Inorg. Chem. **2007**, *46*, 8222–8227

Migration of a *cis*-$(NH_3)_2Pt^{II}$ Moiety along Two Adenine Nucleobases, from N1 to N6, is Markedly Facilitated by Additional Pt^{II} Entities Coordinated to N7

Marta Garijo Añorbe,† Thea Welzel, and Bernhard Lippert*

Fachbereich Chemie, Universität Dortmund, 44221 Dortmund, Germany

Received May 7, 2007

Adenine acidification as a consequence of simultaneous Pt^{II} binding to N1 and N7 facilitates deprotonation of the exocyclic $N(6)H_2$ group and permits Pt^{II} migration from N1 to N6 under mild conditions. Starting from the trinuclear complex *cis*-$[(NH_3)_2Pt(N1\text{-9-MeA-}N7)_2\{Pt(NH_3)_3)\}_2]^{6+}$ (**3**), stepwise migration of *cis*-$(NH_3)_2Pt^{II}$ takes place in the alkaline aqueous solution to give initially *cis*-$[(NH_3)_2Pt(N1\text{-9-MeA-}N7)(N6\text{-9-MeA}^-\text{-}N7)\{Pt(NH_3)_3\}_2]^{5+}$ (**4**) and eventually *cis*-$[(NH_3)_2Pt(N6\text{-9-MeA}^-\text{-}N7)_2\{Pt(NH_3)_3\}_2]^{4+}$ (**5**) (with 9-MeA = neutral 9-methyladenine, 9-MeA^- = 9-methyladenine monoanion, deprotonated at N6). The migration process has been studied by ^1H NMR spectroscopy, and relevant acid–base equilibria have been determined. **5** has been crystallized as its nitrate salt and has been characterized by X-ray crystallography. The precursor of **3**, $[(NH_3)_3Pt\ (9\text{-MeA-}N7)]Cl_2\cdot 2H_2O$ (**2**) has likewise been studied by X-ray analysis.

Introduction

One of the changes in paradigms of Pt^{II}−DNA coordination chemistry in recent years has been that Pt−N bonds with nucleobases can rearrange more readily than anticipated, and consequently metal migration processes can take place. This observation contrasts with earlier views on the relative inertness of such bonds. The new view has developed from a number of observed linkage isomerization processes of Pt^{II} entities with isolated model nucleobases[1] and within DNA fragments.[2] Fundamental steps of platinum migration along or between nucleobases are only beginning to emerge. At this stage, it appears that there are different mechanisms possible to accomplish platinum migration. For example, with the model nucleobase 1-methycytosine we have found that migration from N3 to N4 can be redox-mediated[3] or initiated by high pH.[4] In addition, there is circumstantial evidence that the very same migration can also take place at moderately acidic pH, possibly involving a Pt^{II}−OH entity.[5]

Concerning Pt^{II} migration processes at adenine nucleobases, the group of Arpalahti has demonstrated that migrations of type N1 → N6,[6] N7 → N6,[7] and N7 → N1[8] are possible. Even migration of two N1-bonded 9-methyladenine (9-MeA) nucleobases to give *cis*-$[(NH_3)_2Pt(9\text{-MeA-}N6)_2]^{n+}$ (n = 0, 1, or 2, depending upon pH and the protonation state of 9-MeA) has been reported by these authors.[6a] Without exception, these processes require high pH and elevated temperatures (e.g., 85 °C for the latter linkage isomerization). Under these conditions, partial deamination of 9-MeA to 9-methylhypoxanthine can occur.[6a] More recently, our group has shown that the presence of a second Pt^{II}, attached to N7 of 9-MeA, facilitates migration of Pt^{II} from N1 to N6,[9] consistent with a stronger acidification of the exocyclic amino group by two metal electrophiles. Deprotonation of the exocyclic amino group to give the imido function $N(6)H^-$

* To whom correspondence should be addressed: E-mail: bernhard.lippert@uni-dortmund.de.

† Present address: ISAS-Institute for Analytical Sciences, Bunsen-Kirchhoff-Strasse 11, 44139 Dortmund, Germany.

(1) For a general overview, see: Lippert, B. *Prog. Inorg. Chem.* **2005**, *54*, 385.

(2) (a) Comess, K. M.; Costello, C. E.; Lippard, S. J. *Biochemistry* **1990**, *29*, 2102. (b) Dalbiès, R.; Boudvillain, M.; Leng, M. *Nucleic Acids Res.* **1995**, *23*, 949. (c) Dalbiès, R.; Payet, D.; Leng, M. *Proc. Natl. Acad Sci. U.S.A.* **1994**, *91*, 8147. (d) Yang, D.; van Boom, S. S. G. E.; Reedijk, J.; van Boom, J. H.; Wang, A. H.-J. *Biochemistry* **1995**, *34*, 12912.

(3) Lippert, B.; Schöllhorn, H.; Thewalt, U. *J. Am. Chem. Soc.* **1986**, *108*, 6616.

(4) Sanz Miguel, P. J.; Lax, P.; Lippert, B. *J. Inorg. Biochem.* **2006**, *100*, 980.

(5) Sanz Miguel, P. J.; Lax, P.; Willermann, M.; Lippert, B. *Inorg. Chim. Acta* **2004**, *357*, 4552.

(6) (a) Klika, K. D.; Arpalahti, J. *Chem. Commun.* **2004**, 666. (b) Arpalahti, J.; Klika, K. D. *Eur. J. Inorg. Chem.* **1999**, 1199.

(7) Viljanen, J.; Klika, K. D.; Sillanpää, R.; Arpalahti, J. *Inorg. Chem.* **1999**, *38*, 4924.

(8) Arpalahti, J.; Klika, K. D.; Molander, S. *Eur. J. Inorg. Chem.* **2000**, 1007.

(9) Garijo Añorbe, M.; Lüth, M. S.; Roitzsch, M.; Morell Cerdà, M.; Lax, P.; Kampf, G.; Sigel, H.; Lippert, B. *Chem.—Eur. J.* **2004**, *10*, 1046.

10.1021/ic7008754 CCC: $37.00
Published on Web 09/08/2007

Scheme 1. Synthetic Pathway Applied to Prepare *cis*-$[(NH_3)_2Pt(N6\text{-}9\text{-}MeA^{-}\text{-}N7)_2\{Pt(NH_3)_3\}_2]$ $(NO_3)_4 \cdot 5H_2O$ (**5**)

$[PtCl_4]^{2-} + 9\text{-}MeAH^{+}$

↓

$PtCl_3(9\text{-}MeAH\text{-}N7)$ (**1**)

↓ $+ NH_3$ (exc.)

$[(NH_3)_3Pt(9\text{-}MeA\text{-}N7)]Cl_2 \cdot 2H_2O$ (**2**)

↓

cis-$[(NH_3)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)_2\{Pt(NH_3)_3\}_2](NO_3)_6 \cdot 2H_2O$ (**3**)

↓ OH^-

cis-$[(NH_3)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)(N6\text{-}9\text{-}MeA^{-}\text{-}N7)\{Pt(NH_3)_3\}_2]^{5+}$ (**4**)

↓ OH^-

cis-$[(NH_3)_2Pt(N6\text{-}9\text{-}MeA^{-}\text{-}N7)_2\{Pt(NH_3)_3\}_2](NO_3)_4 \cdot 5H_2O$ (**5**)

9-MeAH = protonated 9-MeA
9-MeA = neutral molecule
$9\text{-}MeA^{-}$ = deprotonated 9-MeA

is believed to precede metal migration. Here, we report that Pt^{II} migration along two 9-MeA ligands, from N1 to N6, occurs in *cis*-$[(NH_3)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)_2\{Pt(NH_3)_3\}_2]^{6+}$ even at room temperature and pH 9−10.

Apart from the phenomenon of metal migration, N6- and N6,N7-platinated adenine nucleobases are also of interest for the fact that they represent metalated forms of the rare imino tautomer of this nucleobase (metal-stabilized rare tautomers[10]) and for their substantial change in pK_a values. While neutral, N9-blocked adenine nucleobases deprotonate with pK_a values of close to 17 (at the exocyclic amino group $N(6)H_2$),[11] the platinated forms have pK_a values as low as ca. 7.65 (N6 coordination[6b]) and ca. 4−5 (N6,N7 coordination[9]), respectively, with the acidic proton originating from the N1 position. Similarly, binding of a dirhodium(II) entity to N6 and N7 of 9-methyladenine yields a species displaying a pK_a ~7.5.[12] As we have pointed out,[13] this feature makes N6 metalated forms of rare adenine tautomers a potential source of protons at physiological pH, possibly relevant to acid−base catalysis in RNAs.[14]

Results and Discussion

Precursor Complex. The synthetic pathway leading to *cis*-$[(NH_3)_2Pt(N6\text{-}9\text{-}MeA^{-}\text{-}N7)_2\{(NH_3)_3Pt\}_2]$ $(NO_3)_4 \cdot 5H_2O$ (**5**) is outlined in Scheme 1. The synthesis of **3** and its X-ray crystal structure have previously been reported.[15] The intermediate $[Pt(NH_3)_3(9\text{-}MeA\text{-}N7)]Cl_2 \cdot 2H_2O$ (**2**) has likewise been prepared before, although suitable crystals were not obtained then, and only the perchlorate salt was structurally analyzed.[16] Single crystals of **2** have now been isolated, and the X-ray structure has been performed (Figure 1). As expected, there are no significant differences in bond lengths and angles between the ClO_4^- salt and the Cl^- salt **2** as far as the geometry of the respective cation is concerned. Differences refer to the dihedral angle between the platinum coordination plane and the adenine plane (69.9° in ClO_4^- salt, 80.5° in **2**), which are a consequence of differences in crystal packing and hydrogen bonding interactions. The hydrogen-bonding pattern in **2** is relatively uncomplicated; it is defined by interactions between the cation with water molecules and the chlorine anions. Specifically, both N1 and N3 sites are hydrogen bonded to water molecules (2.982(6) and 2.924(6) Å), and the exocyclic amino group N6 is involved in hydrogen bonding with a water molecule (O2w, 3.021(7) Å) and a chloride ion (3.449(5) Å). As for the NH_3 ligands of platinum, all three of them are engaged in hydrogen bonding with chloride ions (ca. 3.23−3.44 Å). In addition, N3L forms a hydrogen bond with O1w of 2.922(7) Å. The packing is further dominated by extensive stacking interactions (ca. 3.3 Å), which involve the adenine ligands of pairs of cations (good overlap) and between adjacent pairs (poor overlap) (Supporting Information).

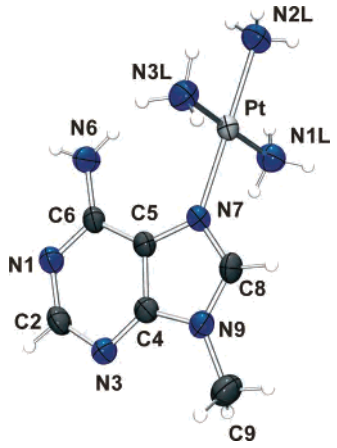

Figure 1. View of cation $[Pt(NH_3)_3(9\text{-}MeA\text{-}N7)]^{2+}$ (**2**) with the atom numbering scheme.

Behavior of 3 in Alkaline Solution. We have previously reported the pK_a values of the two 9-MeA ligands in *cis*-$[(NH_3)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)_2\{Pt(NH_3)_3\}_2]^{6+}$ (**3**) for deprotonation of the exocyclic amino groups.[9] These are 8.7 and 10.7 (converted to H_2O), respectively. The pD-dependent ^1H NMR spectra of **3** display the following features: First, at

(10) Zamora, F.; Kunsman, M.; Sabat, M.; Lippert, B. *Inorg. Chem.* **1997**, *36*, 1583.
(11) Stewart, R.; Harris, M. G. *Can. J. Chem.* **1977**, *55*, 3807.
(12) Chifotides, H. T., personal communication.
(13) Roitzsch, M.; Garijo Añorbe, Sanz; Miguel, P. J.; Müller, B.; Lippert, B. *J. Biol. Inorg. Chem.* **2005**, *10*, 800.
(14) For RNA acid−base catalysis, see, for example (a) Bevilacqua, P. C. *Biochemistry* **2003**, *42*, 2259. (b) Westhof, E. *Science* **1999**, *286*, 61. (c) Nissen, P.; Hansen, J.; Ban, N.; Moore, P. B.; Steitz, T. A. *Science* **2000**, *289*, 920. (d) Muth, G. W.; Ortoleva-Donnelly, L.; Strobel, S. A. *Science* **2000**, *289*, 947. (e) Moore, P. B.; Steitz, T. A. *RNA* **2003**, *9*, 155.
(15) Jaworski, S.; Menzer, S.; Lippert, B.; Sabat, M. *Inorg. Chim. Acta* **1993**, *205*, 31.
(16) Beyerle-Pfnür, R.; Jaworski, S.; Lippert, B.; Schöllhorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1985**, *107*, 217.

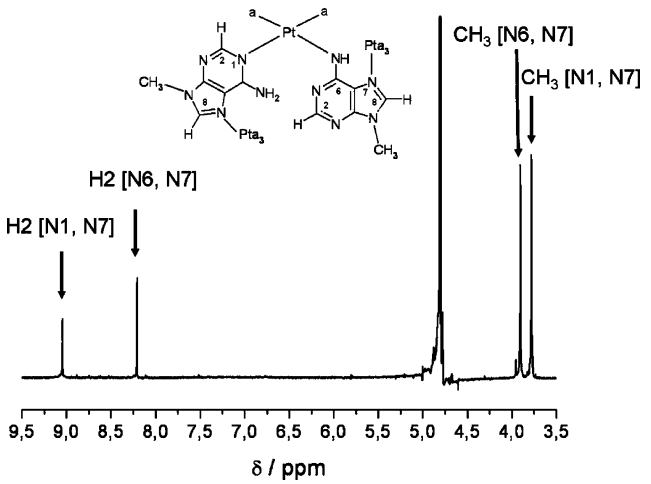

Figure 2. ^{1}H NMR spectrum (D_2O, pD ~10) of compound *cis*-[$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)(*N6*- 9-MeA$^-$-*N7*){Pt$(NH_3)_3\}_2]^{5+}$ (**4**). The spectrum displays two sets of H2 and of methyl resonances, which correspond to one adenine nucleobase with *cis*-a_2Pt^{II} at N1 and the other one with *cis*-a_2Pt^{II} at the N6 position. No H8 resonances are observed as a result of rapid isotopic exchange.

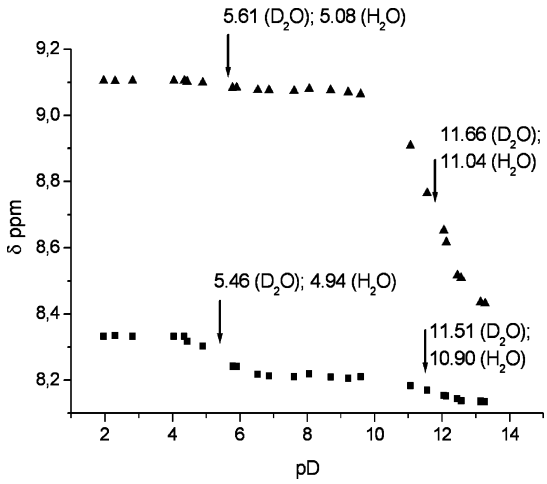

Figure 3. ^{1}H NMR pD-dependence (D_2O, δ) of the two H2 resonances of *cis*-[$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)(*N6*-9-MeA$^-$-*N7*){Pt$(NH_3)_3\}_2]^{5+}$ (**4**).

neutral and acidic pD the ^{1}H NMR spectrum indicates the presence of two rotamers, as reported before.[15] At pD > 7, only single sets of all the protons are detected, however. Second, the H2 resonance of the 9-MeA ligand in **3**, which is downfield from that of H8, undergoes an upfield-shift deprotonation of 9-MeA. Third, H8 is rapidly (within hours) exchanged for deuterium above pD 9, leaving only the H2 and CH_3 resonances.

When an aqueous solution of **3** is kept at pD 9−10 at room temperature or at 40 °C, ^{1}H NMR spectroscopic changes take place, which are indicative of a conversion of **3** into another species. Within two weeks at room temperature or 30 h at 40 °C, the ^{1}H NMR spectrum displays two H2 resonances as well as two CH_3 resonances in a 1:1 ratio with no signals due to the original compound **3** left (Figure 2). On the basis of the pD dependence of the four resonances, we assign the new species formed to *cis*-[$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)(*N6*-9-MeA$^-$-*N7*){Pt$(NH_3)_3\}_2]^{5+}$ (**4**), hence, to a complex with two differently bonded 9-MeA ligands. The pD-dependent ^{1}H NMR spectra (2 < pD < 14) reveal two deprotonation steps ocurring with different pK_a values, namely p$K_{a1} = 5.02 \pm 0.03$ and p$K_{a2} = 10.97 \pm 0.07$ (values converted to H_2O, average of two H2 resonances, see Figure 3). Whereas pK_{a2} is in the expected range for a N1,N7-diplatinated 9-MeA ligand and corresponds to deprotonation of the exocyclic N(6)H_2 group, the low value for pK_{a1} is only consistent with deprotonation of a N(1)H site, hence, with a diplatinated rare tautomer of 9-MeA being present. In other words, this second 9-MeA must be platinated at N7 and N6. The differences in relative shifts of the two acid−base steps of the aromatic (H2) resonances (Figure 2) and of the CH_3 resonances (not shown) suggest the assignment of the two H2 resonances to N1,N7 and N6,N7 diplatinated adenine species as made in Figure 2.

Upon prolonged standing (>3 d at pD 10, 40 °C), the ^{1}H NMR spectra become again more complicated with additional resonances growing between 8.1 and 8.9 ppm as well as in the range of the CH_3 resonances, whereas resonances of **4** slowly decrease. It is quite obvious that it is not a single new compound that is formed, simply because the number of new H2 resonances (ca. 6) is too high for a single species, even if rotamers are taken into consideration. Except for the isolated compound **5** (below), which can be identified by its ^{1}H NMR resonances, the nature of the other species present in solution is unclear. It is possible that adenine deamination to hypoxanthine and/or different migration processes take place as well, as previously reported for mononuclear Pt^{II} complexes by Arpalahti and co-workers.[6−8] We also note that, in the case of 1-methylcytosine complexes of Pt^{II}, deamination of the nucleobase and metal migration can occur simultaneously.[4,17]

X-ray Crystal Structure and Properties of 5. After keeping a sample of **3** in D_2O, pD 9−10, 20 °C for an extended period of time (4−6 weeks), crystals were eventually isolated in low yield, which proved to be *cis*-[$(NH_3)_2$Pt(*N6*-9-MeA$^-$-*N7*)$_2${Pt$(NH_3)_3\}_2$]$(NO_3)_4$·$5H_2O$ (**5**). In this compound, the *cis*-diammineplatinum(II) entity has undergone migration from originally N1 (in starting compound **3**) to N6 in both adenine nucleobases. Because of the high pH of isolation, the N1 sites of both nucleobases are deprotonated in **5**.

Figure 4 gives two views of cation **5**. It has C_2 symmetry with the axis bisecting the N6−Pt1−N6a triangle. The Pt(2)-$(NH_3)_3$ units are still bonded to the N7 sites, like in the starting compound **3**,[15] whereas the *cis*-Pt(1)$(NH_3)_2$ entity now cross-links two exocyclic N6 sites of the adenine bases. Because the two adenine bases are arranged *head-tail*, the cation **5** is chiral, with the two enantiomers present in a 1:1 ratio. Selected distances and angles of cation **5** are listed in Table 1.

The angles about Pt1 and Pt2 are close to ideal square-planar, with slight deviations of the coordinating atoms from the best planes, for example, −0.006(2) (Pt2), 0.029(2) (N21), −0.025(2) (N7), −0.025(2) (N22), and 0.028(2) Å

(17) Šponer, J. E.; Sanz Miguel, P. J.; Rodriguez-Santiago, L.; Erxleben, A.; Krumm, M.; Sodupe, M.; Šponer, J.; Lippert, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 5396.

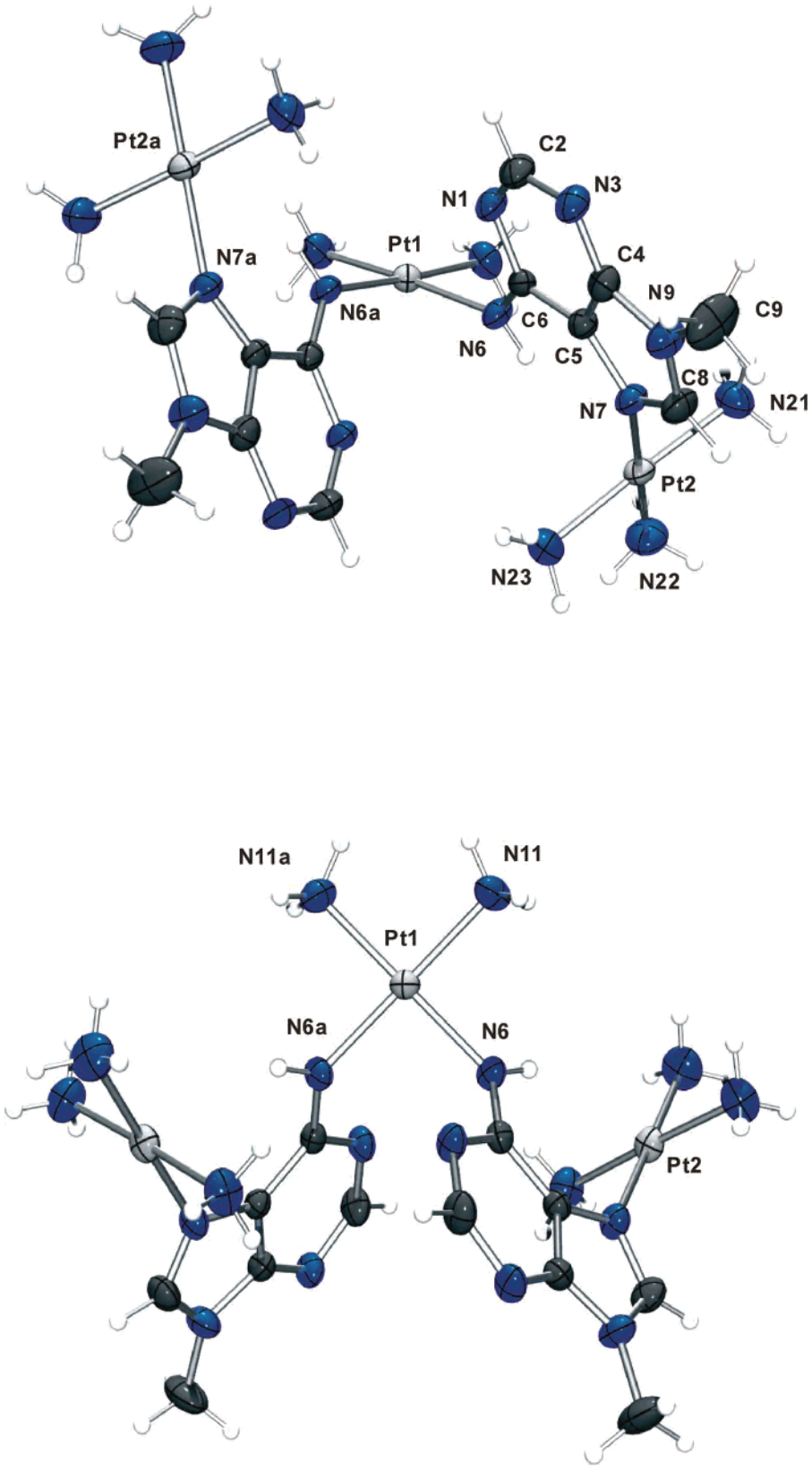

Figure 4. Side and top views of the cation of *cis*-$[(NH_3)_2Pt(N6\text{-}9\text{-}MeA^-\text{-}N7)_2\{Pt(NH_3)_3\}_2](NO_3)_4 \cdot 5H_2O$ (**5**). The anions and water molecules are omitted for clarity.

(N23), with a rms deviation of 0.024. Pt−N distances about the Pt1 center range from 2.016(4) to 2.050(5) Å. Similar Pt−N bond lengths are observed for platinum atom Pt2. The geometry of the 9-MeA^- ligand is normal. In particular, the internal ring angle at N1, which is 119.8(5)° in **5**, is closely similar to that of the free, neutral 9-MeA[18a] and therefore significantly smaller than in the case where this position is protonated.[18b] The adenine ring and the Pt2 coordination

Table 1. Selected Interatomic Distances (Angstroms) and Angles (Degrees) of **5**

Pt1−N6	2.016(4)	N6−Pt1−N11	87.98(19)
Pt1−N11	2.050(5)	N6−Pt1−N6a	92.1(3)
Pt1−N11A	2.050(5)	N6−Pt1−N11a	176.7(2)
Pt1−N6A	2.016(4)	N7−Pt2−N23	90.9(2)
C6−N6	1.296(7)	N7−Pt2−N22	178.4(2)
		N23−Pt2−N22	89.9(2)
		N7A−Pt2−N21	89.4(2)
Pt2−N7	2.012(5)	N23−Pt2−N21	178.1(2)
Pt2−N21	2.043(5)	N22−Pt2−N21	89.9(2)
Pt2−N22	2.046(5)		
Pt2−N23	2.027(5)	C2−N1−C6	119.8(5)

plane are almost perpendicular (dihedral angle 84.7(1)°), similar to the situation in **3**. However, the angle between the adenine base and the other platinum atom Pt1 is considerably smaller, 62.1(1)°. The dihedral angle formed between the two adenine nucleobases is 59.6(1)°.

The packing of **5** is such that pairs of enantiomers interact weakly through the pyrimidine parts of adenine rings (parallel arrangement, distance 3.39 Å), but the overlap is small. There is, however, extensive hydrogen bonding involving the cation of **5**, water molecules, and oxygen atoms of nitrate anions. The shortest hydrogen bond involves N1 of the adenine ring and a water molecule (O1W, 2.744(6)Å).

^{1}H NMR Spectra. In the ^{1}H NMR spectrum of **5**, only a single set of nucleobase signals is present, consistent with the fact that both 9-MeA bases are equivalent and hence have identical metal binding patterns. Because of the conditions of the reaction (alkaline pH values and long reaction time), an isotopic exchange (H→D) is observed for H8 of the adenine base (above). The acidity of the protons at N1 of the two adenine nucleobases of **5** was determined by ^{1}H NMR spectroscopy (pD dependence of CH_3 of adenine and H2 of adenine) and found to be 4.89 ± 0.13 and 6.53 ± 0.11 (calculated for water).

Summary

Both N1 and N7 sites of adenine nucleobase are kinetically favored metal binding sites. N1 is more basic than N7, and, consequently, N1 linkage isomers can be expected to have higher stability constants than the N7 linkage isomers.[19] However, in double-stranded DNA, the N1 site of adenine is statistically disfavored over N7 because it is in the center of the helix and involved in Watson−Crick pairing. Nevertheless, metal binding to this site is possible, as seen for example in a Transplatin interstrand cross-link with a 12/11-mer DNA hybrid.[20] Simultaneous metal binding to N1 and N7 has numerously been demonstrated to occur,[21] and $K[PtCl_3(Me_2SO)]$ has been utilized for some time to recognize adenine in DNA by electron microscopy techniques because of its propensity to bind to both sites.[22] The twofold metal migration process N1 → N6 reported here, which takes place in a moderately alkaline solution at room temperature and leads to a thermodynamically favored product with Pt^{II} located at N7 and N6, is at first glance against intuition gained from the differential stabilities of N1 and N7 linkage isomers. Thus, on the basis of a lower stability of the Pt−N7 product, a migration of $Pt(NH_3)_3^{2+}$ to N6 might have been expected rather than the alternative migration of *cis*-$Pt(NH_3)_2^{2+}$ to N6. Moreover, dinuclear Pt^{II} complexes with a N1,N6 bridging mode are known,[23] and there is no obvious steric problem that could prevent the formation of such a species in the present case. From model building, it is evident that both a syn orientation of *cis*-$Pt(NH_3)_2^{2+}$ and $Pt(NH_3)_3^{2+}$ and an anti orientation are feasible, in principle. It consequently appears that it is the electronic situation in N1,N7-bridged adenine nucleobases that is responsible for the observed migration. In other words, the sequence of stability (Pt−N1 > Pt−N7) seems not to be maintained in the Pt_2−N1,N7 adduct. This conclusion is fully supported by the composition of **4** and also by the X-ray crystal structure analysis of **5**, despite some uncertainties concerning the unknown byproducts accompanying the formation of **5**. Finally, it should be recalled that the preference of N6,N7 bridging is also seen with dinuclear $[Rh^{II}]_2$ entities.[24]

Experimental Section

Instrumentation. 1D ^{1}H NMR spectra were recorded on Varian Mercury 200 FT NMR, Bruker DRX 300, Bruker DRX 400, and Varian Inova 600 MHz instruments in D_2O at ambient temperature (20 °C). TSP (sodium 3-trimethylsilyl-propanesulfonate) ($\delta = 0$) was used as an internal standard.

Determination of Acidity Constants. The pH (uncorrected pH*) of a D_2O solution was determined by the use of a glass electrode on a Metrohm 6321 pH meter. pD values were obtained after the addition of 0.4 units to the value displayed on the pH meter.[25] Measurement of the pD dependences were carried out using identical samples, in which the pD of the solutions was modified in small increments by the addition of small amounts of DNO_3 and/or NaOD. Because of the limitations of the AgCl glass electrodes, it was not possible to get reliable measurements at pH values close to 14. The pK_a values were determined using pH-dependent ^{1}H NMR spectroscopy. Changes in chemical shifts of nonexchangeable protons in the compounds depending on the pD value were followed. The graphs (pD vs chemical shift) were evaluated with a nonlinear least-squares fit according to the Newton−Gauss method.[26] Eventually, the pK_a values obtained in D_2O were converted into pK_a values for water.[27]

(18) (a)Kistenmacher, T. J.; Rossi, M. *Acta Crystallogr*. **1977**, *B33*, 253. (b) Taylor, R.; Kennard, O. *J. Mol. Struct.* **1982**, *78*, 1.

(19) (a) Martin, R. B. *Acc. Chem. Res.* **1985**, *18*, 32. (b) Martin, R. B. *Met. Ions Biol. Syst.* **1996**, *32*, 61.

(20) Andersen, B.; Bernal-Méndez, E.; Leng, M.; Sletten, E. *Eur. J. Inorg. Chem.* **2000**, 1201.

(21) For Pt^{II} complexes, see for example (a) Lock, C. J. L.; Speranzini, R. A.; Turner, G.; Powell, J. *J. Am. Chem. Soc.* **1976**, *98*, 7865. (b) Lüth, M. S.; Freisinger, E.; Glahé, F.; Müller, J.; Lippert, B. *Inorg. Chem.* **1998**, *73*, 3195.

(22) (a) Whiting, R. F.; Ottensmeyer, F. P. *Biochim. Biophys. Acta* **1977**, *474*, 334. (b) Jack, T. R. *Met. Ions Biol. Syst.* **1979**, *8*, 159.

(23) (a) Trovó, G.; Bandoli, G.; Nicolini, M.; Longato, B. *Inorg. Chim. Acta* **1993**, *211*, 95. (b) Prizant, L.; Olivier, M. J.; Rivest, R.; Beauchamp, A. L. *J. Am. Chem. Soc*. **1979**, *101*, 2765, and references cited therein.

(24) (a) Day, E. F.; Crawford, C. A.; Folting, K.; Dunbar, K. R.; Christon, G. *J. Am. Chem. Soc*. **1994**, *116*, 9339. (b) Catalan, K. V.; Mindiola, D. J.; Ward, D. L.; Dunbar, K. R. *Inorg. Chem.* **1997**, *36*, 2458. (c) Chifotides, H. T.; Dunbar, K. R. *Acc. Chem. Res.* **2005**, *38*, 146.

(25) Lumry, R.; Smitz, E. L.; Glantz, R. R. *J. Am. Chem. Soc*. **1951**, *73*, 4335.

Compounds. *cis*-$(NH_3)_2PtCl_2$,[28] 9-methyladenine (9-MeA),[29] and *cis*-[$(NH_3)_2$Pt{(*N1*-9-MeA-*N7*)Pt$(NH_3)_3$}$_2$]$(NO_3)_6\cdot 2H_2O$ (**3**)[15] were prepared as reported.

[(9-MeA-*N7*)Pt$(NH_3)_3$]$Cl_2\cdot 2H_2O$ (2). 9-MeA (4 mmol) was reacted with K_2PtCl_4 (4 mmol) in water (250 mL) at 55 °C for 20 min. After that, the mixture was stirred for 6 h at room temperature. The yellow precipitate was removed by filtration and washed with cold water (5 mL). The yellow compound was [$PtCl_3$(9-MeAH-*N7*)].[30] This compound was dissolved in water, and NH_3 (25%, 80 mL) was added. After stirring for 1 day and removal of some unreacted material, the volume was reduced to 30 mL. The pH of the solution was adjusted to pH 4.0 (HNO_3, 0.1N). The solution was allowed to evaporate at 4 °C. Colorless crystals of **2** were isolated from it and characterized by X-ray crystallography. The yield was 82%. Elemental analysis Calcd for $C_6H_{20}N_8O_2Cl_2Pt$ (502.26 g mol^{-1}): C 14.3, H 4.0, N 22.3; found: C 14.3, H 4.0, N 22.5.

***cis*-[$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)(*N6*-9-MeA$^-$-*N7*){Pt$(NH_3)_3$}$_2$]$^{5+}$ (4).** To a solution of *cis*-[$(NH_3)_2$Pt{(*N1*-9-MeA-*N7*)Pt$(NH_3)_3$}$_2$]$(NO_3)_6\cdot 2H_2O$ (**3**) in D_2O was added 1M NaOH. When the pH was ca. 10, the solution was kept at 40 °C. ^{1}H NMR spectra were recorded at intervals. Within 30 h at 40 °C (or 4 weeks at room temperature, pD 9), signals corresponding exclusively to **4** were seen. **4** has not been isolated.

***cis*-[$(NH_3)_2$Pt(*N6*-9-MeA$^-$-*N7*)$_2${Pt$(NH_3)_3$}$_2$]$(NO_3)_4\cdot 5H_2O$ (5).** *cis*-[$(NH_3)_2$Pt{(*N1*-9-MeA-*N7*)Pt $(NH_3)_3$}$_2$]$(NO_3)_6\cdot 2H_2O$ (**3**) (60 mg) was dissolved in D_2O (1.2 mL). The pH value was raised from 5.4 to 10 by adding 1M NaOD. The sample was lyophilized and subsequently redissolved in D_2O (1 mL), and then the solution was kept in a closed vial until crystals of **5** appeared after several weeks. The composition of **5** was confirmed by X-ray crystallography.

X-ray-Crystallography. Data collection was performed on an Enraf-Nonius Kappa CCD diffractometer at the University of Dortmund using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å).[31] Crystallographic data for **2** and **5** are given in Table 2. Data reduction and cell refinement were carried out using the programs *DENZO* and *SCALE-PACK*.[32] Intensities of the reflections were collected at room temperature, 293(2)°. All of the structures were solved by standard Patterson methods[33] and refined by full-matrix least-squares methods based on F^2 using the *SHELXTL-PLUS*,[34] *SHELXL-97*,[35] and *WinGX*[36] programs. In the refinement process of the X-ray data, all of the non-hydrogen atoms of the crystal were refined anisotropically, except nitrogen and oxygen atoms of the disordered nitrate in **5**. All of the hydrogen atoms except those of the water molecules were included in geometrically calculated positions and refined with isotropic displacement parameters according to the riding model. The production of the diagrams was achieved with the programs *Ortep-3 for Windows*[37] and *Persistence of Vision Raytracer (POV-Ray)*.[38]

Table 2. Crystallographic Data for Compounds **2** and **5**

compound	[(9-MeA-*N7*)Pt$(NH_3)_3$]-$Cl_2\cdot 2H_2O$	*cis*-[$(NH_3)_2$Pt(*N6*−9-MeA-*N7*)$_2$-{Pt$(NH_3)_3$}$_2$]$(NO_3)_4\cdot 5H_2O$
formula	$C_6H_{20}Cl_2N_8O_2Pt$	$C_{12}H_{46}N_{22}O_{17}Pt_3$
fw (g mol^{-1})	502.26	1355.98
cryst color and habit	colorless blocks	colorless blocks
cryst syst	monoclinic	monoclinic
space group	*C*2/*c*	*C*2/*c*
a (Å)	28.133(6)	24.730(5)
b (Å)	7.1110(14)	10.807(2)
c (Å)	17.814(4)	14.505(3)
α (deg)	90.00	90
β (deg)	118.27(3)	95.84(3)
γ (deg)	90.00	90
Z	8	4
V (Å^3)	3138.6(11)	3856.4(13)
ρ_{calcd} (g cm^{-1})	2.109	2.336
μ (Mo Kα) (mm^{-1})	9.293	10.948
F(000)	1888	2568
θ range (deg)	2.32−27.49	2.06−27.89
No. reflns collected	3595	4595
No. reflns observed $I > 2\sigma(I)$	2368	3109
No. params refined	174	242
R1 (obs. data)	0.0406	0.0354
wR2 (obs. data)	0.11	0.0742
GOF, *S*	0.914	0.913
Residual ρ_{max}, ρ_{min} (e Å^{-3})	1.925, −2.617	1.68, −1.76

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft, (D.F.G.), and the Fonds der Chemischen Industrie, (F.C.I.), are gratefully acknowledged. We thank PD Dr. Andrea Erxleben for her assistance with the X-ray diffraction studies. We dedicate this work to Professor Dieter Naumann, University of Köln, on the occasion of his 65th birthday.

Supporting Information Available: X-ray crystallographic file in CIF format and structural details. This material is available free of charge via the Internet at http://pubs.acs.org.

IC7008754

(26) Tribolet, R.; Sigel, H. *Eur. J. Biochem.* **1987**, *163*, 353.
(27) Martin, R. B. *Science* **1963**, *139*, 1198.
(28) (a) Dhara, S. C. *Indian J. Chem.* **1970**, *8*, 193. (b) Raudaschl-Sieber, G.; Lippert, B.; Hoeschele, J. D.; Howard-Lock, H. E.; Lock, C. J. L.; Pilon, P. *Inorg. Chim. Acta* **1985**, *106*, 141.
(29) Krüger, G. *Hoppe Seyler's Z. Physiol. Chemie* **1894**, *18*, 434.
(30) Terzis, A. *Inorg. Chem.* **1976**, *15*, 793.
(31) KappaCCD package; Nonius: Delft, The Netherlands, 1997.
(32) Otwinowsky, Z.; Minor, W.; DENZO and SCALEPACK. *Methods Enzymol.* **1997**, *276*, 307.
(33) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, 467.
(34) Sheldrick, G. M. *SHELXTL-PLUS (VMS)*; Siemens Analytical X-Ray Instruments: Madison, WI, 1990.
(35) Sheldrick, G.-M. *SHELXL-97*, program for crystal structure refinement; University of Göttingen: Göttingen, Germany, 1993.
(36) Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, *837*. Windows programs for the solution, refinement, and analysis of single crystal X-ray diffraction data. http://www.chem.gla.ac.uk/~louis/wingx.
(37) Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.
(38) *Persistence of Vision Raytracer (POV-Ray)*, Ver. 3.6, Persistence of Vision Raytracer Pty. Ltd., PO Box 407, Williamstown, Victoria 3016, Australia, **2005**.