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Dynamic processes in platinum(II)–adenosine complexes. Preparation, NMR spectroscopic characterisation and crystal structure of isomeric Pt^{II}(dien)–adenosine complexes

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The distribution of aquated Pt^{II}(dien) between the adenosine N^1 and N^7 sites has been found to be affected in aqueous solution not only by lowering the pH, but also by equilibration of the mixture of Pt^{II} and nucleoside at high temperature. In the former case Pt^{II} predominantly binds to the N^7 site (**1**), whereas the latter procedure significantly increases the amount of the N^1-bound complex (**2**) at the expense of the N^7 isomer. Both complexes exhibit two ^{195}Pt resonances at ambient temperature, but ^{1}H and ^{13}C NMR spectra recorded in D_2O revealed only signals with expected multiplicities for the adenine moiety. However, in [$^2H_7$]dmf the aromatic protons and the dien NH proton resonances were split into two components at −50 °C and the C^6–NH_2 protons were no longer equivalent in both complexes. This suggests restricted rotation about the platinum–nucleoside bonds and/or conformational changes of the dien ligand. Also rotation of the exocyclic amino group about the C^6–N^6 bond appears to be restricted at low temperatures. Both complexes were crystallised as perchlorate salts and their crystal structures determined. Based on X-ray data, further disturbance in the platinum(II) co-ordination sphere may be induced by close proximity of the exocyclic amino group of the nucleobase and Pt^{II}.

The versatile metal-ion binding capability of N^9-substituted adenine nucleobases has stimulated a great deal of research in the past two decades.[1,2] Of the different binding modes reported, the ring nitrogens N^1 and N^7 are the predominant binding sites for various metal ions,[1–4] but co-ordination to the exocyclic N^6 amino group upon displacement of a proton has also occasionally been reported.[5] The N^3 binding mode appears to be very rare in 9-substituted adenines and becomes significant only when both N^1 and N^7 are sterically blocked, *e.g.* in 6,6,9-trimethyladenine.[6]

The distribution of metal ions between the major binding sites N^1 and N^7 depends on the pH, metal, and additional ligands co-ordinated to the metal.[1] Much attention has been paid to the co-ordination of various platinum(II) compounds to adenine derivatives, in particular, since the adenine N^7 site is one of the major targets in DNA for anticancer platinum drugs.[7] For example, monofunctionally binding Pt^{II}(dien) distributes almost equally between the N^1 and N^7 sites in neutral adenosine, while the faster reacting palladium analogue favours the N^1 site by 5:1.[8] With 5′-AMP (adenosine 5′-monophosphate) Pt^{II}(dien) slightly favours the N^7 site.[9] Similarly, various aquated *cis*-platinum(II) diamines show a slight preference for the adenosine N^7 site,[10] as does *cis*-[$PtCl_2(NH_3)_2$].[11] Although selective N^7 platination in 9-substituted adenines may be achieved in strongly acidic solution, *i.e.* when the N^1 site is blocked by a proton,[1,10] no such procedure that gives N^1-platinated species as a major product appears to have been reported. In this work we show that prolonged treatment of aquated Pt^{II}(dien) with an excess of adenosine at *ca.* 85 °C in aqueous solution considerably increases the amount of N^1-bound species at the expense of the N^7 isomer. The chromatographically purified N^1- and N^7-bound platinum–adenosine complexes were characterised by ^{1}H, ^{13}C and ^{195}Pt NMR spectroscopy, which show that in both cases Pt^{II} exists in two slightly different environments. Both complexes were crystallised as perchlorate salts and their crystal structures determined. To our knowledge they represent the first examples of X-ray structurally characterised platinum(II)–adenosine complexes.

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Experimental

Materials

Adenosine (Ado) was from Sigma and used as received; [Pt(dien)I]I and its aqua derivative were prepared as previously described.[12] For the preparation of [Pt(dien)(Ado-N^7)]$^{2+}$ **1**, adenosine (1.8 mmol) was dissolved in 1 M HNO_3 (2 cm^3), followed by addition of aquated Pt^{II}(dien) (0.36 mmol). After stirring for 3 d at room temperature, NaOH (1.9 mmol) was added and the solution concentrated to about 0.5 cm^3. The residue was fractionated on a preparative RP-18 column (40 μm, 30 × 200 mm) using 10% methanol in aqueous 0.1 M $NaClO_4$ (pH 3) as eluent. The combined fractions of **1** were concentrated to about 0.5 cm^3, and the excess of electrolyte was removed by refractionation with 15% methanol. Upon cooling, the concentrated solution of **1** gave 190 mg (67%) of [Pt(dien)(Ado-N^7)][ClO_4]$_2$·H_2O **1a** as colourless prisms, which had a strong tendency to dim during crystallisation (Found: C, 21.8; H, 3.3; N, 14.4. Calc. for $C_{14}H_{28}Cl_2N_8O_{13}Pt$: C, 21.5; H, 3.6, 14.3%).

For the preparation of [Pt(dien)(Ado-N^1)]$^{2+}$ **2**, adenosine (5.2 mmol) was suspended in water (50 cm^3) and to this was added aquated Pt^{II}(dien) (0.56 mmol) in water (15 cm^3). The mixture was stirred in a stoppered flask for 5 d at 80–85 °C, after which most of the unchanged adenosine was precipitated upon cooling the mixture with ice. The mixture was filtered and the filtrate, after concentration to about 2 cm^3 on a rotary evaporator, was passed through the RP-18 column using 10% methanol in aqueous 0.1 M $NaClO_4$ (pH 3) as eluent. The combined fractions of **2** were then concentrated to about 3 cm^3, which gave 230 mg of thin colourless needles upon cooling at +4 °C. About 150 mg of this product were dissolved in water (1 cm^3), assisted by gentle warming, and [Pt(dien)(Ado-N^1)][ClO_4]$_2$·2.77H_2O **2a** (the amount of crystal water is based on X-ray analysis refinement) slowly crystallised at room temperature as thick, colourless plates which very easily lost water of crystallisation

(Found for dried substance: C, 21.8; H, 3.5; N, 14.6. Calc. for $C_{14}H_{26}Cl_2N_8O_{13}Pt$: C, 22.0; H, 3.4; N, 14.7%). For X-ray analysis, the mother-liquor was removed and the crystals were immediately suspended in paraffin to prevent decomposition. A large plate was cut into pieces under paraffin, and a selected piece sealed in a capillary.

NMR studies

The NMR measurements were carried out in D_2O and [$^2H_7$]dmf (^1H) or in H_2O/D_2O (^{13}C and ^{195}Pt) at different temperatures ranging from −50 to +25 °C [$^2H_7$]dmf and from +25 to +60 °C (D_2O or H_2O/D_2O). Spectra were acquired primarily on a JEOL Alpha 500 spectrometer equipped with a 5 mm tunable probe operating at 500.16 MHz for ^1H, 125.78 MHz for ^{13}C and 107.21 MHz for ^{195}Pt, or a JEOL Lambda 400 spectrometer equipped with a 5 mm CH probe operating at 399.78 MHz for ^1H and 100.54 MHz for ^{13}C. The ^1H and ^{13}C spectra were referenced internally to sodium 4,4-dimethyl-4-silapentanesulfonate (dss), assigned as δ 0.015 for proton and 0 for carbon, and the ^{195}Pt spectra externally to $[PtCl_4]^{2-}$ (δ_{Pt} −1625 from $[PtCl_6]^{2-}$).

One-dimensional high-resolution proton spectra were acquired with normal single-pulse excitation, 45° flip angle, pulse recycle time of 9 s and spectral widths of 8 kHz consisting of 65 k data points (digital resolution 0.11 Hz per point), zero-filled to 128 k prior to Fourier transformation. Spectra were also acquired with presaturation of the water signal (32 k data points and 5 s of presaturation for a total pulse recycle time of 9 s). Exchange spectroscopy (EXSY) difference spectra were acquired using irradiation times of 6–8 s and 8 k data points, zero-filled to 128 k and with 1 Hz exponential weighting applied prior to Fourier transformation. Double quantum filtered (DQF) COSY was acquired in the phase-sensitive mode with spectral widths appropriately optimised from the one-dimensional spectra, and processed with zero-filling (×2, ×4) and exponential weighting (1 Hz) applied in both dimensions prior to Fourier transformation.

One-dimensional carbon spectra were acquired with normal single-pulse excitation, 45° flip angle, pulse recycle time of 3.5 s and spectral widths of 34 kHz consisting of 64 k data points (digital resolution of 0.52 Hz per point), zero-filled to 128 k and with 1 Hz exponential weighting applied prior to Fourier transformation. The DEPT spectra (90 and 135°) were acquired under similar conditions, but with the pulse recycle time reduced to 3 s. The CH shift correlation and heteronuclear multiple bond correlation (HMBC) spectra were acquired in magnitude mode with spectral widths appropriately optimised from the one-dimensional spectra and processed with zero-filling (×2, ×4), 2π/3-shifted sinebell functions, and exponential weighting (1 Hz) applied in both dimensions prior to Fourier transformation.

One-dimensional platinum spectra were acquired with normal single-pulse excitation, 70° flip angle, pulse recycle time of 0.8 s and spectral widths of 118 kHz consisting of 32 k data points (digital resolution 3.6 Hz per point), zero-filled to 64 k and with 50–100 Hz exponential weighting applied prior to Fourier transformation.

Crystallography

All X-ray data were collected on a Rigaku AFC5S diffractometer at ambient temperature using Mo-Kα radiation (λ = 0.710 69 Å). The intensity of three standard reflections remained constant throughout the measurement in both cases. The intensities of the reflections were corrected for Lorentz-polarisation and absorption (empirical) effects. The structures were solved by standard Patterson and Fourier-difference methods and refined by full-matrix least-squares calculations employing the TEXSAN program package[13] (**1a**) or SHELXL 93 (**2a**).[14] In **1a** all atoms except hydrogen and the water oxygen were refined with anisotropic thermal parameters, whereas in **2a** only Pt and Cl were anisotropically refined. Further details of the structure refinement are given in Table 3.

CCDC reference number 186/891.

See http://www.rsc.org/suppdata/dt/1998/1397/ for crystallographic files in .cif format.

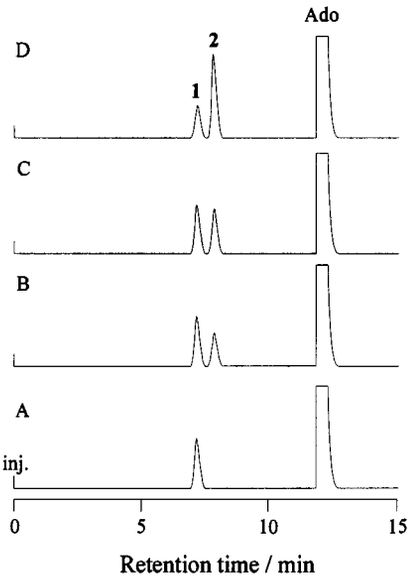


Fig. 1 The HPLC elution profiles of mixtures of aquated Pt^{II}(dien) and adenosine ($[Pt]_T:[L]_T = 1:5$) after 2 h of mixing at pH 2 (A), at pH 5 (B), at pH 5 in the presence of Ni^{2+} ($[Ni]_T:[L]_T = 5:1$) (C) and mixture (B) after 5 d (D). Eluent: 3% MeOH in 0.05 M $NaClO_4$ (pH 3), flow rate 1.0 $cm^3\ min^{-1}$; LiChrospher RP-18 column (4 × 250 mm, 5 μm)

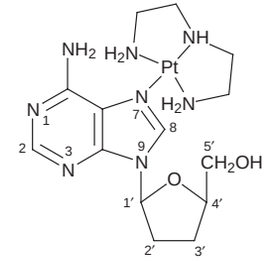
Results and Discussion

Distribution of Pt^{II} between the adenosine N^1 and N^7 sites can be conveniently followed by HPLC. As seen in Fig. 1, the N^7 binding mode of $[Pt(dien)(H_2O)]^{2+}$ predominates at pH 2 because the N^1 site is blocked by a proton.[1,10] At higher pH coordination to the N^1 site becomes significant, and at pH 5 the apparent $N^1:N^7$ ratio based on peak areas at 260 nm is *ca.* 2:3. We have reported earlier that certain 3d metal ions slightly prefer the N^7 over the N^1 site in 9-substituted adenines.[15] However, attempts to block the N^7 site by 3d metal ions were not successful. Only in the presence of a large excess of Ni^{2+} ions the amount of N^1-platinated species increased; other metal ions tested (Co^{2+}, Cu^{2+}) were found to be ineffective. By contrast, prolonged treatment (5 d) of an aqueous solution of $[Pt(dien)(H_2O)]^{2+}$ and adenosine at *ca.* 85 °C significantly increased the amount of N^1-bound species at the expense of the N^7 isomer. According to HPLC analysis the initial $N^1:N^7$ ratio of 2:3 slowly increases to *ca.* 3:1 during this treatment. This process parallels the behaviour of the 10^4–10^5 times faster reacting palladium(II) analogue[8] and reflects the greater thermodynamic strength of the Pt–N^1 bond over the Pt–N^7 bond consistent with the difference in basicity of these sites. In an equimolar mixture of Pt^{II} and adenosine a third (minor) product also appears in the reaction. It is tentatively assigned as the N^1,N^7-diplatinated species because its concentration could be greatly reduced by employing an excess of the nucleoside.[1] This suggests that the N^7 to N^1 isomerisation proceeds *via* breaking and reformation of platinum–nucleobase bonds without participation of the C^6–NH_2 group in the process.

NMR Studies

The ^1H, ^{13}C and ^{195}Pt chemical shifts for complexes **1** and **2** in D_2O are listed in Tables 1 and 2. The assignments of the ^1H and ^{13}C resonances were based on COSY, C–H correlation, DEPT, HMBC, and by comparison to adenosine. Downfield shifts of

Table 1 Proton chemical shifts for complexes **1**, **2** and free adenosine*



	δ_H								
Compound	H^2	H^8	$H^{1'}$	$H^{2'}$	$H^{3'}$	$H^{4'}$	$H^{5'}$	$H^{5''}$	CH_2 of dien
1	8.383	8.901 (br)	6.156 (d) [$J(H^{1'}H^{2'})$ 5.3]	4.786 (t) [$J(H^{1'}H^{2'}) = J(H^{2'}H^{3'})$ 5.0]	4.434 (t) [$J(H^{2'}H^{3'}) = J(H^{3'}H^{4'})$ 4.7]	4.329 (q) [$J(H^{3'}H^{4'}) = J(H^{4'}H^{5'}) = J(H^{4'}H^{5''})$ 3.5]	3.963 [d(AB)d] [$J(H^{5'}H^{5''})$ 12.9; $J(H^{4'}H^{5'})$ 2.7]	3.882 [d(AB)d] [$J(H^{5'}H^{5''})$ 13.1; $J(H^{4'}H^{5''})$ 3.6]	3.26–3.34 (2 H) 3.06–3.16 (4 H) 2.90–2.98 (2 H)
2	8.65 (br)	8.421	6.086 (d) [$J(H^{1'}H^{2'})$ 5.9]	4.766 (t) [$J(H^{1'}H^{2'}) = J(H^{2'}H^{3'})$ 5.5]	4.428 (dd) [$J(H^{2'}H^{3'})$ 5.2; $J(H^{3'}H^{4'})$ 3.8]	4.274 (td) [$J(H^{3'}H^{4'}) = J(H^{4'}H^{5''})$ 3.9; $J(H^{4'}H^{5'})$ 2.9]	3.900 [d(AB)d] [$J(H^{5'}H^{5''})$ 12.8; $J(H^{4'}H^{5'})$ 3.0]	3.835 [d(AB)d] [$J(H^{5'}H^{5''})$ 12.8; $J(H^{4'}H^{5''})$ 4.0]	3.24–3.33 (2 H) 3.02–3.13 (4 H) 2.86–2.95 (2 H)
Adenosine	8.146	8.283	6.029 (d) [$J(H^{1'}H^{2'})$ 6.1]	4.769 (dd) [$J(H^{1'}H^{2'})$ 6.1; $J(H^{2'}H^{3'})$ 5.3]	4.424 (dd) [$J(H^{2'}H^{3'})$ 5.3; $J(H^{3'}H^{4'})$ 3.4]	4.292 (q) [$J(H^{3'}H^{4'}) = J(H^{4'}H^{5''})$; $J(H^{4'}H^{5''})$ 3.2]	3.921 [d(AB)d] [$J(H^{5'}H^{5''})$ 12.9; $J(H^{4'}H^{5'})$ 2.8]	3.839 [d(AB)d] [$J(H^{5'}H^{5''})$ 12.9; $J(H^{4'}H^{5''})$ 3.6]	

* In ppm from dss. Spectra recorded in D_2O at ambient temperature. Coupling constants in Hz in square brackets.

Table 2 Carbon-13 and ^{195}Pt chemical shifts for complexes **1**, **2** and free adenosine[a]

		δ_C										
Compound	δ_{Pt}	C^2	C^4	C^5	C^6	C^8	$C^{1'}$	$C^{2'}$	$C^{3'}$	$C^{4'}$	$C^{5'}$	CH_2 of dien
1	−2861 (0.3)[b] −2875 (0.7)	156.55	150.74	119.60	156.93	145.16	92.20	76.78	72.80	88.62	63.78	56.71; 53.14
2	−2925 (0.4) −2936 (0.6)	156.31	149.80	122.40	158.35	144.45	91.13	76.68	73.02	88.29	64.00	56.53, 53.16
Adenosine		155.20	151.08	121.76	158.27	143.27	91.07	76.43	73.38	88.55	64.25	

[a] In ppm from dss. Spectra recorded in D_2O at ambient temperature. [b] The values in parentheses refer to the relative intensity of the signal.

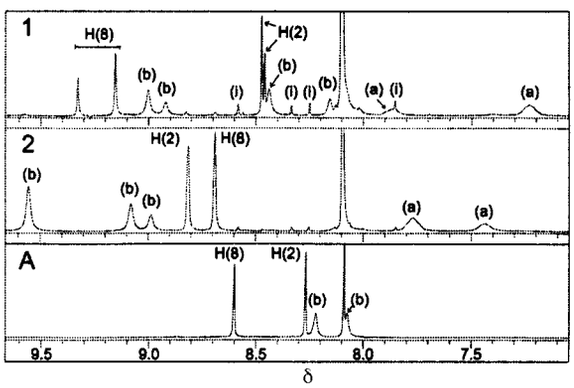


Fig. 2 Downfield section of the ^{1}H NMR spectra of complexes **1**, **2** and free adenosine (**A**) in [$^2H_7$]dmf at −50 °C. Notation: (a) dien NH, assignment made from its observable coupling to the dien CH_2 (confirmed with COSY or homodecoupling experiments); (b) adenosine NH_2, assignment made from one-dimensional EXSY spectra which indicated them to be exchangeable at −25 or −50 °C. Assignment of the two base protons was left by default and distinction between them by comparison with the D_2O spectra. Unknown impurities are denoted as (i)

H^8 (**1**) and H^2 (**2**) of co-ordinated adenosine are in accordance with N^7- and N^1-platinated species, respectively, analogous to those observed earlier for the corresponding complexes of 9-methyladenine.[16–18] Moreover, all signals of the adenosine moiety in **1** and **2** show the expected multiplicity, whereas the proton resonances of the dien group are rather complicated although the eight protons in both cases show the 2:4:2 pattern typical for Pt^{II}(dien) complexes.[16] By contrast, in the ^{195}Pt NMR spectra both compounds exhibit two platinum resonances near δ −2900. This chemical shift is consistent with a PtN_4 co-ordination sphere with a tridentate dien group.[6] For **1** the two signals differ by 14 ppm and for **2** by 11 ppm, significantly less than the difference of about 60 ppm between the major resonances of **1** and **2** suggesting two only slightly different environments for Pt^{II} in the two complexes. Increasing the temperature up to 60 °C causes merging of the ^{195}Pt signals and considerably simplifies the dien region in both cases, suggesting that exchange between the platinum(II) environments becomes fast on the NMR time-scale at higher temperature. However, the merging of the platinum(II) signals may also be due to broadening and/or the significant temperature dependency of the resonances (a *ca*. 20 ppm downfield shift is observed on going from 25 to 60 °C).

Changing the solvent to [$^2H_7$]dmf and lowering the temperature revealed several interesting aspects in the ^{1}H NMR spectra of complexes **1**, **2** and free adenosine, as shown in Fig. 2. First, the aromatic proton resonances of both **1** and **2** are clearly split into two components at −50 °C, whereas those of uncomplexed adenosine remain as singlets. Most notable is the large difference in the chemical shift of the H^8 protons between the two species of **1**. Secondly, the C^6–NH_2 protons of uncomplexed adenosine are no longer equivalent, which indicates restricted rotation about the C^6–NH_2 bond (the signals remain split at −25 °C but have coalesced at +25 °C). For **1**, both adenosine NH_2 proton resonances are further split into two components giving a total of four signals for the NH_2 group. In **2**, instead, one of the NH_2 protons remained as a singlet down to −50 °C. (The small probability of accidental overlap of signals from different protons rather than signals from the same proton in different conformers being isochronous is disregarded.) Thirdly, for both complexes the dien NH proton resonance is also split into two components at −50 °C. Like the NH_2 protons in free adenosine, the NH_2 and dien NH proton resonances of **1** and **2** remain split at −25 °C, but have coalesced at +25 °C. Owing to overlap, the dien NH_2 and CH_2 proton resonances could not be seen to be discernibly split, but they also showed dramatic broadening associated with dynamic processes.

Accordingly, most spectra (*i.e.* all nuclides) showed, to varying extents, dynamic processes primarily due to slow rotation about the platinum–nucleoside bond and/or conformational change of the dien ligand (not discernible in practice). Usually platinum(II)–nucleobase complexes exhibit rapid rotation about the platinum–nucleobase bond on the NMR timescale, unless the other ligands in the platinum(II) co-ordination sphere (usually amines) are bulky.[19,20] With adenine derivatives a few studies have reported restricted rotation about the Pt–N^7 or Pt–N^1 bond, *e.g.* in *cis*-[PtL_2(5′-AMP-N^7)$_2$] even when L_2 is not bulky,[19] and in *cis*-[$Pt(PMe_3)_2$(made)$_2$]$^{2+}$ (made = 9-methyladenine),[21] respectively. In these cases all nuclides studied (^{1}H and ^{195}Pt for the former and ^{1}H, ^{13}C, ^{15}N, ^{31}P and ^{195}Pt for the latter) indicated restricted rotation. On the other hand, a single ^{195}Pt resonance but a very complex set of resonances for the dien group and splitting of the resonances for H^2, H^8 and $N^9(CH_3)$ into two components for [Pt(dien)(tmade-N^3)]$^{2+}$ (tmade = 6,6,9-trimethyladenine) have been attributed to conformation changes of the dien ligand.[6] In addition to the expected change of the labile protons (NH, OH) and the slow rotation of the Pt–N^1 (N^7) bond, slow rotation of the C^6–NH_2 bond was also indicated in both **1** and **2**. In dmf exchange of the labile protons could be slowed, and then effectively stopped at −25 °C; at −50 °C the platinum rotation could also be effectively stopped, but not the C^6–NH_2 rotation which was still comparatively fast.

Crystal structures of complexes 1a and 2a

Selected structural features are shown in Fig. 3 (**1**) and compiled in Table 4 (**2**).

The molecular structure of the cation **1** depicted in Fig. 3 confirms N^7 platination of adenosine. The Pt–N bond lengths are normal, but the angles of the metal co-ordination sphere deviate from the ideal square-planar geometry, as is usual with Pt^{II}(dien)X compounds.[6,16,22,23] In fact, the platinum(II) co-ordination sphere of **1** is very similar to that of the corresponding 9-methyladenine complex.[16] The lattice water molecule forms weak hydrogen bonds to the sugar hydroxyl groups O(3′) [2.85(2)] and O(5′) [2.96(3) Å]. The packing of **1a** is stabilised by hydrogen bonds involving the hydroxyl groups of the sugar moiety and perchlorate oxygens [O(2′)···N(1^{i}) 2.80(2), O(3′)···O(8^{ii}) 2.80 (2), O(4)···O(5′^{iii}) 2.93(2), O(2)···N(12^{iv}) 2.96(2) Å; symmetry operations (i) $-\frac{1}{2} - x$, $1 - y$, $\frac{1}{2} + z$, (ii)

Table 3 Crystal data and data collection parameters for the structures of [Pt(dien)(Ado-N^7)][ClO_4]$_2$·H_2O **1a** and [Pt(dien)(Ado-N^1)][ClO_4]$_2$·2.77H_2O **2a**

	1a	**2a**
Empirical formula	$C_{14}H_{28}Cl_2N_8O_{13}Pt$	$C_{14}H_{31.54}Cl_2N_8O_{14.77}Pt$
M	782.42	814.32
Crystal system	Orthorhombic	Triclinic
Space group	$P2_12_12_1$ (no. 19)	$P\bar{1}$ (no. 1)
a/Å	13.520(6)	12.167(4)
b/Å	14.23(1)	14.644(2)
c/Å	12.914(4)	8.746(2)
α/°		105.170(10)
β/°		108.40(2)
γ/°		70.97(2)
U/Å^3	2484(4)	1375.6(6)
Z	4	2
D_c/g cm^{-3}	2.092	1.966
F(000)	1536	803
μ/mm^{-1}	5.999	5.376
Crystal size/mm	0.20 × 0.20 × 0.20	0.24 × 0.20 × 0.16
θ Range/°	1.83–27.53	1.83–27.53
Index ranges	$0 < h,k < 18$, $0 < l < 17$	$0 < h < 15$, $-18 < k < 19$, $-11 < l < 10$
Reflections collected	3230	6631
Independent reflections (R_{int})		6627 (0.0437)
Data, restraints, parameters	2145, —, 339	6626, 97, 359
Goodness of fit	1.96 (on F)	1.041 (on F^2)
Final R indices	$R = 0.054$, $R' = 0.040$ [$I > 3\sigma(I)$]	$R1 = 0.0441$, $wR2 = 0.1064$ [$I > 2\sigma(I)$]
(all data)		$R2 = 0.0671$, $wR2 = 0.1167$
Largest difference peak and hole/e Å^{-3}	1.75, −1.98	0.941, −0.899

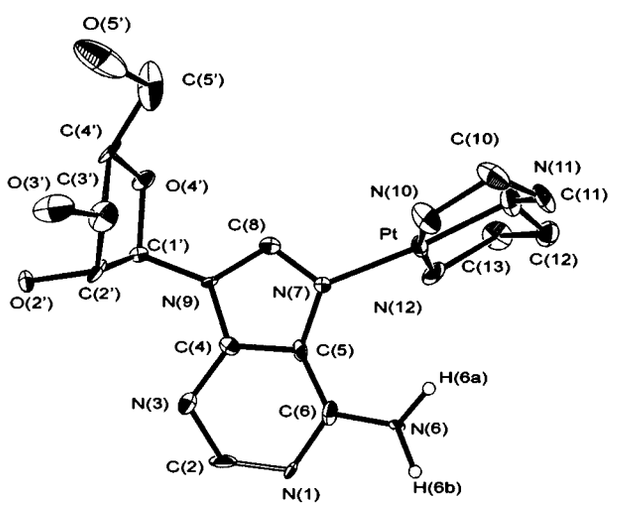


Fig. 3 Molecular structure of [Pt(dien)(Ado-N^7)]$^{2+}$ cation. Selected interatomic distances (Å) and angles (°) with estimated deviations in parentheses: Pt–N(7) 2.05(1), Pt–N(10) 2.06(1), Pt–N(11) 1.98(2), Pt–N(12) 2.00(2) and Pt···N(6) 3.52(2); N(7)–Pt–N(10) 95.4(6), N(7)–Pt–N(11) 175.3(7), N(7)–Pt–N(12) 94.7(6), N(10)–Pt–N(11) 84.2(7), N(10)–Pt–N(12) 169.0(7) and N(11)–Pt–N(12) 86.0(7)

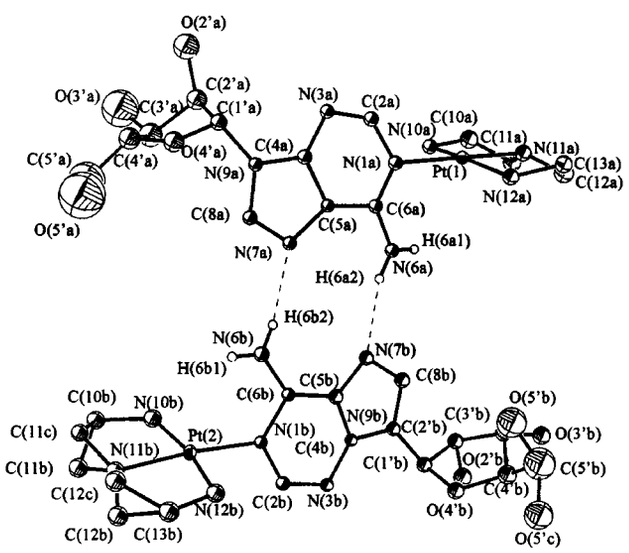


Fig. 4 The two crystallographically different cations of complex **2**. Dashed lines represent proposed hydrogen bonds

$-1 + x, y, z$, (iii) $\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$, (iv) $1 - x, -\frac{1}{2} + z, \frac{1}{2} - z$]. In fact, the size of the unit cell of **1a** is comparable to that of [Pt(dien)(Guo-N^7)][ClO_4]$_2$ (Guo = guanosine),[22] and also similar is that base stacking is not an important packing factor in **1a**.

Fig. 4 shows the two crystallographically different cations of complex **2**. Interestingly, the units show pseudo-symmetry between the base moieties and platinum(II) atoms that is obeyed also by the perchlorate groups. In both units the Pt–N bond lengths and the angles of the platinum co-ordination sphere are normal and similar to those of **1**. The dihedral angles between the PtN_4 co-ordination plane and the adenine moiety are identical within the estimated standard deviations (e.s.d.s) in both units [75.8(2)°]. By contrast, differences between the two units can be seen in the sugar conformation. The unit denoted as A has an *anti* (*-ac*) conformation [torsion angle O(4′a)–C(1′a)–N(9a)–C(4a) −168.0(7)°], while the B has a *high-anti* (*-sc*) conformation [torsion angle O(4′b)–C(1′b)–N(9b)–C(4b) −81.2(8)°].[24] In both units large thermal ellipsoids for the sugar hydroxyl groups indicate structural disorder. In particular, the O(5′) atom is disordered and can even adopt two positions in unit B, which also shows partial disorder in the dien group. The packing of **2** is stabilised by moderate hydrogen bonding between the exocyclic amino group and N^7 of the neighbouring molecules [N(6a)···N(7b) 2.963(8), N(6b)···N(7a) 2.976(8) Å]. Lattice water forms hydrogen bonds to sugar oxygens and dien nitrogens [O(5′c)···O(20) 2.61(3), $x, y, z + 1$; O(3′b)···O(20) 2.68(1), N(12a)···O(17) 2.87(1) Å]. Also the ring nitrogen N^3 may participate in hydrogen bond formation with lattice water [N(3a)···O(18) 2.90(1), $x, y, z - 1$; N(3b)···O(17) 2.99(1) Å; $x + 1, y, z + 1$].

Unfortunately, crystallographic data do not give an unambiguous answer for the observed splitting of ^{195}Pt resonances. It is highly unlikely that the two crystallographically different cations of complex **2** could give rise to two platinum resonances, since similar splitting of platinum(II) signals is seen

Table 4 Selected interatomic distances (Å) and angles (°) of complex **2a** with estimated deviations in parentheses

	Cation A	Cation B
Pt–N(1)	2.037(7)	2.050(7)
Pt–N(10)	2.064(7)	2.018(8)
Pt–N(11)	2.041(8)	2.005(9)
Pt–N(12)	2.085(7)	2.043(8)
Pt · · · N(6)	3.246(6)	3.168(6)
N(1)–Pt–N(11)	174.8(3)	172.6(3)
N(1)–Pt–N(10)	91.7(3)	93.9(3)
N(1)–Pt–N(12)	99.7(3)	97.2(3)
N(10)–Pt–N(11)	83.2(3)	84.0(3)
N(11)–Pt–N(12)	85.4(3)	84.9(3)
N(10)–Pt–N(12)	167.1(3)	168.9(4)

also for **1**. Rather, it is tempting to attribute two platinum(II) environments in **1** and **2** to the exocyclic amino group, which is known sterically to prevent metal-ion binding to both N^1 and N^7 sites.[15] Hover, the angles C(5)–C(6)–N(6) and N(1)–C(6)–N(6) do not indicate that the C^6–NH_2 group and Pt^{II} are mutually pushing away each other. In **1** the former is 126(2)° and the latter 115(2)°, but the difference is within limits of 3σ due to the poor quality of the crystal. In **2** the corresponding angles are rather different to the two units, *viz*. 117.9(6) and 119.5(8) in unit A, and 127.5(7) and 116.1(7)° in unit B, respectively. Also the distances between Pt^{II} and N(6) are quite large; 3.52 Å in **1** and 3.25 (unit A) and 3.16 Å (unit B) in **2**, suggesting no direct interaction between these atoms. Although hydrogen atoms were not located in the structure determination, the distances above give an estimation of the shortest possible separation for Pt^{II} and the C^6–NH_2 hydrogen, *viz*. 2.79 Å for **1**, 2.83 **2** (unit A) and 2.67 Å (unit B) for **2**, assuming that the NH is directed towards Pt. Similar short M–H–N contacts typical of hydrogen rather than agostic bonds have recently been documented for a number of platinum(II) complexes.[25] Thus, an intramolecular hydrogen bond-like interaction of Pt–H–N cannot be excluded in either case. This type of interaction may also be affected by the slow rotation about the platinum–nucleoside bond and/or conformational change of the dien ligand.

Conclusion

The distribution of Pt^{II} between the adenosine N^1 and N^7 sites can be affected in aqueous solution not only by lowering the pH of the solution, but also by equilibration of the mixture of Pt^{II} and nucleoside at high temperature. In the former case, Pt^{II} predominantly binds to the N^7 site, whereas the latter procedure significantly increases the amount of the N^1-bound complex at the expense of the N^7 isomer. Both complexes exhibit two ^{195}Pt resonances at ambient temperature and the ^1H and ^{13}C NMR spectra recorded in D_2O show indications of exchange phenomena through the broadening of ^1H and ^{13}C resonances of those nuclei spatially close to Pt^{II}. Mirroring the splitting of the platinum signal in D_2O for both compounds, in [$^2H_7$]dmf the dien NH, adenosine NH_2 (now non-equivalent) and both aromatic proton resonances were all shown to be split accordingly at low temperatures (some only at −25 °C, all at −50 °C) for both **1** and **2**. The one exception to this was one of the NH_2 protons in **2**, which remained as a singlet down to −50 °C. In dmf, exchange of the labile protons could be slowed, and then effectively stopped at −25 °C; at −50 °C the platinum rotation could also be effectively stopped, but not the C^6–NH_2 rotation which was still comparatively fast. The restricted rotation about the platinum(II)–nucleoside and C^6–NH_2 bonds may also affect the disturbance to the platinum(II) co-ordination sphere induced by an intramolecular hydrogen bond-type interaction of N^6–H · · · Pt, assuming coplanarity between the C^6–NH_2 group and the base moiety. In both **1** and **2** the minimum distance between a NH_2 proton and Pt^{II} is within the range of 2.2–3.25 Å given in literature for this type of interaction.[25a]

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