Platinum−Nitrogen Bond Rearrangements in Isomeric *cis*-$Pt^{II}(NH_3)_2$-bis(9-methyladenine) Complexes under Alkaline Conditions

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The migration of coordinated Pt^{II} in the adenine ring was studied in basic aqueous solutions for the isomeric bis(9-methyladenine) complexes: *cis*-$[Pt(NH_3)_2(9\text{-made-N7})_2]^{2+}$ (**1**) and *cis*-$[Pt(NH_3)_2(9\text{-made-N1})(9\text{-made-N7})]^{2+}$ (**2**). In both compounds, coordinated Pt^{II} migrates from the endocyclic nitrogen N(7) or N(1), respectively, to the exocyclic amino group, upon displacement of an NH_2 proton, to give the same first-generation product, viz. *cis*-$[Pt(NH_3)_2(9\text{-made-N6})(9\text{-made-N7})]^{2+}$ (**3**). Although both reactions undergo an intramolecular reaction, the N(1)→N(6) step is faster and far more efficient than the N(7)→N(6) step. This may be attributed to the more favorable electronic effects and to the spatial positioning of the N(1)-bound Pt^{II} in comparison to the platinum coordinated to the N(7) site. However, the contribution of a Dimroth-type rearrangement to the overall N(1)→N(6) conversion cannot be completely ruled out. Attempts to obtain second migration in the N(6),N(7)-bound species to give the N(6),N(6) species were unsuccessful. Rather, prolonged treatment of the N(6),N(7)-bound complex in strongly basic solution resulted in the deamination of the N(7)-bound 9-methyladenine yielding a mixed ligand complex consisting of N(6)-bound 9-methyladenine and N(7)-bound 9-methylhypoxanthine, i.e. *cis*-$[Pt(NH_3)_2(9\text{-made-N6})(9\text{-mhyp-N7})]^{2+}$ (**4**). To the best of our knowledge, this is the first example of such a deamination reaction in Pt^{II} complexes. Both reaction products, **3** and **4**, were characterized by ^1H and ^{195}Pt NMR spectroscopy and by X-ray crystallography of the diperchlorate. In dicationic **3** and **4**, the N(6)-bound 9-made exists in the rare imino tautomer with the N(1) site bearing a proton.

Introduction

The discovery of the anticarcinogenic activity of *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) by B. Rosenberg in 1969 has led to research interests being focused on the interactions of Pt compounds with nucleic acids and their constituents.[1−3] From a chemical point of view, considerable effort has been paid to the various binding modes[4] of Pt and to the kinetics of complexation.[1,5,6] Due to the general inertness of Pt^{II} and Pt^{IV}, and the high thermodynamic stability of the Pt−N bond, the factors affecting the initial binding step of Pt to DNA are considered crucial for understanding the biological activity of Pt drugs[1,5] and, in this respect, findings on relatively facile Pt−N bond rearrangements at the oligonucleotide level are of prime interest.[7−9] For example, rearrangement of *trans*-$[Pt(NH_3)_2\{d(G^*XG^*)\}]$ intrastrand adducts (where X = A, T, C; * denotes the platination site) into interstrand crosslinks appears as soon as the platinated oligonucleotides are hybridized with their complementary ribonucleotide or deoxyribonucleotide strands.[7] Unfortunately, the exact mechanism for this type of rearrangement is unknown, rendering model studies in this field highly desirable. There have been, however, a few reports on Pt−N bond rearrangements in simple complexes, either within the nucleobase moiety[10,11] or within the auxiliary[12] ligand. Other types of Pt−N bond rearrangements include oxidative Pt migration from the ring nitrogen to the exocyclic amino group in platinated pyrimidine complexes, which involve Pt^{IV} as an intermediate.[13−15] A clear picture, though, is not apparent as regards the factors controlling the migration reactions, and the latter may even require the cooperation of other nucleophiles.[8] In addition, Pt^{II} coordinated to different bioligands has also been found to migrate from the soft S atom to the hard N atom,[16−21] or vice versa.[22]

We have previously examined[23−25] the distribution of Pt^{II} in the adenine ring between the N(7) (kinetically preferred) and N(1) (thermodynamically preferred) binding modes in neutral solutions. Under basic conditions, though, migration of coordinated Pt^{II} to N(6) was observed from both N(1)[10] and N(7)[11] binding sites. In this study we wanted to compare the behavior of *cis*-N(7),N(7) coordinated Pt to the previously examined[11] *trans*-N(7),N(7) system and to contrast directly the N(1) and N(7) binding modes by using a mixed system, namely, *cis*-N(1),N(7) coordinated Pt, by following the reactions of *cis*-$[Pt(NH_3)_2(9\text{-made-N7})_2]^{2+}$ (**1**) and *cis*-$[Pt(NH_3)_2(9\text{-made-N1})(9\text{-made-N7})]^{2+}$ (**2**) under alkaline conditions (9-made = 9-methyl-

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adenine). In both complexes **1** and **2**, Pt^{II} migrates from an endocyclic nitrogen atom to the exocyclic amino group upon displacement of an N(6) proton to give a first-generation product, *cis*-$[Pt(NH_3)_2$(9-made-N6)(9-made-N7)$]^{2+}$ (**3**), which is common to the reactions of both **1** and **2**.[26] Further treatment of **3** at high pH results in the deamination of the N(7)-bound 9-made providing the corresponding 9-methylhypoxanthine (9-mhyp) complex, *cis*-$[Pt(NH_3)_2$(9-made-N6)(9-mhyp-N7)$]^{2+}$ (**4**).[26] Both reaction products **3** and **4** were characterized by ^1H and ^{195}Pt NMR spectroscopy and by X-ray crystallography of the diperchlorate.

Results and Discussion

General Considerations

The reactions of the isomeric *cis*-$Pt^{II}(NH_3)_2$-bis(9-methyladenine) complexes **1** and **2** were studied in strongly alkaline aqueous solutions at 65 and 85 °C employing HPLC equipped with an RP-18 column as an analytical tool. Both complexes **1** and **2** were found to undergo two distinct, consecutive reaction steps, the products of which were well resolved from each other, and from the starting material in both cases. Quite interestingly, the major first-generation product, **3**, is the same for the reactions of both **1** and **2** and possesses a much longer retention time than either of the starting compounds. This first-generation product slowly reacts further to yield the major second-generation product, **4**, which elutes earlier than either of the original complexes (see Figure 1). Both reaction steps also produced a small amount of free 9-methyladenine and several unidentified, weakly UV-absorbing (at 260 nm) side products with short retention times. Since the two consecutive reaction steps differ considerably, they are discussed separately.

Intramolecular Migration of Pt^{II}

Although both **1** and **2** give the same major first-generation product **3**, kinetically they behave in a very different manner. While the reaction **2**→**3** is clean and efficient, the reaction **1**→**3** proceeds less efficiently and produces a number of unidentified side products, particularly under more forcing conditions (see Tables S1 and S2). For example, at 338.2 K the overall decomposition of **1** in 1.0 M NaOH solution is rather fast [$k_{obs} = (4.10 \pm 0.04) \times 10^{-3}$ s^{-1}], but only about 6% of the starting material is converted into **3**, with weakly UV-absorbing side products constituting the remainder. At 358.2 K and in 1.0 M NaOH solution, the overall reaction is about five times faster than at 338.2 K, with **3** representing ca. 15% conversion. By contrast, in all cases the efficacy of the reaction **2**→**3** is greater than 95% of the overall decomposition of **2**, with free 9-methyladenine as the principal side product according to HPLC analysis. In 0.03 M NaOH solution, the reaction **2**→**3** is about 30 times faster than the **1**→**3** conversion (at 338.2 K), whereas in 1.0 M NaOH solution this reactivity difference is only a factor of three (see Figure 2). A similar trend is also in place

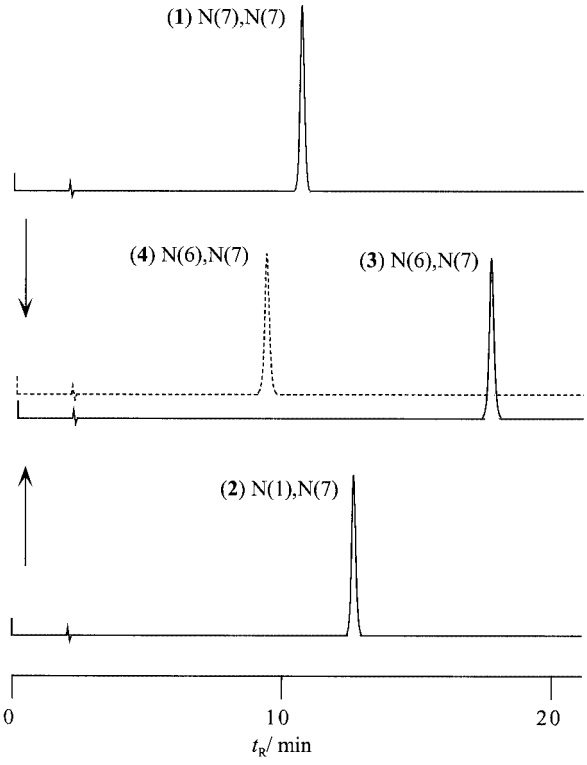


Figure 1. Simplified HPLC traces showing the conversion of **1**→**3** and **2**→**3** under alkaline conditions; the dotted line refers to the second reaction step **3**→**4**; the labeling of the signals refers to the binding sites of Pt^{II}

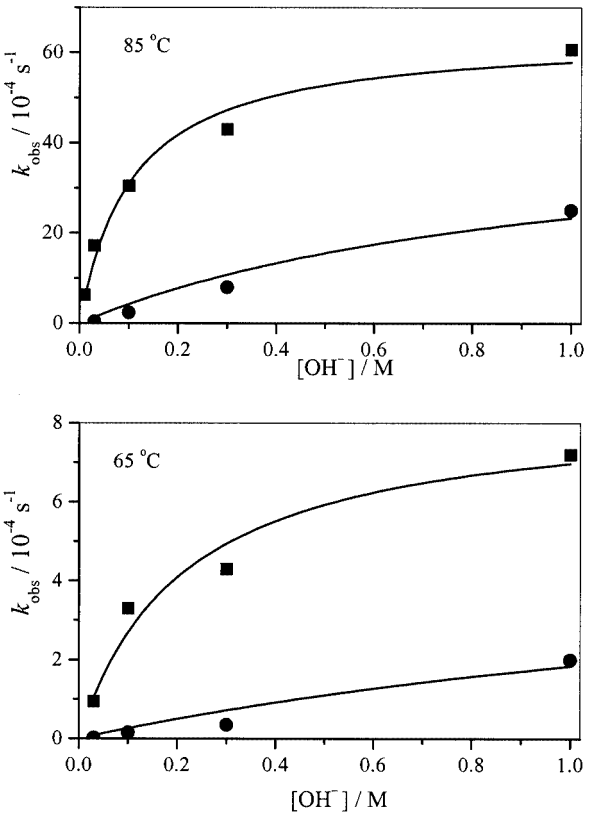


Figure 2. Observed rate constants for the reactions **1**→**3** (●) and **2**→**3** (■) as a function of pH at two different temperatures

Table 1. ^{1}H and ^{195}Pt NMR chemical shifts in ppm for **3**, **4**, and some reference compounds[a]

Compounds		δ_{Pt}	δ_H(H2)	δ_H(H8)	δ_H(CH_3)
3	N(6)[b]	−2530 {−2457}	8.172 {7.995}[c]	7.995[c] {8.224}	3.780 {3.873}[d]
	N(7)[b]		8.328 {8.309}	8.702 {8.576}	3.897 {3.873}[d]
[e]	N(6)[b]	−2463 {−2520}	8.220 {8.315}	8.055 {8.302}	3.861 {3.878}
	N(7)[b]		8.593 {8.611}	8.999 {9.041}	4.023 {4.050}
4	9-made-N(6)[b]	−2524	8.111	7.994	3.785
	9-mhyp-N(7)[b]		8.318	8.570	3.872
[f]			8.30	8.55	3.89

[a] Spectra recorded in D_2O (^{1}H) or in H_2O/D_2O (^{195}Pt); minor species with an intensity of ca. 20% of the major one in braces. [b] Binding site of the nucleobase derivative and associated ^{1}H chemical shifts. [c] Overlapped. [d] Overlapped. [e] *trans*-[Pt(NH_3)$_2$(9-made-N6)(9-made-N7)]$^{2+}$.[11] [f] Pt(dien)(mhyp-N7)]$^{2+}$.[32]

at 358.2 K, where the reaction **2**→**3** is favored over the reaction **1**→**3** by a factor of 20 in 0.03 M NaOH, and by a factor of 2 in 1.0 M NaOH. It is worth noting that the first step in the conversion **2**→**3** was unequivocal: no other product with a retention time close to that of **3** could be detected by HPLC analysis.

Table 2. Crystal data and structure refinement for the complexes *cis*-[Pt(NH_3)$_2$(9-made-N6)(9-made-N7)](ClO_4)$_2$·H_2O (**3**) and *cis*-[Pt(NH_3)$_2$(9-made-N6)(9-mhyp-N7)](ClO_4)$_2$·H_2O (**4**)

	3	**4**
Empirical formula	$C_{12}H_{22}Cl_2N_{12}O_9Pt$	$C_{12}H_{21}Cl_2N_{11}O_{10}Pt$
Molecular mass	744.41	745.39
Crystal system	monoclinic	triclinic
Space group	*P*21/*c*	$P\bar{1}$
a (Å)	13.406(3)	11.428(3)
b (Å)	13.1230(17)	13.878(4)
c (Å)	13.9926(19)	8.2638(14)
α (°)		92.90(2)
β [°]	108.302(14)	108.941(14)
γ (°)		74.94(3)
V (Å^3)	2337.2(7)	1196.3(5)
Z	4	2
$D_{calcd.}$ (g cm^{-3})	2.116	2.069
μ (mm^{-1})	6.304	6.160
F(000)	1448	724
Crystal size (mm)	0.16 × 0.18 × 0.22	0.26 × 0.36 × 0.40
θ_{range} (°)	1.60−25.00	2.71−25.00
Index ranges	+16, +16, ±17	+14, ±17, ±10
Reflections coll.	4302	4432
Independent (R_{int})	4117 (0.0535)	4202 (0.0167)
Observed ($I > 2\sigma I$)	2697	3794
Absorption correction	ψ scan	ψ scan
Transmission	1.000−0.636	1.000−0.594
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4117/−/342	4202/−/354
Goodness-of-fit on F^2	1.014	1.045
R indices[a] ($I > 2\sigma I$)	R_1 = 0.0488	R_1 = 0.0336
	wR_2 = 0.1052	wR_2 = 0.0818
R indices (all data)	R_1 = 0.1076	R_1 = 0.0407
	wR_2 = 0.1219	wR_2 = 0.0845
Largest diff. peak and hole (eÅ^{-3})	1.514 and −1.598	1.623 and −2.248

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma\,[w(F_o^2)^2]\}^{1/2}$ and $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP)]$, where $P = (2F_c^2 + F_o^2)/3$.

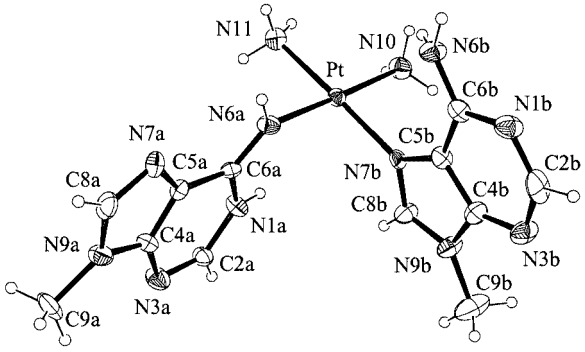


Figure 3. ORTEP plot showing 30% probability ellipsoids of the cation of *cis*-[Pt(NH_3)$_2$(9-made-N6)(9-made-N7)](ClO_4)$_2$·H2O (**3**) with its atom labeling scheme; selected interatomic distances (Å) and angles (°) with estimated deviations in parentheses: Pt−N(6a) 2.016(10), Pt−N(7b) 2.030(9), Pt−N(10) 2.056(9), Pt−N(11) 2.072(10), N(6a)−Pt−N(7b) 93.3(4), N(6a)−Pt−N(10) 177.8(4), N(7b)−Pt−N(10) 88.9(4), N(6a)−Pt−N(11) 86.8(4), N(7b)−Pt−N(11) 177.4(4), N(10)−Pt−N(11) 91.1(4), C(6a)−N(6a)−Pt 129.7(8)

We were able to purify and isolate **3** by fractionating the neutralized reaction solution. It was characterized using ^{1}H and ^{195}Pt NMR spectroscopy (Table 1) and by X-ray crystallography of the diperchlorate (Table 2), thus revealing that the compound is a bis(9-methyladenine) complex of *cis*-$Pt^{II}(NH_3)_2$ where one 9-methyladenine is coordinated to Pt through N(7) and the other through the exocyclic amino group upon displacement of an NH_2 proton which is translocated to N(1) upon acidification. A thermal ellipsoid diagram for the dication of **3** is presented in Figure 3. The platinum atom has nearly square-planar geometry, as is typical for these types of complexes, and lies virtually in the plane defined by the four coordinating nitrogen atoms deviating less than 0.02 Å from this plane. However, the N(6a)−Pt−N(7b) angle is widened [93.3(4)°] at the expense of the N(6a)−Pt−N(11) angle [86.8(4)°]. The Pt−N bond lengths in **3** are comparable to those in **1** and **2** and also to those in the corresponding N(6),N(7)-bound *trans* isomer.[11] It is notable that the Pt−N(6a) bond appears to be significantly shorter by more than three standard deviations[27] than the Pt−NH_3 bonds. Protonation of N(1a) also slightly widens the C(2)−N(1)−C(6) angle [C(2a)−N(1a)−C(6a) 124.5(11)°; C(2b)−N(1b)−C(6b)

119.8(11)°]; a similar widening was also observed in the corresponding *trans* compound.[11] The packing of **3** is stabilized by hydrogen bonding involving primarily the am(m)ine hydrogens and perchlorate oxygens, e.g. N(11)···O(21) 2.974(16) Å, N(6a)···O(24) 3.223(15) Å, and N(10)···O(22[a]) 3.192(17) Å. Other possible H-bonds include: N(6b)···N(1b[b]) 3.105(14) Å, N(1a)···O(14[c]) 2.849(15) Å, and O(1w)···N(3a[d]) 3.285(29) Å. [Symmetry operations: a) $-x + 1, y - 1/2, -z + 1/2$; b) $-x + 1, -y, -z + 1$; c) $x, -y + 1/2, z + 1/2$; d) $-x, y + 1/2, -z + 1/2$.] However, stacking of the base moieties does not play a significant role in stabilizing the crystal lattice.

In aqueous solution, the dication of **3** shows evidence of dynamic processes as indicated by the splitting of the ^{1}H and ^{195}Pt signals. Most probably, the dynamic process in effect is the restricted rotation of the nucleobase(s) about the Pt−N bond, as has been observed frequently with Pt^{II} complexes of adenine derivatives.[10,11,23] The ^{1}H chemical shifts are in line with the proposed binding modes showing significant downfield shifts for those signals near the proposed Pt^{II} coordination site, whereas the δ_{Pt} values close to −2500 ppm are typical for a PtN_4 coordination sphere[28] and are in agreement with those reported earlier for the corresponding *trans* isomer.[11]

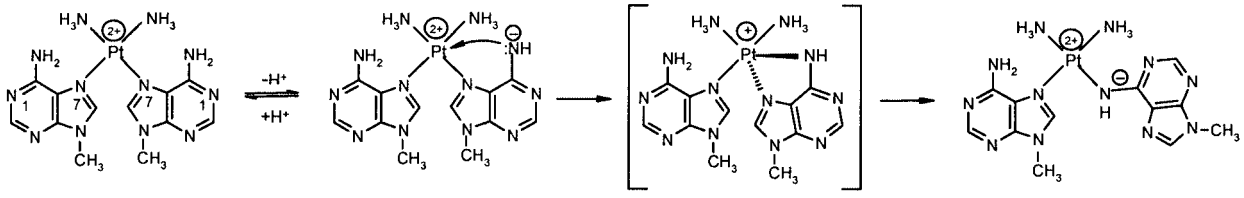
Mechanistically, the formation of **3** is interesting since it forms directly from supposedly inert, isomeric species. The readiness of the reactions **1**→**3** and **2**→**3** rules out the likelihood that the reaction proceeds via hydrolysis of the initial Pt−N bonds and then formation of the Pt−N(6) bond by taking into account the reasoning given earlier for the N(7)→N(6) migration in the N(7)-bound bis(9-methyladenine) complex of *trans*-Pt^{II}(NH$_3$)$_2$.[11] Moreover, the nonlinear dependency of the reactions **1**→**3** and **2**→**3** on [OH$^-$] indicates that the OH$^-$ ion (known as a poor *trans*-labilizing group) does not act as nucleophile on Pt^{II}.[29,30] Rather, the proposed mechanism involves an intramolecular migration of coordinated Pt from endocyclic ring nitrogens, N(7) in **1** or N(1) in **2**, to the exocyclic amino group upon displacement of an NH_2 proton, as depicted in Scheme 1 for the reaction **1**→**3**.

As the first step, deprotonation of the exocyclic amino group provides an imino group close to Pt^{II}, albeit fleetingly transient. Values of 3.430(7) Å and 3.515(7) Å have been reported for the N(6)···Pt distances in the two crystallographically distinct cations of **1**, whilst for **2**, the N(6)···Pt distances are 3.149(8) Å and 3.446(8) Å for the N(1)- and N(7)-bound 9-methyladenines, respectively. For **1**, the attack of the imino group on Pt results in a five-coordinate intermediate, where subsequent cleavage of the presumably weaker Pt−N(7) bond furnishes the N(7)→N(6) migration of Pt in an analogous fashion to the *trans* isomer.[11] Most probably, the same mechanism is also valid for **2** to effect the N(1)→N(6) migration, or at least partly so. Here the efficacy of the migration can be attributed to the shorter N(6)···Pt distance in the N(1)-bound 9-methyladenine and also to the supposedly stronger influence of Pt^{II} on the acidity of the NH_2 protons. However, an alternative mechanistic explanation for the N(1)→N(6) migration of coordinated Pt involves exchanging of the N(1) and N(6) atoms via a Dimroth-type bond rearrangement. It has been proposed that in adenine derivatives, OH$^-$ attacks both protonated (amino form) and deprotonated (imino form) species at C(2), the former being significantly faster than the latter.[31] Although a Dimroth-type bond rearrangement cannot be completely ruled out for **2**, according to our current knowledge, the rate profile nevertheless indicates that the nucleophilic action of the OH$^-$ ion on deprotonated **2** does not play any significant role in the overall migration reaction.

The Second Reaction Step

In **3**, the comparable N(6b)···Pt distance of 3.54(1) Å provided the impetus for attempting a second Pt migration to obtain the N(6),N(6)-bound species. Prolonged treatment of the reaction mixtures of both **1** and **2** ([OH$^-$] > 0.1 M) slowly yielded one major second-generation product, **4**, common to both initial complexes, together with free 9-methyladenine and several unidentified side products. In a 0.1 M NaOH solution (358.2 K), the reaction **3**→**4** is rather inefficient and yields only ca. 15% conversion of **3** to **4**, using **3** as a starting material with the principal side product being 9-methyladenine. However, in 1.0 M NaOH (358.2 K), the yield of **4** rises to ca. 75% and the amount of free 9-methyladenine produced is negligible.

Serendipitously, **4** is virtually insoluble in cold alkali and can thus be easily separated from the reaction mixture. The crude product converts to sparingly soluble in dilute perchloric acid and can be recrystallized as the diperchlorate. The structure provided by X-ray analysis showed Pt^{II} to be bound now to two distinct ligands: 9-made through N(6) and 9-methylhypoxanthine (9-mhyp) through N(7), that is, the N(6),N(7)→N(6),N(6) transformation does not occur and prolonged treatment only results in N(6) deamination of the N(7)-bound ligand. This transformation has not been observed previously for Pt-bound adenines, but substrates have never been subjected to such forcing conditions as they



Scheme 1. Intramolecular N(7)→N(6) migration (**1**→**3**) of coordinated Pt upon displacement of an NH_2 proton

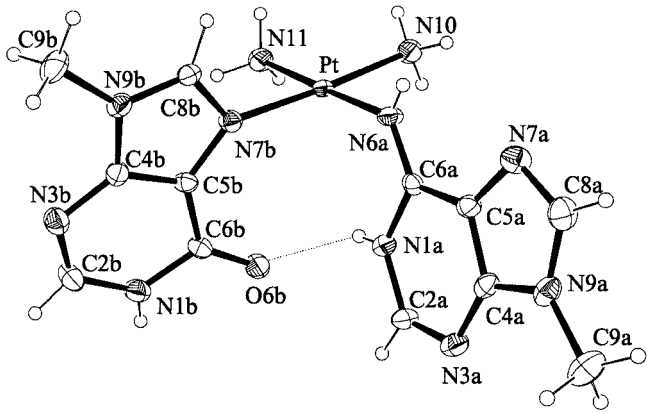


Figure 4. ORTEP plot showing 30% probability ellipsoids of the cation of *cis*-[Pt(NH_3)$_2$(9-made-N6)(9-mhyp-N7)](ClO_4)$_2$·H_2O (**4**) with its atom labeling scheme; selected interatomic distances (Å) and angles (°) with estimated deviations in parentheses: Pt−N(6a) 2.005(6), Pt−N(7b) 2.020(5), Pt−N(10) 2.040(6), Pt−N(11) 2.060(6), N(6a)−Pt−N(7b) 91.6(2), N(6a)−Pt−N(10) 89.3(2), N(7b)−Pt−N(10) 176.9(2), N(6a)−Pt−N(11) 178.6(2), N(7b)−Pt−N(11) 89.6(2), N(10)−Pt−N(11) 89.5(2) C(6a)−N(6a)−Pt 128.4(5)

were here.[11] A thermal ellipsoid diagram for the dication of **4** is shown in Figure 4. The atom bound to C(6b) is best identified as oxygen rather than nitrogen according to the thermal displacement parameters and the *R* values of least-squares refinements. This is supported by the elemental analysis, which provided a composition consistent with this structure.

Only a single platinum signal resonating at δ = −2524 ppm was observed for **4**, which is consistent with a PtN_4 coordination sphere. This species singularity was also evident in the ^{1}H NMR spectrum of **4** where four aromatic protons within the range δ = 7.99−8.57 ppm with nearly equal intensities, together with two methyl groups in a 1:1 ratio further upfield, were observed. These chemical shifts are apt for this structure in comparison to the reference compounds (see Table 2). Finally, treatment of **4** with thiourea (tu), which is known[25] to displace nitrogen-bound ligands from Pt^{II}, provided three HPLC-detectable end products in approximately stoichiometric amounts, namely, $[Pt(tu)_4]^{2+}$-ion, 9-made, and 9-mhyp, identified as such by coelution with authentic samples.

According to the X-ray analysis, the platinum atom in **4** has an almost idealized square-planar geometry with the Pt atom lying in the plane defined by the four coordinating nitrogen atoms, deviating by less than 0.03 Å from this plane. The Pt−N bond lengths in **4** are similar to those in **3**, with the Pt−N(6a) bond being significantly shorter by $> 4.1\sigma$[27] than the Pt−NH_3 distances. The packing of **4** is stabilized by hydrogen bonding involving primarily the am(m)ine hydrogens and the perchlorate oxygens, e.g. N(10)···O(21^a) 3.102(11) Å, N(6a)···O(23^a) 3.092(9) Å, and N(1b)···O(12^b) 2.938(11) Å. Most notable, though, is the intramolecular H-bond N(1a)···O(6b) 2.889(8) Å, where the proton involved was located from the electron density map. Other possible H-bonds include N(10)···O(1w^a) 3.050(9) Å and N(11)···O^a 3.038(12) Å. [Symmetry operations: a) $-x$, $-y+1$, $-z+1$; b) $-x+1$, $-y$, $-z+1$.] The intramolecular H-bond may affect the orientation of the bases in **4**, as seen in the dihedral angle between the base moieties and the Pt coordination sphere, namely 72.5(2)° for the N(6)-bound 9-made and 82.7(2)° for the N(7)-bound 9-mhyp. In **3**, the corresponding angles are 80.5(2) and 86.8(3)°, respectively. Also the dihedral angle between the base moieties is different; 76.5(2)° in **4** and 89.2(2) in **3**. The crystal lattice of **4** is further stabilized by stacking of the six-membered rings of adjacent hypoxanthine bases in a head-to-tail fashion with a distance of 3.44(2) Å between the centers of the rings. Deamination of the N(7)-bound 9-methyladenine and subsequent protonation of N(1b) widens the C(2b)−N(1b)−C(6b) angle from 119.8(11)° to 125.3(7)°, a widening similar to that observed for the N(6)-bound ligand in **3**.

Conclusions

Coordinated Pt^{II} has been found to migrate in the adenine ring from both the N(1) and N(7) sites to the exocyclic amino group, upon displacement of an NH_2 proton in basic aqueous solution. Although both isomeric bis(complexes) of 9-methyladenine with N(7),N(7) and N(1),N(7) binding modes of Pt^{II} undergo an intramolecular reaction and provide the same first-generation product, the N(1)→N(6) migration is faster and far more efficient than the N(7)→N(6) migration. This may be attributed to more favorable electronic effects and to the spatial positioning of the N(1)-bound Pt^{II} in comparison to platinum coordinated to the N(7) site. However, the contribution of a Dimroth-type mechanism to the overall N(1)→N(6) conversion cannot be completely ruled out. Attempts to obtain a second platinum migration from the N(6),N(7)-bound species to produce the N(6),N(6) species were unsuccessful. Rather, the prolonged treatment of the N(6),N(7)-bound complex in strongly basic solution resulted in the deamination of the N(7)-bound 9-methyladenine and yielded the mixed ligand complex consisting of N(6)-bound 9-methyladenine and N(7)-bound 9-methylhypoxanthine. To the best of our knowledge this is the first example of such a deamination reaction in Pt^{II} complexes. By comparison, treatment of free 9-methyladenine in 1.0 M NaOH for 8 h at 85 °C did not provide 9-methylhypoxanthine, though this reaction is known to proceed in the presence of oxidizing agents,[32,33] and thereby it can be concluded that Pt complexation facilitates adenine deamination when migration is not favored. This is quite interesting when considering that for the two major DNA adducts of cisplatin, that is, A-N(7),G-N(7) and G-N(7),G-N(7) (where A = adenine, G = guanine), the former is more mutagenic than the latter, which is cytotoxic.[1,34,35] In addition, in dicationic **3** and **4**, the N(6)-bound 9-made exists in the rare imino tautomer with the N(1) site bearing a proton in an analogous fashion to other N(6)-metalated adenine derivatives.[4,10,11]

Experimental Section

Materials: 9-Methylhypoxanthine (9-mhyp) from Chemogen was used as received. The compounds 9-methyladenine[36] (9-made), $[Pt(tu)_4]Cl_2$[37] (tu = thiourea), *cis*-$[Pt(NH_3)_2(9\text{-made-}N7)_2](ClO_4)_2$ (**1**),[24] and *cis*-$[Pt(NH_3)_2(9\text{-made-}N1)(9\text{-made-}N7)](ClO_4)_2$ (**2**)[24] were obtained as described previously. All other chemicals were of the highest purity available and were used as received. For the preparation of *cis*-$[Pt(NH_3)_2(9\text{-made-}N6)(9\text{-made-}N7)](ClO_4)_2\cdot H_2O$ (**3**), 65 mg of **2** was dissolved in 5 mL of 0.1 M NaOH and the mixture was stirred for 30 min at 85 °C in a stoppered tube. The mixture was neutralized (pH 6) using 1 M $HClO_4$ and the resulting solution concentrated to ca. 1 mL, prior to fractionation using a preparative RP-18 column.[38] After concentration, the combined fractions of **3** afforded 30 mg (50%) of crystalline product upon cooling on ice. $C_{12}H_{22}Cl_2N_{12}O_9Pt$ (744.41): calcd. C 19.36, H 2.98, N 22.58; found C 19.42, H 2.94, N 22.60.

The compound *cis*-$[Pt(NH_3)_2(9\text{-made-}N6)(9\text{-mhyp-}N7)](ClO_4)_2\cdot H_2O$ (**4**) was obtained in a similar manner by dissolving 55 mg of **3** in 5 mL of 1 M NaOH and stirring the mixture for 6 h at 85 °C. Upon cooling to room temperature, crude **4** precipitated from the reaction mixture and was separated by centrifugation. The collected product was first dissolved using a calculated amount of 1 M $HClO_4$ to provide a solution of pH 6 which afforded 28 mg (51%) of **4** as colorless prisms suitable for X-ray analysis upon cooling on ice. $C_{12}H_{21}Cl_2N_{11}O_{10}Pt$ (745.39): calcd. C 19.34, H 2.84, N20.67; found C 19.14, H 2.90, N 20.67.

Methods: NMR measurements were conducted in D_2O (^1H) or in H_2O/D_2O (^{195}Pt) at ambient temperature. Spectra were acquired on a JEOL Alpha 500 spectrometer equipped with a 5 mm tunable probe operating at 500.16 MHz for ^1H, and 107.21 MHz for ^{195}Pt as described earlier.[23,24,38] ^1H spectra were referenced internally to sodium 4,4-dimethyl-4-silapentanesulfonate (δ_H = 0.015 ppm); ^{195}Pt spectra were referenced externally to $[PtCl_4]^{2-}$ (δ_{Pt} = −1625 ppm from $[PtCl_6]^{2-}$). HPLC analyses were conducted on a Merck-Hitachi chromatograph using an end-capped RP-18 column (5 μm, E. Merck AG) and water−methanol mixtures (0.05 M $NaClO_4$, pH 3) as eluents.

Migration Studies: The reactions of the Pt^{II} complexes were followed at 65 and 85 °C at various $[OH^-]$ by HPLC. Samples withdrawn from the aqueous reaction mixtures (I = 1 M, adjusted with $NaClO_4$) were diluted with an appropriate mixture of cold 1 M $HClO_4$ and HOAc/NaOAc buffer (pH 4) prior to chromatographic analysis. First-order rate constants, $k_{1,obs}$, for the disappearance of the starting material were obtained by Equation (1), where $[S]_0$ denotes the initial concentration of the complex and $[S]_t$ the concentration at time t.

$$\ln[S]_t = -k_{1,obs}t + \ln[S]_0 \quad (1)$$

In a few cases the rate constants, $k_{2,obs}$, for the decomposition of **3** were obtained by Equation (2) from the time-dependent concentration of **3**, denoted as $[P]_t$, using $k_{1,obs}$ values obtained from Equation (1) where $[P]_{max}$ is the maximum observed concentration of **3** at moment t_{max}.

$$\frac{[P]_t}{[P]_{max}} = \frac{e^{-k_{1,obs}t} - e^{k_{2,obs}t}}{e^{-k_{1,obs}t_{max}} - e^{k_{2,obs}t_{max}}} \quad (2)$$

When possible, the amount of **3** or **4** formed was approximated by HPLC analysis employing a standard solution of the desired species. In all cases, the signal area was used as the measure of the concentration.

X-ray Diffraction Studies: All X-ray data were collected on a Rigaku AFC5S diffractometer at ambient temperature using Mo−K_α radiation (λ = 0.71069 Å). Unit cell parameters were obtained from a least-squares fit of 20 reflections [11.07 < 2θ < 15.96° (**3**) and 10.70 < 2θ < 16.14° (**4**)]. Intensity data were collected by the ω/2θ scan technique to a maximum 2θ value of 50°. The intensities of three standard reflections were measured every 150 data points in all cases [intensity decays, 3.4% (**3**) and 1.2% (**4**)]. The intensities of the reflections were corrected for Lorenz, polarization, and absorption (empirical) effects.[39] The structures were solved by standard Patterson and difference Fourier methods and refined by full-matrix least-squares calculations employing SHELXL-97.[40] All atoms other than hydrogen were refined with anisotropic temperature factors. The positions of the hydrogen atoms in **3** were calculated except for those located at N(1a), N(6a) and N(6b) which were found from electron density maps. For **4**, the proton at N(6a) and those at the C and N atoms of the aromatic rings were also found from the electron density maps. The water hydrogens could not be located. The final cycle of refinement yielded for the structure of **3**, R_1 = 0.0448 and wR_2 = 0.1052 for the observed data [$I > 2\sigma(I)$] and 342 parameters, and R_1 = 0.1076 and wR_2 = 0.1219 for all data. For **4**, refinement converged at R_1 = 0.0336 and wR_2 = 0.0819 for the observed data and 354 parameters, and R_1 = 0.0407 and wR_2 = 0.0846 for all data. Crystallographic data and experimental details are presented in Table 2. Data reduction and subsequent calculations were performed with *teXsan for Windows*.[41] Figures were drawn with *Ortep-3 for Windows*.[42] CCDC-212435 and CCDC-212436 for **3** and **4**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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