Aqua Group Acidity in Complexes of the Type *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ (with L = Substituted Pyridines). Linear, yet Weak Dependence of pK_a of the Aqua Ligand from L Basicity

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Dedicated to Professor Hubert Schmidbaur on the occasion of his 75th birthday

The pK_a of the aqua ligand in complexes of the type *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{n+}$ depends on the nature of the ligand *trans* to H_2O, as expected. With L = NH_3 or NH_2R and n = 2, the pK_a is around 6.0 – 6.4. With L = *N*-heterocyclic ligands generally higher acidities of the aqua ligands are observed, with pK_a values being in the range of 4.7 – 5.4. These values are between those for L = H_2O, n = 2 (4.4) and L = Cl^-, n = 1 (5.7). For differently substituted pyridine ligands L a linear relationship exists between the pK_a of the H_2O ligand and the basicity of the heterocyclic ligand L, which is relatively weak, however.

Key words: Transplatin, Pyridine Ligands, Aqua Ligand Acidity, *trans* Influence

Introduction

There is good reason to assume that metal-hydroxo complexes $M(OH)L_x$ (L = ligand) play a similarly important role in nucleic acid chemistry as they do in catalytic processes of metalloproteins. In protein chemistry numerous examples exist, where M(OH) entities catalyze essential reactions (*e. g.* the role of Zn^{II} in hydrolytic enzymes, of Fe^{III} or Zn^{II} in purple acid phosphatases, of Ni^{II} in urease, *etc.*) [1]. In many cases, details regarding the chemical processes (coordination number of M and effect on pK_a of the H_2O ligand, nucleophilicity of the OH^- ligand, pK_a shift due to local environment, *etc.*) are reasonably well understood. However, the number of examples of $M(OH)L_x$ species accomplishing important reactions with nucleic acids is at present considerably smaller. RNA diester cleavage reactions, as observed in the hepatitis delta virus (HDV) ribozyme, which involves a $Mg(OH)^+$ species [2], or $Pb(OH)^+$-mediated hydrolysis of the backbone of tRNAs [3] are such cases. Moreover, the basics of acid-base chemistry of metal-aqua species in a nucleobase environment are less well studied. Even the generation of a $[Mg(OH)(H_2O)_x]^+$ (x = 5 or 4) species under physiological conditions is not fully understood, considering the fact that in water the pK_{a1} of $[Mg(H_2O)_6]^{2+}$ is 11.4 and consequently far from 7 [4]. Mixed aqua/nucleobase complexes are special in that, in principle, both types of ligands may undergo acid-base chemistry and, in addition, may mutally influence their individual pK_a values [5]. We have recently reported on the varying acidities of aqua ligands in complexes of types *cis*- and *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{n+}$ (L = nucleobase) [6]. It was noticed that, depending on L, pK_a values of the aqua ligand were variable in the case of the *cis* isomers (4.8 – 7), while they were essentially constant (5.2±0.1) with the *trans* isomers. These findings were interpreted by us in terms of a major influence of the microenvironment (hydrogen bonding) of the aqua/hydroxo ligand in the case of the *cis* isomers, and in a relatively minor *trans*-influence of the *N*-heterocycle on the H_2O ligand in the *trans* isomers. In order to put these observations on a broader basis, we decided to prepare a series of structurally related complexes of composition *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ with L = pyridine ligands of varying basicities, and to study the influence of L on the acidity of the respective aqua ligand.

As the pK_a values of the H_2O ligands in metal-aqua complexes are "experimental indicators for the electron density around a metal center" [7], in principle insight in the donor/acceptor properties of the co-ligands can be gained. Van Eldik and coworkers

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have extensively studied the interrelationship between chelating *N*-heterocyclic ligands (bipyridine, terpyridine, aminomethylpyridine) and the rate of substitution of aqua ligands [7–9]. It was one goal of the present study to learn more about the electronic properties of *N*-heterocyclic ligands L bonded in a monodentate fashion to Pt in *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{n+}$ compounds. Unlike in the aforementioned chelating *N*-heterocycles, which are coplanar within the Pt coordination plane, the here discussed monodentate *N*-heterocyclic ligands have their planes at moderate to large dihedral angles (*ca.* 45–90°) with respect to the Pt coordination plane, depending on the possibility of interactions between the NH_3 ligands and exocyclic groups of L.

Apart from these questions relating to basic aspects of metal-ligand interactions, there has been recently renewed interest in pK_a values of aqua complexes derived from compounds of the type *trans*-$PtCl_2(A)(A')$ (with A, A′ representing aliphatic amines, iminoethers or planar amines) [10] following reports on the unexpected antitumor activity of such Pt^{II} complexes having a *trans* geometry [11]. As the speciation inside a cell is governed by the pK_a of the aqua complexes, and because reactivity towards biological targets depends on the presence of H_2O or OH^- ligands at the Pt, this topic is of substantial importance.

Results and Discussion

Aqua group acidities in trans-[Pt(A)(A′)(L)(H$_2$O)]$^{n+}$

The acidity of the aqua ligand in *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{n+}$ is, to a first approximation, influenced by the ligand L *trans* to H_2O (Table 1). "Consensus" values [12] are *ca.* 4.4 for L = H_2O, n = 2, 5.7 for L = Cl, n = 1, and 6.4 for L = NH_3, n = 2. Substitution of the NH_3 ligands by aliphatic amines, *e. g.* methylamine, dimethylamine, isopropylamine [10] or mixing NH_3 with an aliphatic amine [13] has a relatively minor effect only or none at all [14]. Even replacement of one of the two NH_3 ligands by a picoline ligand (2-pic, 3-pic, 4-pic), hence a ligand without the potential of forming hydrogen bonds with the aqua or hydroxido ligand in *cis*-position, has no effect (mono aqua complex) or a small effect at most (diaqua species) [15]. This situation changes drastically, once the am(m)ine ligand is substituted by a ligand capable of forming intramolecular hydrogen bonds with H_2O or OH^- ligands. Thus the mentioned [6] variations in aqua ligand acidities in *cis*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ (L = model nucleobases) have been primarily attributed to differences in hydrogen bonding interactions with exocyclic groups of the nucleobases and H_2O and OH^- ligands.

Table 1. Literature pK_a values of aqua ligands in complexes of the type *trans*-$[Pt(A)(A')X(H_2O)]^{n+}$ in water.

A	A′	X	n	pK_a [a]	Ref.
NH_3	NH_3	H_2O	2	4.4	[12]
NH_3	am[b]	H_2O	2	4.2	[14]
NH_3	2-pic	H_2O	2	4.0	[15]
NH_3	3-pic	H_2O	2	4.0	[15]
NH_3	4-pic	H_2O	2	3.9	[15]
am[c]	am′ [c]	H_2O	2	4.4	[10]
NH_3	NH_3	Cl	1	5.7	[12]
NH_3	am[b]	Cl	1	5.9	[14]
NH_3	2-pic	Cl	1	5.6	[15]
NH_3	3-pic	Cl	1	5.4	[15]
NH_3	4-pic	Cl	1	5.4	[15]
NH_3	am[d]	Cl	1	5.4	[13]
am[c]	am′ [c]	Cl	1	5.9[e]	[10]
NH_3	NH_3	NH_3	2	6.4	[12]

[a] For diaqua species, only pK_{a1} value considered; [b] am = 2-methylbutylamine; [c] am, am′ = methylamine, dimethylamine, isopropylamine; [d] am = cyclohexylamine; [e] average value of three mixed amine complexes.

Syntheses and characterization of pyridine complexes

1 : 1-Complexes of composition *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ (with L = substituted pyridine) were prepared in water from the corresponding chloro complexes *trans*-$[Pt(NH_3)_2(L)Cl]^+$ upon treatment with $AgNO_3$. 1 : 1-Complexes for L = 2-methylpyridine (2-pic) (**1**), 3-methylpyridine (3-pic) (**2**), pyridine (py) (**3**), 4-chloropyridine (4-Clpy) (**4**), 3-chloropyridine (3-Clpy) (**5**), 4-cyanopyridine (4-CNpy) (**6**), 2-chloropyridine (2-Clpy) (**7**) as well as 2-aminopyridine(2-ampy) (**8**) were obtained this way. *trans*-$[Pt(NH_3)_2(L)Cl]^+$ compounds were either prepared

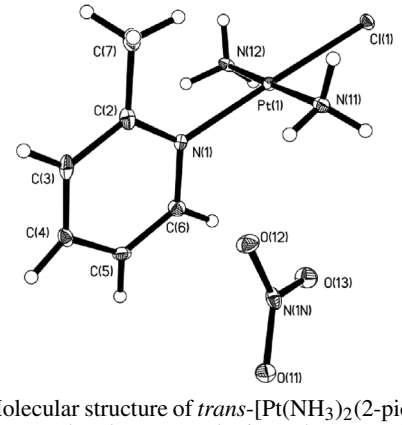

Fig. 1. Molecular structure of *trans*-$[Pt(NH_3)_2(2\text{-pic})Cl]NO_3$ (**1**) in the crystal and atom numbering scheme used.

Table 2. Crystallographic data for compounds **1**, **9** and **10**.

Compound	**1**	**9**	**10**
Name	*trans*-$[Pt(NH_3)_2$(2-pic)Cl$](NO_3)$	*trans*-$[Pt(NH_3)_2$(2-pic)$_2](NO_3)_2$	*cis*-$[Pt(NH_3)_2$(2-pic)Cl]Cl
Formula	$C_6H_{13}ClN_4O_3Pt$	$C_{12}H_{20}N_6O_6Pt$	$C_6H_{13}Cl_2N_3Pt$
Formula weight, g mol^{-1}	419.74	539.43	393.18
Crystal color and habit	colorless cubes	colorless cubes	colorless cubes
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$C2/c$
a, Å	12.200(2)	6.3320(13)	17.308(4)
b, Å	8.1840(16)	8.0920(16)	12.502(3)
c, Å	11.793(2)	9.2670(19)	10.379(2)
α, deg	90	98.64(3)	90
β, deg	105.95(3)	96.01(3)	95.27(3)
γ, deg	90	106.50(3)	90
Z	4	1	8
V, Å^3	1132.1(3)	444.63(16)	2236.4(8)
ρ_{calc}, g cm^{-1}	2.46	2.02	2.34
μ(MoK_α), cm^{-1}	12.6	7.9	13.0
F(000), e	784	260	1456
Temperature, K	153(2)	293(2)	293(2)
hkl range	±16, +10, ±15	±8, ±10, −11/+12	±22, ±16, ±13
Refl. meas. / unique / R_{int}	2824 / 1920 / 0.0458	7982 / 2044 / 0.0259	2568 / 2063 / 0.0518
Param. refined	140	115	81
$R1(F)/wR2(F^2)$[a] (all refls.)	0.0479 / 0.0975	0.0203 / 0.0404	0.0484 / 0.0736
Goodness-of-fit, S[b]	0.964	1.071	1.312
Residual ρ_{max}/ρ_{min}, e Å^{-3}	3.72 / −4.03	0.51 / −0.81	1.58 / −1.23

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$ and A and B are constants adjusted by the program; [b] $S = \mathrm{GoF} = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$, where n_{obs} is the number of data and n_p the number of refined parameters.

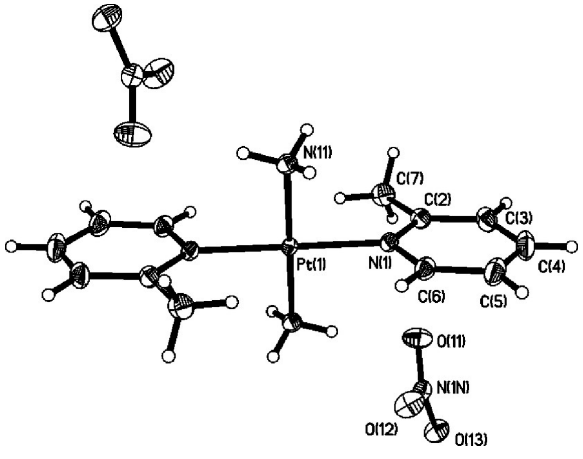

Fig. 2. Molecular structure of *trans*-$[Pt(NH_3)_2$(2-pic)$_2]$-$(NO_3)_2$ (**9**) in the crystal and atom numbering scheme used. In the solid state the two 2-pic ligands adopt a *head to tail* arrangement.

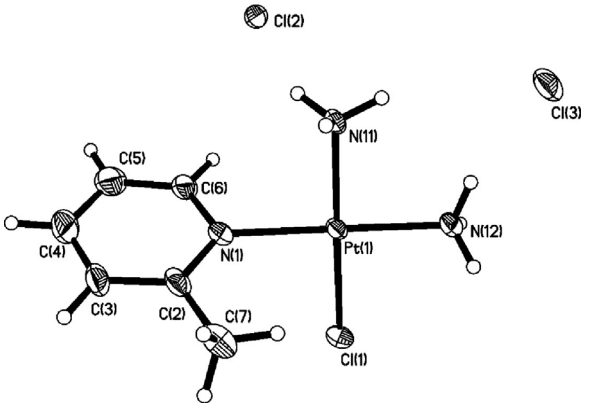

Fig. 3. Molecular structure of *cis*-$[Pt(NH_3)_2$(2-pic)Cl]Cl (**10**) in the crystal and atom numbering scheme used. The chloride counter ion is distributed over two positions [Cl(2), Cl(3)].

from *trans*-$Pt(NH_3)_2ICl$ (*c.f.* Experimental) or *trans*-$Pt(NH_3)_2Cl_2$ [16] in water. In one instance, with L = 2-pic, attempts to prepare *cis*-$[Pt(NH_3)_2$(2-pic)Cl]Cl from *cis*-$PtCl_2(NH_3)_2$ in DMF, led to the corresponding *trans*-isomer **1a**, as unambiguously established by ^{1}H NMR spectroscopy of the isolated compound. Similar *cis* → *trans* isomerization reactions for Pt^{II} complexes have been reported before, but in general these occur with compounds containing ligands with a high *trans*-effect (*e. g.* phosphines) and/or with DMSO as solvent [17]. The mechanism of the present process has not been further studied.

With 2-methylpyridine (2-pic) as ligand, X-ray crystal structures were performed for *trans*-$[Pt(NH_3)_2$(2-

Table 3. Selected bond lengths (Å) and angles (deg) for compounds **1**, **9**, and **10**.

	1	**9**	**10**
Pt1–N1	2.033(6)	2.028(3)	2.034(6)
Pt1–N12	2.037(8)		2.014(5)
Pt1–N11	2.045(7)	2.049(3)	2.043(5)
Pt1–Cl1	2.2969(19)		2.3000(16)
N1–Pt1–N12	91.2(3)		179.4(3)
N1–Pt1–N11	90.4(3)	89.42(11)/90.58(11)[a]	89.3(2)
N12–Pt1–Cl1	89.75(18)		88.15(15)
N11–Pt1–Cl1	88.64(18)		91.58(18)
2-picoline/Pt plane	76.11(23)	77.58(10)	73.76(17)

[a] $-x+1, -y, -z$.

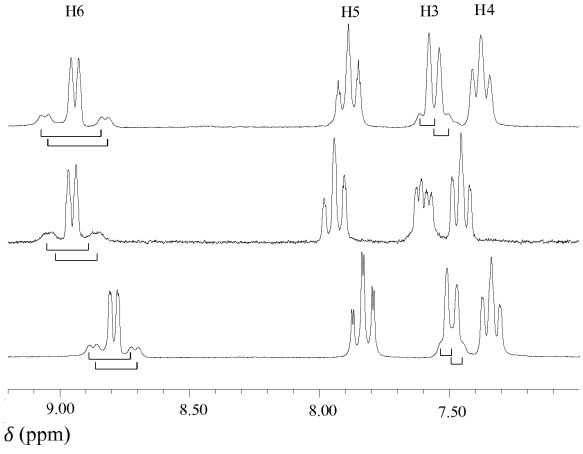

Fig. 4. Low-field sections of the ^{1}H NMR spectra (200 MHz, D_2O) of *trans*-$[Pt(NH_3)_2(2\text{-pic})Cl]NO_3$ (**1**) (top), *trans*-$[Pt(NH_3)_2(2\text{-pic})_2](NO_3)_2$ (**9**) (middle), and *cis*-$[Pt(NH_3)_2(2\text{-pic})Cl]Cl$ (**10**) (bottom). ^{195}Pt satellites of H6 and H3 resonances are indicated.

pic)Cl]NO_3 (**1**), *trans*-$[Pt(NH_3)_2(2\text{-pic})_2](NO_3)_2$ (**9**), and *cis*-$[Pt(NH_3)_2(2\text{-pic})Cl]Cl$ (**10**). Views of the cations are given in Figs. 1 – 3, and crystallographic data as well as selected bond lengths and angles are provided in Tables 2 and 3.

In all cases the 2-picoline ligands form large dihedral angles with the Pt coordination planes (73.8 – 77.6°). There are no unusual features as far as bond lengths and angles about the Pt are concerned. Specifically, Pt−NH_3 and Pt−(2-pic) bond length are identical within standard deviations. Geometrical details of the 2-picoline ligands compare well with published data on other Pt^{II} complexes [18, 19].

Fig. 4 shows the lowfield sections of the ^{1}H NMR spectra (200 MHz) of **1**, **9**, and **10** in D_2O. They consist of the expected resonances (dd for H3 and H6, ddd for H4 and H5). Typically, ^3J (^{1}H-^{1}H) coupling constants in these types of ligands are around 7.5 – 8 Hz, and long-range ^4J(^{1}H-^{1}H) coupling constants are *ca.* 1.6 Hz. Long-range coupling is not always well resolved, and consequently dd signals can appear as doublets only and ddd signals can look triplet-like. In the spectrum of **9** some of the resonances are doubled, *e. g.* H3 and CH_3, which suggests the presence of two rotamers (*head-head* and *head-tail*) in a 1 : 1 ratio. The H6 signals, which occur furthest downfield, are readily identified by their ^{195}Pt satellites due to ^3J coupling. ^4J coupling between the ^{195}Pt isotope, and proton resonances are also observed for the methyl groups in 2-pic compounds (**1**, **9**, **10** and **1′**, see below) as well as for H3 of some of the 2-pic compounds (**1**, **10**; *c. f.* Fig. 4). The size of these ^{195}Pt-^{1}H coupling constants not only is influenced by the number of bonds between the nuclei, but also by the nature of the ligand *trans* to the pyridine, as previously demonstrated by us for 9-ethylguanine complexes of Pt^{II} [20]. For example, $^3J(^{195}Pt\text{-}^1H6)$ is largest in the case of *trans*-$[Pt(NH_3)_2(2\text{-pic})(D_2O)]^{2+}$ (**1′**) (51 Hz), followed by *trans*-$[Pt(NH_3)_2(2\text{-pic})Cl]^+$ (**1**) (46 Hz), and by complexes **9** (36 Hz) and **10** (32 Hz), both of which have *N*-donors in *trans* position. As the aqua ligand becomes deprotonated to the hydroxo ligand, *e. g.* in *trans*-$[Pt(NH_3)_2(2\text{-pic})(OD)]^+$, ^3J coupling with H6 is decreased (37 Hz) as a consequence of the better donor properties of the hydroxo ligand. Similar trends are to be seen with the ^4J values, albeit they are considerably smaller in magnitude and typically in the range 12 – 9 Hz. These findings are in agreement with data on compounds of composition *cis*- and *trans*-$PtX_2(2\text{-pic})_2$ with X = Cl or I [19]. In general, ^{195}Pt satellites become ill-resolved in spectra recorded at high field strength, *e. g.* at 400 MHz.

Aqua group acidities

pK_a values of the aqua ligands of the here described compounds *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ (assigned as **1′**, **2′**, *etc.*) were determined by pD-dependent ^{1}H NMR spectroscopy, as described elsewhere [21], and pK_a values of individual ^{1}H resonances obtained for D_2O, were converted to H_2O [22]. A typical example (complex **1′**) of a pD dependence of aromatic protons is shown in Fig. 5.

In cases where the 1 : 1-complexes were contaminated with small amounts of the 1 : 2-complex (*e. g.* with compounds **2**, **5**, and **6**), the identity of the aqua complex could nevertheless be determined, as its resonances were pD dependent, unlike those of the 1 : 2-complex.

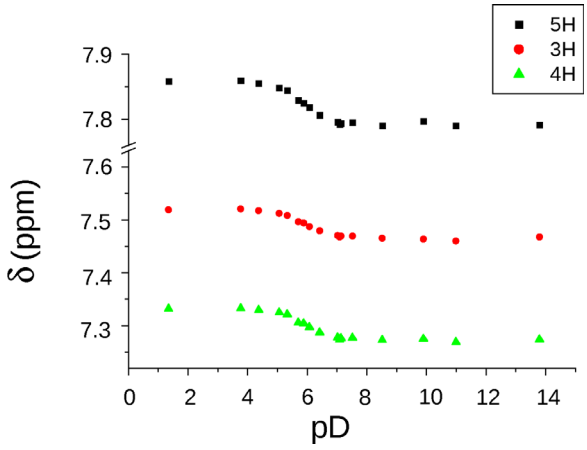

Fig. 5. pD dependence of the chemical shifts (δ) of the aromatic proton resonances of the 2-pic ligand in *trans*-$[Pt(NH_3)_2(2\text{-pic})(D_2O)]^{2+}$ (**1′**).

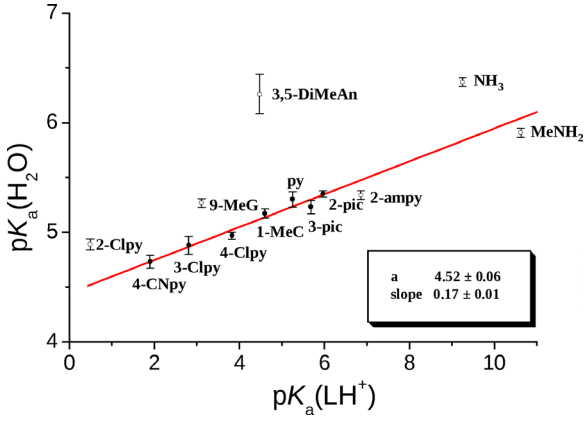

Fig. 6. Relationship between pK_a of the H_2O ligand in *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ and basicity of L [expressed as pK_a(LH^+)]. The least-squares straight line was calculated for complexes (filled circles) with the following ligands L: 2-pic, 3-pic, py, 4-Clpy, 3-Clpy, and 4-CNpy. Complexes deviating significantly from the straight line (open circles) are discussed in the text. Error bars refer to estimated errors in pK_a value determinations.

Fig. 6 gives the relationship of pK_a values of aqua ligands of the respective pyridine complexes **1′**–**8′** in dependence on the basicity of the free, uncoordinated ligands L. As a measure of basicity of L the pK_a for the equilibrium shown in Eq. 1 is given.

$$LH^+ \rightleftharpoons L + H^+ \tag{1}$$

The higher the pK_a is, the more basic is L. The pK_a values of LH^+ were taken from the literature [23–26]. Included in Fig. 6 are also values for L = NH_3 (**11′**), $MeNH_2$ (**12′**), and 3.5-dimethylaniline (3.5-DiMeAn) (**13′**), as well as the previously determined values for *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ [with L = 1-methylcytosine-*N*3 (**14′**) and 9-methylguanine-*N*7 (**15′**)] [6].

As can be seen, there is a good linear relationship between the pK_a of most pyridinium ligands (LH^+) and the pK_a of the aqua ligand in *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$, hence for the equilibrium in Eq. (2).

$$\begin{aligned} &\textit{trans}\text{-}[Pt(NH_3)_2(L)(H_2O)]^{2+} + H^+ \\ &\rightleftharpoons \textit{trans}\text{-}[Pt(NH_3)_2(L)(OH)]^{+} + H^+ \end{aligned} \tag{2}$$

The straight-line equation, derived from six data points (**1′**–**6′**), gave the following relationship (Eq. 3):

$$pK_a(H_2O) = (4.52 \pm 0.06) + (0.17 \pm 0.01)pK_a(LH^+) \tag{3}$$

It reveals that the slope of the line is small. In other words: the dependence of pK_a (H_2O) from pK_a (LH^+) is relatively weak. A comparison between formation constants of 1 : 1-transition metal complexes of substituted pyridine ligands shows generally steeper dependies of pK_a (LH^+), unless *ortho*-substituents at the pyridine, for steric reasons, affect complex formation negatively [24]. Plots of formation constant logarithms of 1 : 1-complexes of Pd^{II}(dien) [27] or of Ni^{II} [28] with nucleobases likewise display steeper slopes, implying that a high ligand basicity translates into high complex stability.

As is evident from Fig. 6, of the pyridine complexes studied, the 2-chloropyridine compound **7′** deviates significantly in its pK_a (H_2O) from the straight line. Concerning reasons, at least two possibilities, can be put forward: An "axial" interaction between the Cl substituent and the Pt, and/or a hydrogen bonding interaction between the Cl substituent and one of the NH_3 groups. While in the first instance a large ($\sim 90°$) dihedral angle between the pyridine ligand and the Pt plane can be expected, in the second case the dihedral angle is likely to be smaller. Steric hindrance between the Cl substituent and the two NH_3 groups and as its consequence, a longer Pt–N(2-Clpy) bond, appears to be less likely as an explanation, as it should cause an increase in H_2O acidity rather than the observed decrease. Moreover, considering the square-planar coordination geometry of Pt^{II}, steric clash could be avoided by a perpendicular arrangement of the pyridine lig-

and. The 2-aminopyridine complex **8′** likewise deviates from the straight line, yet less pronounced, and opposite to the situation with the 2-Clpy compound. As the 2-ampy ligand has a lone electron pair at its exocyclic amino group, in principle similar arguments as for **7′** could be raised. In contrast the 2-pic compound **1′**, despite its methyl substituent, fits the straight line very well.

Of the two nucleobase complexes included in this comparison, the 1-methylcytosine complex **14′** behaves "pyridine-like" and is well on the straight line. The 9-methylguanine complex **15′**, on the other hand, deviates from the straight line. Considering the more profound difference between pyridine and purine ligands, this is not too surprising. In absolute values, the pK_a (H_2O) values of **14′** and **15′** are very close, however, unlike in the corresponding *cis* isomers [6].

The available data points for the L = NH_2R compounds (**11′**–**13′**) are not sufficient to draw conclusions concerning the relationship between ligand basicity and pK_a of the aqua ligand. In any case it is evident that *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ compounds containing L = *N*-heterocyclic ligands and hence sp^2-hybridized *N*-donors are significantly more acidic than those having sp^3-hybridized NH_2R donors.

Summary

Our data show that a linear relationship exists between the basicity of a family of closely related ligands L – here of differently substituted pyridines – and the acidity of the aqua ligand *trans* to the py ligand L in *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$. All complexes studied are of identical charge (+2) and differ by the L ligand only. There is no influence of the microenvironment in stabilizing either the H_2O or the OH^- ligand [6, 29], and consequently the observed differences in pK_a values of the aqua ligand essentially reflect the transmission of electronic effects from L *via* Pt to H_2O. The expected qualitative trend, that a higher basicity of the pyridine ligand L lowers the acidity of the aqua ligand, is confirmed. However, the transmission effect of L is relatively weak: A ΔpK_a (LH^+) of *ca.* 5 units translates into a ΔpK_a (H_2O) of *ca.* 0.65 units only. In a study on the influence of substituted pyridine ligands on the acidity of the NH_2 group of chelating 8-aminoquinoline, the response between pK_a of the amino group and pK_a of LH^+ in terms of slope of the straight line is almost twice as high [30]. Nevertheless there is an important difference between the ligands L studied here, including the two model nucleobases, and the L = NH_2R compounds **11′**–**13′** in that the heterocyclic N ligands acidify the *trans*-positioned aqua ligand considerably more than do the NH_2R ligands. The observed pK_a values of 4.7 – 5.4 are substantially lower than those for L = NH_2R (6.0 – 6.4) and in between those for L = H_2O (4.4) and L = Cl^- (5.7). Unfortunaly single crystal data on complexes of type *trans*-$[Pt(NH_3)_2(L)(H_2O)]^{2+}$ are presently not available, and consequently a distinct structural *trans*-influence of *N*-heterocycles over NH_2R ligands on the Pt–OH_2 bond cannot be proven. Nevertheless, the differential aqua ligand acidities in the here discussed complexes may very well be related to π-acceptor properties of the *N*-heterocyclic ligands. Well established for C_2H_4 and CO ligands for example [31], as well as for chelating *N*, *N′*-heterocycles (*e. g.* 2,2′-bipyridine or 2,2′:6′,2″-terpyridine) [7 – 9], there appear to be controversial views concerning the significance of π back-donotion from Pt to coordinated nucleobases [32, 33]. It must be taken into account, however, that the overlap between filled π orbitals of the heterocycle and Pt^{II} involves different *d* orbitals of the metal, depending on the dihedral angle between the Pt plane and the plane of the heterocycle.

Experimental Section

Starting compounds and syntheses

All chemicals were of reagent grade and were used without further purification. *trans*-$Pt(NH_3)_2Cl_2$ [34], *trans*-$PtICl(NH_3)_2$ [35], *cis*-$Pt(NH_3)_2Cl_2$ [36] and *trans*-$[Pt(NH_3)_2(2\text{-ampy})Cl]Cl$ (**8**) [37] were prepared as reported. Compounds **2** – **7** as well as **12** and **13** were synthesized by slight modification of the method given in the literature for *trans*-$[Pt(NH_3)_2(py)Cl]Cl$ [16]. **2**, **5**, **6** and **12** were not obtained analytically pure but were rather contaminated with the respective *trans*-$[Pt(NH_3)_2(L)_2]Cl_2$ complex. The determination of the pK_a value of the aqua complexes was not hampered by this fact, however (*c. f.* text above). In the following accurate ^1H–^1H coupling patterns are given only if resolved (*e. g.* with **1**, **9**, **10**). Frequently, coupling was not resolved, and in these cases the resonance is described by its appearance, *e. g.* as a doublet instead of a doublet-of-doublet *etc.*

*trans-[$(NH_3)_2$Pt(2-pic)Cl](NO_3) (**1**)*

1 was obtained as follows: *trans*-$PtICl(NH_3)_2$ (27 mmol) was suspended in water (720 mL), $AgNO_3$ (27 mmol), dissolved in water (45 mL) was added and the mixture stirred for 2 h in the dark. Yellow AgI was then separated by filtration and washed three times with 50 mL of hot water. To the

filtrate 2-picoline (32.4 mmol), dissolved in water (45 mL), was added dropwise over a period of 2 h and the solution stirred at 40 °C for 28 h. Concentration of the solution to *ca.* 80 mL volume produced a white crystalline material, which was recrystallized from water. The yield was 28 %. – Elemental analysis for $C_6H_{13}ClN_4O_3Pt$: calcd. C 17.15, H 3.13, N 13.35; found C 17.2, H 3.1, N 13.4. – ^{1}H NMR (D_2O): δ = 8.93 (dd, H6, ^3J (^{195}Pt-^{1}H) = 46 Hz), 7.87 (ddd, H5), 7.54 (dd, H3, ^4J (^{195}Pt-^{1}H) = 11 Hz), 7.36 (ddd, H4), 3.09 (s, CH_3, ^4J (^{195}Pt-^{1}H) = 11 Hz).

At a later stage, upon further concentration, *trans*-$[(NH_3)_2Pt(2\text{-pic})_2](NO_3)_2$ (**9**) was isolated in 32 % yield. Characterization was achieved by X-ray crystallography. – ^{1}H NMR (D_2O): δ = 8.95 (dd, H6, ^3J (^{195}Pt-^{1}H) = 36 Hz), 7.94 (ddd, H5), 7.62 (dd, H3), 7.58 (dd, H3′), 7.45 (ddd, H4), 3.2 (s, CH_3, ^4J (^{195}Pt-^{1}H) *ca.* 10 Hz), 3.19 (s, CH_3, ^4J (^{195}Pt-^{1}H) *ca.* 10 Hz).

*trans-[(NH$_3$)$_2$Pt(2-pic)Cl]Cl (**1a**)*

1a was obtained as follows: *cis*-$Pt(NH_3)_2Cl_2$ (1 mmol) in DMF (20 mL) was reacted with $AgNO_3$ (1 mmol) for 24 h in the dark, filtered from AgCl, and 2-pic (0.95 mmol), dissolved in DMF (5 mL), was added dropwise during 2 – 3 h. The mixture was then kept at 40 °C for 1 d, concentrated to 5 mL by rotary evaporation and allowed to stay at r. t. Colorless crystals of **1a** appeared within 2 d. ^{1}H NMR spectroscopy proved the *trans* geometry of the product.

*trans-[(NH$_3$)$_2$Pt(py)Cl]Cl (**3**)*

Yield 76 %. – Elemental analysis for $C_5H_{11}Cl_2N_3Pt$: calcd. C 15.84, H 2.92, N 11.08; found C 15.8, H 3.1, N 11.0. – ^{1}H NMR (D_2O): δ = 8.82 (d, H2), 8.01 (dd, H4), 7.56 (dd, H3).

*trans-[(NH$_3$)$_2$Pt(4-Clpy)Cl]Cl (**4**)*

Yield 40 %. – Elemental analysis for $C_5H_{10}Cl_3N_3Pt$: calcd. C 14.52, H 2.44, N 10.16; found C 14.4, H 2.6, N 10.2. – ^{1}H NMR (D_2O): δ = 8.78 (d, H2), 7.65 (d, H3).

*trans-[(NH$_3$)$_2$Pt(2-Clpy)Cl]Cl (**7**)*

Yield 56 %. – Elemental analysis for $C_5H_{10}Cl_3N_3Pt$: calcd. C 14.52, H 2.44, N 10.16; found C 14.4, H 2.6, N 10.2. – ^{1}H NMR (D_2O): δ = 8.95 (d, H6), 8.02 (dd, H4), 7.81 (d, H3), 7.54 (dd, H5).

*cis-[Pt(NH$_3$)$_2$Cl(2-pic)Cl]Cl (**10**)*

10 was prepared as follows: *cis*-$(NH_3)_2PtCl_2$ (10 mmol) was dissolved in H_2O (500 mL), and 2-picoline (10 mmol) was added. The solution was stirred for 2 d at 55 °C. The solution was then reduced in volume (rotavapor, 45 °C) to 5 mL and filtered. The filtrate was then brought to dryness, yielding a viscous material, which within several days gave a crystalline material, admixed with viscous [2-picH]Cl. Following treatment with EtOH (5 mL), a white solid was obtained, which was filtered off. A according to ^{1}H NMR spectroscopy it consisted of a mixture of **10** and *cis*-$[Pt(NH_3)_2(2\text{-pic})_2]Cl_2$. The mixture was recrystalized twice from EtOH. The yield of **10** was 38 %. – Elemental analysis for $C_6H_{13}Cl_2N_3Pt$: calcd. C 18.32, H 3.3, N 10.69; found C 18.4, H 3.3, N 10.8. – ^{1}H NMR (D_2O): δ = 8.79 (dd, H6, ^3J (^{195}Pt-^{1}H) = 32 Hz), 7.83 (ddd, H5), 7.49 (d, H3, ^4J (^{195}Pt-^{1}H) = 9 Hz), 7.34 (ddd, H4), 3.09 (s, CH_3, ^4J (^{195}Pt-^{1}H) = 10 Hz).

*trans-[(NH$_3$)$_2$Pt(3,5-DiMeAn)Cl]NO$_3$ (**13**)*

Yield 80 %. – Elemental analysis for $C_8H_{17}ClN_4O_3Pt$: calcd. C 21.46, H 3.83, N 12.51; found C 21.6, H 4.0, N 12.5. – ^{1}H NMR (D_2O): δ = 7.01 (s, H4), 6.98 (s, H2), 2.31 (s, CH_3).

^{1}H NMR chemical shifts of *trans*-$[(NH_3)_2Pt(L)Cl]^+$ complexes not isolated in pure form:

*trans-[Pt(NH$_3$)$_2$(3-Mepy)Cl]Cl (**2**)*. – ^{1}H NMR (D_2O): δ = 8.69 (s, H2), 8.60 (d, H6), 7.83 (d, H4), 7.42 (dd, H5), 2.37 (s, CH_3).

*trans-Pt(NH$_3$)$_2$(3-Clpy)Cl]Cl (**5**)*. – ^{1}H NMR (D_2O): δ = 9.01 (d, H2), 8.82 (d, H6), 8.16 (d, H4), 7.65 (dd, H5).

*trans-Pt(NH$_3$)$_2$(4-CNpy)Cl]Cl (**6**)*. – ^{1}H NMR (D_2O): δ = 9.15 (d, H2), 7.94 (d, H3).

*trans-Pt(NH$_3$)$_2$(MeNH$_2$)Cl]Cl (**12**)*. – ^{1}H NMR (D_2O): δ = 2.45 (s, CH_3)

NMR measurements

^{1}H NMR spectra were recorded in D_2O on Varian Mercury 200 FT-NMR, Bruker DPX 300 and Bruker DPS 400 spectrometers, with TSP used as an internal reference. pD values were determined by use of a glass electrode and addition of 0.4 to the pH-meter reading. D_2O solutions of NaOD and DNO_3 were used to adjust pD values.

Crystal structure determination

Crystal data for compounds **1**, **9**, and **10** were collected on an Enraf-Nonius KappaCCD diffractometer [38] using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) at low temperature (150 K) for compound **1** or at r. t. for compounds **9** and **10**. None of the crystals reported showed evidence of crystal decay during data collection. For data reduction and cell refinement, the programs DENZO and SCALEPACK were used [39]. Corrections for incident and diffracted beam absorption effects were applied using SADABS [40]. The structures were solved by standard conventional Direct Methods and refined by full-matrix least-squares based on F^2 using the programs SHELXTL-PLUS [41] and SHELXL-97 [42]. The positions of all non-hydrogen atoms were deduced from difference Fourier maps

and were refined anisotropically. Hydrogen atoms except those of the water molecules were generated geometrically and given isotropic thermal parameters equivalent to 1.2 or 1.5 times those of the atom to which they were attached. The distances and angles were calculated by using PLATON [43], and the CIF files [44] were generated using the Software WINGX [45].

CCDC 748589 – 748591 contain the supplementary crystallographic data for compounds **1**, **9**, and **10**. They can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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