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Short Communication

Interaction of [(dien)PtBr]Br with 6-oxopurine nucleosides

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Abstract

Complexes of the general formulae $[(dien)Pt(nucl)]Br_2$, with nucl = guanosine (guo), inosine (ino), xanthosine (xao) and 9-methyl guanine (9-MeG) were first isolated from the reactions of [(dien)PtBr]Br with the nucleosides. Further reactions between the $[(dien)Pt(nucl)]Br_2$, [(dien)PtBr]Br and K_2PtX_4 (X = Cl, Br) complexes produced new ones of formulae $[(dien)Pt(nucl\text{-}H^+)]Br$, $[\{(dien)Pt\}_2(nucl\text{-}H^+)](ClO_4)_3$, $[(dien)Pt(nucl\text{-}H^+)PtX_3]$ and $[(dien)Pt(nucl)](PtX_4)$ (X = Cl, Br). All complexes were characterized by elemental analysis, conductivity measurements, IR and ^{1}H NMR spectra. All the nucleosides are firstly coordinated through their N_7 atoms. This is followed by an attack of a second Pt(II) atom at N_1, after deprotonation of this site in the dinuclear complexes.

Introduction

Purine nucleobases like guanine (guo) or adenine (ado) are known to coordinate preferentially through their N_7 positions with Pt(II) [1, 2]. The N_1 site is also a potential coordination site in adenines [3, 4], and also in guanines after deprotonation of this position [5–7]. Complexes with the guanine nucleobases coordinated with both N_7 and N_1 simultaneously with two different Pt(II) atoms, have also been characterized, both in the solid state [7] and in solution [5, 6, 8–10]. In one case, 9-ethylguanine was found to coordinate with all three sites N_1, N_3 and N_7 with Pt(II) [9].

Deprotonation of the N_1 site of guanines becomes easier after coordination of the base through N_7 with Pt(II), the pK_a of N_1–H being lowered by 1,5-2 logarithmic units [5–10].

In the present note, we report first the preparation of mononuclear complexes of [(dien)PtBr]Br (dien = diethylenetriamine) with the nucleosides inosine (ino), guanosine (guo) and xanthosine (xao). Binuclear complexes of these N_7 coordinated mononuclear complexes with $[(dien)Pt]^{2+}$ and $[PtCl_3]^-$ involving also the N_1 site following deprotonation were subsequently prepared and characterized. For comparison purposes the known complexes with 9-MeG were also prepared [7].

Results and discussion

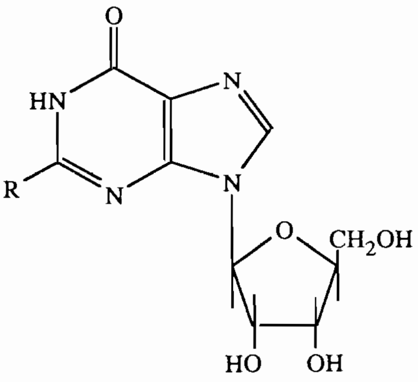
The structures of the nucleosides used in the present study are shown in Fig. 1.

The 1:1 complexes of the nucleosides guo, ino, xao and 9-MeG with [(dien)PtBr]Br were prepared in aqueous solutions, according to the reaction

$$[(dien)PtBr]Br + nucl \longrightarrow [(dien)Pt(nucl)]Br_2 \qquad (1)$$

The nucleosides were N_7 coordinated in all cases as expected [11–13] and as their ^{1}H NMR spectra revealed (see below). The pK_a values of the N_1–H protons of the N_7 coordinated nucleosides were subsequently determined with pH metric titrations and are included in Table 1, together with their elemental analysis. They were found about 1.5–2 logarithmic units lower than the ones of the corresponding free nucleosides [5–10].

Based on the lowering of the pK_as of the N_1–H protons after complexation of N_7 with Pt(II), we at-



R = -H, inosine
-NH_2, guanosine
-OH, xanthosine

Fig. 1. The oxopurine nucleosides used in this study.

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TABLE 1. Elemental analysis, molar conductance and pK_a values of the compounds

Compound	C (%)	H (%)	N (%)	Pt (%)	X (%)	pK_a	Λ_M (Ω^{-1} cm^2 mol^{-1})
[(dien)Pt(guo)]Br_2	23.23(22.68)	3.50(3.54)	15.14(15.12)	26.60(26.32)	22.1(21.56)	7.65	197 (H_2O)
[(dien)Pt(ino)]Br_2	23.41(23.15)	3.93(3.47)	11.70(13.50)	27.30(26.86)	22.45(22.0)	7.00	195 (H_2O)
[(dien)Pt(xao)]Br_2	22.12(22.65)	3.42(3.39)	13.60(13.21)	26.70(26.28)	22.10(21.53)	4.65	238 (H_2O)
[(dien)Pt(9-MeG)]Br_2	19.20(19.27)	3.15(3.23)	17.58(17.98)	30.93(31.31)	26.10(25.64)	8.15	192 (H_2O)
[{(dien)Pt}$_2$(guo-H^+)](ClO_4)$_3$	17.87(18.37)	3.35(3.25)	12.20(13.09)				290 (H_2O)
[{(dien)Pt}$_2$(ino-H^+)](ClO_4)$_3$	18.33(18.60)	3.51(3.21)	11.63(12.05)				281 (H_2O)
[(dien)Pt(guo-H^+)$PtCl_3$]				43.25(44.24)	12.60(12.06)		19 (DMSO), 41 (DMF)
[(dien)Pt(ino-H^+)$PtCl_3$]				45.20(45.01)	12.40(12.27)		15 (DMSO), 33 (DMF)
[(dien)Pt(xao-H^+)$PtCl_3$]				44.30(44.19)	12.90(12.05)		15 (DMSO), 30 (DMF)
[(dien)Pt(9-MeG-H^+)$PtCl_3$]				50.60(51.07)	14.01(13.93)		22 (DMSO)
[(dien)Pt(guo-H^+)$PtBr_3$]				38.40(38.43)	23.90(23.61)		
[(dien)Pt(ino-H^+)$PtBr_3$]	15.95(16.81)	2.18(2.42)	9.35(9.80)	38.80(39.01)			
[(dien)Pt(xao-H^+)$PtBr_3$]				37.93(38.39)	23.20(23.59)		
[(dien)Pt(9-MeG-H^+)$PtBr_3$]	13.50(13.39)	1.80(2.13)	12.90(12.49)	43.10(43.49)	27.15(26.71)		
[(dien)Pt(9-MeG)][$PtBr_4$]	13.10(12.28)	1.91(2.06)	11.92(11.46)	40.20(39.89)	32.00(32.67)		36 (DMSO)

Calculated values of the elemental analysis are given in parentheses.

tempted reactions of the obtained complexes with [(dien)Pt(H_2O)](ClO_4)$_2$ [7] and K_2PtCl_4 or K_2PtBr_4 in neutral aqueous solutions, as follows

$$[(\text{dien})\text{PtBr}]\text{Br} + 2\text{AgClO}_4 \xrightarrow{(\text{H}_2\text{O})} [(\text{dien})\text{Pt}(\text{H}_2\text{O})](\text{ClO}_4)_2 + 2\text{AgBr} \quad (2)$$

$$[(\text{dien})\text{Pt}(\text{H}_2\text{O})](\text{ClO}_4)_2 + [(\text{dien})\text{Pt}(\text{nucl})](\text{ClO}_4)_2 \xrightarrow[-\text{H}_2\text{O}]{-\text{HClO}_4} [\{(\text{dien})\text{Pt}\}_2(\text{nucl-H}^+)](\text{ClO}_4)_3 \quad (3)$$

$$[(\text{dien})\text{Pt}(\text{nucl})]\text{X}_2 + \text{K}_2\text{PtX}_4 \xrightarrow[(\text{X}=\text{Cl, Br})]{\text{KX}} [(\text{dien})\text{Pt}(\text{nucl})](\text{PtX}_4) \quad (4)$$

$$[(\text{dien})\text{Pt}(\text{nucl})](\text{PtX}_4) \xrightarrow[\text{pH}\sim 6]{-\text{HX}} [(\text{dien})\text{Pt}(\text{nucl-H}^+)(\text{PtX}_3)] \quad (5)$$

The elemental analysis of the isolated compounds agree with their assigned formulae (see Table 1).

The molar conductance values (Λ_M), also included in Table 1, indicate that the [(dien)Pt(nucl)]Br_2 complexes are 1:2 electrolytes, while the binuclear ones are non-electrolytes as expected. The complexes [(dien)Pt(nucl)](PtX_4) however, have Λ_M values in DMSO, approaching the 1:1 electrolytes (see Table 1).

Characteristic IR bands of all the complexes are included in Table 2. The complexes [(dien)Pt(nucl)]Br_2 show the bands in the region of 1600–1700 cm^{-1} slightly shifted to lower frequencies, due to a Pt(II)–N_7 monodentate coordination [12–14] and the retention of the double bond character of the C_6=O group (see Table 2). The band near 1700 cm^{-1}, due to the νC_6=O vibration, however, disappears and a new band appears near 1635 cm^{-1} in the dinuclear complexes containing ino, while in the deprotonated [(dien)Pt(ino-H^+)]Br complex, this band appears near 1600 cm^{-1}.In the guo derivatives on the other hand, the near 1700 cm^{-1} νC_6=O band of [(dien)Pt(guo)]Br_2 appears at 1600 cm^{-1} in the N_1–H deprotonated and N_7 coordinated complex [(dien)Pt(guo-H^+)]Br and again near 1635 cm^{-1} in both dinuclear species. The situation in the series of complexes with xao is similar. This behaviour was explained as indicating N_7O_6 chelation, in earlier studies [13, 14], of 6-oxopurine nucleosides with Pt(II) or Pd(II). Possible polymeric structures involving all potential sites (N_1, N_7, O_6) of the 6-oxopurine nucleosides could not be excluded however [13], on the basis of the IR spectra alone. A similar conclusion was also made in the case of the copper(II)–inosine–monophosphate-*o*-phenanthroline complex [15], with a simultaneous N_1, N_7, O_6 bonding with the metal, as well as in the case of Hg(II)–guo complexes [16].

TABLE 2. Characteristic IR and ^1H NMR bands of the compounds

Compound	IR bands (cm^{-1})	^1H NMR bands (ppm)		
		H_2	H_8	$H_{1'}$
guo	1735, 1647, 1605, 1545, 775		8.07	5.98
$[(dien)Pt(guo)]Br_2$	1699, 1643, 1595, 1539, 797		8.30	5.90
$[(dien)Pt(guo\text{-}H^+)]Br$	1600, 1556, 797		8.21	5.85
$[(dien)Pt(guo\text{-}H^+)PtCl_3]$	1630, 1595, 1530, 785, 325			
$[\{(dien)Pt\}_2(guo\text{-}H^+)](ClO_4)_3$	1635, 1600, 1530, 782		8.36	5.98
ino	1700, 1598, 1555, 786	8.11	8.22	5.98
$[(dien)Pt(ino)]Br_2$	1699, 1592, 1560, 788	8.03	8.59	5.90
$[(dien)Pt(ino\text{-}H^+)]Br$	1601, 1535, 804	7.86	8.37	5.88
$[(dien)Pt(ino\text{-}H^+)PtCl_3]$	1638, 1537, 792, 325			
$[\{(dien)Pt\}_2(ino\text{-}H^+)](ClO_4)_3$	1635, 1535, 792	8.47	8.71	6.15
xao	1700, 1680, 1610, 1580, 717		7.97	5.96
$[(dien)Pt(xao)]Br_2$	1700, 1580, 750		8.42	5.98
$[(dien)Pt(xao\text{-}H^+)PtCl_3]$	1630, 1585, 720, 320			
$[\{(dien)Pt\}_2(xao\text{-}H^+)](ClO_4)_3$	1638, 1580, 728		8.60	5.95

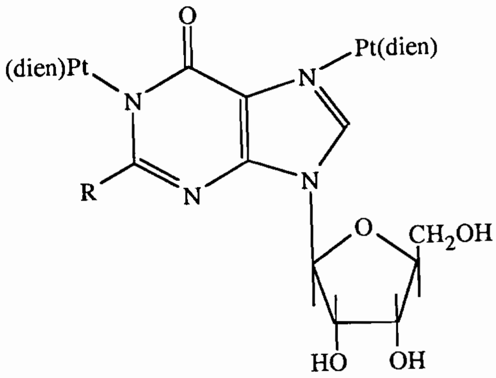

Fig. 2. Proposed structures of the dinuclear complexes.

Lippert and co-workers [7] found a band near 1640 cm^{-1} for the N_1,N_7 diplatinated complex of 9-MeG of formula $[\{(dien)Pt\}_2(9\text{-MeG-}N_7,N_1)](ClO_4)_3 \cdot 2H_2O$, prepared in exactly the same way as our complexes. This frequency is intermediate between the N_7 monocoordinated and N_1–H protonated ligand (~1700 cm^{-1}) and the N_7 monocoordinated and N_1–H deprotonated one (1600 cm^{-1}) [7]. An N_7O_6 chelation is not possible in the present case, though an O_6 over N_1 coordination or a simultaneous N_1O_6 coordination with Pt(II) cannot be excluded. The approximately similar intermediate frequencies of our dinuclear complexes, e.g. 1630–1640 cm^{-1} (Table 2), however, as well as their similar method of preparation to the complex with 9-MeG (see 'Experimental'), indicates a similar simultaneous N_7,N_1 coordination also here (Fig. 2). At present, such an IR behaviour should be taken as indicating a simultaneous N_7,N_1 coordination with Pt(II), rather than an N_7O_6 chelation [13, 14]. It should be noted, however, that in the postulated Pd–N_7O_6 chelates with ino or guo, this band was observed at slightly lower frequency, e.g. 1625 cm^{-1} [14].

Other sensitive IR bands include the 1555 cm^{-1} of free ino, shifted to 1535 cm^{-1} in the N_7 monocoordinated and N_1–H deprotonated or N_1,N_7 dicoordinated species and the 1545 cm^{-1} of free guo, shifted analogously to 1530 cm^{-1}. Also, the ring breathing motions of free ino, guo and xao, occurring at 786, 785 and 717 cm^{-1}, respectively, are shifted to higher frequencies upon metal coordination, but to intermediate ones in the N_7, N_1 dinuclear species (higher frequencies in the Pt–N_7 coordinated ligands and the free ligands). Finally, the appearance of a band near 330 cm^{-1} due to νPt–Cl should be mentioned for the complexes containing the $PtCl_3^-$ and $PtCl_4^{2-}$ species, but not found in the case of $PtBr_3^-$ and $PtBr_4^{2-}$.

The ^1H NMR chemical shifts of the various complexes in the aromatic proton region are also included in Table 2. Only the ^1H NMR spectra of the $[(dien)Pt(nucl)]Br_2$ and the dinuclear $[\{(dien)Pt\}_2(nucl\text{-}H^+)](ClO_4)_3$ complexes could be obtained; these are also presented in Table 2. The ^1H NMR spectra of the dinuclear complexes $[(dien)Pt(nucl\text{-}H^+)(PtX_3)]$, however, showed broad lines, possibly due to either polymerization involving both N_1 and N_3 sites, besides N_7 of the nucleosides in bonding with Pt(II), or to a metal–metal interaction. The H_8 aromatic protons of guo, ino and xao, shift downfield in the complexes $[(dien)Pt(nucl)]Br_2$ by 0.3–0.4 ppm, compared to the free ligands. The 60 MHz spectra of the compounds also show the satellites of ^{195}Pt (33%) around H_8 (coupling constant of about 35 Hz). These are in agreement with an N_7–Pt(II) coordination in all the complexes [11–14]. In the N_1,N_7 dinuclear complexes on the other hand, a further downfield shift of the H_2

proton is observed in the ino complexes, and a smaller one for the H_8 proton in the guo complexes (Table 2). Finally, both H_2 and H_8 protons of the N_7 monocoordinated and N_1-deprotonated complexes are shown upfield compared to the non-deprotonated ones (Table 2).

Experimental

Materials

The nucleosides ino, guo and xao and $AgClO_4$ were purchased from Sigma Chem. Co and used without further purification. K_2PtCl_4 was from Johnson Matthey and Mallory.

Methods

The elemental analysis of Pt and Cl were made by us, as previously described [13, 14] and of C, H, N with a Beckmann elemental analyser. The conductivity measurements were performed in an E365 B conductoscope, Metrohm Ltd., Herisau, Switzerland. The IR spectra were recorded on a Perkin-Elmer model 883 spectrophotometer. The ^1H NMR spectra are obtained on Brucker 200 MHz and Varian T60 spectrometers.

Preparation of the complexes

(i) The complexes [(dien)Pt(nucl)]Br$_2$

0.5 mmol of [(dien)PtBr]Br and 0.5 mmol of the nucleoside were heated at 80 °C for 7–8 h under stirring, in about 20 ml of H_2O. The aqueous solutions were subsequently evaporated to small volumes and left in the refrigerator. In the cases with guo and 9-MeG, a white powder was precipitated after a few hours and was then filtered. It was washed with cold water, acetone and ether and dried over P_2O_5 under vacuum. In the cases with ino and xao an amount of acetone was added to the aqueous solutions, and the precipitate obtained after cooling, was filtered and dried as above. Yield 85–90%.

(ii) The complexes [(dien)Pt(nucl)](PtX$_4$) and [(dien)Pt(nucl-H$^+$)(PtX$_3$)] (X=Cl, Br)

In 25–30 ml of H_2O, 0.2 mmol of the complex [(dien)Pt(nucl)]Br_2 and 5 mmol of KX (X=Cl, Br) were dissolved. 0.2 mmol of K_2PtCl_4 were then added. The mixing was followed by precipitation of the corresponding salt [(dien)Pt(nucl)][$PtCl_4$] of light pink colour, which can be isolated by filtration at this stage, washing with H_2O, acetone and ether, and drying. To obtain the [(dien)Pt(nucl-H^+)($PtCl_3$)] complexes, the suspensions were allowed to react with stirring for 8 h at 80 °C. During the reaction, the pH falls to acidic values and is kept constant to about 6 by addition of 0.1 M KOH or NaOH. This procedure results in the dissolution of the initial precipitates. Finally the clear solution was evaporated to a small volume and upon cooling, an orange coloured precipitate separated out, which was filtered, washed with ice cold water, acetone and ether, and dried over P_2O_5 in a dessicator under vacuum. Yield 80%.

(iii) The complexes [(dien)Pt(nucl-H$^+$)Pt(dien)]-(ClO$_4$)$_3$

0.2 mmol of [(dien)PtBr]Br were allowed to react with 0.39 mmol of $AgClO_4$ and the resulting AgBr was filtered off by centrifugation. The resulting solution, containing [(dien)Pt(H_2O)]$(ClO_4)_2$, was allowed to react with 0.2 mmol of [(dien)Pt(nucl)]$(ClO_4)_2$ (exchange of Br^- with ClO_4^-, in a similar fashion) by heating for 8 h at 80–90 °C, with stirring, in 20–30 ml of water. The pH of the reaction mixture is kept constant to about 6, with 0.1 M NaOH. At the end of the reaction, the solutions were evaporated to small volumes. To these, acetone was added and the resulting precipitate was separated from the liquid by filtration. The precipitate was washed with acetone and ether, and dried over P_2O_5 in a vacuum dessicator. Yield 50–60%.

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