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Varying Acidity of Aqua Ligands in Dependence on the Microenvironment in Mononucleobase (nb) Complexes of Type *cis*- and *trans*-$[Pt(NH_3)_2(nb)(H_2O)]^{n+}$

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Aqua ligands in mixed aqua/nucleobase metal complexes are potential sites of acid–base catalysis and/or, when present as hydroxo ligands, can directly be involved in hydrolysis reactions. pK_a values of close to 7 are consequently of particular interest and potential significance. Here we report on the differential acidity of aqua complexes in model nucleobase (nb) complexes of *cis*- and *trans*-$[Pt(NH_3)_2(nb)(H_2O)]^{n+}$ and discuss reasons as to why the nb in cis complexes influences the pK_a (pK_a 4.8–7.0), whereas in trans complexes the pK_a values are rather constant (pK_a $\sim$ 5.2–5.3). The results of DFT calculations of a series of mono(nucleobase) complexes derived from *cis*-$Pt(NH_3)_2$ are critically examined with regard to the role of exocyclic groups of nucleobases in stabilizing aqua/hydroxo ligands through intracomplex hydrogen bond formation. This applies in particular to the exocyclic amino groups of nucleobases, for which gas-phase calculations suggest that they may act as H bond acceptors in certain cases, yet in the condensed phase this appears not to be the case.

Introduction

Among the many functions metal ions (M) exercise in living systems, acid−base chemistry involving aqua ligands, hence release of protons from $M-OH_2$ or acceptance of protons by the conjugate base M−OH as well as nucleophilic attack of the M-bonded hydroxo ligand on a substrate, are the most simple ones. The efficiency of such processes is particularly high, when the pK_a of the bound aqua ligand approaches 7, hence the physiological pH. For metalloproteins[1] and likewise for their models[2,3] numerous examples are known. This is not so in metal−nucleic acid chemistry: although metal-catalyzed hydrolysis reactions of phosphodiester bonds follow similar rules,[4,5] mechanistic details have been less intensively studied. It is worthwhile mentioning that it was the Pb−OH-catalyzed cleavage of the backbone of $tRNA^{phe}$, incidentally observed during the X-ray crystal structure determination of crystals soaked in Pb^{2+} salt solutions, which provided evidence for RNA backbone hydrolysis by a metal−hydroxo species.[6] The discovery of catalytically active RNA (ribozymes) in the 1980s[7] and later of catalytically active DNA molecules (DNAzymes)[8] has spurred renewed interest in this topic, even though the role of metal ions is not necessarily restricted to a function in the active site.[9]

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Table 1. pK_a Values of Aqua Ligands in Selected Am(m)ine Complexes of Pt^{II} [a]

compd[b]	pK_{a1}	pK_{a2}	method	ref
trans-[PtCl(H$_2$O)(NH$_3$)$_2$]$^+$	5.63		^{15}N NMR	12
	5.94(2)		potentiometry	13
cis-[PtCl(H$_2$O)(NH$_3$)$_2$]$^+$	6.6		"consensus"[a]	14
[Pt(H$_2$O)(trpy)]$^{2+}$	4.42 ± 0.05		kinetic	15
	4.62 ± 0.04		potentiometry	15
[Pt(H$_2$O)(dien)]$^{2+}$	6.3 ± 0.05		kinetic	15
	6.26 ± 0.10		potentiometry	15
[Pt(H$_2$O)(NH$_3$)$_3$]$^{2+}$	6.37(10)		^{15}N NMR	16
trans-[Pt(H$_2$O)$_2$(NH$_3$)$_2$]$^{2+}$	4.4	7.3	"consensus"[a]	14
cis-[Pt(H$_2$O)$_2$(NH$_3$)$_2$]$^{2+}$	5.5	7.3	"consensus"[a]	14
[Pt(H$_2$O)$_2$(2,2-bpy)]$^{2+}$	4.80	6.32	UV, vis	17
cis-[Pt(H$_2$O)$_2$(NH$_3$)(2-pic)]$^{2+}$	3.90	4.78	^{1}H and ^{15}N NMR	18

[a] Given the many different methods (e.g., potentiometry, UV−vis spectroscopy, NMR spectroscopy, kinetic methods) and, in part, different conditions applied, so-called "consensus" values are provided in several cases (cf. ref 14). [b] Abbreviations used: trpy = 2,2′:6′,2″-terpyridine; dien = diethylenetriamine; 2,2′-bpy = 2,2′-bipyridine; 2-pic = 2-(2-hydroxyethyl)pyridine.

While the acidifying effects of metal ion binding on ligand acidity in general[10] and on nucleobase ligands in particular[11] have been investigated in detail, little attention has been paid to the question of aqua group acidities in mixed nucleobase, aqua complexes. It occurred to us that this question is definitely relevant to both biological aspects (e.g., "why can metal ions displace weakly acidic NH protons at physiological pH?" or "is the metal-ion specificity of certain DNAzymes related to the pK_a of its metal aqua entity?") and to numerous questions arising from model chemistry (e.g., "how are multinuclear complexes containing bridging anionic nucleobases formed?"). Here we report on aqua ligand acidities in a series of model nucleobase complexes of composition *cis-* or *trans*-[Pt(NH$_3$)$_2$(H$_2$O)(nb)]$^{n+}$ with nb being the model nucleobases 1-methylcytosine (1-MeC), 9-methyladenine (9-MeA), 9-methylguanine (9-MeGH), and 1-methyluracilate (1-MeU) as well as the related heterocyclic ligand 2-aminopyridine (2-ampy).

Results and Discussion

Basic Principles of Aqua Ligand Acidity. Factors influencing the acidity of ligands in the coordination sphere of a metal ion in general and that of an aqua ligand in particular are numerous: charge of the metal, its coordination number, spectator ligands (trans-influence, σ-donor and π-acceptor properties), steric hindrance and its effect on metal−ligand bond length, solvent, etc. Thus, a high effective positive charge of the metal ion and/or low coordination number causes a particularly high acidification of a ligand. The large variety of oxo and hydroxo complexes of many transition (e.g., Fe^{III}) and main group elements (e.g., Al^{III}) is a direct consequence of this propensity. In square-planar complexes of Pt^{II}, to which the following discussion shall be limited, both the coordination number and the oxidation state of the metal remain constant. Electronic effects of coligands, in particular when positioned trans to the aqua ligand ("trans-influence") and π-bonding properties of these are of importance, but in addition the microenvironment (via stabilization of either the OH$_2$ or the OH$^-$ ligand through specific hydrogen bonding interactions with a coligand, possibly mediated by one or more solvent molecules) can have a profound influence. Examples (Table 1):[12−18] (1) The acidities of aqua ligands in simple complexes of *cis-* and *trans*-Pt^{II}(NH$_3$)$_2$ can be qualitatively rationalized based on the concept of the trans-influence. Thus, the trans isomers of [PtCl(NH$_3$)$_2$(H$_2$O)]$^+$ and of [Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ are always more acidic than the corresponding cis isomers because of the trans-influence order O < Cl < N. Differences in aqua ligand acidities in such compounds are in the order of a factor of 10 (1 log unit). (2) A π-acceptor ligand acidifies the aqua ligand by increasing the effective positive charge at the metal and by stabilizing the electron-richer hydroxo species. Consequently, [Pt(trpy)(H$_2$O)]$^{2+}$ is substantially more acidic, by almost 2 log units, than the corresponding [Pt(dien)(H$_2$O)]$^{2+}$ complex (trpy = 2,2′:6′,2″-terpyridine and dien = diethylenetriamine) and the pK_{a1} of [Pt(2,2′-bpy)(H$_2$O)$_2$]$^{2+}$ (with 2,2′-bpy = 2,2′-bipyridine) is lower by 0.7 log units as compared to that of *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$. However, simple monodentate pyridine (py) ligands have relatively little influence on aqua ligand acidity when compared to NH$_3$[17] as a consequence of a different, namely, an essentially perpendicular, orientation of the py plane with respect to the Pt coordination plane. (3) The surprisingly low pK_{a1} and

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Table 2. pK_a Values of Aqua Ligands in Mono(nucleobase) Complexes

compd	pK_a (H_2O ligand)	other pK_a values
cis-$[Pt(NH_3)_2(H_2O)(9\text{-MeA-}N7)]^{2+}$	4.8 ± 0.1	1.23 ± 0.04[a]
cis-$[Pt(NH_3)_2(H_2O)(1\text{-MeC-}N3)]^{2+}$	5.78 ± 0.03	>13[b]
	5.9 ± 0.05[c]	
cis-$[Pt(NH_3)_2(H_2O)(9\text{-MeGH-}N7)]^{2+}$	6.2 ± 0.1	8.7 ± 0.1[d]
cis-$[Pt(NH_3)_2(H_2O)(1\text{-MeU-}N3)]^{+}$	7.0 ± 0.1[e]	0.9[f]
trans-$[Pt(NH_3)_2(H_2O)(1\text{-MeC-}N3)]^{2+}$	5.17 ± 0.1	>13[b]
trans-$[Pt(NH_3)_2(H_2O)(9\text{-MeGH-}N7)]^{2+}$	5.27 ± 0.05	8.87 ± 0.06[d]
trans-$[Pt(NH_3)_2(H_2O)(2\text{-ampy-}N1)]^{2+}$	5.34 ± 0.01	

[a] Deprotonation of N(1) of the adeninium ligand. [b] Deprotonation at exocyclic N(4)H_2 of cytosine. [c] Taken from ref H. [d] Deprotonation at N(1)H of guanine. [e] Taken from ref 24. [f] Deprotonation of O(4) of the rare uracil tautomer; cf. ref 23.

pK_{a2} values of *cis*-$[Pt(NH^3)(H_2O)_2\{2\text{-(2-hydroxyethyl)pyridine}\}]^{2+}$ [17] have been attributed to a stabilization of the hydroxo species by favorable hydrogen bonding between the OH^- ligand and the 2-hydroxyethyl substituent, as mediated by a solvent (H_2O) molecule.

The effects of the microenvironment on ligand acidity have received wide attention in recent years, in particular with regard to biological phenomena of metal ion catalysis.[19−21] Similarly, the acidity of metal-carrying nucleobases can in certain cases be rationalized on the basis of intramolecular ligand−ligand interactions leading to a stabilization of the deprotonated nucleobase.[11c−e]

pK_a Values of Mixed Nucleobase, Aqua Complexes of Pt^{II}. pK_a values of the complexes studied here are listed in Table 2. In the large majority of cases pK_a values were determined by ^{1}H

NMR spectroscopy. Details of the method are reported elsewhere.[22] The advantage of applying ^{1}H NMR spectroscopy is that the presence of either impurities or condensation products essentially does not influence the chemical shift of the aqua species of interest. On the other hand, if potentiometry or UV−vis spectroscopy are applied, only the equivalents of added acid or base are monitored and analyzed which, of course, can be markedly influenced by other species present or formed in solution. As pointed out by Martin,[14] a likely explanation of different pK_a values of Pt aqua complexes as reported in the literature is due to impurities and/or the formation of condensation products.

For both adenine and guanine containing complexes, in addition to the acid−base equilibrium involving the aqua group, protonation/deprotonation reactions of these nucleobases take place. Thus, the 9-methyladeninium (9-$MeAH^+$) undergoes deprotonation with a p$K_a = 1.23 \pm 0.04$ in *cis*-$[Pt(NH_3)_2(H_2O)(9\text{-MeAH-}N7)]^{3+}$ and the 9-methylguanine deprotonates with p$K_a = 8.7 \pm 0.1$ in *cis*-$[Pt(NH_3)_2(OH)(9\text{-MeGH-}N7)]^+$ and 8.87 ± 0.06 in *trans*-$[Pt(NH_3)_2(OH)(9\text{-MeGH-}N7)]^+$. Both values are in the usual range.[22] Deprotonation of the methylcytosine ligands (exocyclic NH_2 groups) takes place at pH > 13 only, and protonation of the 1-methyluracilate ligand in *cis*-$[Pt(NH_3)_2(H_2O)(1\text{-MeU-}N3)]^+$ to give the platinated rare 2-oxo-4-hydroxo tautomer (1-MeUH*) occurs below pH 1.[23]

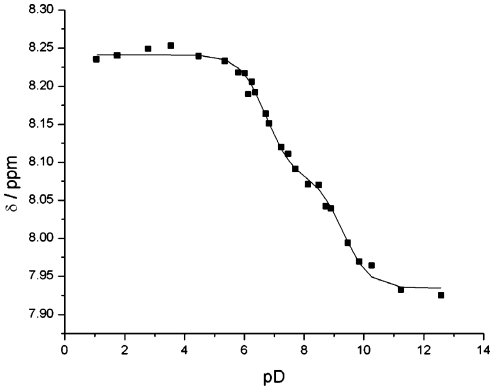

Figure 1. pD dependence of H8 resonance of 9-methylguanine ligand in *cis*-$[Pt(NH_3)_2(9\text{-MeGH-}N7)(H_2O)]^{2+}$. Two deprotonation steps (of aqua ligand, pK_a 6.2 ± 0.1; of 9-MeGH, p$K_a = 8.7 \pm 0.1$) are observed.

The pK_a values of the aqua ligands in the model nucleobase (nb) complexes *cis*-$[Pt(NH_3)_2(nb)(H_2O)]^{n+}$ decrease in the order nb = 1-MeU^--*N3* > 9-MeGH-*N7* > 1-MeC-*N3* > 9-MeA-*N7*. The relatively high pK_a of 7 for *cis*-$[Pt(NH_3)_2)(1\text{-MeU-}N3)(H_2O)]^+$, hence its low aqua group acidity, appears to be mainly affected by the lower charge (+1) of this complex as compared to the three others of charge +2.[24] Comparison with the +1 charged species *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ (p$K_a = 6.6$)[14] suggests that the better donor properties of the negatively charged 1-MeU ligand over Cl^- plays a role to account for this difference. As to a possible contribution of the microenvironment, this will be discussed later.

Of the three +2 charged complexes with 9-MeA, 1-MeC, and 9-MeGH, the two latter display a lower aqua acidity as compared to *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (p$K_{a1} = 5.5$), namely 5.8 for nb = 1-MeC-*N3* and 6.2 for nb = 9-MeGH-*N7*. In Figure 1, as a representative example, the pD dependence of the H8 resonance of the guanine nucleobase in *cis*-$[Pt(NH_3)_2(9\text{-MeGH-}N7)(H_2O)]^{2+}$ is given. Interestingly, the 9-MeA-*N7* compound is more acidic (p$K_a = 4.8$) than the diaqua species (pK_{a1}). Since the sequence of aqua ligand acidities in these three nucleobase complexes does not correlate with the intrinsic basicity of the nucleobase donor sites (pK_a of 9-$MeGH_2^+$ protonated at N7, 3.27 ± 0.03; pK_a of 9-$MeAH^+$ protonated at N7, 4.10 ± 0.01;[22] pK_a of 1-$MeCH^+$ protonated at N3, 4.78 ± 0.03), alternative explanations are required. As will be outlined below, we propose that differences in the stabilization of aqua/hydroxo ligands by the microenvironment could be responsible.

The replacement of an aqua ligand in *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ by a nucleobase (1-MeC-*N3*, 9-MeGH-*N7*) or a

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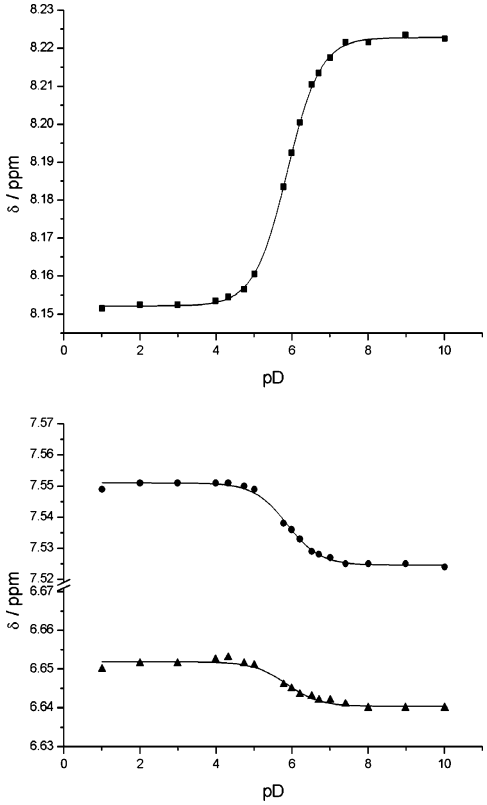

Figure 2. pD dependence of resonances of 2-aminopyridine ligand in *trans*-$[Pt(NH_3)_2$(2-ampy-*N1*)$(H_2O)]^{2+}$ giving a $pK_a = 5.34 \pm 0.01$. Surprisingly, the H6 resonance (■) undergoes a downfield shift with increasing pD. H3 (▲) and H4 (●) resonances are shifted into opposite directions.

structurally related heterocycle (2-aminopyridine, 2-ampy) (Figure 2) causes a decrease in aqua group acidity from 4.4 (pK_{a1} of diaqua species) by approximately 1 unit for the neutral ligands (1-MeC, 5.2; 9-MeGH, 5.3; 2-ampy, 5.3). Unfortunately no corresponding 9-MeA-*N7* complex could be studied because of rapid condensation reactions of *trans*-$[Pt(NH_3)_2$(9-MeA-*N7*)$(H_2O)]^{2+}$, which led to a large number of different species and problems of proper identification of the remaining mononuclear compound. Despite the limited number of compounds studied, it appears that the variations in pK_a values of the *trans*-$[Pt(NH_3)_2$(ligand)$(H_2O)]^{2+}$ complexes are considerably smaller than those of the corresponding cis isomers. A possible reason for this finding is that no immediate interactions between functional groups of the nucleobases and the two NH_3 ligands at the Pt with the aqua/hydroxo ligands are possible in the trans compounds; hence, no differential stabilization of aqua or hydroxo ligands can be expected.

DFT Calculations of Nucleobase Complexes of *cis*-Pt-$(NH_3)_2$. Geometry-optimized energy minimum gas-phase structures were calculated for pairs of mixed nucleobase/aqua as well as mixed nucleobase/hydroxo complexes of *cis*-$Pt(NH_3)_2$. Only the most stable forms (rotamer I for each species) are depicted in Figure 3. Structural details of a additional rotamers of the aqua complexes with different intramolecular hydrogen bonding interactions are given in the Supporting Information. The aim of this study was to get a more detailed understanding of intracomplex interactions involving aqua and hydroxo ligands of *cis*-$[Pt(NH_3)_2$-

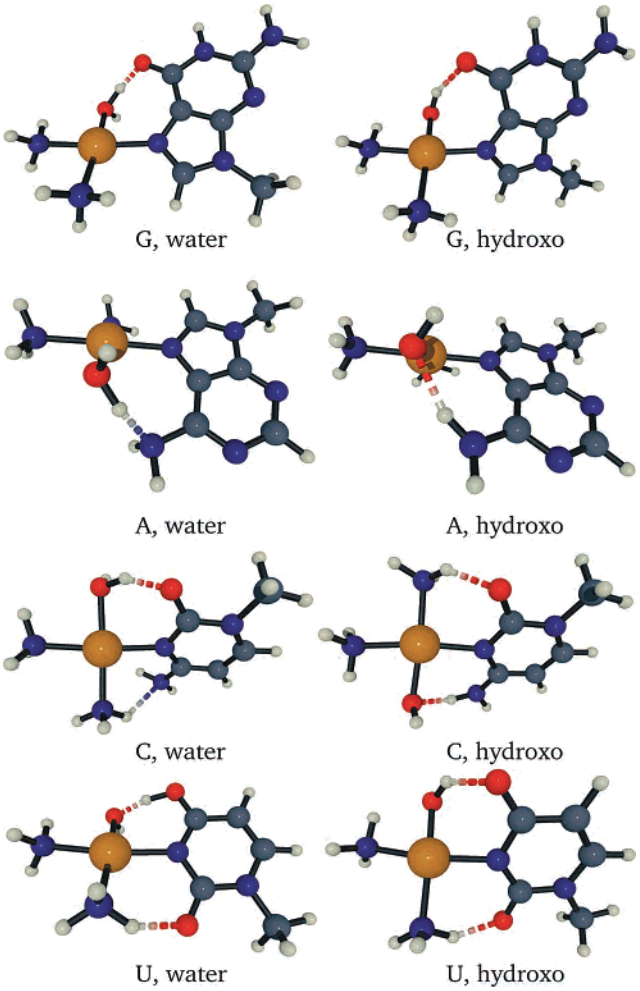

Figure 3. Calculated lowest energy structures of *cis*-$[Pt(NH_3)_2$(nb)$(H_2O)]^{n+}$ (left) and of *cis*-$[Pt(NH_3)_2$(nb)$(OH)]^{(n-1)+}$ (right) for nb = 9-MeGH, 9-MeA, 1-MeC, and 1-MeU^- (top to bottom).

(nb)(OH_2)/$(OH)]^{n+}$ and coligands in general and with functional groups of the nucleobase ligands in particular. We are aware that hydration of the various cations will have an influence on their structure. However, we believe that the conclusions concerning the varying acidities of Pt−aqua groups can nevertheless been rationalized on the basis of the intracomplex interactions derived from the calculated gas-phase structures.

In the most stable structure of *cis*-$[Pt(NH_3)_2$(9-MeGH-*N7*)-$(H_2O)]^{2+}$ (rotamer I), there is a short intramolecular hydrogen bond between the aqua ligand and O(6) of the nucleobase ($O_{aq}\cdots$O(6), 2.455 Å) which is almost linear $O_{aq}-H\cdots$O(6), 170.5°). The dihedral angle between the plane of the guanine nucleobase and the Pt coordination plane is 40.7°. Pt−N and Pt−O bonds are in the expected range, 2.06−2.10 Å. In the second most stable rotamer (rotamer II), which is higher in energy by 23.69 kJ/mol (ΔG_{298}), the NH_3 ligand trans to the aqua ligand is involved in intramolecular hydrogen bonding with O(6) ($N_{am}\cdots$O(6), 2.711 Å; $N_{am}-H_{am}\cdots$O(6), 161.6°). The dihedral angle 9-MeGH/Pt-plane amounts to 50.5°. In the hydroxo complex *cis*-$[Pt(NH_3)_2$(9-MeGH-*N7*)$(OH)]^+$ again intramolecular hydrogen bonding between the OH group and O(6) of guanine is realized, but the H bond becomes much longer (O−H···O(6), 3.081 Å; O−H···O(6),

144.6°), and the dihedral angle between 9-MeGH and the Pt plane is 58.9°. A major difference as far as Pt−ligand bond lengths are concerned refers to the Pt−OH_2/OH bond lengths, which shortens in the sequence 2.155 Å (rotamer II) > 2.068 Å (rotamer I) > 1.989 Å (OH complex). The last value reflects the increase in Coulomb attraction between Pt^{2+} and OH^-.

In *cis*-$[Pt(NH_3)_2(1\text{-MeC-}N3)(H_2O)]^{2+}$ the most stable form (rotamer I) displays intramolecular hydrogens bonds between the aqua ligand and O(2) of the nucleobase ($O_{aq}\cdots O(2)$, 2.528 Å; $O_{aq}-H\cdots O(2)$, 152.3°) as well as between the NH_3 ligand trans to H_2O and $N(4)H_2$ of the cytosine base, with the latter acting as the acceptor ($N_{am}\cdots N(4)$, 3.072 Å; $N_{am}-H_{am}\cdots N(4)$, 129.0°). The dihedral angle between the nucleobase and the Pt coordination plane is 49.2°. In the second most stable rotamer (rotamer II) the hydrogen-bonding groups are reversed, hence O(2) of the 1-MeC forms a hydrogen bond with NH_3 (2.744 Å; 141.3°), and there is H bonding between the aqua ligand (acting as H donor) and the $N(4)H_2$ group of 1-MeC (acting a acceptor), with $O_{aq}\cdots N(4) = 2.884$ Å and $O_{aq}-H_{aq}\cdots N(4) = 130.6°$. The energy of rotamer II is higher by 20.28 kJ/mol (ΔG_{298}). The hydroxo complex reveals intramolecular hydrogen bond formation between NH_3 and O(2) of 1-MeC (2.720 Å; $N_{am}-H_{am}\cdots O(2)$, 141.6°) and between OH and $N(4)H_2$ with the amino group being the H donor and OH^- being the acceptor (2.659 Å, 153.8°).

Of all the compounds discussed here, *cis*-$[Pt(NH_3)_2(1\text{-MeC-}N3)(H_2O)]^{2+}$ and *cis*-$[Pt(NH_3)_2(1\text{-MeC-}N3)(OH)]^+$ are the only ones for which X-ray crystal structures exist.[26] However, in neither of the two solid-state structures intramolecular hydrogen bonds are observed but rather intermolecular ones. As a consequence, in these solid-state structures the 1-MeC base forms large dihedral angles with the Pt coordination planes, 90.9(5)° in the case of the aqua complex and 79.8(5)° with the hydroxo complex. The H_2O ligand is involved in two short H bonds with nitrate oxygen atoms (2.60(1) and 2.74(1) Å), whereas the OH^- ligand acts as a H bond acceptor for two protons from two different water molecules in the crystal lattice.

The hydrogen bonds between a NH_3 ligand (rotamer I) and the H_2O ligand (rotamer II), respectively, and the exocyclic amino group of 1-MeC as suggested by the DFT calculations deserve some comment. Both hydrogen bonds cause a pyramidalization of the $N(4)H_2$ group of 1-MeC and imply the presence of a lone electron pair at N(4) to act as an acceptor. This feature of pyramidalized nitrogen atoms of nucleobase amino groups has been found in gas-phase calculations[27] and may even be relevant to nucleic acid structures.[28,29] Nevertheless it should be noted that the basicity of exocyclic amino groups in cytosine, guanine, and adenine nucleobases is poor (protonation not possible in aqueous solution) and that metal coordination to a ring N atom, because of its electron-withdrawing effect, is expected to further diminish it. Moreover, to the best of our knowledge, X-ray crystal data of a large number of metal−nucleobase complexes do not reveal cases of these amino groups acting as acceptors in hydrogen bonding interactions. There are, however, numerous cases where nucleobase amino groups acts as hydrogen bond donors. On the basis of these arguments, it would therefore appear to us that both calculated structures of *cis*-$[Pt(NH_3)_2(1\text{-MeC-}N3)(H_2O)]^{2+}$ are not relevant to the situation in condensed phase. On the other hand, considering the marked difference in the two calculated hydrogen bond lengths ($O_{aq}\cdots O(2)$, 2.528 Å; $N_{am}\cdots N(4)$, 3.072 Å), only a slight increase in dihedral angle between the Pt plane and 1-MeC, albeit weakening the $O_{aq}\cdots O(2)$ hydrogen bond somewhat, would lengthen the $N_{am}\cdots N(4)$ distance anyway beyond a value that is generally considered a hydrogen bond[30] and would be consistent with expectations. As in the calculated structure of *cis*-$[Pt(NH_3)_2(1\text{-MeC-}N3)(OH)]^+$, the amino group behaves as hydrogen bond donor; these results are thus feasible.

A similar "problem" concerning the function of the exocyclic $N(6)H_2$ group of adenine arises from the calculated structures of *cis*-$[Pt(NH_3)_2(9\text{-MeA-}N7)(H_2O)]^{2+}$. Thus, in the lowest energy structure, there is a hydrogen bond from the aqua ligand to the amino group of adenine ($O_{aq}\cdots N(6)$, 2.580 Å; $O_{aq}-H_{aq}\cdots N(6)$, 162.9°), and in the other rotamer, which is higher in energy by 20.28 kJ/mol (ΔG_{298}), a hydrogen bond exists between the NH_3 ligand and the amino group of adenine ($N_{am}\cdots N(6)$, 2.925 Å; $N_{am}-H_{am}\cdots N(6)$, 151.4°). Dihedral Pt plane/9-MeA angles are 42.5° (rotamer I) and 53.4° (rotamer II). For arguments laid out above for the 1-MeC complex, the relevance of both structures for solid-state conditions is questionable. While there is no X-ray crystal structure analysis of a related adenine, aqua complex available, the X-ray crystal structures of 9-MeA complexes of $Pt(NH_3)_3$[31] and *cis*-$Pt(NH_3)_2$[32] give no indication whatsoever for intra- or intermolecular hydrogen bonding interactions between NH_3 ligands and the exocyclic $N(6)H_2$ group. Like in the case of 1-MeC, the calculated structure of the hydroxo complex *cis*-$[Pt(NH_3)_2(9\text{-MeA-}N7)(OH)]^+$ reveals a situation consistent with chemical intuition, namely intramolecular hydrogen bonding between the donor $N(6)H_2$ and the acceptor OH^- ($O\cdots N(6)$, 2.867 Å; $O-H\cdots N(6)$, 160.1°; dihedral angle between 9-MeA and Pt plane, 55.0°).

Differential Stabilization of Aqua and Hydroxo Complexes of Guanine and Adenine. The pK_a values of the aqua complex *cis*-$[Pt(NH_3)_2(nb)(H_2O)]^{2+}$ differ by 1.3 log units between 9-MeA-*N7* (4.8 ± 0.1) and 9-MeGH-*N7* (6.2 ± 0.1). If we ignore differences in electronic interactions between Pt^{II} and the two nucleobases and take into consideration the

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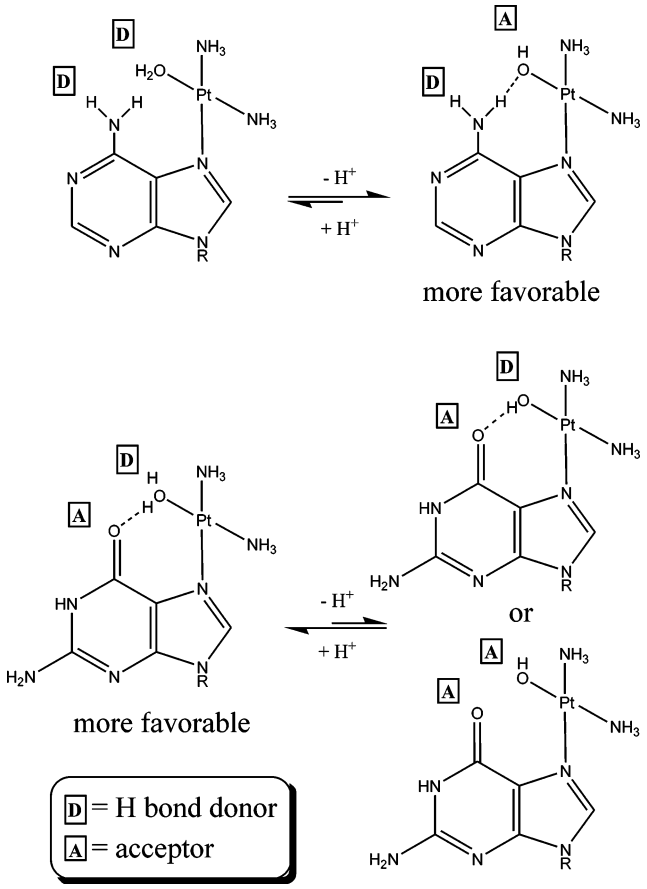
Scheme 1



critical comments made on the possibility of N(6)H$_2$ of 9-MeA acting as a hydrogen bond acceptor, it would appear to us that a simplistic, qualitative interpretation of the differences in aqua ligand acidity could be derived from a consideration of the microenvironment of the aqua ligands in the two complexes (Scheme 1). Thus, the "low" pK_a of the 9-MeA complex might be seen in terms of an efficient stabilization of the hydroxo ligand by intramolecular H bond formation, with the amino group of adenine acting as a H donor, whereas the higher pK_a of the 9-MeGH complex might arise from the fact that in the aqua complex the water ligand is involved in favorable hydrogen bonding already in the aqua complex. This view is in agreement with interpretations used to rationalize shifts in pK_a of other metal aqua complexes,[19−21] some of which are also relevant to biology. This interpretation would explain, at the same time, the fact that the aqua pK_a values in the corresponding *trans*-[Pt(NH$_3$)$_2$(nb)(H$_2$O)]$^{2+}$ are identical within the error limits (ca. 5.2−5.3). In the absence of any intramolecular contacts between the H$_2$O/OH ligands and the nucleobase, no influence of the microenvironment is to be expected.

Comparison of the acidity of [Pt(H$_2$O)(NH$_3$)$_3$]$^{2+}$ (pK_a = 6.37(10)[16]) with that of *trans*-[Pt(H$_2$O)(ligand)(NH$_3$)$_2$]$^{2+}$ (pK_a 5.17−5.34 for 1-MeC, 9-MeGH, and 2-ampy) suggests a rather *constant influence* of the N-heterocyclic ligands studied, which may either be due to a weaker σ-donor strength as compared to the NH$_3$ ligand and/or the capacity of the N-heterocycle to act as a π-acceptor. On the basis of a computational study involving [Pt(NH$_3$)$_3$]$^{2+}$, *cis*-[Pt(H$_2$O)(NH$_3$)$_2$]$^{2+}$, and *cis*-[PtCl(NH$_3$)$_2$]$^{+}$ complexes with CO, it was concluded that Pt−ammine fragments do not engage in any significant π-back-donation to π-acids such as CO or possibly purine bases,[33] although the latter has been proposed.[34]

Assuming rather modest π-back-donating properties of Pt^{II} entities with NH$_3$, H$_2$O, and Cl ligands would be consistent with our view that the presence or absence of hydrogen bonding interactions between exocyclic nucleobase functions and H$_2$O/OH ligands in complexes of type *cis*-[Pt(NH$_3$)$_2$(nb)(H$_2$O/OH)]$^{2+/+}$; hence, the microenvironment has a marked influence on the pK_a of the H$_2$O ligand.

DFT Calculations of Uracil Complex of *cis*-Pt(NH$_3$)$_2$. The geometry optimization of *cis*-[Pt(NH$_3$)$_2$(1-MeU$^-$-*N3*)(H$_2$O)]$^+$ gave a structure in which a proton transfer from the aqua ligand to O4 of 1-MeU had occurred, thus leading to a structure with a neutral 4-hydroxo, 2-oxo-tautomer (1-MeUH*) and a hydroxo ligand, *cis*-[Pt(NH$_3$)$_2$(1-MeUH*-*N3*)(OH)]$^+$. Both groups interact via a short H bond (O···O(4), 2.424 Å; O···H−O, 167.3°; dihedral angle Pt plane/uracil, 31.9°). Rare uracil tautomers can indeed be generated in the coordination sphere of Pt^{II},[23] but because of the relatively low basicity of the N3-platinated uracil anion only at low pH, hence upon protonation.[35] We therefore believe that the results of the DFT calculations with H$^+$ transfer occurring in the gas phase are not relevant to conditions found in the solid state or in solution. The second exocyclic oxygen atom of the uracil anion, O2, forms a hydrogen bond with a NH$_3$ ligand (N$_{am}$···O(2), 2.682 Å; N$_{am}$−H$_{am}$···O(2), 146.5°).

In the hydroxo species, *cis*-[Pt(NH$_3$)$_2$(1-MeU$^-$-*N3*)(OH)], the 1-MeU is present as an anion, hydrogen bonded via O4 to the OH ligand (OH···O(4), 2.838 Å; O−H···O(4), 138.1°) and via O2 to the NH$_3$ ligand trans to OH$^-$ (N$_{am}$···O(2), 2.721 Å; N$_{am}$−H$_{am}$···O(2), 147.5°). The dihedral angle between the Pt plane and 1-MeU is 45.5°.

Summary and Conclusions

As has been demonstrated here, the substitution of an aqua ligand in *cis*- or *trans*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ by a neutral or an anionic nucleobase leads to mixed nucleobase/aqua complexes with pK_a values of the aqua ligand approaching physiological pH values. This feature makes such compounds potential candidates for proton relays, hence for catalysis in acid−base chemistry. It might be argued that given the pK_{a2} values (∼7.3) of the diaqua species (cf. Table 1), binding to a nucleobase is not required at all to achieve such a function at physiological pH. However, under realistic conditions, hence in the presence of a large excess of potential nucleobase ligands in RNA or DNA, a diaqua species is unlikely to survive for any length of time without being

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complexed by nucleobases. On the other hand, as reported by Kozelka, Chottard, and co-workers,[36] the lifetime of mono(aqua) species of *cis*-Pt$(NH_3)_2$ complexed to DNA may be quite high, and a similar situation could be anticipated for Pt−RNA species. If eventually a bis(nucleobase) complex is formed, shifts in pK_a values (of the nucleobases) can likewise be substantial,[11,37] but this shall not be further discussed here. As indicated above, any mixed nucleobase, aqua complex of *cis*- or *trans*-Pt$(NH_3)_2$ with a pK_a reasonably close to 7 could be a potent acid−base catalyst in either DNA or, more likely, RNA. Although generally not believed a primary binding site of Pt^{II} at nucleic acids, the N3 sites of thymine in DNA[38] or of uracil in RNA must be taken into consideration as potential candidates fur such a function, mainly because of their expected inertness.[39] Even a 1:1 complex of *cis*-Pt$(NH_3)_2$ with a guanine nucleobase could be a potential candidate, provided some extra stabilization of the aqua ligand by a suitable H bond acceptor in the neighborhood would further shift the pK_a from 6.2 toward 7.

There is a second aspect relevant to the feature of metal−aqua group acidity, which refers to numerous reports in the literature on condensation products of metal−aqua/hydroxo species with weakly acidic nucleobase functions such as imido protons of endocyclic N atom groups[37,38] or exocyclic amino groups.[40] Typically, NH_2 groups of the nucleobases have pK_a values in the order of 17, yet metalation reactions can occur in the pH range 2−9. They are readily rationalized, however, if the fact is taken into consideration that any M−OH species represents a base, capable of removing a proton (NH, NH_2, even CH) from a weakly acidic ligand. Similarly, the formation of metal−N3 (uracil or thymine) bonds at weakly acidic pH, and much below the pK_a value of the free nucleobase (9−10), reflects the very same principle.[38,41,42]

With regard to the influence of hydrogen-bonding interactions between coligands of Pt (NH_3, nb) on aqua ligand acidity or OH group stabilization, we wish to reiterate our view that exocyclic amino groups of nucleobases, despite suggestions from gas-phase calculations, behave as H bonding donors in condensed matter, very much like Pt−NH_3 and Pt−OH_2 groups. With Pt−OH groups, however, the situation is differently, as they can act either as hydrogen acceptors or as donors.

We have recently pointed out[11d,37] that metal binding to nucleobases in their canonical or their rare tautomeric forms can have profound consequences for the nucleobase pK_a values. In essence, the introduction of one or more coordinated metal ion(s) can make available a much wider pH range for acid base chemistry than the pH ranges, where nucleobases are either protonated (low pH) or deprotonated (high pH). As we have shown here, the addition of a metal-bonded aqua ligand further increases the possibilities of fine-tuning pK_a values. In fact, acid−base equilibria of mixed aqua/nucleobase complexes of metal entities in general (and not just of Pt^{II} as in this study) are potentially more exciting than those of either metal−aqua or metal−nucleobase complexes alone because of the possibility to differently "distribute" the polarizing power of the metal on the H_2O or the nb ligand. Features of this kind may very well play an important role in catalytically active RNA and DNA molecules.

Experimental Section

Compounds. Unless data were taken from the literature, pK_a values of the compounds were determined with samples obtained from the corresponding mixed chloro, nucleobase complexes following abstraction of the Cl ligand with $AgNO_3$ in water and centrifugation of AgCl. The compounds were prepared as reported elsewhere: *cis*-[Pt$(NH_3)_2$Cl(9-MeAH-*N7*)]$(NO_3)_2$;[32] *cis*-[Pt$(NH_3)_2$Cl(1-MeC-*N3*)]NO_3;[43] *cis*-[Pt$(NH_3)_2$Cl(9-MeGH-*N7*)]Cl;[44] *cis*-[Pt$(NH_3)_2$Cl(1-MeU-*N3*)]·H_2O;[24] *trans*-[Pt$(NH_3)_2$Cl(1-MeC-*N3*)]Cl·1.5H_2O;[45] *trans*-[Pt$(NH_3)_2$Cl(9-MeGH-*N7*)]Cl·1.5H_2O;[46] *trans*-[Pt$(NH_3)_2$Cl(2-ampy-*N1*)]NO_3.[47]

Methods and Instruments. The pK_a values of the aqua complexes were determined using pH-dependent ^{1}H NMR spectroscopy measurements in D_2O (20 °C). Sodium 3-(trimethylsilyl)-propanesulfonate was used as internal reference. pD values were obtained by adding 0.4 to the pH meter reading.[48] DNO_3 and NaOD solutions were applied to vary the pD. Changes in chemical shifts of nonexchangeable protons at different pD values were determined and analyzed by a Newton-Gauss nonlinear least-squares curve-fitting procedure.[49] The pK_a values obtained for D_2O were then converted into pK_a values in water using a relationship published by Martin.[50] The pK_a value for 1-MeC was determined in an analogous way.

Computations. The calculations were carried out using the Gaussian 98 suite of programs.[51] The geometries were preoptimized with the B3LYP method[52] and the LANL2DZ basis set.[53] The final structures were obtained with a 631+G** basis set[54] for nonmetal atoms and LANL2DZ for platinum and verified by frequency calculations to be minimum geometries.

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Using the 631+G** basis set is crucial for these compounds, as LANL2DZ insufficiencies are clearly demonstrated by our following observation. While with the LANL2DZ basis set *cis*-[Pt(NH$_3$)$_2$(1-MeU$^-$-*N3*)(H$_2$O)]$^{2+}$ yields a Pt(OH)···H$_3$N geometry (O···H, 1.271 Å; HN, 1.223 Å), the larger basis set 631+G** leads to a Pt(OH$_2$)···H$_2$N geometry (OH, 1.058 Å; H···N, 1.550 Å). This proton shift is reversible if the geometry is reoptimized with the other basis set. So, while the optimization with the 631+G** basis set reproducibly leads to a chemically reasonable structure, the LANL2DZ basis set yields a structure in which a rare uracil tautomer is generated.

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Supporting Information Available: Calculated structures of disfavored cations *cis*-[Pt(NH$_3$)$_2$(nb)H$_2$O)]$^{2+}$ (with nb = 9-MeGH, 1-MeC, 9-MeA) and coordinates of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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