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Intrinsic Acid–Base Properties of Purine Derivatives in Aqueous Solution and Comparison of the Acidifying Effects of Platinum(II) Coordinated to N1 or N7: Acidifying Effects Are Reciprocal and the Proton "Outruns" Divalent Metal Ions

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The effect of Pt^{2+} coordination, in particular of (dien)Pt^{2+} or *cis*-$(NH_3)_2Pt^{2+}$, on the acid–base properties of the purine ligands 9-ethylguanine (9EtG), 9-methylhypoxanthine (9MeHx), inosine (Ino), 9-methyladenine (9MeA), and N6′,N6′,N9-trimethyladenine (TriMeA) is quantitatively evaluated. The corresponding acidity constants of the complexes are calculated by curve-fitting procedures using previously published ^{1}H NMR shift data which had been measured in aqueous solution (D_2O) in dependence on pH (pD). Comparison of the pK_a values of the ligands with those of the Pt^{2+} complexes reveals the expected behavior for the (N7)-platinated complexes; i.e., the (N1)$H^{0/+}$ sites are acidified due to charge repulsion. However, Pt^{2+} coordination at $(N1)^{-/0}$ sites leads to an (already previously observed) apparent increase in the basicity of the N7 sites for the guanine, hypoxanthine, and adenine residues; this is also the case if Pt^{2+} is bound to N3. Coordination of Pt^{2+} to both the $(N1)^-$ and N7 sites of 9EtG results apparently in an enhanced basicity of N3 if compared with the release of the proton from the (N3)H^+ site in $H_2(9EtG)^{2+}$. For the former cases in aqueous solution (H_2O) it is now proven for a comprehensive set of data (seven examples), by taking into account the intrinsic basicities of the various N7 sites via micro acidity constants, that the acidifications are reciprocal and identical. This means Pt^{2+} coordinated to $(N1)^{-/0}$ sites in guanine, hypoxanthine, or adenine residues acidifies the (N7)H^+ unit to the same extent as (N7)-coordinated Pt^{2+} acidifies the (N1)$H^{0/+}$ site. In other words, the apparently increased basicity of N7 upon Pt^{2+} coordination at $(N1)^{-/0}$ sites disappears if the micro acidity constants of the appropriate isocharged tautomers of the ligand are properly taken into account. It is further proven, on the basis of the evaluations of the nucleotide analogue 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), that these given conclusions are also valid for nucleotides. In addition, it is shown that the mentioned apparent basicity increase, which results from the use of macro acidity constants, has its origin in the fact that the proton–metal ion (Pt^{2+}) interaction (the extent of which depends on the kind of metal ion involved) is less pronounced than the proton–proton interaction. Finally, the proven reciprocal behavior will now allow one to determine micro acidity constants of ligands by studying complexes formed with kinetically inert metal ions. A further result of interest is the proof that the competition of Pt^{2+} (or Pd^{2+}) with the proton for the $(N1)^-$ and N7 binding sites of inosinate results in the isomer where the metal ion is at N7 with the proton relegated to $(N1)^-$; this isomer is favored by a factor of about 2000 compared with the one having the metal ion at $(N1)^-$ and the proton at N7.

1. Introduction

The effect which divalent metal ions including Pt^{2+}, if coordinated to the N7 site of purines, exert on the acidic properties of the corresponding (N1)$H^{0/+}$ site[1] is nowadays relatively well understood,[2,3] and some quantum chemical calculations for the gas phase also exist.[4] This is not

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surprising since the discovery of the powerful antitumor agent cisplatin,[5,6] *cis*-$(NH_3)_2PtCl_2$, fostered tremendously research on platinum complexes.[7−11] Furthermore, the binding of metal ions to N7 of purines has been in the focus already for many years[12] since these N7 sites are the main binding loci for *cis*-$(NH_3)_2Pt^{2+}$ to DNA.[5,7,10] Indeed, as one would expect, N7 coordination of Pt^{2+} leads to an increased acidity of the $(N1)H^{0/+}$ site of purines compared with that of the free ligands.[3]

However, if N1 coordination of Pt^{2+} is considered, it appears that the basicity of the N7 site increases compared with the situation in the free purines.[13−16] At first sight this result is astonishing, yet if one bears in mind that a deprotonated free purine like 9-methyladenine or 9-methylguaninate is always first protonated at the $(N1)^{0/-}$ position and only thereafter at N7, one realizes[3] that a N7 coordination of Pt^{2+} gives rise to an effect which is due to two positively charged units, if compared with the acidity of the $(N1)H^+$/(N1)H sites in the free ligands, whereas binding of Pt^{2+} at $(N1)^{0/-}$ leads only to the effect of one extra charged unit, if compared with the acidic properties of $(N7)H^+$ of the free ligand which has $(N1)H^+$/(N1)H sites (see sections 3.2 and 3.3 for details).

Indeed, recently we have shown[3] that in (dien)Pt(Ino-*N7*)$^{2+}$ the (N1)H site is acidified to the extent commonly expected ($\Delta pK_a \simeq 1.5$),[3] but that the same is true if the effect of $(N1)^-$-bound (dien)Pt^{2+} on the $(N7)H^+$ site in (dien)Pt(H*N7*;Ino-*N1*−H)$^{2+}$ is considered provided the comparison is made with the acid−base properties of the uncomplexed zwitterionic species H*N7*(Ino−H*N1*)$^{\pm}$. The difficulty with such a comparison is that micro acidity constants for the various sites[17,18] need to be known; only then the intrinsic basicity/acidity of a given site is properly quantified.

To this end we have recently studied[19,20] the acid−base properties of several purine derivatives in great detail to derive the various micro acidity constants.[19] These results enable us to provide, e.g., the intrinsic basicity of N7 in uncharged 9-methyladenine, i.e., N1 does not carry a proton, or of N7 in N1-deprotonated guanosine, i.e., of H*N7*(Guo−H*N1*)$^{\pm}$. The macro and micro acidity constants previously obtained are compared now with acidity constants which we calculated for several Pt^{2+} complexes on the basis of published ^{1}H NMR shift data.[13,14,21−24] The core ligands considered in the present study are depicted in Figure 1.[25] Combination of all these results allows a quantitative evaluation of the acidifying effects which Pt^{2+} exerts, if bound to the N1 or N7 sites of various purines, on the remaining acidic (N)H sites.

2. Experimental Section

The materials, equipment, and computer facilities employed in this study are the same as used previously.[19]

Several very careful ^{1}H NMR shift studies are available in the literature which deal with complexes formed by platinum(II) and nucleobase derivatives and which provide detailed data[13,14,21−24] about measurements in D_2O. We enlarged these published figures which show the chemical shift of a system in dependence on pD (or pH*) and read from these the experimental data, transformed where necessary the pH-meter reading pH* to pD, by adding[26] 0.40, and applied then our previously described[20,27] nonlinear least-squares fitting procedure (for examples see Figures 2 and 3 as well as Figures S1−S4 of the Supporting Information). In all instances, we always proved first the reliability of the literature data by fitting the previously measured ^{1}H NMR shifts given in dependence on

(1) Abbreviations (see also Figure 1 and its legend): dien, diethylenetriamine = 1,4,7-triazaheptane; *I*, ionic strength; K_a, (macro) acidity constant; k_a, micro acidity constant; M^{2+}, general divalent metal ion; 1MeC, 1-methylcytosine; NB, nucleobase residue; pH*, pH-meter reading with the electrode in a D_2O solution; TriMeA, N6′,N6′,N9-trimethyladenine. The expression $(N1)H^{0/+}$ represents the (N1)H site in hypoxanthine and guanine derivatives as well as the $(N1)H^+$ unit in adenine derivatives. The Pt(II) complexes are written in the following convention, e.g., as $[(dien)Pt]_2[\mu$-(H*N3*;9EtG-*N7,N1*−H)$]^{4+}$; this means that two (dien)Pt^{2+} units (μ) are coordinated to a single 9-ethylguanine (9EtG) via the *N7* and (*N1*)$^-$ sites, that a proton resides at *N3* of 9EtG, and that in addition 9EtG has lost a proton from the (N1)H unit where now a Pt^{2+} is located.

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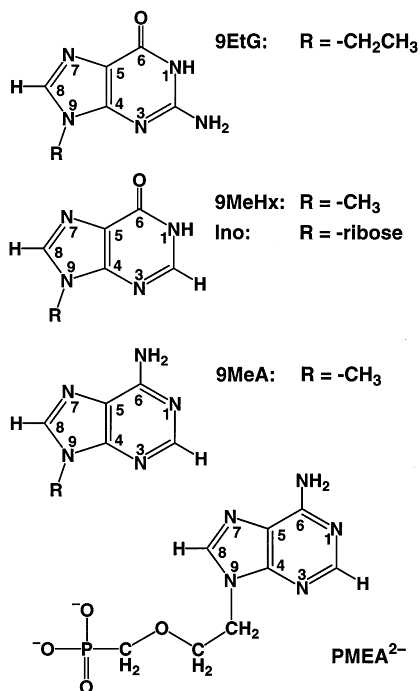


Figure 1. Chemical structures of purine derivatives considered in this study: 9-ethylguanine (9EtG), 9-methylhypoxanthine (9MeHx), and inosine (Ino), as well as 9-methyladenine (9MeA). Also shown is the structure of the dianion of the antivirally active nucleotide analogue 9-[2-(phosphonomethoxy)ethyl]adenine ($PMEA^{2-}$)[25] which is considered in section 3.4.

pD for the free nucleobase ligands with the acidity constants we had measured via potentiometric pH titrations.[19] To this end we transformed our pK_a values valid for water (H_2O) to D_2O as solvent by applying eq 1:[28]

$$pK_{a/D_2O} - 0.45 = pK_{a/H_2O} \times 1.015 \quad (1)$$

When the fits were excellent, we evaluated all data and transformed the results for the Pt(II) complexes valid for D_2O (see Table S1 in the Supporting Information) as solvent with eq 1 to water (see Table 1; vide infra in section 3.1). Hence, all comparisons made in this study refer to aqueous solution (H_2O) with a temperature and an ionic strength close to 25 °C and I = 0.1 M, respectively. In a few instances where data at pH (or pH*) $\lesssim$ 0 had to be evaluated (Figure 2 and Figure S3), the H_0 (D_0) scale was applied by using the listings given in ref 29 between acid concentration and H_0 (for further details see ref 19).

In one case, namely with 9-ethylguanine (9EtG), the plot of the chemical shift of H8 of unbound 9EtG versus pH*, which is shown in Figure 3 of ref 14, is somewhat out of scale. For this reason these ^{1}H NMR measurements were repeated using a DPX 300 spectrometer at 300 MHz and a 9EtG concentration of 0.4 mM in D_2O (24 °C). Two series of experiments were performed, one without adjusting the ionic strength and one with I = 0.1 M ($NaNO_3$); both series gave practically identical results, and therefore, the data of both series were combined for the evaluation. These experimental data obtained now could be excellently fitted with the acidity constants determined by potentiometric pH titrations[19] (see Table 1 in section 3.1) after their transformation with eq 1 to D_2O as solvent: $pK^D_{D(9EtG)} = 3.77 \pm 0.03$ and $pK^D_{9EtG} = 10.16 \pm 0.05$. The corresponding fit is shown in part A of Figure S1 (and Figure S2 as well) in the Supporting Information. All the other original data available for this ligand[14] could be evaluated in a straightforward manner.

There are three symmetrical Pt(II) complexes, like *cis*-$(NH_3)_2$-Pt(9EtG-*N7*)$_2^{2+}$, considered in this study, in which two protons may be released "simultaneously" from equivalent sites; in these instances the difference between the pK_a values was fixed to 0.6, corresponding to the expected statistical factor of 4 between $K_{a/1}$ and $K_{a/2}$ of a diprotonic acid.[30] This treatment was applied to the complexes of entries 5c, 7b, and 7c in Table 1 below in section 3.1.

3. Results and Discussion

3.1. Definition of the Acidity Constants of the Nucleobase Derivatives and of Their Platinum(II) Complexes. In principle, a 9-substituted adenine residue can be protonated at N1, N7, and N3 in that order.[19,31−33] Consequently, the following three deprotonation reactions, where NB represents

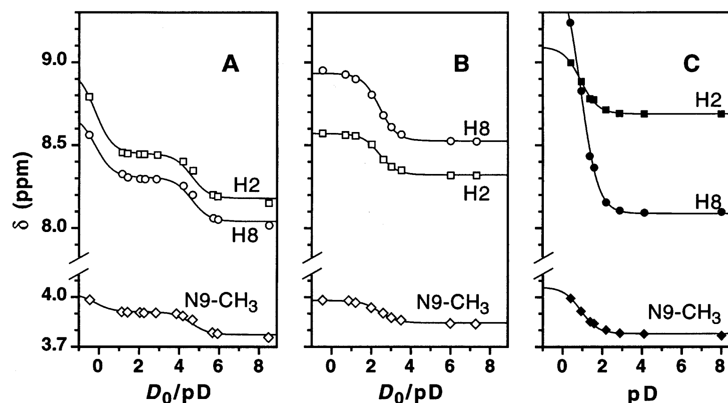
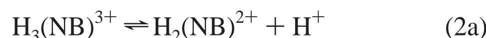


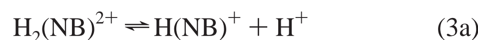
Figure 2. Variation of the chemical shift in dependence on D_0/pD (see section 2) for 9MeA (Figure 1) (A) and several of its Pt(II) complexes (B and C). The solid curves in (A) show the excellent fit of the experimental data pairs taken from refs 13 and 23 (ppm vs pD) with $pK^D_{D_2(9MeA)} = -0.20$ and $pK^D_{D(9MeA)} = 4.61$; these values follow (eq 1) from $pK^H_{H_2(9MeA)} = -0.64$ and $pK^H_{H(9MeA)} = 4.10$ (Table 1, entry 4a) as obtained from NMR and potentiometric titrations.[19] For the *cis*-$(NH_3)_2$Pt(1MeC-*N3*)(H*N1*;9MeA-*N7*)$^{3+}$ (B) and *cis*-$(NH_3)_2$Pt(1MeC-*N3*)(H*N7*;9MeA-*N1*)$^{3+}$ (C) systems and their H2 (□, ■), H8 (○, ●) and (N9)-CH_3 (◇, ◆) protons an independent fitting procedure was carried out and in each case the weighted mean of the three resulting values was calculated; with these acidity constants (i.e., $pK_{a/D_2O} = 2.41$ for (B) and $pK_{a/D_2O} = 0.91$ for (C)) the solid curves seen in parts B and C have been computed. These acidity constants (B, C) valid for D_2O as solvent (see Supporting Information: Table S1; entries 4b, 4c) were transformed with eq 1 to H_2O as solvent; these results are given in entries 4b and 4c of Table 1, respectively (see also section 2).

a general nucleobase residue, can be defined (eqs 2–4):



$$H_3(NB)^{3+} \rightleftharpoons H_2(NB)^{2+} + H^+ \quad (2a)$$

$$K^H_{H_3(NB)} = [H_2(NB)^{2+}][H^+]/[H_3(NB)^{3+}] \quad (2b)$$



$$H_2(NB)^{2+} \rightleftharpoons H(NB)^+ + H^+ \quad (3a)$$

$$K^H_{H_2(NB)} = [H(NB)^+][H^+]/[H_2(NB)^{2+}] \quad (3b)$$

$$H(NB)^+ \rightleftharpoons NB + H^+ \quad (4a)$$

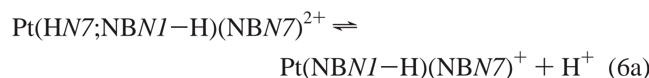
$$K^H_{H(NB)} = [NB][H^+]/[H(NB)^+] \quad (4b)$$

Similarly, a 2-fold protonation of guanine or hypoxanthine residues at N7 and N3 is possible, but only very little information exists about the latter (see also below). Hence, in the present context only eq 4 is of relevance except that these nucleobases can also lose a proton from their (N1)H site (see Figure 1) as is expressed in eq 5:

$$NB \rightleftharpoons (NB-H)^- + H^+ \quad (5a)$$

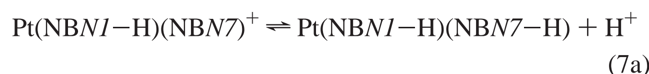
$$K^H_{NB} = [(NB-H)^-][H^+]/[NB] \quad (5b)$$

Once a Pt(II) unit is coordinated to N7 and/or $(N1)^{0/-}$ sites of one or two nucleobase residues, in general one or two deprotonation reactions occur. As an example, let us consider the situation for *cis*-$(NH_3)_2$Pt(H*N7*;9EtG-*N1*–H)(9EtG-*N7*)$^{2+}$. In this complex Pt^{2+} is coordinated to the deprotonated $(N1)^-$ site of one 9-ethylguanine (9EtG) and this same 9EtG also carries a proton at N7 having thus a $(N7)H^+$ site; in addition, the Pt^{2+} is bound via N7 to a second 9EtG which also has a (N1)H site. Consequently, two sites can be deprotonated, namely first $(N7)H^+$ and next (N1)H. If we abbreviate this complex as Pt(H*N7*;NB*N1*–H)(NB*N7*)$^{2+}$, the following two equilibria can be written:



$$Pt(HN7;NBN1-H)(NBN7)^{2+} \rightleftharpoons Pt(NBN1-H)(NBN7)^+ + H^+ \quad (6a)$$

$$K^H_{Pt(HN7;NBN1-H)(NBN7)} = \frac{[Pt(NBN1-H)(NBN7)^+][H^+]}{[Pt(HN7;NBN1-H)(NBN7)^{2+}]} \quad (6b)$$



$$Pt(NBN1-H)(NBN7)^+ \rightleftharpoons Pt(NBN1-H)(NBN7-H) + H^+ \quad (7a)$$

$$K^H_{Pt(NBN1-H)(NBN7)} = \frac{[Pt(NBN1-H)(NBN7-H)][H^+]}{[Pt(NBN1-H)(NBN7)^+]} \quad (7b)$$

Quite generally, the acid–base properties of a given (N)H site can be compared between the free NB ligand and its Pt(II) complex to quantify the effect of the, e.g., N7-coordinated Pt^{2+} on the $(N1)H^{0/+}$ site. This is expressed in a general way in eq 8:

$$\Delta pK'_a = pK_{a/ligand} - pK_{a/complex} \quad (8)$$

In Table 1 the acidity constants of 19 Pt(II) complexes are listed and the values for 13 of these systems were determined now as described in section 2 on the basis of the published[13,14,21–24] ^{1}H NMR shift data. In Figures 2 and 3 representative examples of our evaluations are shown, one each for complexes with the adenine and the hypoxanthine residues, respectively. The evaluation of the other systems is summarized in Figures S1–S4 of the Supporting Information. The values for the remaining six systems are from the literature.[3,15] The acidity constants of the corresponding free nucleobase ligands, which are used for comparisons and which were mostly determined recently by potentiometric pH titrations,[19] are always listed under the entries "a" in Table 1.[34,35]

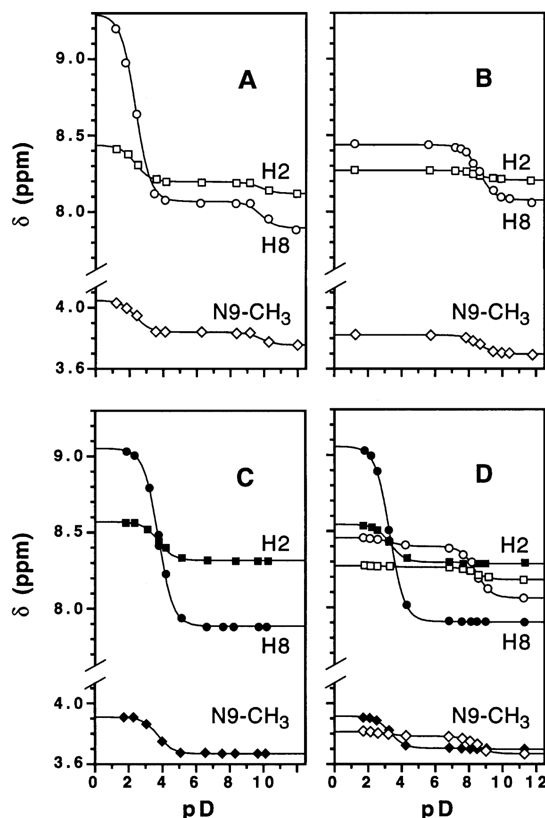


Figure 3. Variation of the chemical shift in dependence on pD for 9MeHx (Figure 1) (A) and several of its Pt(II) complexes (B–D). The solid curves in (A) show the excellent fit of the experimental data pairs taken from ref 21 (ppm vs pD = pH* + 0.40)[26] ($pK^D_{D(9MeHx)}$ = 2.35 and pK^D_{9MeHx} = 9.80; these values follow (eq 1) from $pK^H_{H(9MeHx)}$ = 1.87 and pK^H_{9MeHx} = 9.21 (Table 1, entry 7a) as obtained from potentiometric pH titrations.[19] For the *cis*-$(NH_3)_2$Pt(9MeHx-*N7*)$_2^{2+}$ (B), *cis*-$(NH_3)_2$Pt(H*N7*;9MeHx-*N1*–H)$_2^{2+}$ (C), and *cis*-$(NH_3)_2$Pt(H*N7*;9MeHx-*N1*–H)(9MeHx-*N7*)$^{2+}$ (D) systems and their H2 (□, ■), H8 (○, ●), and (N9)-CH_3 (◇, ◆) protons an independent fitting procedure was carried out and in each case the weighted mean of the three resulting values was calculated; with these acidity constants [i.e., pK_{a/D_2O} = 8.34 and 8.94 (see section 2) for (B), pK_{a/D_2O} = 3.44 and 4.04 (see section 2) for (C), and $pK_{a/N7/D_2O}$ = 3.29 and $pK_{a/N1/D_2O}$ = 8.42 for (D)] the solid curves seen in parts B–D have been computed. These acidity constants (B–D) valid for D_2O as solvent (see Supporting Information: Table S1; entries 7b–d) were transformed with eq 1 to H_2O as solvent; these results are given in entries 7b–d of Table 1, respectively (see also section 2).

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Table 1. Negative Logarithms of the Acidity Constants[a,b] for the (N1)H$^{0/+}$ and (N7)H$^+$ Sites of Free and Pt^{2+}-Coordinated Purine Nucleobases (See, E.g., Eqs 2−7) As Determined by Potentiometric pH Titrations (Ligands) or ^{1}H NMR Shift Measurements (Complexes)[c] with the Extent of the Acidification of the (N1)H$^{0/-}$ Site by (N7)-Coordinated Pt^{2+} and of the (N7)H$^+$ Site by (N1)-Coordinated Pt^{2+} Expressed by $\Delta pK'_a$ (Analogous to Eq 8)

no.	protonated ligand or complex	pK_a for (N3)H$^+$	pK_a for (N7)H$^+$	pK_a for (N1)H$^{0/+}$	$\Delta pK'_a$
1a	H$_2$(9EtG)$^{2+}$	−1.0 ± 0.3[d]	3.27 ± 0.03	9.57 ± 0.05	
b	(dien)Pt(9EtG-*N7*)$^{2+}$			8.35 ± 0.20	1.22 ± 0.21
c	(dien)Pt(H*N7*;9EtG-*N1*−H)$^{2+}$		4.42 ± 0.09		−1.15 ± 0.09
d	[(dien)Pt]$_2$[*μ*-(H*N3*;9EtG-*N7,N1*−H)]$^{4+}$	0.7 ± 0.4			−1.7 ± 0.5
2a	H(9MeHx)$^+$		1.87 ± 0.01	9.21 ± 0.01	
b	(dien)Pt(9MeHx-*N7*)$^{2+}$			7.67 ± 0.08	1.54 ± 0.08
c	(dien)Pt(H*N7*;9MeHx-*N1*−H)$^{2+}$		3.02 ± 0.25		−1.15 ± 0.25
3a	H(Ino)$^+$		1.06 ± 0.06	8.76 ± 0.03	
b	(dien)Pt(Ino-*N7*)$^{2+}$			7.24 ± 0.10	1.52 ± 0.10
c	(dien)Pt(H*N7*;Ino-*N1*−H)$^{2+}$		2.30 ± 0.15		−1.24 ± 0.16
4a	H$_3$(9MeA)$^{3+}$	−2.83 ± 0.30	−0.64 ± 0.06	4.10 ± 0.01	
b	*cis*-(NH$_3$)$_2$Pt(1MeC-*N3*)(H*N1*;9MeA-*N7*)$^{3+}$			1.93 ± 0.10	2.17 ± 0.10
c	*cis*-(NH$_3$)$_2$Pt(1MeC-*N3*)(H*N7*;9MeA-*N1*)$^{3+}$		0.45 ± 0.11		−1.09 ± 0.13
5a	H(9EtG)$^+$		3.27 ± 0.03	9.57 ± 0.05	
b[e]	*cis*-(NH$_3$)$_2$Pt(9EtG-*N7*)(X)$^+$			8.58 ± 0.17	0.99 ± 0.18
c	*cis*-(NH$_3$)$_2$Pt(9EtG-*N7*)$_2$$^{2+}$			7.76 ± 0.09/8.36 ± 0.09	1.81 ± 0.10/1.21 ± 0.10
d	*cis*-(NH$_3$)$_2$Pt(H*N7*;9EtG-*N1*−H)(9EtG-*N7*)$^{2+}$		4.42 ± 0.07	8.47 ± 0.09	−1.15 ± 0.08/1.10 ± 0.10
6a	H$_2$(9EtG)$^{2+}$	−1.0 ± 0.3[d]	3.27 ± 0.03	9.57 ± 0.05	
b	(NH$_3$)$_3$Pt(H*N3*;9EtG-*N7*)$^{3+}$	−0.35 ± 0.4		8.1 ± 0.2	−0.65 ± 0.5/1.47 ± 0.21
c	[(NH$_3$)$_3$Pt]$_2$[*μ*-(H*N3*;9EtG-*N7*,*N1*−H)]$^{4+}$	1.14 ± 0.16			−2.14 ± 0.34
7a	H(9MeHx)$^+$		1.87 ± 0.01	9.21 ± 0.01	
b	*cis*-(NH$_3$)$_2$Pt(9MeHx-*N7*)$_2$$^{2+}$			7.77 ± 0.10/8.37 ± 0.10	1.44 ± 0.10/0.84 ± 0.10
c	*cis*-(NH$_3$)$_2$Pt(H*N7*;9MeHx-*N1*−H)$_2$$^{2+}$		2.94 ± 0.13/3.54 ± 0.13		−1.07 ± 0.13/−1.67 ± 0.13
d	*cis*-(NH$_3$)$_2$Pt(H*N7*;9MeHx-*N1*−H)(9MeHx-*N7*)$^{2+}$		2.80 ± 0.09	7.85 ± 0.15	−0.93 ± 0.09/1.36 ± 0.15
8a	H$_3$(TriMeA)$^{3+}$	−2.7 ± 0.4[f]	−0.77 ± 0.13	4.18 ± 0.04	
b	(dien)Pt(H*N1*,H*N7*;TriMeA-*N3*)$^{4+}$		0.26 ± 0.12	−3.9 ± 0.25	−1.03 ± 0.18/8.1 ± 0.3
9a$_1$	H(9EtG)$^+$	−1.0 ± 0.3[d]	3.27 ± 0.03	9.57 ± 0.05	
a$_2$	H$_3$(TriMeA)$^{3+}$	−2.7 ± 0.4[f]	−0.77 ± 0.13	4.18 ± 0.04	
b	*trans*-(NH$_3$)$_2$Pt(H*N3*;9EtG-*N7*)-	−0.4 ± 0.4		8.12 ± 0.36	−0.6 ± 0.5/1.45 ± 0.36
	(H*N7*;TriMeA-*N3*)$^{3+}$		0.08 ± 0.10		−0.85 ± 0.16

[a] The error limits given are three times the standard error of the mean value (3σ) or the sum of the probable systematic errors, whichever is larger. The error limits of the derived data, in the present case for $\Delta pK'_a$ (eq 8), were calculated according to the error propagation after Gauss. [b] So-called practical, mixed, or Brønsted constants are listed.[19,34] [c] The acidity constants of the protonated ligands (entries 'a') were determined[19] by potentiometric pH titrations (25 °C; $I = 0.1$ M, NaNO$_3$) with the exception of $pK^H_{H(Ino)} = 1.06$ (entry 3a) and of $pK^H_{H_3(9MeA)} = -2.83$ and $pK^H_{H_2(9MeA)} = -0.64$ (entry 4a), which were obtained from NMR[35] and UV measurements,[19] respectively. The result $pK^H_{H_3(TriMeA)} = -0.77$ (entry 8a, column 4) is based also on spectrophotometric measurements.[19] For all instances with pK_a > 1 $I = 0.1$ M (NaNO$_3$) and 25 °C.[19] The same temperature and ionic strength holds for entries 3b,c, which are taken from the work (kinetic experiments) of Arpalahti and Lehikoinen.[15] Evidently, $I > 0.1$ M in those cases where pK_a < 1. The acidity constants of the Pt^{2+} complexes considered under the entry numbers 1, 4−7, and 9 were calculated now as described in section 2 on the basis of published ^{1}H NMR shift data (see Figures 2 and 3 as well as Figures S1−S4 of the Supporting Information). Entry 8b presents a reevaluation, based on the H_0 scale (see ref 19), of spectrophotometric measurements (see Figure 10 of ref 24); previously[24] concentration constants were given. The results for entries 2b,c and 7d are taken from our earlier evaluation[3] of also published ^{1}H NMR shift data.[21] Entries 3b,c are from ref 15 (see also above); the error limits of these acidity constants, derived from kinetic measurements, are estimated. All NMR measurements were made close to 25 °C and $I = 0.01-0.1$ M. [d] This value is from ref 32 and refers to H$_2$(guanine)$^{2+}$. Since the acidity constants of N7-protonated H(guanine)$^+$ and H(9EtG)$^+$ are identical[3] within their error limits and since the pK_a values for the deprotonation of the (N1)H site in guanine and 9EtG differ[3] by only $\Delta pK_a = 0.2$, we consider $pK^H_{H_2(guanine)} = -1.00 \pm 0.3$ (average from the values in ref 32) with a large error limit as a reliable estimate for the pK_a of H$_2$(EtG)$^{2+}$. [e] In ref 14 one reads "X denotes an unknown ligand. ... Since this product elutes just between species with charge +1 and +2 under neutral conditions, it is difficult to deduce the charge of the unknown group. ... Coordination of a hydroxo group (X), however, is unlikely since the amount of the product increases when the reaction is performed under neutral conditions". Tentatively we attribute a negative charge to X because then the complex of entry 5b fits in its properties with those of entries 5c,d (see also text in section 3.2). [f] This value is an estimate on the basis of the result obtained for 9MeA (entry 4a) as well as on those obtained for 1,9- and 7,9-dimethyladenine (for details see ref 19).

3.2. Comparison of the Acid−Base Properties of the Free Nucleobase Ligands with Those of Their Platinum(II) Complexes. Many comparisons are possible among the results listed in Table 1; a few will follow. It had previously[3] been concluded that a Pt^{2+} unit coordinated to N7 of a guanine derivative increases the acidity of (N1)H by $\Delta pK'_a = 1.4 \pm 0.1$. The present data, including those for the hypoxanthine moiety, fall to the largest part within their error limits into the given range (see the final column to the right for entries 1b, 2b, and 3b; the second value of 6b, the first value of 7b, and the second value of 9b).[36] If platinum(II) is coordinated to an anionic ligand like (9EtG−H*N1*)$^-$, the overall charge of the Pt(II) unit is decreased to +1 and then the acidification is somewhat smaller, i.e., $\Delta pK'_a = 1.2 \pm 0.15$ (average of entry 5b and of the second values of entries 5c, 5d, and 7d). This trend agrees with theoretical expectations[4] and also with the results of entry 4b, where a Pt^{2+} unit at N7 of an adenine residue acidifies the *positively* charged (N1)H$^+$ site by $\Delta pK'_a = 2.17$, a value in reasonable accord with that observed previously for *cis*-(NH$_3$)$_2$Pt-(H*N1*;Ado*N7*)$^{3+}$ ($\Delta pK'_a = 1.9 \pm 0.1$).[3,37] Hence, overall we have the interaction series 2+/NH$^+$, 2+/NH, and 1+/NH with $\Delta pK'_a \simeq 2.0 \pm 0.2$, 1.4 ± 0.1, and 1.2 ± 0.15, respectively (error limits estimated). It may be added that at present there are not enough examples[3] to allow a clear distinction between the acidification properties of *cis*-(NH$_3$)$_2$-Pt^{2+} and *trans*-(NH$_3$)$_2$Pt^{2+}.

In the preceding paragraph only the effect of (N7)-coordinated Pt^{2+} on the (N1)H$^{0/+}$ site of purine derivatives

(34) Sigel, H.; Zuberbühler, A. D.; Yamauchi, O. *Anal. Chim. Acta* **1991**, *255*, 63−72.
(35) Corfù, N. A.; Sigel, H. *Eur. J. Biochem.* **1991**, *199*, 659−669.
(36) An exception seems to be the first value in the final column of entry 5c in Table 1, which appears to be too high; the reason for this is at present not clear.
(37) Lemaire, D.; Fouchet, M.-H.; Kozelka, J. *J. Inorg. Biochem.* **1994**, *53*, 261−271. See Table S1 in their Supporting Information.

was considered. How does $(N1)^{0/-}$-bound Pt^{2+} affect the properties of the $(N7)H^+$ site? From entry 1c in Table 1 it follows that in (dien)Pt(H*N7*;9EtG-*N1*−H)$^{2+}$ the N7 site is more basic than in the free ligand; this is why $\Delta pK'_a$ carries a negative sign, $\Delta pK'_a = (3.27 \pm 0.03) - (4.42 \pm 0.09) = -1.15 \pm 0.09$ (see eq 8). There are more such examples in Table 1 (entries 2c, 3c, 4c, and 7c), the most fascinating case in this context being entry 5d with the coordination of the *cis*-$(NH_3)_2Pt^{2+}$ unit to N1 of one 9EtG and to N7 of the second one giving the *cis*-$(NH_3)_2$Pt(H*N7*;9EtG-*N1*−H)(9EtG-*N7*)$^{2+}$ complex, in which the (N7)-coordinated 9EtG is acidified at its (N1)H site whereas in the $(N1)^-$-coordinated case the N7 site becomes apparently again *more* basic than the free ligand. A further corresponding case is given in entry 7d of Table 1.

Though there is one previous quantitative example[15] and a few qualitative ones,[13,14] as well as a recent discussion,[3] this is for the first time that the apparent basicity-enhancing effect of $(N1)^{0/-}$-coordinated Pt^{2+} on the N7 site is described in a quantitative manner for in total 7 examples, making the result unequivocal. From the given examples in Table 1 it becomes in addition clear that the effect operates in all three important types of purines, i.e., in guanines, hypoxanthines, and adenines.

Though no evaluation is possible, as described in the next section 3.3 for the above $(N1)^{0/-}$-coordinated examples, due to the lack of data, it is still evident from entry 8b in Table 1 that (N3)-coordination of a Pt^{2+} unit leads to an analogous basicity-increasing effect at N7 of the adenine residue ($\Delta pK'_a = -1.03 \pm 0.18$); of course, the acidity-promoting effect of the (N3)-coordinated (dien)Pt^{2+} on the neighboring $(N1)H^+$ site is tremendous ($\Delta pK'_a = 8.1$). The mentioned basicity-increasing effect of (N3)-coordinated Pt^{2+} on the (N7)-adenine site is confirmed by entry 9b, where (N3)-coordination of *trans*-$(NH_3)_2$Pt(9EtG-*N7*)$^{2+}$ leads to $\Delta pK'_a = -0.85 \pm 0.16$, in excellent agreement with the preceding example. Furthermore, the effect of *cis*-$(NH_3)_2$Pt(1MeC-*N3*)$^{2+}$ if coordinated to N1 of (N7)-protonated 9MeA amounts to $\Delta pK'_a = -1.09 \pm 0.13$ (Table 1, entry 4c) and this value is within the error limits also identical with the two mentioned $\Delta pK'_a$ values which means that the effect of Pt^{2+} coordinated either at N1 or at N3 of an adenine residue on the $(N7)H^+$ site is very much alike. Considering that the distances (three bonds in each case) between N1 and N7 as well as between N3 and N7 are very similar, this result is understandable.

Equally interesting is the example given in entry 1d of Table 1, where it is shown that the coordination of two (dien)Pt^{2+} units, one each to $(N1)^-$ and N7 of (9EtG−H*N1*)$^-$, makes the N3 site of this ligand more basic ($\Delta pK'_a = -1.7 \pm 0.5$); i.e., deprotonation of $(N3)H^+$ in the complex occurs with a higher pK'_a value if compared with that for the release of the proton from the same site in $H_2(9EtG)^{2+}$ or more specifically H*N3*,H*N7*(9EtG)$^{2+}$. This observation is corroborated by a further example given in entry 6c, where two $(NH_3)_3Pt^{2+}$ units are coordinated to the $(N1)^-$ and N7 sites of (9EtG−H*N1*)$^-$ and where a proton resides at N3; again, the N3 site experiences an apparent increase in basicity ($\Delta pK'_a = -2.14 \pm 0.34$).

Though we are far from being able to obtain the necessary micro acidity constants allowing evaluations analogous to those described in section 3.3 for the cases mentioned in the last two paragraphs, it is clear that the conclusions given below apply also here and that the N3 sites in neutral purine residues must have a remarkable basicity. This observation is meaningful regarding the metal ion-binding properties of DNA since such N3 sites are exposed to the solvent in the minor grove of DNA.

3.3. Micro-Acidity-Constant Evaluation. The Apparent (N7)-Basicity Increase Due to Platinum(II) Coordination at N1 Disappears! What is the reason for the apparent basicity enhancement of the N7 site upon Pt^{2+} coordination to $(N1)^{0/-}$ of a purine-type residue as seen in entries 1c, 2c, 3c, 4c, 5d, 7c, and 7d of Table 1? Evidently substitution at the (N1)H site by Pt^{2+}, if we consider a guanine or hypoxanthine derivative, also means that the $(N1)^-Pt^{2+}$ site carries an overall charge of only one whereas that of the $(N7)Pt^{2+}$ site amounts to two (entries 1b, 2b, 3b, 5c, 6b, 7b, 7d). Hence, if a valid comparison between the effect of Pt^{2+} at N7 versus that at N1 is attempted, one has to consider equally charged ligands and complexes! Of course, the analogous request holds for adenines: Here the $(N7)Pt^{2+}/(N1)H^+$ interaction is compared with the $N7/(N1)H^+$ situation of the free ligand, whereas the $(N1)Pt^{2+}/(N7)H^+$ interaction refers to that of $(N1)H^+/(N7)H^+$; i.e., the charges in the settings used for comparisons are again different.

In other words, we need to know in the case of the guanines and hypoxanthines the acidity of the $(N7)H^+$ site when (N1)H is deprotonated, i.e., when it is present as $(N1)^-$, and for the adenines we need to know the acidity of the $(N7)H^+$ site when N1 is free. These intrinsic acid−base properties of a given site cannot directly be measured because, e.g., in the latter case N1 will always be protonated under conditions where $(N7)H^+$ exists, but they can indirectly be determined via micro-acidity-constant schemes where use is made of the properties of cyclic systems.[17] The micro acidity constants for the ligands considered here have recently been determined[19] by employing methylated derivatives. For example, for 7,9-dimethyladenine the effect of a positive charge residing at N7, thus simulating the $(N7)H^+$ site, on the release of the proton from the $(N1)H^+$ unit can be measured providing thus the needed information for 9MeA:

$$^{+}H{\cdot}N7\text{-}N1{\cdot}H^{+} \rightleftharpoons {}^{+}H{\cdot}N7\text{-}N1 + H^{+} \quad (9a)$$

$$pk^{H\cdot N7\text{-}N1}_{H\cdot N7\text{-}N1\cdot H} = [^{+}H{\cdot}N7\text{-}N1][H^{+}]/[^{+}H{\cdot}N7\text{-}N1{\cdot}H^{+}] \quad (9b)$$

This result in combination with the experimentally accessible (macro) acidity constants allows then to calculate the micro acidity constant for equilibrium 10a:

$$^{+}H{\cdot}N7\text{-}N1 \rightleftharpoons N7\text{-}N1 + H^{+} \quad (10a)$$

$$pk^{N7\text{-}N1}_{H\cdot N7\text{-}N1} = [N7\text{-}N1][H^{+}]/[^{+}H{\cdot}N7\text{-}N1] \quad (10b)$$

The analogous kind of evaluation is possible for guanine and

Table 2. Negative Logarithms of the Acidity Constants[a] for the $(N7)H^+$ and $(N1)H^{0/+}$ Sites of Pt^{2+}-Coordinated Purine Nucleobases (See, E.g., Eqs 6 and 7) in Comparison with the Micro Acidity Constants of the Corresponding Sites in the Free Ligands (Analogous to Eq 10) with the Effect of the Coordinated Pt^{2+} on These Sites Expressed by ΔpK_a (Eq 11)[b]

no.[b]	acidic species	$pk^{N7\text{-}N1}_{H\cdot N7\text{-}N1}$	$pk^{N7\text{-}N1}_{N7\text{-}N1\cdot H}$ [c]	pK_a for $(N7)H^+$	pK_a for $(N1)H^{0/+}$	ΔpK_a
1a	$^+$H*N7*(9EtG)*N1*H	5.62 ± 0.06	9.57 ± 0.05			
b	(dien)Pt(9EtG-*N7*)$^{2+}$				8.35 ± 0.20	1.22 ± 0.21
c	(dien)Pt(H*N7*;9EtG-*N1*−H)$^{2+}$			4.42 ± 0.09		1.20 ± 0.11
2a	$^+$H*N7*(9MeHx)*N1*H	4.62 ± 0.02[d]	9.21 ± 0.01[d]			
b	(dien)Pt(9MeHx-*N7*)$^{2+}$				7.67 ± 0.08	1.54 ± 0.08
c	(dien)Pt(H*N7*;9MeHx-*N1*−H)$^{2+}$			3.02 ± 0.25		1.60 ± 0.25
3a	$^+$H*N7*(Ino)*N1*H	3.62 ± 0.07	8.76 ± 0.03			
b	(dien)Pt(Ino-*N7*)$^{2+}$				7.24 ± 0.10	1.52 ± 0.10
c	(dien)Pt(H*N7*;Ino-*N1*−H)$^{2+}$			2.30 ± 0.15		1.32 ± 0.17
4a	$^+$H*N7*(9MeA)*N1*H$^+$	2.96 ± 0.10	4.07 ± 0.08			
b	*cis*-$(NH_3)_2$Pt(1MeC-*N3*)(H*N1*;9MeA-*N7*)$^{3+}$				1.93 ± 0.10	2.14 ± 0.13
c	*cis*-$(NH_3)_2$Pt(1MeC-*N3*)(H*N7*;9MeA-*N1*)$^{3+}$			0.45 ± 0.11		2.51 ± 0.15
5a	$^+$H*N7*(9EtG)*N1*H	5.62 ± 0.06	9.57 ± 0.05			
c	*cis*-$(NH_3)_2$Pt(9EtG-*N7*)$_2^{2+}$				7.76 ± 0.09/8.36 ± 0.09	1.81 ± 0.10/1.21 ± 0.10
d	*cis*-$(NH_3)_2$Pt(H*N7*;9EtG-*N1*−H)(9EtG-*N7*)$^{2+}$			4.42 ± 0.07	8.47 ± 0.09	1.20 ± 0.09/1.10 ± 0.10
7a	$^+$H*N7*(9MeHx)*N1*H	4.62 ± 0.02[d]	9.21 ± 0.01[d]			
b	*cis*-$(NH_3)_2$Pt(9MeHx-*N7*)$_2^{2+}$				7.77 ± 0.10/8.37 ± 0.10	1.44 ± 0.10/0.84 ± 0.10
c	*cis*-$(NH_3)_2$Pt(H*N7*;9MeHx-*N1*−H)$_2^{2+}$			2.94 ± 0.13/3.54 ± 0.13		1.68 ± 0.13/1.08 ± 0.13
d	*cis*-$(NH_3)_2$Pt(H*N7*;9MeHx-*N1*−H)(9MeHx-*N7*)$^{2+}$			2.80 ± 0.09	7.85 ± 0.15	1.82 ± 0.09/1.36 ± 0.15

[a] For the error limits, see footnote *a* of Table 1. [b] The micro acidity constants are from ref 19, and the acidity constants of the complexes are from Table 1. The entry numbers in this table correspond to those in Table 1 to facilitate comparisons. [c] The values of these micro acidity constants are close to those directly measured for the macro acidity constants; hence, the latter values describe overwhelmingly the deprotonation of the $(N1)H^{0/+}$ site. In fact, a difference (0.03 p*K* unit) between the macro and micro constant occurs for the listed ligands only for 9MeA; for details see ref 19. [d] The corresponding micro acidity constant scheme is given in Figure 4 as an example.

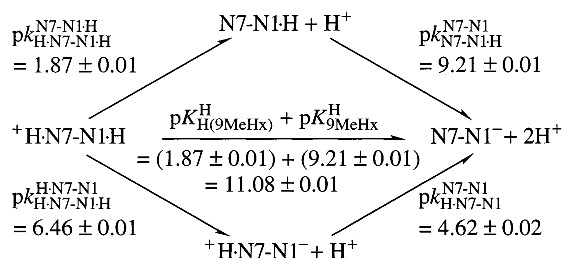

Figure 4. Micro acidity constant scheme for 9-methylhypoxanthine (9MeHx). The scheme defines the micro acidity constants (*k*) and shows their interrelation with the measured macro acidity constants (*K*) and the connection between N7-N1·H and $^+$H·N7-N1$^-$ and the other species present. In N7-N1·H and $^+$H·N7-N1$^-$ the proton is bound to N1 or to N7, respectively; $^+$H·N7-N1·H represents H(9MeHx)$^+$ (Table 1, entry 2a) sometimes also written as H*N7*(9MeHx)$^+$ or $^+$H*N7*(9MeHx)*N1*H (Table 2, entry 2a). The arrows indicate the direction for which the acidity constants are defined (cf. with eqs 9 and 10). Use of the value measured[19] for 7,9-dimethylhypoxanthine (7,9DiMeHx$^+$), $pK^H_{7,9DiMeHx} = 6.46 \pm 0.01$, for the microconstant $pk^{H\cdot N7\text{-}N1}_{H\cdot N7\text{-}N1\cdot H}$ permits calculation of the other microconstants including those given in entry 2a of Table 2 (for details see ref 19; the above scheme is from the Supporting Information for this reference). The error limits of the measured values correspond to three times the standard error; the error limits of the derived constants were calculated according to the error propagation after Gauss (see also Table 1; footnote *a*); however, the error limit of the value given for $pk^{N7\text{-}N1}_{H\cdot N7\text{-}N1}$ was deliberately enlarged from ±0.01 to ±0.02, since the latter appears to us as more realistic.

hypoxanthine derivatives,[19] and for the latter ones an example of a microconstant scheme is given in Figure 4 for 9-methylhypoxanthine (9MeHx) to facilitate understanding of the procedure employed for the ligands. The relevant acidity constants of the complexes taken from Table 1 are now assembled in Table 2 together with the micro acidity constants[19] of the nucleobase ligands.

Let us consider the first entry in Table 2 in detail and use the neutral 9EtG ligand as an example to explain the kind of comparisons made: (dien)Pt^{2+} coordination to N7 of 9EtG gives (dien)Pt(9EtG-*N7*)$^{2+}$ (Tables 1 and 2, entry 1b). To obtain a complex of the same overall charge upon (dien)-Pt^{2+} coordination at $(N1)^-$ one needs an equally charged ligand; i.e., one has to consider the tautomer of 9EtG^0, namely the zwitterionic H*N7*(9EtG−H*N1*)$^\pm$ species, and this gives the complex (dien)Pt(H*N7*;9EtG-*N1*−H)$^{2+}$ (Tables 1 and 2, entry 1c). Of course, the tautomeric H*N7*(9EtG−H*N1*)$^\pm$ ⇌ 9EtG^0 equilibrium is far over to its right side,[19] but its intrinsic or micro acidity constant was determined[19] in the way indicated above and it is given in the third column of Table 2 in entry 1a, $pk^{N7\text{-}N1}_{H\cdot N7\text{-}N1} = 5.62 \pm 0.06$. This value describes the acidity of the $(N7)H^+$ proton in the zwitterion and its comparison according to eq 11 with $pK_a = 4.42 \pm 0.09$ of the (dien)Pt(H*N7*;9EtG-*N1*−H)$^{2+}$ complex gives $\Delta pK_a = 1.20 \pm 0.11$ (Table 2, entry 1c). In other words, if the intrinsic acidity of the $(N7)H^+$ site as quantified by the micro acidity constant is considered, the problem regarding an increased basicity as described in section 3.2 based on the macro acidity constants of the ligand no longer exists, but the system behaves normally and (dien)Pt^{2+} coordination at $(N1)^-$ in H*N7*(9EtG−H*N1*)$^\pm$ gives rise to an acidification at the $(N7)H^+$ site which is within its error limits identical with that observed for the N7-coordinated (dien)Pt(9EtG-*N7*)$^{2+}$ complex, $\Delta pK_a = 1.22 \pm 0.21$ (cf. in Table 2, entries 1b and 1c).

$$\Delta pK_a = pk^{microconstant}_{ligand} - pK_{a/complex} \tag{11}$$

In fact, that the acidification effects of Pt^{2+} are reciprocal and identical for N1 coordination on $(N7)H^+$ and for (N7) coordination on $(N1)H^{0/+}$ is confirmed by the other results listed in Table 2. All those systems which previously had negative values for $\Delta pK'_a$ (eq 8; Table 1) have in the comparisons made now with the micro acidity constants (eq 11) values for ΔpK_a with a *positive* sign (Table 2; entries 1c, 2c, 3c, 4c, and 7c, as well as the first values in the final column of entries 5d and 7d). It is most remarkable to see the identity and equivalency of the values in entries 1−3 of

Table 3. Negative Logarithms of the Acidity Constants for the (N7)H$^+$ and (N1)H$^+$ Sites of the Complexes Formed by (dien)Pt^{2+} Coordination to 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA; See Figure 1) in Comparison with the Macro Acidity Constants of the Ligand as Well as with Its Estimated Micro Acidity Constants (25 °C; for pK_a > 1, I = 0.1 M, NaNO$_3$)[a]

no.	acidic species	pK_a for (N7)H$^+$	pK_a for (N1)H$^+$	ΔpK'_a(eq 8)	ΔpK_a(eq 11)
1[b]	$H_4(PMEA)^{2+}$	−0.7 ± 0.5			
2[c]	$H_2(PMEA)^{\pm}$		4.16 ± 0.02		
3[d]	H[(dien)Pt(H*N1*;PMEA-*N7*)]$^{2+}$		1.80 ± 0.10	2.36 ± 0.10	2.27 ± 0.13
4[e]	H$_2$[(dien)Pt(H*N7*;PMEA-*N1*)]$^{3+}$	0.52 ± 0.10		−1.2 ± 0.5	2.44 ± 0.14
5[f]	$H_2(9MeA)^{2+}$	−0.64 ± 0.06	4.10 ± 0.01		
6[f]	$^+$H*N7*(9MeA)*N1*H$^+$	2.96 ± 0.10	4.07 ± 0.08		

[a] For the error limits see footnote *a* of Table 1. I > 0.1 M, where pK_a < 1. [b] From ref 20. The proton is released from the (N7)H$^+$ site, and the phosphonate group is still 2-fold protonated. The four pK_a values of $H_4(PMEA)^{2+}$ are −0.7 [(N7)H$^+$] (the concentration constant of −0.35 given in ref 20 was now transformed to the H_0 scale to be consistent with the other data), 1.22 [-P(O)(OH)$_2$], 4.16 [(N1)H$^+$], and 6.90 [-P(O)$_2$(OH)$^-$].[20,41] [c] From ref 41; see also footnote *b*. [d] From ref 42. The phosphonate group is monoprotonated under these conditions. [e] From ref 43. The phosphonate group is 2-fold protonated under the conditions where (N7)H$^+$ releases its proton. [f] The macro acidity constants are from entry 4a of Table 1, and the micro acidity constants are from entry 4a of Table 2.

Table 2, thus proving that the acidifying effect is reciprocal. The agreement between the values for the 9MeA systems in entry 4 is somewhat less satisfying though both values are positive; the small discrepancy in size is clearly attributable to experimental errors: the determination of the micro acidity constant for N7 is in this case not trivial since pK_a values ≤0.5 are involved in the cyclic calculations,[19] though a minor error in the pK_a values determined via NMR experiments (Figure 2) for the Pt(II) complexes seems more likely (see also the results of Table 3 discussed below).

A further remarkable observation is that the ΔpK_a values of entries 2 and 3 in Table 2 for systems with a hypoxanthine residue are quite alike, and those of the other related systems (the first values of entries 7c and 7d) are similar. The ΔpK_a values involving a guanine residue are also alike but somewhat smaller (entries 1 and the first value of 5d); the largest ΔpK_a values are observed for the systems with an adenine residue (entries 4b and 4c). Overall, the consistency of the results of this evaluation for the various systems based on micro acidity constants is very satisfying.

3.4. Microconstant Evaluation of a Nucleotide Analogue−Platinum(II) System. Not many purine−nucleotide systems are available for which both the N1 and N7 isomers of their platinum(II) complexes have been synthesized and their solution chemistry studied. One of the rare examples are the complexes of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA; see Figure 1); this ligand may be considered as an analogue of (2′-deoxy)adenosine 5′-monophosphate, and indeed, this compound has useful antiviral properties (see ref 25 for details). Since enzymatic reactions involving nucleotides usually also depend on the presence of metal ions,[6a,b] the coordination chemistry of PMEA has been studied in great detail[38−41] with the aim to shed some light on its possible biological action in the reactions with nucleic acid polymerases.[25] In an effort to modify the biological properties of PMEA, the (dien)Pt^{2+} unit was coordinated to N1 and also to N7, and in this context the solution properties of these two isomeric complexes were studied.[42,43] The pertinent acidity constants are given in Table 3 together with some related data.[20,41−43]

Comparison according to eq 8 of the release of the proton from the (N1)H$^+$ site in the free ligand, $H_2(PMEA)^{\pm}$ (Table 3, entry 2), and in the H[(dien)Pt(H*N1*;PMEA-*N7*)]$^{2+}$ complex (entry 3) to give ΔpK'_a = 2.36 is straightforward because both species are monoprotonated at the phosphonate group and the charge difference between the two species is +2 indeed, corresponding to the charge of the (N7)-coordinated (dien)Pt^{2+} unit. The comparison between the species in entries 1 and 4 regarding the deprotonation of the (N7)H$^+$ site is less straightforward even though in both instances the phosphonate groups are diprotonated because the same problem arises as discussed already in section 3.2; i.e., in $H_4(PMEA)^{2+}$ also N1 is protonated and therefore the increase in charge in the (N1)-platinated complex, H$_2$[(dien)-Pt(H*N7*;PMEA-*N1*)]$^{3+}$, amounts only to +1. The consequence is again that a negative value for ΔpK'_a (=−1.2) is observed. However, both pK'_a differences (Table 3, entries 3 and 4) are very close to those observed for the systems with the phosph(on)ate-free 9-methyladenine ligand (see entries 4b and 4c in Table 1) confirming thus the conclusions reached in section 3.2.

Commonly a further evaluation of nucleotide systems is hardly possible because of the lack of micro acidity constants; yet in the present case the circumstances are fortunate because the macro acidity constants for the (N7)H$^+$ and (N1)H$^+$ sites in $H_2(9MeA)^{2+}$ are nearly identical with the corresponding values in $H_4(PMEA)^{2+}$ and $H_2(PMEA)^{\pm}$ as can be seen from a comparison of the data in entry 5 with those in entries 1 and 2 of Table 3. Hence, one may conclude that the same applies for the micro acidity constants of the mentioned N sites and, thus, the values of entry 6 may be used for calculating according to eq 11 the ΔpK_a values listed in the final column of Table 3. These calculations give

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(40) Ternary complexes: (a) Gómez-Coca, R. B.; Kapinos, L. E.; Holý, A.; Vilaplana, R. A.; González-Vílchez, F.; Sigel, H. *J. Inorg. Biochem.* **2001**, *84*, 39−46. (b) Gómez-Coca, R. B.; Kapinos, L. E.; Holý, A.; Vilaplana, R. A.; González-Vílchez, F.; Sigel, H. *Met.-Based Drugs* **2000**, *7*, 313−324.
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Table 4. Comparison of the Effect of the Proton and of Several Divalent Metal Ions on Deprotonation Reactions of Purines (Aqueous Solution; 25 °C; $I = 0.1$ M, $NaNO_3$)[a]

no.	purine	deprotonation reaction	pK_a or pk_a	ΔpK_a[b]
1a[c]	9EtG	$^{+}$H·N7-N1·H ⇌ $^{+}$H·N7-N1^{-} + H^{+}	7.22 ± 0.01	2.35 ± 0.05
b[d]		$^{2+}$Cu·N7-N1·H ⇌ $^{2+}$Cu·N7-N1^{-} + H^{+}	7.3 ± 0.4	2.27 ± 0.40
c[d]		$^{2+}$Ni·N7-N1·H ⇌ $^{2+}$Ni·N7-N1^{-} + H^{+}	7.85 ± 0.17	1.72 ± 0.18
d[e,f]		$^{2+}$Pt·N7-N1·H ⇌ $^{2+}$Pt·N7-N1^{-} + H^{+}	8.35 ± 0.20	1.22 ± 0.21
e[e,f]		N7-N1·H ⇌ N7-N1^{-} + H^{+}	9.57 ± 0.05	
2a[e]	9EtG	$^{+}$H·N7-N1·H ⇌ N7-N1·H + H^{+}	3.27 ± 0.03	2.35 ± 0.07
b[g]		$^{+}$H·N7-N1^{-}·Cu^{2+} ⇌ N7-N1^{-}·Cu^{2+} + H^{+}	(3.35 ± 0.40)	(2.27 ± 0.40)
c[g]		$^{+}$H·N7-N1^{-}·Ni^{2+} ⇌ N7-N1^{-}·Ni^{2+} + H^{+}	(3.90 ± 0.19)	(1.72 ± 0.20)
d[e,f]		$^{+}$H·N7-N1^{-}·Pt^{2+} ⇌ N7-N1^{-}·Pt^{2+} + H^{+}	4.42 ± 0.09	1.20 ± 0.11
e[f]		$^{+}$H·N7-N1^{-} ⇌ N7-N1^{-} + H^{+}	5.62 ± 0.06	
3a[h]	9MeA	$^{+}$H·N7-N1·H^{+} ⇌ $^{+}$H·N7-N1 + H^{+}	0.50 ± 0.08	3.57 ± 0.11
b[i,j]		$^{2+}$Pt·N7-N1·H^{+} ⇌ $^{2+}$Pt·N7-N1 + H^{+}	1.93 ± 0.10	2.14 ± 0.13
c[j]		N7-N1·H^{+} ⇌ N7-N1 + H^{+}	4.07 ± 0.08	
4a[i]	9MeA	$^{+}$H·N7-N1·H^{+} ⇌ N7-N1·H^{+} + H^{+}	−0.64 ± 0.06	3.60 ± 0.12
b[i,j]		$^{+}$H·N7-N1·Pt^{2+} ⇌ N7-N1·Pt^{2+} + H^{+}	0.45 ± 0.11	2.51 ± 0.15
c[j]		$^{+}$H·N7-N1 ⇌ N7-N1 + H^{+}	2.96 ± 0.10	

[a] For the error limits, see footnote *a* of Table 1. Ni^{2+} or Cu^{2+} are coordinated to the indicated ligand binding sites; their remaining coordination positions are occupied by H_2O. In the case of Pt^{2+} the remaining three positions are occupied either by dien (entries 1d, 2d) or by two NH_3 and one 1MeC-*N3* (entries 3b, 4b); see also the relevant entries in Table 1. [b] The difference is always calculated with the final entry of a data set. [c] Micro acidity constant taken from Figure S9 of the Supporting Information for ref 19. [d] From ref 3. [e] From Table 1, entry 1. [f] From Table 2, entry 1. [g] These values are given in parentheses because they have not been measured directly; they were calculated assuming "reciprocity" (see sections 3.3 and 3.4) by using the ΔpK_a values of entry 1, e.g.: $pK^{H}_{Ni(HN7;9EtG\text{-}N1)} = (5.62 \pm 0.06) - (1.72 \pm 0.18) = 3.90 \pm 0.19$. [h] Micro acidity constant taken from Figure 6 of ref 19. [i] From Table 1, entry 4. [j] From Table 2, entry 4.

positive values of a comparable size for both acidifications, and they are also identical within the error limits with entries 4b and 4c of the related systems in Table 2. Furthermore, in the present case the difference of 0.17 ± 0.19 [=(2.44 ± 0.14) − (2.27 ± 0.13) (Table 3, entries 3 and 4)] between the ΔpK_a values of the two Pt^{2+} complexes, if taken as real, can be attributed to a charge effect because in the N7 isomer (entry 3) the phosphonate group is monoprotonated and carries a charge of −1 whereas in the N1 isomer (entry 4) the phosphonate group is 2-fold protonated and thus this species is neutral; such a −/+ charge effect amounts to about 0.22 (±0.05; error estimated) p*K* units,[44] and this means that the difference between the two values in the final column of Table 3 disappears and becomes equal within the error limits. This observation then confirms the conclusion of section 3.3 that the acidification by Pt^{2+} is reciprocal, meaning that a (N7)-coordinated Pt^{2+} acidifies a (N1)H^+ unit to the same extent as a (N1)-coordinated Pt^{2+} acidifies a (N7)H^+ site.

3.5. Comparison of the Acidifying Properties of H^+ and M^{2+}. The Proton Wins! In the two preceding paragraphs we have seen that the acidifying properties of Pt^{2+}, if one considers metal ion and proton binding at N1 versus N7, are reciprocal, provided the comparison is based on the coordination of Pt^{2+} and H^+ to the two isocharged tautomers of a given purine ligand. However, the micro acidity constants employed in these sections for the ligands allow further comparisons. For these we have selected 9EtG as a representative for guanines and hypoxanthines because for this ligand the largest set of data is available; a few comparisons are also made with 9MeA, an adenine representative.

From entries 1 in Table 4, where H^+ or M^{2+} binding to N7 and their effect on the deprotonation of the (N1)H site is considered, one sees that different divalent metal ions have a different acidifying effect, which means that they have a different polarizing power ($Cu^{2+} > Ni^{2+} > Pt^{2+}$). However, the largest effect is clearly achieved by the single-charged proton as is also seen from entries 2 and confirmed by entries 3 and 4 in Table 4; this illustrates the known[45] stronger polarizing power of the proton over almost any divalent metal ion. Overall, these results conform to the general principle[46] that a proton−proton interaction is of greater magnitude than a metal ion−proton interaction which in turn is greater than a metal ion−metal ion interaction.

There is a further interesting point to be noted: a comparison between the data of Tables 2 and 4 reveals that the ΔpK_a values of entries 1d, 2d, 3b, and 4b of Table 4 also appear in Table 2 (entries 1b, 1c, 4b, 4c). However, a corresponding comparison with Table 1 only reveals a single identical difference, namely entry 1d of Table 4, which is identical with entry 1b of Table 1; the reason is that in Tables 2 and 4 micro acidity constants of the ligands are used in the calculations whereas in Table 1 only macroconstants are employed. However, in this context the negative $\Delta pK'_a$ values of Table 1 experience a "natural" explanation: the difference between the ΔpK_a values of entries 2d and 2a of Table 4 amounts to −1.15 ± 0.13 p*K* units, and this is exactly the value found under entry 1c in Table 1, though the error limits are different because of the different calculation pathways. Similarly, the difference of −1.09 ± 0.19 between entries 4b and 4a of Table 4 appears in entry 4c of Table 1. In other words, the negative $\Delta pK'_a$ values in Table 1, which reflect an apparent increase in basicity at N7 upon Pt^{2+} coordination at $(N1)^{-/0}$, have their origin in the smaller polarizing power of Pt^{2+} compared with that of the proton.

(44) Bastian, M.; Sigel, H. *J. Coord. Chem.* **1991**, *23*, 137−154.

(45) (a) Martin, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2501−2502. (b) Noszál, B.; Scheller-Krattiger, V.; Martin, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 1078−1081.

(46) See page 84 in ref 33.

3.6. Metal Ion or Proton: Which Gets N1 and Which Gets N7? Generally speaking, metal ions and protons compete for binding at $(N1)^{-/0}$ and N7 of purine-nucleobase derivatives. Both, protons and metal ions such as Pd^{2+} bind more strongly at $(N1)^-$ in the proton-free bases of guanine or hypoxanthine derivatives.[12,33] What happens if both a metal ion and a proton are forced to compete for the $(N1)^-$ site of a proton-free base? Which ion is relegated to N7? The answer to this question amounts to finding the molar ratio for the isomeric equilibrium 12, for which the intramolecular equilibrium constant K_I is defined in eq 13:

$$^{+}H{\cdot}N7\text{-}N1^{-}{\cdot}M^{2+} \rightleftharpoons {}^{2+}M{\cdot}N7\text{-}N1{\cdot}H \qquad (12)$$

$$K_I = [^{2+}M{\cdot}N7\text{-}N1{\cdot}H]/[^{+}H{\cdot}N7\text{-}N1^{-}{\cdot}M^{2+}] \qquad (13)$$

This ratio of eq 13 may be found from the equilibrium constants for the deprotonations of the ligand metalated once at $(N1)^-$ and once at N7 and the stability constants for metal ion binding at $(N1)^-$ and N7 in the proton-free nucleobase. These stability constants are not known for the kinetically nearly inert Pt^{2+} complexes but have been determined for the more labile complexes formed with $(dien)Pd^{2+}$. For inosinate, $(Ino-HN1)^-$, and $(dien)Pd^{2+}$, binding at $(N1)^-$ occurs with $\log K_{M(N1)} = 8.33 \pm 0.05$ and for inosinate at N7 with the smaller $\log K_{M(N7)} = 6.80 \pm 0.05$ (errors estimated).[12] These stability constants may be combined with the acidity constants determined for the two isomeric complexes formed between $(dien)Pt^{2+}$ and inosine, $pK^H_{(dien)Pt(Ino\text{-}N7)} = 7.24 \pm 0.10 = pK_{a/N1}$ and $pK^H_{(dien)Pt(HN7;Ino\text{-}N1-H)} = 2.30 \pm 0.15 = pK_{a/N7}$ (Table 1, entries 3b,c), as given in eq 14:

$$\frac{[^{2+}M{\cdot}N7\text{-}N1{\cdot}H]}{[^{+}H{\cdot}N7\text{-}N1^{-}{\cdot}M^{2+}]} = K_I = \frac{K_{M(N7)}{\cdot}K_{a/N7}}{K_{M(N1)}{\cdot}K_{a/N1}} = \frac{10^{(6.80\pm0.05)}{\cdot}10^{-(2.30\pm0.15)}}{10^{(8.33\pm0.05)}{\cdot}10^{-(7.24\pm0.10)}} = 10^{(3.41\pm0.19)} = \frac{2570 \pm 1125}{1} \qquad (14)$$

Since Pt^{2+} and Pd^{2+} have very similar acidifying effects as shown recently[3] for the corresponding complexes of adenosine and inosine and, equally important, since the metal ion stability constants and the pK_a values of the complexes appear as a ratio each in eq 14, intermingling of the two systems should have little effect on the result. Thus, for inosinate and Pt^{2+} or Pd^{2+}, the isomer with the proton at $(N1)^-$ and the metal ion at N7 predominates by a factor of about 2000 over the isomer with the metal ion at $(N1)^-$ and the proton at N7.

4. Conclusions

The comprehensive set of data discussed in this study allows the unequivocal conclusion that, provided the intrinsic acid−base properties are considered via micro acidity constants, Pt^{2+} coordinated in guanine, hypoxanthine, or adenine residues to N7 acidifies the $(N1)H^{0/+}$ site to the same extent as $(N1)^{-/0}$-coordinated Pt^{2+} acidifies the $(N7)H^+$ unit. This means, the acidification is reciprocal (sections 3.3 and 3.4) and the so-called increased basicity of N7 upon Pt^{2+} coordination to $(N1)^{-/0}$ results only if comparisons are made on the basis of the macro acidity constants of the ligands (section 3.2). In fact, this observation is a result of the more pronounced proton−proton interaction compared to the metal ion−proton interaction (section 3.5). In this context it is of further interest that for inosinate, $(Ino-HN1)^-$, a representative hypoxanthine and guanine derivative, the isomer with Pd^{2+} or Pt^{2+} at N7 and the proton at $(N1)^-$ predominates strongly (section 3.6).

Of course, a consequence of the reciprocity is that proton binding at $(N1)^{-/0}$ decreases metal ion binding at N7 to the same extent as proton binding at N7 decreases metal ion binding at $(N1)^{-/0}$. Furthermore, provided the macro acidity constants are known for the free ligand and for both the (N1)- and (N7)-platinated isomers, the present results showing that the effects are reciprocal should prove helpful to establish the micro acidity constant for the $(N7)H^+$ site of the free purine derivative because those of the $(N1)H^{0/+}$ site are close or even identical with the macroconstants. Considering that obtaining micro acidity constants in other ways[19] is difficult and time-consuming, the indicated procedure via the coordination of kinetically inert metal ions is appealing.

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Supporting Information Available: Figures S1−S4, showing the evaluations of the ^1H NMR shift data to give the results listed in Table 1 in entries 1, 5, 6, and 9, respectively, as well as Table S1, which lists the acidity constants calculated for D_2O as solvent. This material is available free of charge via the Internet at http://pubs.acs.org.

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