Perturbation of the NH_2 pK_a Value of Adenine in Platinum(II) Complexes: Distinct Stereochemical Internucleobase Effects[‡]

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Dedicated to Professor Jan Reedijk on the occasion of his 60th birthday

Abstract: The degree of acidification of the exocyclic N6 amino group of the model nucleobase 9-methyladenine (9MeA) in relation to the number and site(s) of Pt^{II} binding has been studied in detail. It is found that twofold Pt^{II} binding to N1 and N7 lowers the pK_a value from 16.7 in the free base to 12–8. The lowest pK_a values are observed when the resulting $N6H^-$ amide group is intramolecularly stabilized by an H-bond donor such as the $N6H_2$ group of a suitably positioned second 9MeA ligand. Deprotonation of the N6 amino group facilitates Pt migration from N1 to N6, and subsequent reprotonation of the N1 position yields a twofold *N*7,*N*6-metalated form of the rare imino tautomer of 9MeA, which has a pK_a value of 5.03. These findings demonstrate a principle that is of potential relevance to the topic of "shifted pK_a" values of adenine nucleobases, which is believed to be important with regard to acid–base catalysis of RNAs at physiological pH values. The principle states that a nucleobase pK_a value can be sufficiently lowered to reach near-neutral values and that the pK_a value of the protonated base does not necessarily have to be increased to accomplish this effect.

Keywords: acidity · hydrogen bonds · nucleobases · platinum

Introduction

The heterocyclic rings of nucleobases are generally not involved in acid–base equilibria of nucleic acids, since the pK_a values ($4 > pK_a > 9$) are outside the physiological pH range.[1] This picture changes if the nucleobases are modified, for example, through alkylation or metal coordination. For example, the N1H group in 7,9-dimethylguaninium has a pK_a value of 7.22 ± 0.01,[2] compared to a value of 9.56 for 9-methylguanine,[3] and metal binding to N7 generally lowers the pK_a value of this proton by one to two log units, depending on the metal, net charge, etc.[2–4] It is known that in biological macromolecules the environment of an acidic proton can likewise modify its pK_a value, in either direction. In special nucleic acid structures, for example, the i motif of hemiprotonated cytosine or DNA triplex structures containing cytosine·guanine·CH^+ triplets, this phenomenon is well established.[5] Shifts of the pK_a values of nucleobase protons into the physiological pH range are currently of great interest in that they potentially permit acid–base catalysis.[6] Thus, it has been reported that an adenine residue in ribosomal RNA with the highly unusual pK_a value of 7.6 ± 0.2 acts as a catalyst in the ribosomal peptidyl transferase center,[7] and nucleobase functions with near-neutral pK_a values have been associated with ribozyme catalysis of the hepatitis delta virus.[8] Similarly, an unusual pK_a value of 6.5 for an adenine base close to the active site of a Pb-dependent ribozyme ("leadzyme") has been described.[9] Other authors[10–12] and ourselves[3,4,13,14] have demonstrated in numerous instances that metal binding to a nucleobase acidifies protons of NH groups and, conversely, causes an apparent increase in nucleobase basicity upon metal coordination to a deproto-

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[‡] Abbreviations: 9EtA = 9-ethyladenine, 9MeA = 9-methyladenine, $9MeA^-$ = 9-methyladenine anion, $9MeAH^+$ = 9-methyladeninium, 1MeU = 1-methyluracil anion, 1MeC = 1-methylcytosine, 9EtGH = 9-ethylguanine, 9MeGH = 9-methylguanine, 1MeT = 1-methylthymine anion, A = adenine nucleobases, GH = guanine nucleobases, C = cytosine nucleobases, U = uracil anion nucleobases, T = thymine anion nucleobases, a = NH_3, ma = CH_3NH_2.

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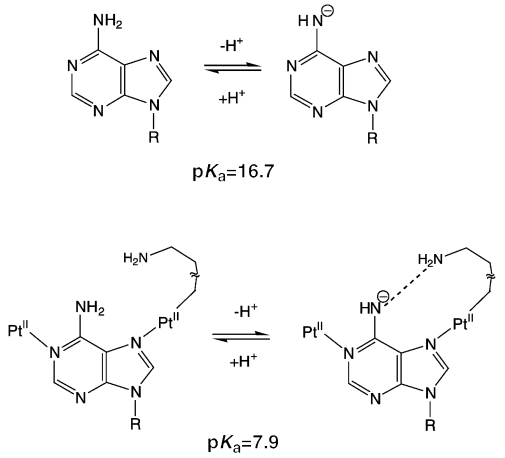
nated, and hence anionic, nucleobase,[15,16] because the proton has a stronger polarizing effect than (most) divalent metal ions.[13a] The effect depends on a combination of factors such as the charge of the metal(s), the number of metal ions, the coligands, the distance between the metal center and the proton, and hence the site(s) of metal binding.[10c]

Here we report on "normal" as well as unexpectedly low pK_a values of the adenine N6H$_2$ group in cross-linking adducts with a variety of Pt^{II} entities. The work originated from our previously reported finding of a 10^9-fold acidification of this group in a trinuclear Pt^{II} complex containing four nucleobases, two of which were adenines.[17] The drop in the pK_a value from 16.7[18] in free 9-ethyladenine (9EtA) to approximately 7.9 in *trans*,*trans*,*trans*-[(NH$_3$)$_2$Pt(*N*7-9EtA-*N*1)$_2${(CH$_3$NH$_2$)$_2$Pt(1MeU-*N*3)}$_2$](ClO$_4$)$_4$ was attributed to a synergy of electronic effects (Lewis acidification by two metal ions) *and* favorable geometrical conditions, that is, an efficient stabilization of the deprotonated adenine by intramolecular H-bond formation with the neutral adenine ligand (Scheme 1). In a sense, the situation is reminiscent of



Scheme 1. Acid–base equilibria of N9-blocked adenine involving neutral and anionic species: the free nucleobase (top) and the *N*1,*N*7-diplatinated complex with a record-low pK_a value (bottom).

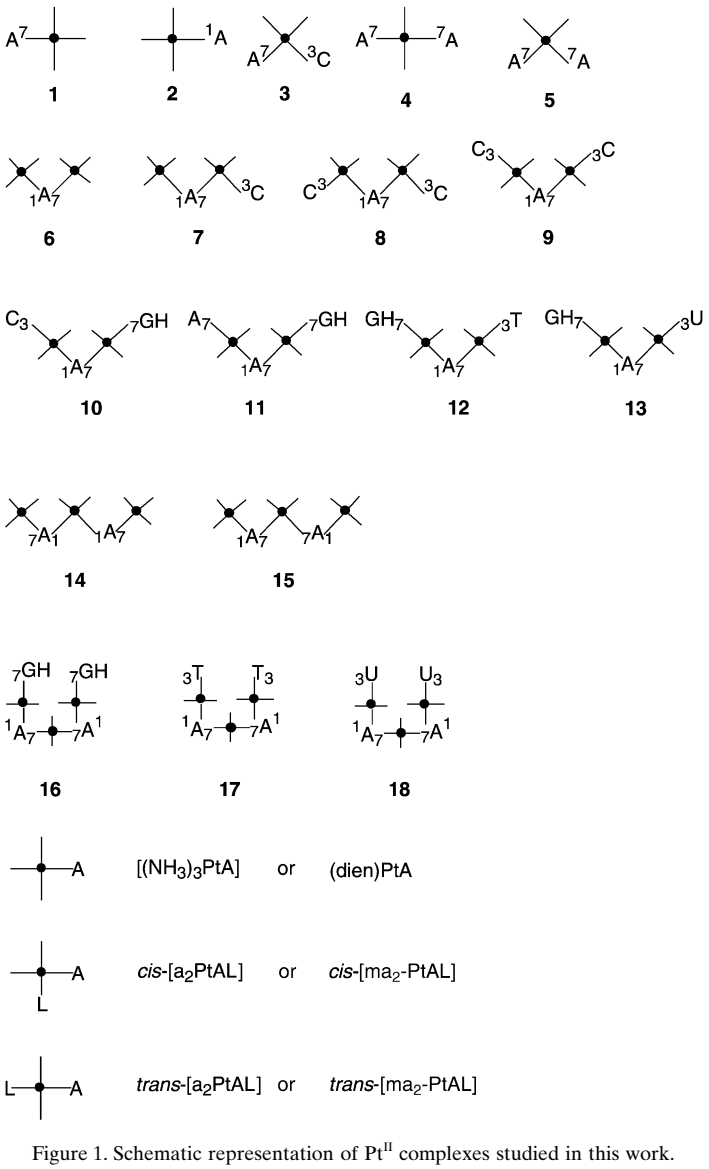


Figure 1. Schematic representation of Pt^{II} complexes studied in this work. Coordination sites are indicated. L = a nucleobase other than an adenine nucleobase, A = 9MeA or 9EtA, C = 1MeC, T = 1MeT, U = 1MeU, GH = 9MeGH or 9EtGH, dien = diethylenetriamine.

that found in dinuclear complexes of Pt^{IV} containing the amido–ammine bridging ligands $H_5N_2^-$ that give Pt–NH$_3$···$^-$H$_2$N–Pt.[19] In continuation of this earlier work, we have extended our studies of Pt^{II}–adenine complexes to different geometries (*cis*-[a$_2$Pt^{II}], [a$_3$Pt^{II}], *trans*-[ma$_2$Pt^{II}], and [dien$_3$Pt^{II}], where a = NH$_3$ and ma = NH$_2$CH$_3$). In addition, we employed other nucleobases as coligands (Figure 1). We were particularly interested in the effect of cytosine since this nucleobase also contains a suitably located exocyclic amino group for stabilization of an NH$^-$ group of adenine.

Results

"Normal" N6H$_2$ acidification of adenine by a single Pt^{II}: The acidification of adenine nucleobases by a coordinated metal ion can be expressed in terms of a loss in basicity for accepting a proton at one of the three available endocyclic nitrogen atoms, N1 (preferably), N7, or N3. Pt^{II} binding to N7 of an N9-substituted adenine, for example, 9-methyladenine (9MeA), makes protonation of the preferred N1 position more difficult by approximately 2 log units, that is, the pK_a value of N1H drops from 4.10 in free 9-methyladeninium (9MeAH$^+$) to approximately 2 in its Pt^{II} complexes.[13] If Pt^{II} is bonded to N1, protonation occurs at N7 with a pK_a value of approximately 1.2,[20] and if the N3 site is carrying a Pt^{II} entity, the overall basicity of the adenine ring drops by 4 log units, with N7 then being more basic than N1.[13a,21]

The acidifying effect of metal coordination on any of the ring nitrogen atoms is also reflected by a drop in the pK_a value of the exocyclic amino group (Table 1). Of course, this is numerically different from the ΔpK_a values measured for the protonated endocyclic nitrogen atoms but it also depends on the site of metal binding. It appears that N1 Pt^{II}

Table 1. pK_a values of the N6H$_2$ group in 9-alkyladenine complexes of Pt^{II}.[a,b]

Compd	Cation composition	pK_{a1}	pK_{a2}[c]	Other pK_a values[d]	Ref.
1	[(dien)Pt(A-*N*7)]$^{2+}$	>13	–		[11]
2	[(dien)Pt(A-*N*1)]$^{2+}$	>11	–		[11]
3	*cis*-[a$_2$Pt(A-*N*7)(C-*N*3)]$^{2+}$	>12.6[e]			this work
4	*trans*-[a$_2$Pt(A-*N*7)$_2$]$^{2+}$	>12.8[e]	n.d.		this work
5	*cis*-[a$_2$Pt(A-*N*7)$_2$]$^{2+}$	>13[f]	n.d.		this work
6	[{(dien)Pt}$_2$(A-*N*1,*N*7)]$^{4+}$	ca. 11	–		[11]
7	*cis*-[a$_2$Pt(C-*N*3)(*N*7-A-*N*1)Pt(dien)]$^{4+}$	10.79			this work
8	*cis*-[{a$_2$Pt(C-*N*3)}$_2$(A-*N*1,*N*7)]$^{4+}$	11.03	–		this work
9	*trans*-[{a$_2$Pt(C-*N*3)}$_2$(A-*N*1,*N*7)]$^{4+}$	10.00	–		this work
10	*trans*,*trans*-[(ma)$_2$Pt(C-*N*3)(*N*1-A-*N*7)Pta$_2$(GH-*N*7)]$^{4+}$	10.66	–	7.92 (N(1)H of GH)	this work
11	*trans*,*trans*-[(ma)$_2$Pt(A-*N*7)(*N*1-A-*N*7)Pta$_2$(GH-*N*7)]$^{4+}$	10.08	–	7.94 (N(1)H of GH)	this work
12	*trans*,*trans*-[a$_2$Pt(T-*N*3)(*N*7-A-*N*1)Pt(ma)$_2$(GH-*N*7)]$^{3+}$	12.06	–	8.33 (N(1)H of GH)	[22]
13	*trans*,*trans*-[a$_2$Pt(U-*N*3)(*N*7-A-*N*1)Pt(ma)$_2$(GH-*N*7)]$^{3+}$	12.62	–	8.61 (N(1)H of GH)	[22]
14	*cis*-[a$_2$Pt{(*N*1-A-*N*7)Pta$_3$}$_2$]$^{6+}$	8.7,[g] 9.10[h]	10.7,[g] 10.99[h]	−4.4[i] (N(3)H of AH)	this work
15	*cis*-[a$_2$Pt{(*N*7-A-*N*1)Pt(dien)}$_2$]$^{6+}$	9.23[h]	10.56[h]	−4.3[i] (N(3)H of AH)	this work
16a	*trans*,*trans*,*trans*-[a$_2$Pt(*N*7-A-*N*1)$_2${a$_2$Pt(GH-*N*7)}$_2$]$^{6+}$	8.67[h]	10.96[h]	7.13; 7.59 (N(1)H of GH)	this work
16b	*trans*,*trans*,*trans*-[a$_2$Pt(*N*7-A-*N*1)$_2${(ma)$_2$Pt(GH-*N*7)}$_2$]$^{6+}$	8.57[h]	10.61[h]	7.28; 7.49 (N(1)H of GH)	this work
17	*trans*,*trans*,*trans*-[a$_2$Pt(*N*7-A-*N*1)$_2${a$_2$Pt(T-*N*3)}$_2$]$^{4+}$	8.61[h]	11.31[h]		this work
18	*trans*,*trans*,*trans*-[a$_2$Pt(*N*7-A-*N*1)$_2${(ma)$_2$Pt(U-*N*3)}$_2$]$^{4+}$	7.94	11.66		[17]

[a] Abbreviations: A = 9MeA or 9EtA, C = 1MeC, T = 1MeT, U = 1MeU, GH = 9MeGH or 9EtGH, a = NH$_3$, ma = CH$_3$NH$_2$, n.d. = not determined. [b] Determined by ^{1}H NMR spectroscopy unless otherwise stated; values obtained for D$_2$O are converted into values for H$_2$O. [c] For a second 9MeA ligand. [d] For ligands other than 9MeA. [e] Estimated; deprotonation not yet complete at pD 13. [f] Estimated; deprotonation starts at pD 12.5. [g] ^{1}H NMR spectroscopy. [h] Potentiometry. [i] UV spectroscopy.

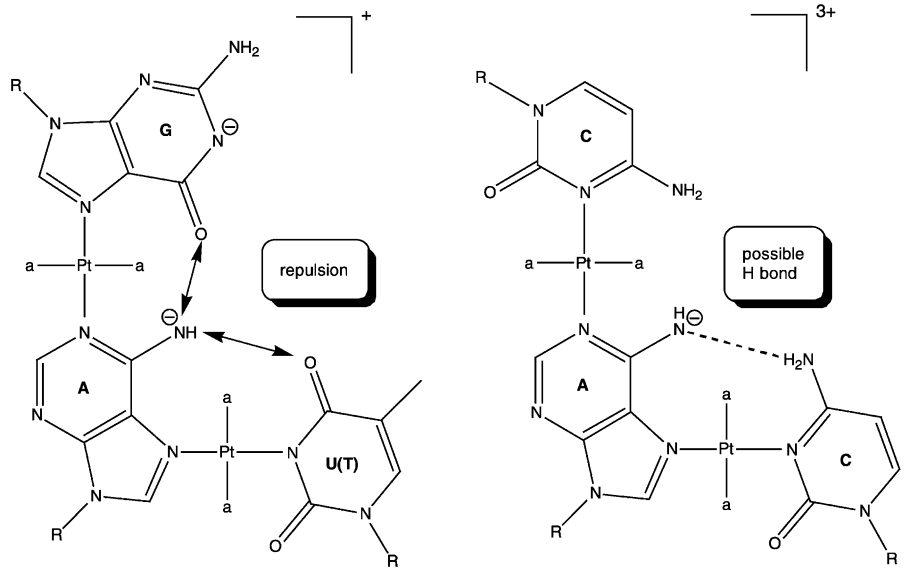
binding to adenine nucleobases causes a larger acidification of the N6H$_2$ group than N7 Pt^{II} binding: In the (dien)Pt^{II} complex of 9MeA (**2**) deprotonation starts above pH* 11,[11] and with [(NH$_3$)$_3$Pt(adenosine-*N*1)]$^{2+}$ a pK_a value of 12.4 has been reported.[12] Our own findings with *cis*-[(NH$_3$)$_2$Pt(9MeA-*N*7)(1MeC-*N*3)](ClO$_4$)$_2$·H$_2$O (**3**) and with *trans*-[(NH$_3$)$_2$Pt(9-MeAH-*N*7)$_2$](ClO$_4$)$_4$·2H$_2$O and *cis*-[(NH$_3$)$_2$Pt(9MeA-*N*7)$_2$](NO$_3$)$_2$·2H$_2$O (**4** and **5**, respectively) are also consistent with a relatively moderate effect of the metal ion at N7 (pK_a values >12.6), although it might be argued that the charge effect of the metal is reduced in the bis(nucleobase) complex relative to that in a mono(nucleobase) complex.

N6H$_2$ acidification of adenine by twofold Pt^{II} binding through N1 and N7: Coordination of a second Pt^{II} entity to an adenine nucleobase causes a more pronounced acidification of the exocyclic adenine amino group and permits ready detection in water. In early studies, pK_a values of 11.0–11.3 have been determined for [{(dien)Pt}$_2$(9MeA-*N*1,*N*7)]$^{4+}$ (**6**),[11] and 10.8 was the value reported for [{(NH$_3$)$_3$Pt}$_2$(adenosine-*N*1,*N*7)]$^{4+}$.[12] The dinuclear mixed adenine/cytosine complexes **7**–**9** studied by us (Figure 1) essentially confirm this picture. Still, there is an interesting detail to be noted: For the *trans*-[(NH$_3$)$_2$Pt^{II}] compound **9** a pK_a value of 10.0 ± 0.1 is observed, which is significantly lower than the corresponding pK_a value of 11.1 ± 0.1 for the *cis* isomer **8** (see below). In two previously described nucleobase triplets containing a central Pt(*N*1-adenine-*N*7)Pt unit,[22] *trans*,*trans*-[(NH$_3$)$_2$Pt(1MeT-*N*3)(*N*7-9MeA-*N*1)Pt(NH$_2$CH$_3$)$_2$(9EtGH-*N*7)](ClO$_4$)$_3$·5.2H$_2$O (**12**) and *trans*,*trans*-[(NH$_3$)$_2$Pt(1MeU-*N*3)(*N*7-9EtA-*N*1)Pt(NH$_2$CH$_3$)$_2$-(9EtGH-*N*7)]$^{3+}$ (**13**), the pK_a values for deprotonation of the exocyclic amino group of the adenine nucleobase in water were found to be substantially higher, around 12.1–12.6 in both cases. This difference of two log units from the value for **9** clearly suggests a substantial internucleobase effect (Scheme 2).

Although a charge influence is also likely to play a role (**9** has a charge of +4; **12** and **13** have charges of +2 once the guanine ligands have undergone deprotonation), it is probably not dominant. For example, **11** has almost the same pK_a value (10.08 ± 0.22) as **9**, although it has a charge of only +3 once the guanine ligand is deprotonated. An internucleobase effect on the pK_a value of the adenine is further suggested by a comparison of **10** and **11**: Both compounds have identical charges (and identical pK_a values of the guanine ligands), yet the pK_a values of the bridging adenine ligand are different (10.66 ± 0.03 and 10.08 ± 0.22, respectively).

Acidification of N6H$_2$ in trinuclear bis(adenine-*N*1,*N*7) complexes: We have prepared several complexes of general composition Pt$_3$A$_2$ (A = 9MeA or 9EtA), with formally 1.5 Pt entities per adenine base and either a *cis*- or a *trans*-[a$_2$Pt^{II}] or -[ma$_2$Pt^{II}] entity cross-linking two central adenine bases. Surprisingly, pK_a values in the compounds studied are substantially lower than in the cases with two Pt entities per adenine (compare with the above results). This rules against the charges of the metal entities being the major determinants of ligand acidity.

Several examples of trinuclear Pt^{II} complexes containing a single *cis*-[a$_2$Pt^{II}] as well as two monofunctional a$_3$Pt^{II} units have been studied. In *cis*-[(NH$_3$)$_2$Pt{(*N*1-9MeA-*N*7)Pt(NH$_3$)$_3$}$_2$](NO$_3$)$_6$·2H$_2$O (**14**), the X-ray crystal structure of which has been reported before,[23] pD-dependent ^{1}H NMR spectra in D$_2$O and potentiometric titrations in H$_2$O gave pK_{a1} values of approximately 8.7 (^{1}H NMR spectroscopy) and 9.10 ± 0.03 (potentiometry) for deprotonation of the first adenine base and pK_{a2} values of approximately 10.7 (^{1}H NMR spectroscopy) and 10.99 ± 0.10 (potentiometry) for deprotonation of the second adenine. In the NMR spectra, the two deprotonation steps of **14** are particularly



Scheme 2. Internucleobase effects on deprotonated adenine group N6H$^-$ in **12** and **13** on one hand and **9** on the other.

well separated for the adenine H2 resonance (Figure 2). It is noted that above pD 7.5 and at ambient temperature only single sets of H2 and H8 resonances are observed; this is unlike the situation at lower pH values, where resonance doubling (with an intensity ratio of about 1:3) is observed due to slow nucleobase rotation. While the pK_{a2} value is in the range expected for a Pt_2(9MeA-*N*1,*N*7) species (see above), pK_{a1} is significantly shifted to lower values. We propose that the first proton loss from the exocyclic amino group is facilitated by an efficient stabilization of the deprotonated species involving donation of a proton from the N6H2 group of the second 9MeA in a hydrogen bond (Scheme 3).

This scenario is supported by structural arguments: In the solid-state structure of **14**[23] the two adenine bases are in a *head–head* arrangement with the two exocyclic amino groups 3.35 Å apart (N6A···N6A′) and essentially perpendicular to each other. Following removal of a single proton only a slight tilting of the two bases would be required to lower the separation of the two exocyclic nitrogen atoms to well below 3 Å and to permit stabilization of the deprotonated species by H-bond formation. Removal of a second proton (from the other adenine base) is expected to lead to mutual repulsion of the NH^- groups, to a larger separation of these groups, and probably, as a consequence, to base rotation into a *head–tail* orientation. With no extra stabilization of the deprotonated species possible, the pK_{a2} value is again in the "normal" range for diplatinated adenines, namely close to 11.

When the positions of the *cis*-[a_2Pt^{II}] and the [a_3Pt^{II}] entities on the adenine bases are interchanged, that is, in *cis*-[$(NH_3)_2$Pt{(*N*7-9MeA-*N*1)Pt(dien)}$_2$]$(NO_3)_6$ (**15**), differences between the pK_{a1} and pK_{a2} values are somewhat lower than in **14**, but the values are still significantly apart (9.23 ± 0.08 and 10.56 ± 0.17, respectively; potentiometry). The low pK_a value of the first deprotonation step calls for a similar interpretation as in the case of **14**. Although X-ray crystal structures are not available for **15** or for the *cis*-[$(NH_3)_2$Pt(9MeA-*N*7)$_2$]$^{2+}$ fragment (**5**) with a *head–head* arrangement of the two bases, comparison with the positions of the O6 atoms in *cis*-[$(NH_3)_2$Pt(9EtGH-*N*7)$_2$]$^{2+}$ (two guanines in the *head–head* orientation)[24] leaves no doubt that hydrogen bonding between the NH^- and NH_2 groups in **15** is feasible on steric grounds.

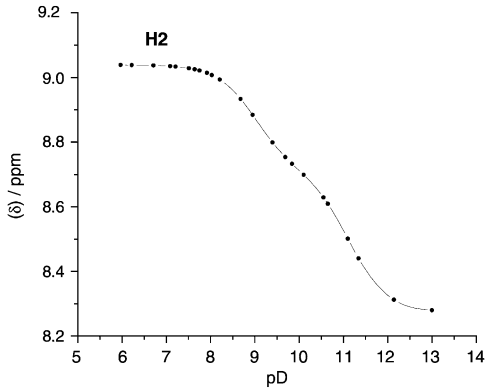
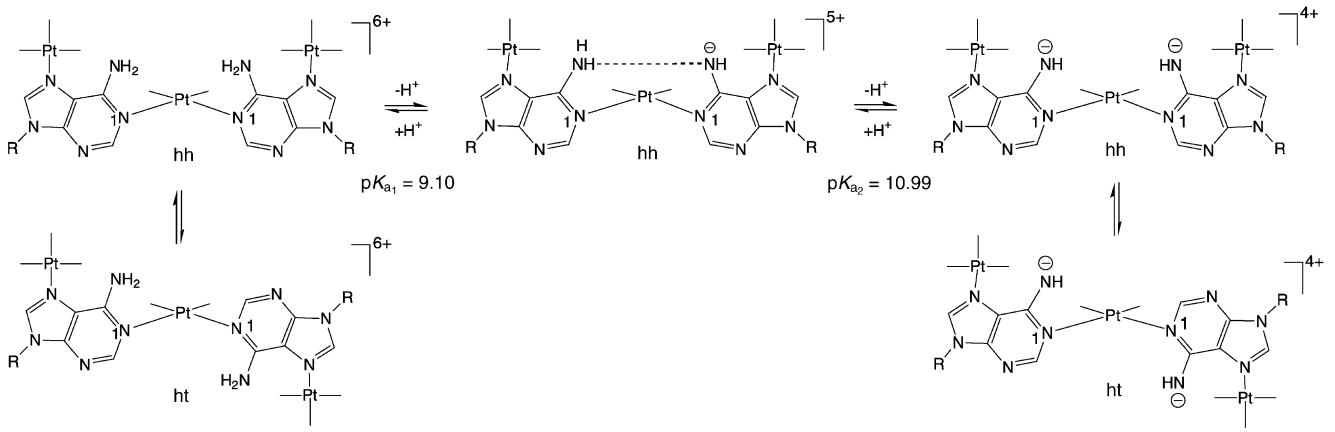


Figure 2. pD dependence of the H2 resonance of **14** in the NMR spectra. Two distinct deprotonation processes for the two adenine ligands are indicated, with pK_a values of 9.10 and 10.99.

Altogether, four compounds containing a central *trans*-[a_2Pt^{II}] unit bridging two adenine nucleobases through their N7 positions were studied: *trans,trans,trans*-[$(NH_3)_2$Pt(*N*7-9MeA-*N*1)$_2${$(NH_3)_2$Pt(9EtGH-*N*7)}$_2$]$(ClO_4)_6 \cdot 6H_2O$ (**16a**), *trans,trans,trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N*1)$_2${$(CH_3NH_2)_2$Pt(9MeGH-*N*7}$_2$]$(ClO_4)_6$ (**16b**), *trans,trans,trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N*1)$_2${$(NH_3)_2$Pt(1MeT-*N*3)}$_2$]$(ClO_4)_4 \cdot 11H_2O$ (**17**), and *trans,trans,trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N*1)$_2${$(CH_3NH_2)_2$Pt(1MeU-*N*3)}$_2$]$(ClO_4)_4 \cdot 4H_2O$ (**18**). As can be seen from Table 1,



Scheme 3. Proposed rotamer distribution of **14** according to the pH of the solution. hh = *head–head*, ht = *head–tail*.

there is a further drop in the pK_{a1} value of 9MeA for these compounds compared to the examples containing a central *cis*-[a_2Pt^{II}] unit, with a minimum of 7.9 ± 0.3 (^{1}H NMR spectroscopy) reached in the case of **18**.

With the mixed guanine/adenine complexes **16a** and **16b** deprotonation takes place at the two guanine ligands (N1 positions) prior to deprotonation at the bridging adenine ligands ($N6H_2$). The pK_a values for the guanine bases in **16a** and **16b** are between 7.1 and 7.6 and are thus also remarkably lower than in other cases of guanine model nucleobase complexes with Pt^{II}.[3,22] Interestingly, hemideprotonation and stabilization of the guanine anion through three hydrogen bonds with a neutral guanine ligand[25] could again be the reason for the observed low pK_a values of the two bases, although the scenario of anion stabilization is radically different from that seen in the case of adenine bases. In principle, the argument of guaninate stabilization should hold up for *any* Pt^{II} complex containing guanine ligands. However, as an inspection of a model of deprotonated **16** reveals, there is the possibility of formation of a loop structure with intermolecular stacking of H-bonded guanines, which would make hemideprotonated **16** different from all *mononuclear* Pt complexes previously studied by us. Additional work is required to verify or disprove such a scenario.

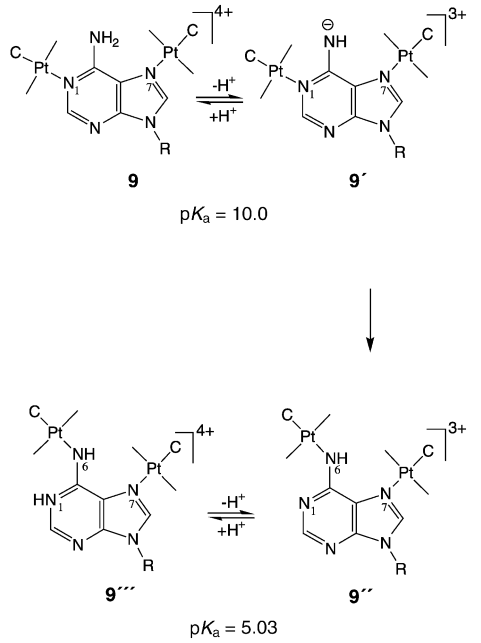
Extent of formation of H-bonded species: If one accepts the idea that intramolecular hydrogen bonding, either directly or indirectly (through an H_2O molecule, see below), is responsible for stabilization of the $N6H^-$ species and for the extra lowering of the pK_a value, it is possible to estimate the degree of formation of the H-bonded structure. According to such an analysis[26] an extra acidification of 2 log units, say from 11 to 9 (the effect of two metals only, modified by charge considerations), corresponds to a degree of formation of the H-bonded species of more than 99%, and a ΔpK_a value of 1.6 still requires a degree of formation of 97%.

Protonation of 14 and 15: The relative ease of deprotonating the exocyclic amino group of the two 9MeA nucleobases in **14** and **15** is contrasted by the superacidic conditions required to accomplish protonation of the 9MeA ligands. According to results obtained from UV spectroscopy, protonation of **14** and **15** occurs with pK_a values of -4.4 ± 0.3 and -4.3 ± 0.3, respectively (H_o scale). It is assumed that protonation takes place at the N3 position of 9MeA. These values are somewhat lower than that of threefold protonated adenine, which loses its first proton from N3.[2]

Pt^{II} migration following $N6H_2$ deprotonation: In the course of our ^{1}H NMR studies with platinated adenine nucleobases we noticed in many instances a complication in the spectra of samples kept at high pH conditions ($pH^* > 10$). We considered two scenarios, both of which are precedented in nucleobase chemistry, namely deamination of adenine and conversion into a hypoxanthine ligand, and/or migration of Pt^{II} from N1 or N7 to N6. The latter aspect has been studied in detail by Arpalahti and co-workers.[27–29] Only in one case were we successful in isolating a reaction product: By applying compound **9** and titrating it with NaOH to pH 11.1, we aimed to obtain crystals of the deprotonated form **9′**. The isolated crystals **9″** proved, however, to be a linkage isomer of **9′** (Scheme 4) in which the Pt entity, which originally resided at N1, had moved to N6. **9″** can be reprotonated to give **9‴**, which is formally the twofold-platinated rare imino tautomer of adenine.[13b,28,30,31]

The cation of *trans*-[{$(NH_3)_2$Pt(1MeC-*N*3)}$_2$(9MeA$^-$-*N*7,*N*6)]$(ClO_4)_3 \cdot 3.5\,H_2O$ (**9″**) is depicted in Figure 3. Selected distances and angles are provided in Table 2. As can be seen, the *trans*-[$(NH_3)_2$Pt(1MeC-*N*3)] residue has migrated from N1 to N6 and adopts a *syn* conformation with respect to N1 of the adenine nucleobase. While the cytosine ring opposite to N7 of the adenine ring is close to coplanar with adenine (dihedral angle of 12.3°) and involved in weak H-bond formation (O(2B)···N(6A) 3.13(1) Å; O(2B)···N(4L) 2.944(9) Å; numbering as given in Figure 3), the cytosine opposite to N6 is at a substantial angle (45.5°) with the adenine plane. The N1 position of adenine is deprotonated in **9″** (internal ring angle of 119.1(6)°, very similar to the value of 118.8(1)° in neutral 9MeA[32]) but is involved in weak H-bond formation (3.06(1) Å) with the NH_3 ligand of Pt2 (N(3L) in Figure 3).

Pairs of cations of **9″** are arranged in such a way as to permit stacking of the adenine ring with the cytosine ring B



Scheme 4. Linkage isomerization of **9′** to **9″** and relevant pK_a values of the protonated forms, **9′** and **9‴**. Note the large difference of 5 log units.

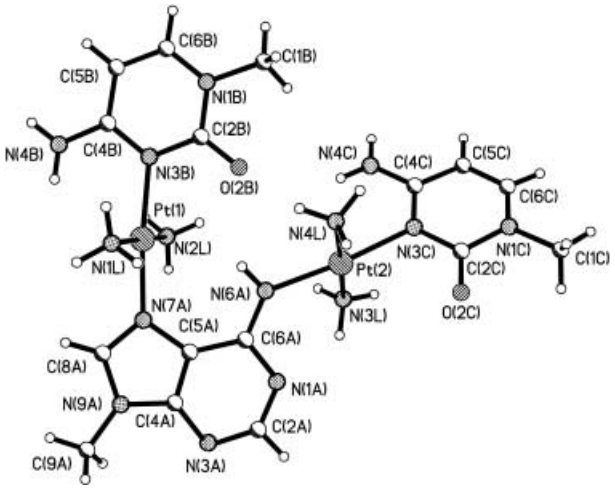


Figure 3. View of the cation of *trans*-[{$(NH_3)_2$Pt(1MeC-*N*3)}$_2$(9MeA$^-$-*N*7,*N*6)]$(ClO_4)_3$ (**9″**).

of an adjacent cation (3.5–3.7 Å). Additional contacts between cations of **9″** are mediated by numerous hydrogen-bonding interactions, which involve ClO_4^- anions, NH_3 groups, and water molecules. None of these contacts is unusually short. With a single exception, direct contacts between bases of adjacent cations are not seen. The exception is a short contact between the oxygen atom of the cytosine ring coordinated to the N6-bonded Pt and the H8 atom of an adjacent adenine (2.53 Å; symmetry operation $-x$, $-{}^1/_2+y$, $-{}^1/_2-z$).

The *syn* orientation of the N6-bonded Pt (Pt2) is also seen in [(dien)Pt(9MeA-*N*6)]$^{2+}$, in which the 9MeA ligand is neutral but carries a proton at N1.[28] From modeling studies, it appears that an *anti* orientation of Pt2 in **9″** is unfavorable because of the presence of the coligands of Pt1 at N7.

Table 2. Selected distances [Å] and angles [°] in **9″**.[a]

Pt(1)–N(3B)	2.018(7)	N(3B)-Pt(1)-N(7A)	174.6(3)
Pt(1)–N(7A)	1.988(6)		
Pt(1)–N(1L)	2.043(6)		
Pt(1)–N(2L)	2.034(7)		
Pt(2)–N(3C)	2.046(5)	N(3C)-Pt(2)-N(6A)	174.7(2)
Pt(2)–N(6A)	1.993(6)		
Pt(2)–N(3L)	2.025(6)		
Pt(2)–N(4L)	2.033(6)		
N(6A)–C(6A)	1.316(9)	C(2A)-N(1A)-C(6A)	119.1(6)
		C(2A)-N(3A)-C(4A)	109.2(7)
O(2B)···N(4L)	2.944(9)		
O(2B)···N(6A)	3.126(9)		
N(3L)···N(1A)	3.064(9)		

[a] Numbering as given in Figure 3.

Of course, in the absence of a metal at N7, *anti* orientations of N6-bonded metal ions are possible,[27,31] sometimes in equilibrium between both forms,[33] and an *anti* orientation is realized if dinuclear, metal–metal bonded units (Rh_2,[34] Mo_2[35]) are attached to N7 and N6 simultaneously.

The ^{1}H NMR spectrum of a freshly dissolved sample of **9″** in D_2O (pD 7.8, ambient temperature) indicates the presence of two different rotamer forms, but given the various possibilities (rotation about the Pt(1)–N(7A) bond, the Pt(2)–N(6A) bond, or the C(6A)–N(6A) bond; numbering as given in Figure 3), a straightforward interpretation is difficult. Aromatic adenine proton resonances are observed at $\delta = 8.36$, 8.14, and 8.07 ppm with relative intensities of approximately 0.2:1:0.2, and two methyl resonances of 9MeA$^-$ occur at $\delta = 3.86$ and 3.81 ppm (ca. 3:0.6). As to cytosine resonances, two H6 and two H5 doublets (ca. 1:1) are clearly discernable (H6: $\delta = 7.69$ and 7.65 ppm; H5: $\delta = 6.10$ and 6.09 ppm), as are two CH_3 singlets at $\delta = 3.51$ and 3.47 ppm (ca. 1:1). There are indications for two additional weak doublets at approximately $\delta = 7.63$ and 6.12 ppm, which are, however, superimposed with the other doublets. Partial isotopic exchange appears to be responsible for the weak intensities of two of the three aromatic protons of 9MeA$^-$. On the basis of a 2D NOESY spectrum we can assign the intense singlet at $\delta = 8.14$ ppm to the H2 proton of 9MeA$^-$ as it does not exhibit a cross-peak with the methyl group at N9. This finding tentatively suggests that there is hindered rotation about the Pt(1)–N(7A) bond.

pK_a Value of *N*7,*N*6-diplatinated 9MeA in 9‴: The acidity of the proton at N1 of **9‴** was determined by ^{1}H NMR spectroscopy (pD dependence of CH_3 of adenine and H2 of adenine) and found to be 5.0 ± 0.1 (calculated for H_2O). This value is lower by 2.6 log units than that of [(dien)Pt(9MeA-*N*6)]$^{2+}$, which is 7.65 ± 0.05,[28] and is a consequence of the second Pt^{II} at N7. The difference is reasonably close to the ΔpK_a values for *N*1-protonated residues carrying a Pt^{II} at N7 (2.17 ± 0.1).[13] This suggests that the acidifying effect of multiple metal ion binding is roughly additive.

Comparison with other metal ions reveals that the acidification brought about by Pt^{II} at N6 is moderate: For an

RHg^{II} complex the pK_a value for N1H has been found to be 4.5,[31] for an Ru^{II} chelate (*N*7,*N*6) the value was 6.5,[36] and for $[(NH_3)_5Ru^{III}]$ values of 2.5 and 4.9 have been estimated,[10a,c] depending on the rotamer state (metal *syn* or *anti* with respect to N1H).[37]

Quantum-mechanical calculations: Geometry-optimized structures for the cation *cis*-$[(NH_3)_2Pt\{(N1\text{-}9MeA\text{-}N7)Pt(NH_3)_3\}_2]^{6+}$ (**14**) and several feasible forms of its deprotonated species were calculated with the Gaussian 98 suite of programs.[38] The geometry of the cation **14** was optimized in two ways, by using the LanL2DZ basis set for all atoms and alternatively by applying the LanL2DZ basis set for Pt only and a 6-31G* basis set for nonmetal atoms. Both structures differ only slightly. They are, however, different from the solid-state structure of **14** (nitrate salt, dihydrate)[23] in that one of the two adenine bases is strongly tilted with respect to the central *cis*-$[(NH_3)_2Pt^{II}]$ plane (A(N1)–Pt(1)–A′(N1)–A′(C2) dihedral angle of 42.5° for the mixed basis set, 43.9° for LanL2DZ). In the crystal structure of **14** this adenine is almost perpendicular to the central Pt coordination plane (87.7°). As a consequence of this difference, which we attribute to the absence of anions in the calculations, the intracomplex separation between the exocyclic NH_2 groups of the two adenine bases is considerably larger in the calculated structure, namely 5.58 Å (mixed basis set), than in the solid state (3.34 Å). Other features (angles of $(NH_3)_3Pt^{II}$ to the adenine plane and of *cis*-$[(NH_3)_2Pt^{II}]$ to the other adenine) deviate less dramatically.

Several feasible structures of deprotonated species of **14** (single deprotonation of one of the 9MeA ligands; *head–head* arrangement of two bases) were optimized by using a LanL2DZ basis set for all atoms. In the first set of calculations a proton of the exocyclic $N6H_2$ group was removed *anti* (I) or *syn* (II) with respect to N1. In a third calculation (III) a starting structure was chosen in which the intracomplex separation between the amido and the amino group of the two adenine bases had been set to 4 Å and the proton had been removed from a *syn* position. Optimizations converged in all three cases toward geometries in which the $N6H^-$ group is stabilized by hydrogen bonding with an NH_3 group, either from the $(NH_3)_3Pt^{II}$ unit at N7 (proton removed from *anti* position; I) or from the *cis*-$[(NH_3)_2Pt^{II}]$ unit at N1 (proton removed from *syn* position; II, III). The latter two structures are about 50 kJ mol^{-1} more stable than the first one (see the Supporting Information). The H-bond lengths between N6 and the NH_3 groups are 2.75, 2.58, and 2.58 Å, respectively. In no instance was there a close approach of the $N6H^-$ and $N6H_2$ groups of the two adenines. This picture changed dramatically when a water molecule was inserted between the two N6 positions (calculation IV): Then, the two exocyclic amino groups were at a distance of 4.79 Å and indirectly interconnected through hydrogen bonds extending from the water molecule, with distances of 2.69 (N6′···OH_2) and 2.74 Å (N6···OH_2), respectively (Figure 4). An additional hydrogen bond of 2.80 Å is formed between the exocyclic N6 amide group and the *cis*-oriented NH_3 ligand (N_{am}).

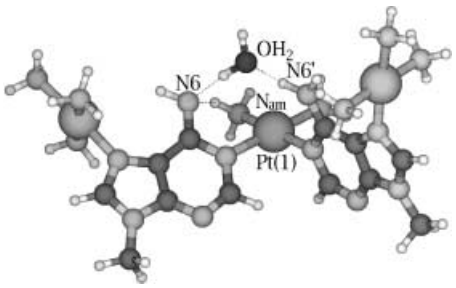


Figure 4. Geometry-optimized gas-phase structure of cation **14** with the H-bonding pattern involving $N6H^-$, N6′H_2, the water molecule, and one of the central NH_3 ligands (N_{am}).

Discussion

Protonation of neutral adenine bases occurs predominantly at the N1 position (preferred tautomer)[2] in moderately acidic solution, with a pK_a value of 3–4 for the adeninium cation, while deprotonation of the exocyclic amino group $N6H_2$ to give an amido species takes place in strongly alkaline solution only, with a pK_a value of approximately 16.7.[18] Thus, there is a range of 13–14 units between the two pK_a values (Figure 5a) with at least the second pK_a value far removed from physiological pH conditions.

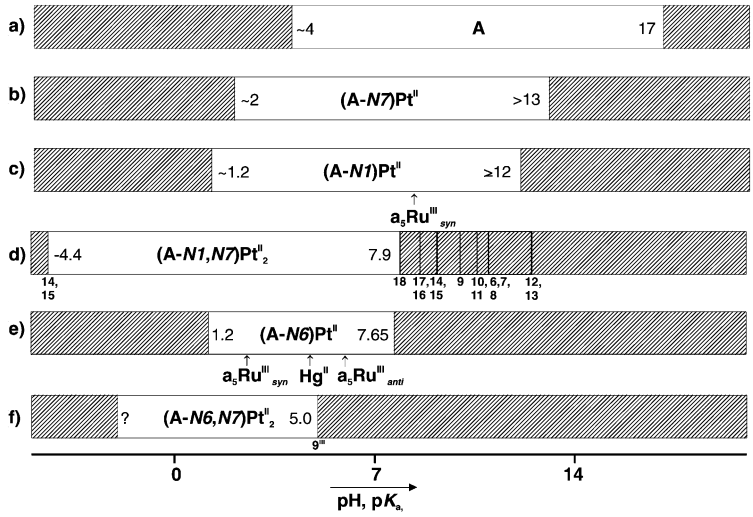


Figure 5. Approximate existence ranges of neutral 9MeA as a free nucleobase (a) or in its various platinated forms (b–f). For simplicity, the pK_a values are given as boundaries. Data for (A-*N*6)Pt^{II} (e) are taken from work of Arpalahti and Kilka.[28] For comparison, pK_a values of selected examples of other metal complexes ($(NH_3)_5Ru^{III}$,[11d,39] Hg^{II}[31]) are also given (c,e).

Metal coordination to any of the endocyclic ring nitrogen atoms, that is, to N1, N7, or N3, shifts *both* pK_a values to lower values, but how pronounced this effect is depends on the nature of the metal ion (charge, back-bonding properties, coligands) *and* the site of coordination. Although there is an influence of the charge of the metal entity for a given coordination pattern on the ΔpK_a values, for example, Pt^{II} at N7,[13,14] its effect is moderate. Thus, the acidifying effect on N1 is smaller in the case of the anionic $[PtCl_3]^-$ species (1.5 log units) than the dicationic $[Pt(NH_3)_3]^{2+}$ species (2.45 log units).[13b] In any case, pK_a values of metalated adeninium species move from 3–4 units to less positive values and thus become less relevant for processes occurring in a buffer medium kept at pH 7. This applies even more to adenine bases carrying metal ions at two endocyclic nitrogen atoms.

The second option for involvement of an adenine nucleobase in acid–base catalysis in physiological pH conditions is a shift of the pK_a value of the exocyclic amino group toward 7. With various Pt^{II}–am(m)ine complexes, the acidifying effect amounts to 3 log units (estimated) for metal binding to N7 and 5 log units for N1 coordination[11] (Figure 5b). However, for $[(NH_3)_5Ru^{III}]$ binding to N1, a dramatic acidification of the amino group by more than eight units has been reported, with the pK_a value then being 8.2.[39] Interestingly, despite the high positive charge of Pt in the Pt^{IV} complex $[(dien)Pt(OH)_2(9MeA\text{-}N1)]^{3+}$ the acidification of the $N6H_2$ group is rather moderate ($pK_{a2} \approx 13$–14),[40] probably because the dien ligand undergoes deprotonation with a rather low pK_a value of 8.3. The three anionic ligands (two OH^-, $dien^-$) obviously reduce the effective charge of the metal ion substantially. As is shown in this paper, twofold Pt^{II} binding (*N*1,*N*7) expectedly increases the acidity of the $N6H_2$ group by more than a single Pt^{II} at either of these positions. However, it is surprising to see the wide range that is spanned for deprotonation of the first adenine ligand (pK_a = 12.0 in **12** and **13**, yet 7.94 in **18**). We attribute this spread in pK_a values primarily to different degrees of stabilization of the resulting amido group at the adenine in the various complexes and specifically propose that stabilization of the amido group by a hydrogen bond from an H-bond donor is important. We have previously suggested that in (9MeA-*N*7)Pt(*N*7-9MeA$^-$-*N*1)PtX compounds direct $N6H^-\cdots H_26N$ hydrogen bonding between a neutral and an anionic adenine is of importance.[17] In a related system we could meanwhile verify such a possibility.[41] Alternatively hydrogen bonding mediated by a water molecule, $N6H^-\cdots H_2O\cdots H_26N$ (see calculations above) could take place. A proton of the water molecule is then donated to the $N6H^-$ group, while the oxygen atom of the H_2O molecule accepts a proton from $N6H_2$. A critical survey of the adenine $N6H_2$ pK_a values reported in this study suggests the following: 1) With 9-alkyl adenines, twofold Pt^{II} binding, to N7 and N1, is required to lower the $N6H_2$ pK_a value to 12.6 or below. 2) Cross-linking of two adenine N7 sites by a linear *trans*-$[a_2Pt^{II}]$ is particularly efficient in reducing the pK_a value to below 9 (**16**–**18**) and is superior to the effect of *cis*-$[a_2Pt^{II}]$ (**14**, **15**). 3) An adenine N7 ligand *trans* to N1 of the diplatinated adenine is less efficient in lowering the pK_a value than if it is *trans* to N7 (**11** versus **16**–**18**). 4) Cytosine coligands in μ-adenine complexes likewise lower the pK_a value of $N6H_2$ of adenine (**7**–**10**), although not to the extent seen with adenine coligands. 5) Nucleobase coligands without an exocyclic amino group (uracil, thymine) or without an exocyclic amino group suitably positioned (for example, $N2H_2$ in Pt(guanine-*N*7)) do not cause this effect (**12**, **13**). Taken together, these observations strongly support the notion that lowering of the pK_a value depends on the efficiency of interbase H-bond formation.

The theoretical calculations carried out with **14** suggest that an efficient stabilization of the amido group in platinated adenine may also be brought about by intramolecular hydrogen bonding with either of the ammine ligands of Pt^{II} at N1 or N7. This is, in a way, reminiscent of the additional stabilization of anionic adenine in adenine N6 complexes of $[(NH_3)_5Ru^{III}]$ if the metal entity adopts a *syn* orientation with respect to the deprotonated N1 position.[10c] Similarly, intramolecular hydrogen bonding between an NH_3 ligand and the N6H proton in $[(NH_3)_3Pt(A^*\text{-}N7)]^{2+}$ (where A^* = the rare imino tautomer of adenine) has been calculated to stabilize the rare tautomer in the gas phase.[42] We do not consider such a possibility to be of prime importance in the present case and in solution, simply because it does not explain the spread in pK_a values over 4 log units in the various complexes. Without exception, in all compounds studied such a possibility is feasible. If important, it should eventually lead to pK_a values within a rather narrow range, modulated by differences in charge only.

There is a third scenario of how adenine can shift one of its pK_a values into the near-physiological pH range: It involves metal binding to the exocyclic N6 position and concomitant shift of the proton originally at N6 to an endocyclic nitrogen position, preferably N1. This situation corresponds to formation of a metal-stabilized rare adenine tautomer and results in pK_a values very much different from those seen in metal complexes of the (normal) major tautomer. Reported pK_a values for a proton loss from the neutral adenine ligands, which formally correspond to pK_a values of complexes containing the major tautomer and hence give adenine $N6H_2$ deprotonation, are in the range 2.5–7.65 (see above and Figure 5d). Protonation of such species occurs in strongly acidic medium only, for example, with $pK_a = 1.2 \pm 0.1$ in the case of $[(dien)Pt(9MeA\text{-}N6)]^{2+}$,[28] and therefore is not expected to be relevant for any acid–base catalysis under physiological conditions.

Acidity constants for dimetal complexes of adenine with one binding site being N6 and the other one an endocyclic ring nitrogen atom are available only for the case of N*6*,N*7* (Pt^{II} compound **9‴**), where it is 5.03 (Figure 5d). Again, the pK_a value for protonation is expected to be low (< 0, estimated) and irrelevant for reactions occurring in the physiological pH range.

Conclusion

Nucleobases with unusual ("shifted") pK_a values, notably adenine and cytosine, have recently been implicated in acid–

base catalysis involving RNAs, with examples being cleavage reactions of the hepatitis delta virus ribozyme and protein synthesis in the ribosomes. It is presently not fully clear which factors eventually contribute to the observed shift in pK_a values of the nucleobases, but it has been proposed that the pK_a shift is a consequence of a stabilization of a protonated nucleobase, which leads to a rise of pK_a values from the normal values of 3–4 for AH^+ and CH^+ to approximately 7. As far as adenine ribonucleotides are concerned, protonation/deprotonation is discussed at either the N1 or N3 positions, and the transient existence of rare nucleobase tautomers during the catalytic cycle has been proposed.[8] Any (indirect) role of metal ions in these processes also remains largely unclear. A possible involvement of the protons of the exocyclic amino group of adenine, leading to a shift of the pK_a value of these protons, has not been discussed to the best of our knowledge. Similarly, the existence of "metal-stabilized rare tautomers" with pK_a values in the physiological pH range appears not to have been considered in possible scenarios of acid–base catalysis brought about by nucleobases.

Here we have demonstrated a principle, namely that twofold metal coordination to adenine (*N*1,*N*7), in combination with suitably positioned H-donor groups of coligands, can lead to dramatic shifts in the pK_a value of the exocyclic amino group. Even a single metal ion, binding to N6 and forcing one of the two amino groups from this site to N1 ("metal-stabilized rare tautomer"), is capable of achieving a pK_a value that is in the physiological pH range or even lower. A second coordinated metal ion reinforces this effect. In the present study the metal entities were Pt^{II}. We believe that the effects are qualitatively similar for many, if not all, metal ions that bind in an inner-sphere fashion to adenine. We are also aware that there are cases where a single metal ion (for example, $[(NH_3)_5Ru^{III}]$) brings about an acidification of A–NH_2 comparable to that of two Pt^{II} ions,[39] but this feature leads to rapid linkage isomerization and eventually to metal binding to N6. It should also be emphasized that the effect seen in our study occurs with small, simple systems and in water, with major influences of the medium, as expected to play a role in large biomolecules, absent. The main question at this stage is whether these scenarios apply also to the "natural" counterions of RNAs, which are essentially Mg^{2+}, K^+, and Na^+. There is presently no crystallographic evidence for the existence of inner-sphere complexes of Mg^{2+} with adenine nucleobases, even though quantum mechanical calculations strongly suggest their existence.[43] Consequently, there are also no solution data available on the acidifying effect of a coordinated Mg^{2+} on adenine protons. However, there are strong indications that Mg^{2+} can indeed exert such an effect.[44] Irrespective of this uncertainty, the generation of oligonucleotides (ribozymes or DNAzymes) capable of acid–base catalysis in the presence of nonphysiological metal ions based on this principle is feasible. The large variety of RNA tertiary structure elements certainly seems to be advantageous for this purpose. The recent development of a new sensor for Pb which is based on gold nanoparticles and a DNAzyme which is activated by lead is an example, even though the function of the metal ion in this case is different from what is discussed in our paper.[45]

Experimental Section

Instrumentation: ^{1}H NMR spectra were recorded with Bruker AC 200 or Bruker DRX 400 instruments in D_2O at ambient temperature (20 °C). Sample concentrations were typically 0.005 M. Chemical shifts are referenced to internal sodium 3-(trimethylsilyl)propanesulfonate (TSP). ^{195}Pt NMR spectra (Bruker AC 200) were referenced to external Na_2PtCl_6. Elemental analyses were performed with a Carlo Erba Model 1106 Strumentazione elemental analyzer.

Determination of acidity constants: The pK_a values were determined by using pH-dependent ^{1}H NMR spectroscopy, potentiometric pH titration, and UV spectroscopy. ^{1}H NMR spectroscopy: Changes in chemical shifts of nonexchangeable protons in the compounds depending on pD value were recorded. The pD value was obtained by adding 0.4 to the pH meter reading (uncorrected = pH*). It was adjusted by addition of NaOD or DNO_3 solutions. Frequently the N9–CH_3 resonance of the 9MeA ligands proved to be more suitable for pK_a determination than the aromatic protons H2 and H8 because it did not undergo isotopic exchange with time. It was determined that the pK_a values reported corresponded to species prior to subsequent alternations such as metal migration (see the text). The graphs (pD versus chemical shift) were evaluated with a nonlinear least-squares fit according to the Newton–Gauss method.[4,46] The acidity constants obtained this way (for D_2O) were subsequently transformed to values valid for H_2O.[47] Error limits given correspond to three times the standard deviation (3σ). Potentiometry: The pH titrations were carried out with a Metrohm E536 potentiograph equipped with a Metrohm 665 Dosimat and a 6.0222.100 combined macro glass electrode. The buffer solutions (pH 4.00, 7.00, and 9.00, based on the NIST scale; for details see ref. [48]) used for calibration were also from Metrohm, Herisau (Switzerland). The direct pH-meter readings were used to calculate the acidity constants; that is, these constants are so-called practical, mixed, or Brønsted constants.[48] Their negative logarithms given for aqueous solutions at $I = 0.1$ M ($NaNO_3$) and 25 °C may be converted into the corresponding concentration constants by substracting 0.02 from the listed pK_a values;[48] this conversion term contains both the junction potential of the glass electrode and the hydrogen-ion activity.[48,49]

The ionic product of water (K_w) and the above-mentioned conversion term do not enter into the calculations because we evaluate the *differences* in NaOH consumption between solutions with and without ligand[48,50] (see also below); this procedure also directly furnishes the concentration of the acid in the present case of complexes **14** and **15**.

The acidity constants of compounds **14** and **15** in the alkaline region were determined by titrating aqueous 0.04 mM HNO_3 (25 mL; $I = 0.1$ M, $NaNO_3$, 25 °C) in the presence and absence of 0.3 or 0.6 mM complex under N_2 with 0.02 or 0.04 M NaOH (2.4–3.7 mL), respectively. For both compounds, each sample was titrated twice, which means that after the first titration the solutions were reacidified to their original pH value (about 4) by addition of 0.03 M HNO_3 and then titrated again to obtain a second pair of curves. In this way, six and four titration pairs were obtained for compounds **14** and **15**, respectively.

The pH range used for the calculations corresponded to about 2–96 % deprotonation for pK_{a1} and about 24 % deprotonation for pK_{a2} (pH 7.4–10.5) of **13**; 2–96 % deprotonation for pK_{a1} with 52 % deprotonation for pK_{a2} was reached for **15** (pH 7.5–10.6). All constants were calculated with an IBM compatible desktop computer with an Intel Pentium-IV processor by a curve-fit procedure with a Newton–Gauss nonlinear least-squares program. The final results are the averages of all titrations carried out for each substance.

Spectrophotometry: In acidic medium, the acidity constants were determined by spectrophotometry. The UV spectra (observed wavelength range of 200–400 nm) were recorded with a two beam (sample and reference beam) UV/Vis Varian Cary 3C spectrophotometer by using 2-cm Suprasil cuvettes (Hellma, Germany), where only the differences in the absorbances between sample and reference cuvette were recorded. The samples were measured in aqueous solution for their dependence on the

pH value, which was adjusted with 12 M $HClO_4$; the studied pH range was from −5.7 to +4.

As long as the pH value was >0.5 it was determined with a Metrohm 713 digital pH meter by using a 6.0234.110 combined micro glass electrode. Lower pH values were obtained by calculating the H^+ activity of $HClO_4$ (H_0 scale) in the solutions in the way described recently.[2,51]

The ionic strength was adjusted to $I=0.1$ M ($NaClO_4$) when [$HClO_4$]< 0.1 M; no further adjustments were made with higher acid concentrations. For each pH value both the sample solution (complex, $HClO_4$, and $NaClO_4$ when appropriate) and the reference solution ($HClO_4$ and $NaClO_4$ when appropriate) were individually prepared.

All calculations were carried out by using the computer equipment mentioned above and by again applying a Newton–Gauss nonlinear least-squares curve-fit procedure.[46]

For both compounds one experimental series was carried out, which was evaluated at three different wavelengths, namely 245, 275, and 290 nm for **14** and 248, 276, and 290 nm for **15**. The final result for both compounds is the average of the values obtained from the three evaluated wavelengths.

Compounds: *cis*-$(NH_3)_2PtCl_2$,[52] [(dien)PtI]I,[53] 9EtA,[54] and 9MeA[55] were prepared as reported. All the Pt complexes studied, except those explicitly described below, were previously prepared: *cis*-[$(NH_3)_2$Pt(9MeA-*N*7)(1MeC-*N*3)]$(ClO_4)_2\cdot H_2O$ (**3**),[20] *trans*-[$(NH_3)_2$Pt(9MeAH-*N*7)$_2$]$(ClO_4)_4\cdot 2H_2O$ (**4**),[56] *cis*-[$(NH_3)_2$Pt(9MeA-*N*7)$_2$]$(NO_3)_2\cdot 1.5H_2O$ (**5**),[57] *cis*-[{$(NH_3)_2$Pt(1MeC-*N*3)$_2$}(9MeA-*N*1,*N*7)]$(ClO_4)_4$ (**8**),[20] *trans*-[{$(NH_3)_2$Pt(1MeC-*N*3)}$_2$(9MeA-*N*1,*N*7)]$(ClO_4)_4$ (**9**),[20] *trans*,*trans*-[$(NH_3)_2$Pt(1MeT-*N*3)(*N*7-9MeA-*N*1)Pt$(NH_2CH_3)_2$(9EtGH-*N*7)]$(ClO_4)_3\cdot 5.2H_2O$ (**12**),[22] *trans*,*trans*-[$(NH_3)_2$Pt(1MeU-*N*3)(*N*7–9MeA-*N*1)Pt$(NH_2CH_3)_2$(9EtGH-*N*7)]$^{3+}$ (**13**),[22] *cis*-[$(NH_3)_2$Pt{(*N*1-9MeA-*N*7)Pt$(NH_3)_3$}$_2$]$(NO_3)_6\cdot 2H_2O$ (**14**),[23] *trans*,*trans*,*trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N*1)$_2$]{$(CH_3NH_2)_2$Pt(1MeU-*N*3)}$_2$]$(ClO_4)_4\cdot 4H_2O$(**18**).[17]

***cis*-[$(NH_3)_2$Pt(1MeC-*N*3)(*N*7-9MeA-*N*1)Pt(dien)]$^{4+}$ (7) and *cis*-[$(NH_3)_2$Pt{*N*7-9MeA-*N*1)Pt(dien)}$_2$]$(NO_3)_6$ (15)**: Compounds **7** and **15** were prepared on an NMR spectroscopy scale in D_2O solution from **3** and **5**, respectively, by treating them with [(dien)Pt$(D_2O)]^{2+}$ (1:1 and 1:2, respectively, 3 d, 40 °C). At this stage in both cases formation of a single new species was evident, clearly separated from the starting compound, the resonances of which had disappeared. **7**: ^{1}H NMR (200 MHz, D_2O, pD = 4.8): δ = 8.76 (br s; H2 9MeA), 8.70 (s, H8 9MeA), 7.56 (d, ^3J = 7.2 Hz; H6 1MeC), 6.22 (d, ^3J = 7.2 Hz; H5 1MeC), 3.89 (s; CH_3 9MeA), 3.36 (s; CH_3 1MeC), 3.35, 3.29, 3.12, 3.09, 2.93, 2.90 ppm (m; dien); the assignment of H8 of 9MeA was confirmed by a 1D NOE experiment (cross-peak with CH_3 of 9MeA); the relative intensities of all resonances are as expected for the composition. **15**: ^{1}H NMR (200 MHz, D_2O, pD = 5.6): δ = 8.80 (br s; H2), 8.72 (s; H8 9MeA), 3.84 (s; CH_3 9MeA), 3.34, 3.31, 3.14, 3.11, 2.93, 2.90 ppm (m; dien); the assignment of H8 of 9MeA was again established by an NOE experiment; at pD > 8.2, the H2 resonance disappears because of isotopic exchange.

***trans*-[{$(NH_3)_2$Pt(1MeC-*N*3)}$_2$(9MeA$^-$-*N*6,*N*7)](ClO$_4$)$_3\cdot$3.5 H$_2$O (9″)**: Compound **9** (50 mg) was dissolved in water (2 mL, brief heating) and the pH value was raised from 4.4 to 11 by adding 1 M NaOD. The sample was lyophilized and subsequently dissolved in D_2O (1 mL), and then the solution was kept in a closed vial until crystals of **9″** appeared after several days. If the sample was kept for 6 h at 50 °C instead and subsequently allowed to crystallize at 4 °C, the isolated yield of **9″** was 8 mg. According to ^{1}H NMR spectroscopy, the linkage isomerization **9**→**9″** is virtually complete, however. ^{1}H NMR (200 MHz, D_2O, pD = 7.8): δ = 8.36, 8.14, 8.07 (3 × s; H2, H8 9MeA$^-$; see text), 7.69 (d, ^3J = 7.4 Hz; H6 1MeC), 7.65 (d, ^3J = 7.4 Hz; H6 1MeC), 6.10 (d; H5 1MeC), 6.09 (d; H5 1MeC), 3.85, 3.81 (2 × s, 5:1; CH_3 9MeA$^-$), 3.51 (s; CH_3 1MeC), 3.47 ppm (s; CH_3 1MeC).

***trans*,*trans*-[$(NH_2CH_3)_2$Pt(1MeC-*N*3)(*N*1-9MeA-*N*7)Pt$(NH_3)_2$(9MeGH-*N*7)](ClO$_4$)$_4\cdot$3H$_2$O (10)**: Compound **10** was prepared from *trans*,*trans*-[$(NH_2CH_3)_2$PtCl(*N*1-9MeA-*N*7)Pt$(NH_3)_2$(9MeGH-*N*7](ClO$_4$)$_3\cdot$2.5 H$_2$O[58] (200 mg in 25 mL H_2O) by removing the Cl^- ligand with 1 equiv of $AgNO_3$ (24 h, 40 °C, exclusion of daylight) and by treatment with 1 equiv of 1MeC (5 days, 40 °C, exclusion of daylight). After filtration of a small amount of unidentified black material the colorless filtrate was concentrated in a stream of nitrogen, $NaClO_4$(aq) was added in excess, and the solution was allowed to further evaporate. Eventually long needles of **10** were harvested. Elemental analysis calcd (%) for $C_{19}H_{43}N_{17}Pt_2O_{21}Cl_4$ (1377.57): C 16.6, H 3.2, N 17.3; found: C 16.4, H 3.2, N 17.2; ^{1}H NMR (200 MHz, D_2O, pD = 5.8): δ = 9.28, 9.24 (2 × s; H2 9MeA, rotamers 0.8:1), 8.98, 8.96 (2 × s; H8 9MeA, rotamers 1:0.8), 8.37 (s; H8 9MeGH), 7.75, 7.74 (2 × d, ^3J = 7.4 Hz; rotamers 1:0.8), 6.15, 6.14 (2 × d; rotamers 1:0.8), 4.03 (s; CH_3 9MeA), 3.80 (s; CH_3 9MeGH), 3.54, 3.52 (2 × s; CH_3 1MeC, rotamers 1:0.8), 2.24, 2.23 ppm (2 × s; CH_3NH_2); assignment made by means of ROESY; relative intensities were as expected; ^{195}Pt NMR (42.95 MHz, D_2O, pD = 5.8): δ = −2466, −2636, −2644 ppm (ca. 1:0.5:0.5).

***trans*,*trans*-[$(NH_2CH_3)_2$Pt(9EtA-*N*7)(*N*1-9MeA-*N*7)Pt$(NH_3)_2$(9MeGH-*N*7)](ClO$_4$)$_4\cdot$2.5 H$_2$O (11)**: Compound **11** was obtained in analogy to **10**, with EtA substituting for 1MeC and with the pH value adjusted to 1.5 (HNO_3) to direct platination of N7. After addition of excess $NaClO_4$, the protonated form of **11**, *trans*,*trans*-[$(NH_2CH_3)_2$Pt(9EtAH-*N*7)(*N*1-9MeA-*N*7)Pt$(NH_3)_2$(9MeGH-*N*7)](ClO$_4$)$_5$ (**11′**) was obtained as a colorless solid in 46% yield. Elemental analysis calcd (%) for $C_{21}H_{40}N_{19}Pt_2O_{21}Cl_5$ (1462.0): C 17.3, H 2.8, N 18.2; found: C 17.3, H 3.0, N 18.3. Recrystallization of **11′** from D_2O (pD 4.8) gave colorless crystals of **11**, which were characterized by X-ray crystal analysis. ^{1}H NMR (200 MHz, D_2O, pD = 4.0): δ = 9.21 (s; H2 9MeA), 9.13 (s; H8 9EtA), 8.97 (s, H8 9MeA), 8.46 (s; H2 9EtA), 8.37 (s; H8 9MeGH), 4.49 (q, ^3J = 8 Hz; CH_2 9EtA), 4.04 (s; CH_3 9MeA), 3.80 (s; CH_3 9MeGH), 2.17 (s, CH_3NH_2), 1.61 ppm (t; CH_3 9EtA); assignment based on ^{1}H–^{1}H NOESY; relative intensities as expected; ^{195}Pt NMR (42.95 MHz, D_2O, pD = 4.0): δ = −2470, −2610 ppm (ca. 1:1).

***trans*,*trans*,*trans*-[$(NH_3)_2$Pt(*N*7-9MeA-*N*1)$_2$]{$(NH_3)_2$Pt(9EtGH-*N*7}$_2$](ClO$_4$)$_6\cdot$6 H$_2$O (16a) and *trans*,*trans*,*trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N*1)$_2$]{$(CH_3NH_2)_2$Pt(9MeGH-*N*7}$_2$](ClO$_4$)$_6$ (16b)**: Compounds **16a** and **16b** were obtained by removal of the Cl ligand of *trans*,*trans*,*trans*-[{Cla_2Pt}(*N*1-9RA-*N*7)$_2$Pt$(NH_3)_2$](ClO$_4$)$_4$ (where a = NH_3 and R = Me for **16a**; a = CH_3NH_2 and R = Et for **16b**)[56] by treatment with $AgNO_3$ in aqueous solution, filtration of AgCl, and reaction with 2 equiv of the corresponding 9-alkylguanine. After seven days at 35 °C and subsequent addition of excess $NaClO_4$ **16a** and **16b** were isolated in 40% and 48% yield, respectively, as white powders. **16a**: Elemental analysis calcd (%) for $C_{26}H_{62}N_{26}Pt_3O_{32}Cl_6$ (2048.8): C 15.2, H 3.1, N 17.8; found: C 15.1, H 2.8, N 17.5; ^{1}H NMR (200 MHz, D_2O, pD = 4.7): δ = 9.23 (s; H8 9MeA), 9.01 (s; H2 9MeA), 8.44 (s; H8 9EtGH), 4.24 (q, ^3J = 8 Hz; CH_2 9EtGH), 4.09 (s; CH_3 9MeA), 1.51 ppm (t; CH_3 9EtGH). **16b**: Elemental analysis calcd (%) for $C_{30}H_{58}N_{26}Pt_3O_{26}Cl_6$ (1996.9): C 18.1, H 2.9, N 18.2; found: C 18.1, H 3.2, N 18.3; ^{1}H NMR (200 MHz, D_2O, pD = 5.1): δ = 9.35 (s; H8 9EtA), 9.07 (s; H2 9EtA), 8.49 (s; H8 9MeGH), 4.55 (q, ^3J = 8 Hz; CH_2 9EtA), 3.84 (s; CH_3 9MeGH), 1.65 ppm (t, CH_3 9EtA).

***trans*,*trans*,*trans*-[$(NH_3)_2$Pt(*N*7-9EtA-*N1*)$_2$]{$(NH_3)_2$Pt(1MeT-*N*3)}$_2$](ClO$_4$)$_4\cdot$(8H$_2$O (17)**: Compound **17** was prepared in analogy to **18**[17] and isolated in 18 % yield. **17**: Elemental analysis calcd (%) for $C_{26}H_{66}N_{20}Pt_3O_{28}Cl_4$ (1833.9): C 17.0, H 3.6, N 15.3; found: C 16.9, H 3.3, N 15.3; ^{1}H NMR (200 MHz, D_2O, pD = 4.0): δ = 9.28 (s; H8 9EtA), 9.19, 9.17 (2 × s; H2 9EtA, rotamers 1:1), 7.38 (s; H5 1MeT), 4.50 (q; ^3J = 8 Hz; CH_2 9EtA), 3.40 (s; N-CH_3 1-MeT), 1.90 (s; C-CH_3 1-MeT), 1.61 ppm (t, CH_3 9EtA).

Crystal structure analysis: Diffraction data of **9″** were collected at 150 K on a Bruker–Nonius KappaCCD[59] apparatus ($Mo_{K\alpha}$, λ = 0.71069 C, graphite monochromator) with a sample-to-detector distance of 34 mm and a ω-scan data collection mode with a HKL 2000-Suite program package.[59] The exposure time was 200 s per frame. Preliminary orientation matrices and unit cell parameters were obtained from the peaks of the first ten frames and refined by using the whole data set. Frames were integrated and corrected for Lorentz and polarization effects by using DENZO-SMN.[60] The scaling as well as the global refinement of crystal parameters were performed with SCALEPACK.[60] Reflections, which were partly measured on previous and following frames, are used to scale these frames on each other. Merging of redundant reflections in part eliminates absorption effects and also considers crystal decay if present. The SHELXTL 5.1 package[61] was used to solve and refine the structure by direct methods. All non-hydrogen atoms were treated anisotropically, and hydrogen atoms were placed in calculated positions and refined with isotropic displacement parameters according to the riding model.

Crystal data: $C_{16}H_{39}Cl_3N_{15}O_{17.5}Pt_2$, M_r = 1211.04, monoclinic, space group $P2_1/c$, a = 11.845(2), b = 15.317(3), c = 21.292(4) Å, β = 94.43(3)°, V = 3851.5(12) Å^3, T = 150 K, Z = 2. Refinement of 512 parameters converged

at final $R_1 = 0.0476$ and $\omega R_2 = 0.1097$ for 6064 reflections with $J = 2\sigma(j)$, min. and max. features in difference Fourier ma: 2.49 and -2.14 e Å^3.

CCDC-216093 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

Theoretical calculations: Geometry-optimized structures for the cation of *cis*-[$(NH_3)_2$Pt{(*N*1-9MeA-*N*7)Pt$(NH_3)_3$}$_2$]$(NO_3)_6 \cdot 2H_2O$ (**14**) and several feasible forms of its deprotonated species were calculated by using the Gaussian 98 suite of programs.[38] Each optimization was followed by a frequency calculation in order to confirm every geometry to be a minimum structure. The DFT calculations were performed by using Becke's three parameter hybrid exchange functional (B3LYP) and a LanL2DZ basis set. For the nondeprotonated species **14**, these calculations were also performed with a LanL2DZ basis set for only Pt and a 6–31G* base set for the nonmetal atoms.

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