
trans-[Pd(tpH)(guoH)Cl$_2$]		270 (25375)		395 (257)
[Pd(tp)(inoH)Cl]		280 (36960)	320 (11200)	
[Pd(tp)(guoH)Cl]		274 (43297)	328 (7040)	

[a]Solvent DMSO. [b]Recorded in nujol.

of tpH. Both νC(6)=O and νC(2)=O of tpH remain unchanged in the spectra of these complexes thus ruling out the possibility of carbonyl groups in bonding. The combination modes of νC=N and νC=C due to tpH shift to higher or lower wave numbers by 15–30 cm^{-1} in all the complexes suggesting the coordination of tpH through N9, the only available ring nitrogen atom. In the mixed ligand complexes involving adenine, guanine, cytosine and guanosine, the δNH_2 of the nucleobase/guanosine at 1665 cm^{-1}, shifts to a lower wave number region only by 5 cm^{-1}, indicating the non-involvement of the NH_2 group in bonding to the metal [14]. Similarly, the νC=O of guanine and guanosine at 1700 cm^{-1} appear around 1710 cm^{-1} in the complexes mixed with νC(6)=O of tpH suggesting that the carbonyl group is not involved in bonding [15]. The combinations of νC=C, νC=N and ring stretching frequencies of adenine, guanine, cytosine, guanosine and inosine shift by 10–30 cm^{-1} to lower energy region compared to their positions in the free ligand spectrum (Table 3) indicating that the ring nitrogen atoms of these nucleic bases are involved in bonding [16–19]. The atom N3 is the only available binding site of cytosine while in adenine and guanine both N7 and N9 are equally probable. The nucleosides may coordinate [20] to the metal either through N7 or N1. The assignments of metal–ligand stretching frequencies are made in comparison with the spectra of free ligands in this region. The complexes prepared with tpH and adH, guaH or cytH, by procedure (c), exhibit two Pd–Cl stretching frequencies around 340 cm^{-1} corresponding to the *cis* orientation of the chloro ligands while the other complexes show only

TABLE 3. Infrared spectral data[a]

	ν_{as}(COO) (tpH)	νC(6)=O (tpH)	νC(2)=O (tpH)	νC=N, νC=C (tpH)	νC=N, νC=C, ring stretching of the nucleobase/nucleoside	νPd–N	νPd–Cl	νPd–O
trans-[Pd(tpH)$_2$Cl$_2$]	1745vs	1710vs	1660vs, b	1610m, 1555s, 1510s		550w	340m	
cis-[Pd(tpH)(cytH)Cl$_2$]	1727m	1710vs, b	1660vs, b[b]	1625sh, 1560s, 1510s	1568sh (1590s)	548w, 425sh	339m, 347m	
trans-[Pd(tpH)(cytH)Cl$_2$]	1750s	1720vs, 1710vs, 1700	1665vs[b]	1595sh, 1555s,b	1555s,b (1590s)	550m	352m	
cis-[Pd(tpH)(adH)Cl$_2$]	1734m	1707s	1658vs,b[c]	1615sh, 1552m, 1480m	1592sh (1600s)	550m, 488w	350m, 342m	
trans-[Pd(tpH)(adH)Cl$_2$]	1736m	1705s	1660vs,b[c]	1610sh, 1555s, 1488s	1637s, 1585sh (1600s)	549m	330sh	
cis-[Pd(tpH)(guaH)Cl$_2$]	1730sh	1710vs[d], 1690vs	1660sh[c] 1650vs	1620s, 1540s, 1478s	1620s (16325)	487m 480m	340m, 330m	
trans-[Pd(tpH)(guaH)Cl$_2$]	1735sh	1710vs[d] 1690vs	1660[c]	1601s, 1552s, 1475vs	1625s (16325)	495m	342m	
trans-[Pd(tpH)(inoH)Cl$_2$]	1745s	1690vs[d], 1710vs	1666vs	1606m, 1557s,b, 1510s,b	1557s,b (1582s) 1510s (1540s)	540m	345m,b	
trans-[Pd(tpH)(guOH)cl$_2$]	1746s	1722vs[d], 1710vs	1665vs[c]	1590s,b, 1557s, 1509s	1590s,b (1610s,b) 1545m (1580m) 1511sh (1535s)	472m	350sh	
[Pd(tp)(guoH)Cl]		1700vs[d]	1665sh[c] 1640s, 1657s	1600sh, 1550s, 1500s	1580s (1610s) 1550sh (1580m) 1510sh (1535s)	470m	340m	407w
[Pd(tp)(inoH)Cl]		1700vs[d]	1660s, 1635s,b	1600sh, 1554m, 1493m	1555sh (1582s) 1530sh (1545s)	480m	343m	420m

[a]vs, very strong; s, strong; m, medium; w, weak; b, broad, sh, shoulder. Values in parentheses are free ligand (nucleobase/nucleoside) vibrational frequencies. [b]Includes δNH_2 cytosine. [c]Includes δNH_2 of nucleobase/nucleoside. [d]Includes νCO of guanine/guanosine/inosine.

one band around 340 cm^{-1} and are therefore assigned a *trans* geometry [21].

The proton NMR spectrum of tpH shows four singlets at 7.57, 4.72, 3.19 and 2.96 ppm in the intensity ratio 1:2:3:3 which are accordingly assigned to H8, CH_2 and the two methyl group protons, respectively. A downfield shift of about 0.1 ppm is observed in H8 of tpH in all the complexes (Table 4). This may arise due to coordination of tpH through the adjacent nitrogen atoms [20] namely, N7 or N9. Since, N7 is blocked with acetic acid group, the shift in the H8 signal may be taken as an indication of coordination through N9. In the cytosine complexes, the H5 and H6 doublets shift downfield by 0.1 ppm each suggesting [22] coordination through N3 of cytH. The inosine complexes, $Pd(tpH)(inoH)Cl_2$ and Pd(tp)(inoH)Cl, show a downfield shift of H2 of inosine by 0.88 and 0.97 ppm, respectively and a downfield shift of H8 of inosine by 0.44 and 0.2 ppm, respectively, suggesting that coordination takes place through N1 of inosine [19]. The downfield shift of the H8 of guanosine by 0.66 and 0.79 ppm in $Pd(tpH)(guoH)Cl_2$ and Pd(tp)(guoH)Cl, respectively, similarly implies coordination through N7 of guanosine [19].

The NMR spectra of tpH show the tendency of downfield shifts of $-CH_2$ and $-CH_3$ protons as the concentration of tpH increases. This may probably be due to the hydrogen bonding involving –COOH and –CO groups since hydrogen bonding is reported to produce downfield shifts of protons attached to the atoms α to the functional groups involved in hydrogen bonding [23]. It has been observed that the CH_2 protons (α to COOH) and CH_3 protons (α to carbonyl) of tpH are shifted downfield by 0.05–0.1 ppm in *trans*-$[Pd(tpH)_2Cl_2]$, *trans*-$[Pd(tpH)(cytH)Cl_2]$ and *trans*-$[Pd(tpH)(guoH)Cl_2]$. However, the infrared results on these complexes rule out the involvement of COOH in bonding and therefore the observed downfield shift of the CH_2 protons, coupled with the infrared results, indicates that the carboxyl group may be involved in hydrogen bonding with the carbonyl oxygens of tpH by either an intra- or intermolecular mechanism. However, in the complexes *cis*-$[Pd(tpH)(cytH)Cl_2]$ and *trans*-$[Pd(tpH)(inoH)Cl_2]$, while the CH_2 protons undergo small downfield shifts, the CH_3 protons are found to undergo upfield shift by 0.05–0.2 ppm. In [Pd(tp)(inoH)Cl] and [Pd(tp)(guoH)Cl], the CH_2 protons shift upfield by 0.05 ppm. These upfield shifts may have resulted from stacking of aromatic rings of tpH and cytosine/inosine/guanosine, as unlike hydrogen bonding, stacking brings about upfield shifts of hydrogen atoms or alkyl protons attached to the aromatic rings involved in stacking [24].

The ^{13}C NMR spectra of *trans*-$[Pd(tpH)_2Cl_2]$ and *trans*-$[Pd(tpH)(CytH)Cl_2]$ suggest that the C8 of tpH undergoes a downfield shift of 0.4 and 0.6 ppm while the C4 also shifts downfield by 0.38 and 0.47 ppm, respectively (Table 5). However, C5 and C2 carbons of tpH suffer upfield shifts of 0.48 and 0.54 ppm in $[Pd(tpH)_2Cl_2]$ and 0.65 and 0.16 ppm in $[Pd(tpH)(cytH)Cl_2]$, respectively. The larger downfield shifts of C8 and C4 confirm [25] coordination of tpH through the adjacent nitrogen atom, N9.

Thermogravimetric and differential thermal analyses have been carried out in order to understand the thermal behaviour of the complexes (Table 6). All the complexes show a single step decomposition, giving rise to PdO as the final residue. An endothermic peak in the range 269–284 °C is a common feature in all the complexes and is characteristic of decomposition of theophylline-7-acetic acid. One more endotherm is observed in the same region in the *cis*-cytosine complex which arises due to the loss of CO from the cytosine unit [26]. This indicates that the two ligands decompose almost simultaneously.

TABLE 4. ^1H NMR chemical shift data (ppm)

Complexes	tpH protons			CytH/inoH/guoH protons		
	H8	CH_2	CH_3	H5/H2	H6/H8	NH_2
tpH	7.57	4.72	3.19, 2.96			
trans-$[Pd(tpH)_2Cl_2]$	7.68	4.83	3.27, 3.07			
cis-$[Pd(tpH)(cytH)Cl_2]$	7.66	4.76	3.16, 2.96	5.39	7.13	8.09
trans-$[Pd(tpH)(cytH)Cl_2]$	7.66	4.76	3.27, 3.03	5.43	7.13	8.08
trans-$[Pd(tpH)(inoH)Cl_2]$	7.65	4.76	2.99, 2.81	8.44	8.23	
trans-$[Pd(tpH)(guoH)Cl_2]$	7.67	4.82	3.24, 2.97		8.16	6.44
[Pd(tp)(guoH)Cl]	7.67	4.65	3.21, 2.95		8.29	6.51
[Pd(tp)(inoH)Cl]	7.68	4.65	3.21, 2.95	8.53	8.00	

TABLE 5. ^{13}C NMR chemical shift data (ppm)

Complexes	tpH carbons									Cytosine carbons			
	C2	C4	C5	C6	C8	CH_2 (triplet)	CH_3 (quartet)	CH_3 (quartet)	COOH	C2	C4	C6	C5
tpH	153.91	147.63	107.21	151.04	142.78	46.76	28.99	27.03	168.43				
trans-$[Pd(tpH)_2Cl_2]$	153.85	148.01	106.73	151.09	143.18	47.30	29.58	27.58	169.03				
trans-[Pd(tpH)(cytH)Cl_2]	153.75	148.10	106.56	151.19	143.38	47.50	29.73	27.67	169.17	165.11	93.71	154.65	152.84

The initial decomposition temperatures of *trans*-$[Pd(tpH)_2Cl_2]$, *cis*- and *trans*-adenine, *cis*- and *trans*-guanine and *cis*- and *trans*-cytosine complexes are 236, 266, 247, 265, 248, 274 and 239 °C, respectively while the *trans*-inosine and guanosine complexes start decomposing around 200 °C. The lower stability of the nucleoside complexes over the adH, cytH complexes and $[Pd(tpH)_2Cl_2]$ may be due to the presence of the sugar moiety. The decomposition temperatures of the *cis*- and *trans*-adH and cytH complexes indicate that the *cis* complexes have a higher decomposition temperatures over the *trans* and also the decomposition of the *cis* isomer is faster, accompanied by a sharp exotherm. In contrast to the above, the *cis*-guanine complex decomposes at 265 °C while the *trans* isomer starts decomposing only by 248 °C.

Thus, the complexes, $[Pd(tpH)(BH)Cl_2]$ and $[Pd(tpH)(B'H)Cl_2]$ have two terminal Pd–Cl bonds either in *cis* or *trans* positions and an N9 coordinated tpH. The fourth coordination site of Pd(II) in these complexes is satisfied by N3 of cytosine, N9 of guanine, either N7 or N9 of adenine, N1 of inosine or N7 of guanosine. Both N9 and COO of the theophylline-7-acetate ion are found to participate in coordination in the complexes, [Pd(tp)(B'H)Cl]. A chelate mode of bonding through N9 and the carboxylate oxygen of the theophylline-7-acetate ion is not geometrically favoured. Hence a dimeric structure, $[Pd(tp)(B'H)Cl_2]$, is proposed for these complexes, with two tp^- ions bridging the two palladium atoms through N9 and COO groups. A terminal chloro ligand and a N7 coordinated guoH or a N1 coordinated inoH satisfy the other two coordinating sites of each palladium atom.

EHMO calculations have been made on tpH and a few structurally related xanthines (Table 7). The various interatomic distances, bond angles and dihedral angles of the molecules, needed for the calculation of the cartesian coordinates are assumed from the crystal structure data on theophylline [1]. The values of the valence orbital ionization energies [27] for carbon, oxygen, nitrogen and hydrogen and the orbital exponent values [28] used in the calculation are taken from the literature. The charge density (q_j) on various atoms of the molecules is calculated from the formula $q_j = n_r C_{rj}$ where n_r is the occupancy of the rth molecular orbital and C_{rj} are the coefficients of the basis orbitals of the atoms. The charge densities at the various nitrogen sites of the xanthine derivatives are given in Table 7.

It follows that N9 is the most electron rich site whenever the imidazole hydrogen is placed at the N7 site and in N(9)-H xanthine, where the imidazole hydrogen is at N9, the atom N7 is found to be the

TABLE 6. Thermal analysis data

Complexes	Weight loss (%)		Decomposition temperature range (°C)	DTA peak temperatures (°C) (−endotherm, +exotherm)
	Found	Calc.		
trans-[Pd(tpH)$_2$Cl$_2$]	81.12	81.28	235–523	−269; −286; +447
cis-[Pd(tpH)(cytH)Cl$_2$]	76.10	76.77	274–486	−284; −292; +443
trans-[Pd(tpH)(cytH)Cl$_2$]	76.00	76.77	239–519	−274; +411
cis-[Pd(tpH)(guaH)Cl$_2$]	77.90	78.41	265–491	−267; +450
trans-[Pdt(tpH)(guaH)Cl$_2$]	78.37	78.41	248–496	−284; +490
cis-[Pd(tpH)(adH)Cl$_2$]	77.03	77.78	266–499	−269; +449
trans-[Pd(tpH)(adH)Cl$_2$]	77.24	77.78	247–458	−260; +449
trans-[Pd(tpH)(inoH)Cl$_2$]	81.33	82.10	201–486	−260; +312; +434
trans-[Pd(tpH)(guoH)Cl$_2$]	82.00	82.49	203–468	−276; +404
[Pd(tp)(inoH)Cl]	80.88	81.09	207–477	−274; +382; +401
[Pd(tp)(guoH)Cl]	81.30	81.52	211–440	−266; +379

TABLE 7. Charge densities at nitrogen

Molecules	N1	N3	N7	N9
Xanthine-N(7)-H	−0.42	−0.37	−0.29	−1.02
Xanthine-N(9)-H	−0.41	−0.35	−0.96	−0.21
1-Methylxanthine-N(7)-H	−0.20	−0.32	−0.29	−1.02
Theophylline-N(7)-H	−0.20	−0.19	−0.29	−1.01
Caffeine	−0.20	−0.18	−0.17	−1.02
Theophylline-7-acetic acid	−0.35	−0.37	−0.22	−1.02

most electron rich centre. In tpH, the atom N9 with maximum electron density is predicted to be the preferred metal binding site which agrees with the experimental results.

The anticancer activity studies on *cis*-[Pd(tpH)(cytH)Cl$_2$] against Dalton's lymphoma in Swiss mice indicate that the complex is marginally active. Different dose schedules were followed in the treatment. Solutions of the complex in 20% DMSO (80% water) at various concentrations were prepared and injected intraperitoneally in a volume of 0.4 ml/30 g mouse. In each schedule a control group of mice was maintained which received only 20% DMSO. The administration of the complex at a dosage of 10 mg/kg body weight on the 1st, 3rd, 5th, 7th and 9th days after transplantation, produced a reduction in tumor size [29] as determined on the 7th ($T/C = 76.7\%$) and 10th ($T/C = 80.6\%$) day after transplantation. The increased survival time [30] was found to be 136%. Lower concentrations of the complex were found ineffective while higher concentrations of the complex resulted in cell death due to the precipitatiion of the complex from the medium. A single dose treatment of Dalton's lymphoma bearing mice, a day after tumor transplantation did not leave any effect on the tumor growth. Treatment of mice for 10 days from the 9th to 17th day after transplantation also did not leave any effect on tumor growth or the survival time. However, the solubility of the complex in water, if improved by converting into a potassium salt may result in higher activity of the complex; this is being investigated.

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