The N3 Position of N9-Substituted Adenine as a Metal Ion Binding Site: Structural and Solution Studies with Pd^{II} and Pt^{II} Complexes of N6′,N6′,N9-Trimethyladenine

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Abstract: Steric blockage of the N1 and N7 sites of 9-methyladenine for metal complexation is achieved by twofold methylation of the exocyclic amino group. With 6′,6′,9-trimethyladenine (TrimeA), binding of M^{II}(dien) (M = Pt, Pd) as well as of *trans*-$[Pt(NH_3)_2Cl]^+$ therefore takes place through N3. X-ray crystal structure determinations and NMR spectroscopic studies of three compounds are reported, and the effects of Pt^{II} and Pd^{II} on the geometry and the acid–base properties of the TrimeA ligand have been measured and compared with those of the free base. TrimeA has a very pronounced self-stacking tendency in water ($K = 85\,M^{-1}$ according to the isodesmic model of indefinite noncooperative self-association). Acidity constants derived from potentiometric pH titrations, spectrophotometry, and NMR shift experiments display excellent agreement with each other. Twofold protonated TrimeA, that is $H_2(TrimeA)^{2+}$, carries protons at the N7 and N1 sites; the acidity constants are $pK^H_{H_2(TrimeA)} = -0.75$ and $pK^H_{H(TrimeA)} = 4.15$. These values compare well with those of other adenine residues. Protonation of [Pt(dien)(TrimeA-N^3)]$^{2+}$ occurs at the N7 position, as shown by spectrophotometry and NMR spectroscopy. The acidity constant of the H^+(N7) site in this complex is low, that is $pK^H_{H[Pt(dien)(TrimeA)]} = 0.3$ (as determined by spectrophotometry), but it is not as low as that for the same site when a proton resides at N1 of unmetalated TrimeA. The pK_a of the doubly protonated complex, $pK^H_{H_2[Pt(dien)(TrimeA)]}$, in which the second acidic proton is situated at N1, is about -1.2 ± 0.3. These findings indicate that upon metalation of N3, the sequence of adenine protonation is reversed. While the N7 site still displays basic properties, the N1 site has undergone a dramatic loss in basicity.

Keywords
acid–base equilibria · adenine · palladium · platinum · structure elucidation

Introduction

The preferred metal ion binding sites of natural adenine nucleobases and their N9-substituted models such as 9-methyladenine are the N7 and N1 positions.[1–3] Occasionally, metal binding to the exocyclic N6 amino group with substitution of a proton has been observed,[4] also in combination with N1,[5] N7[6] or N1, N7.[7] As far as double-stranded DNA is concerned, these positions are located in the major groove of DNA (N6, N7) and the helix center (N1). Virtually nothing is known about metal binding to the N3 position of adenine in DNA, which is in the minor groove. However, alkylation of this site (N3) by small molecules and by some antitumor antibiotics is well established, and leads to a destabilization of the glycosidic bond and subsequent depurination,[8] unless repaired by a DNA glycosylase.[9] Moreover, the involvement of adenine N3 sites in the cleavage reaction of a hammerhead ribozyme has recently been demonstrated.[10]

Metal binding to N3 of isolated adenine nucleobases has been reported in a number of cases (Figure 1): i) with unsubstituted adenine,[11] ii) with unsubstituted adenine in conjunction with the N9 position[12–14] or an additional site (N7),[15] and iii) in conjunction with a donor ligand attached to N9.[16] With regard to the last, solution studies have provided evidence that this arrangement is also encountered with adenosine 2′-monophosphate (2′-AMP^{2-})[17] and 9-[2-(phosphonomethoxy)ethyl]-adenine ($PMEA^{2-}$).[18] Finally, [Rh(1,10-phenanthroline)$_2$]$^{2+}$ binding to 2-deoxyadenosine has been proposed to take place through N3.[19]

There has been a report on a dinuclear Pd^{II} complex with metal binding to both N3 and N9, which was isolated upon reaction of DNA with a cyclometalated Pd^{II} complex.[20] The

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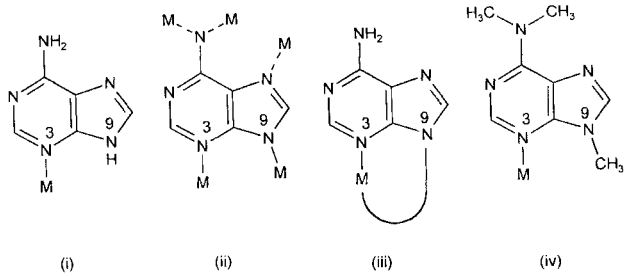

Figure 1. Types of adenine metal complexes containing N3-bonded metal entities.

authors proposed that initial N3 metalation, followed by depurination and addition of a second metal entity to N9 could explain the formation of the product. Alternatively, however, the harsh reaction conditions (HCl, 95 °C) could have been responsible for the initial depurination, which was then followed by metal binding to N9 and N3.

Here we report on what appear to be the first unequivocal examples of metal complexes containing the metal coordinated to the N3 position of a N9-blocked adenine (see Figure 1, iv). The ligand applied, N6′,N6′,N9-trimethyladenine (TrimeA), directs the metal to the N3 position by sterically blocking the N1 and N7 sites to metal coordination. As we have previously shown,[21] a single methyl substituent at N6, as in 6,9-dimethyladenine (6,9-DimeA), does not prevent Pt^{II} binding to N7, since the methyl group can adopt an *anti* orientation with respect to this site.

The only other well-characterized complex of a N9-blocked purine complex containing a metal ion bound to N3 is the threefold platinated 9-ethylguanine complex $[\{(NH_3)_3Pt\}_3(9\text{-EtG-}N^7,N^1,N^3)]^{5+}$ (9-EtG = 9-ethylguanine anion).[22] A characteristic feature of this complex is the dramatic downfield shift of the ^{1}H NMR resonance of the CH_2 group of the ethyl group opposite to the metal at N3. During our work with TrimeA we observed a similar effect on the 9-methyl group in the presence of Pt^{II} and Pd^{II} electrophiles (Figure 2). This observation led us to conclude that these metal entities bind through N3 and initiated our subsequent X-ray structural studies.

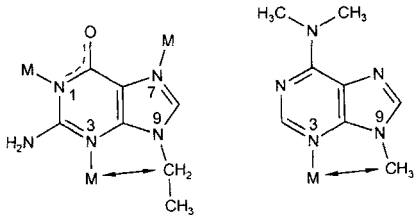

Figure 2. Schematic representation of the close approach between an N3-bound metal entity and a substituent at the N9 position in the 9-ethylguaninate (left) and N6′,N6′,N9-trimethyladenine complexes (right).

Results and Discussion

Solution behavior of 6′,6′,9-trimethyladenine (TrimeA): Spectrophotometric measurements with TrimeA were carried out in the range between 250 and 300 nm to determine the relevant pK_a values of the nucleobase. The average of the computer-calculated best fits of these data (Figure 3) gives $pK^H_{H_2(TrimeA)} = -0.75 \pm 0.20$ (25 °C; $I \approx 5$ M, $HClO_4$) and $pK^H_{H(TrimeA)} = 4.15 \pm 0.05 (3\sigma)$ (25 °C; $I = 0.1$ M, $NaClO_4$). The second value, which is attributed to the deprotonation of the H^+(N1) site of monoprotonated TrimeA in accord with observations on related adenine derivatives[2, 23, 24] as well as the ^{1}H NMR shift experiments (see below), was also determined by potentiometric pH titration. The result $pK^H_{H(TrimeA)} = 4.18 \pm 0.04 (3\sigma)$ (25 °C; $I = 0.1$ M, $NaNO_3$) is in excellent agreement with the value obtained by spectrophotometry. The first value given above, $pK^H_{H_2(TrimeA)} = -0.75 \pm 0.20$, is attributed to the H^+(N7) site of $H_2(TrimeA)^{2+}$. This interpretation regarding the sites of protonation, and the order of the acidity constants is in agreement with the results of studies on threefold protonated adenine (Ade), $H_3(Ade)^{3+}$:[25] $pK^H_{H_3(Ade)} = -4.2$ [for H^+ (N3)], $pK^H_{H_2(Ade)} = -0.4$ [for H^+ (N7)], $pK^H_{H(Ade)} = 4.2$ [for H^+ (N1)]. Similar results are reported for 9-methyladenine ($pK^H_{H(9-MeA)} = 4.3$[21]) and adenosine ($pK^H_{H_2(Ado)} = -1.5$;[25b] $pK^H_{H(Ado)} = 3.6$[26]), even though the pK_a value for the threefold protonated adenosine could not be determined due to decomposition.[25b]

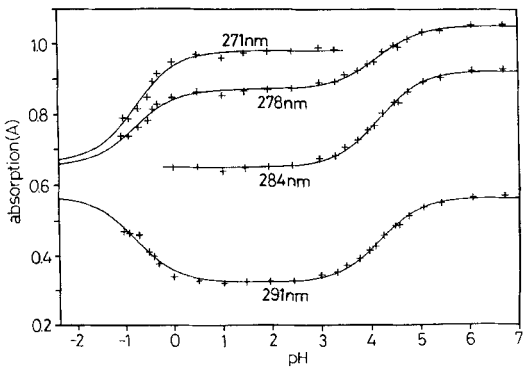

Figure 3. Evaluation of the dependence of the UV absorption of TrimeA on the pH value at different wavelengths. The solid curves represent the computer-calculated best fits of the experimental data points (see also Experimental Section).

The evaluation of the chemical shifts in the ^{1}H NMR spectra of TrimeA (0.13 M) measured in D_2O as a function of the pD value gave the result $pK^D_{D(TrimeA)} = 4.09 \pm 0.06 (3\sigma)$ (20 °C; $I \approx 0.15$ M). The details are summarized in Table 1. The downfield shift ($\Delta\delta$) upon protonation of TrimeA is somewhat more pronounced for H2 than for H8,[27] which is in accordance with the above conclusion that the proton is located at N1. Of course, the shift differences between H2 and H8 are not very pronounced (Table 1), as is expected for the aromatic purine system and in agreement with previous observations.[26, 28] The reason why no pK_a value could be obtained from the resonances of the N6(CH_3)$_2$ group (Table 1) will be discussed below. At this

Table 1. Acidity constant $pK^D_{D(TrimeA)}$ and chemical shifts of various hydrogens of 6′,6′,9-trimethyladenine as calculated from ^{1}H NMR shift data (D_2O, $I = 0.13$ M, 20 °C). $pK_{av} = 4.09 \pm 0.06 (3\sigma)$/weighted mean.

H	$pK^D_{D(TrimeA)}(1\sigma)$	δ(D-TrimeA)(3σ)	δ(TrimeA)(3σ)	$\Delta\delta(3\sigma)$
H2	4.050 ± 0.018	8.404 ± 0.019	7.591 ± 0.011	0.813 ± 0.022
H8	4.118 ± 0.020	8.294 ± 0.016	7.571 ± 0.009	0.723 ± 0.018
N9(CH_3)	4.096 ± 0.019	3.917 ± 0.010	3.474 ± 0.006	0.443 ± 0.012
N6(CH_3)$_2$	–	– [a]	3.000 ± 0.093	–

[a] The reason why these resonance signals were not evaluated is evident from the final paragraph in the first part of the Results and Discussion section.

point it needs to be emphasized that the above pK_a value valid for D_2O as solvent may be transformed to an aqueous solution (H_2O) with Equation (a)[29] to give $pK^{H}_{H(TrimeA)} = 3.59 \pm 0.06$.

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

This acidity constant is much lower ($\Delta pK_a \approx -0.6$) than the previous two results given above, which were obtained from UV spectrophotometry and potentiometric pH titration. The only obvious difference in the experimental conditions is the concentration employed for TrimeA. From our previous experience[30] we suspected that this observation could be a consequence of self-stacking of TrimeA.

This difference in pK_a values prompted us to study the self-association of TrimeA in D_2O by ^1H NMR spectroscopy. Indeed, both aromatic adenine protons undergo dramatic upfield shifts with increasing concentrations of TrimeA, and this demonstrates that the self-association in fact occurs by stacking. Furthermore, the size of the upfield shifts for H2 and H8 of $\Delta\delta = 0.87$ and 0.57 ppm, respectively (Table 2), also proves[31] that the self-stacking occurs beyond the dimer stage. The experimental data, that is the relationship between chemical shift and TrimeA concentration, were analyzed according to the isodesmic model of indefinite noncooperative self-association;[31] thus, the association constant $K = [(TrimeA)_{n+1}]/([(TrimeA)_n][TrimeA])$, from equilibrium (b). The measured self-

$$(TrimeA)_n + TrimeA \rightleftharpoons (TrimeA)_{n+1} \quad (b)$$

association constant, $K_{av} = 85 \pm 9\,M^{-1}$ (Table 2), is substantially higher than those of adenosine ($K = 15 \pm 3\,M^{-1}$)[31d] or 1,10-phenanthroline ($K = 31.1 \pm 3.4\,M^{-1}$);[32] this is a consequence of the methyl substituents at the exocyclic amino group and is in accordance with previous observations at N6′,N6′-dimethyladenosine.[33] The species distribution (that is formation of the monomers, dimers, trimers, etc.) as a function of the concentration of TrimeA is shown in Figure 4.

Table 2. Self-association constant K according to the isodesmic model and chemical shifts of H2 and H8 of 6′,6′,9-trimethyladenine as calculated from ^1H NMR shift data (D_2O, $I \approx 0$ M, 20 °C). $K_{av} = 85 \pm 9(2\sigma)$/weighted mean (by log K).

H	$K(1\sigma)$	$\delta_0(2\sigma)$	$\delta_x(2\sigma)$	$\Delta\delta(2\sigma)$
H2	85.18 ± 5.66	8.212 ± 0.017	7.346 ± 0.029	0.866 ± 0.034
H8	83.57 ± 8.09	8.020 ± 0.013	7.446 ± 0.022	0.574 ± 0.026

Calculations analogous to those whose results are illustrated in Figure 4 demonstrate that under the conditions of the pK_a-NMR experiment, that is [TrimeA] = 0.13 M, only 6.7% of the nucleobase is present in the monomeric form; consequently, the pK_a value determined in this experiment does not really refer to $H(TrimeA)^+$, but to associated species. This situation contrasts with the spectrophotometric experiments ([TrimeA] = 5.6×10^{-5} M), in which more than 99% is present as a monomer, and also with the potentiometric pH titrations ([TrimeA] = 4.6×10^{-4} M), in which about 93% exist as monomers. Hence, only these latter two experiments provide acceptable values for $pK^{H}_{H(TrimeA)}$, whereas the NMR experiment proves that stacking interactions alter the acid–base properties of a nucleobase.

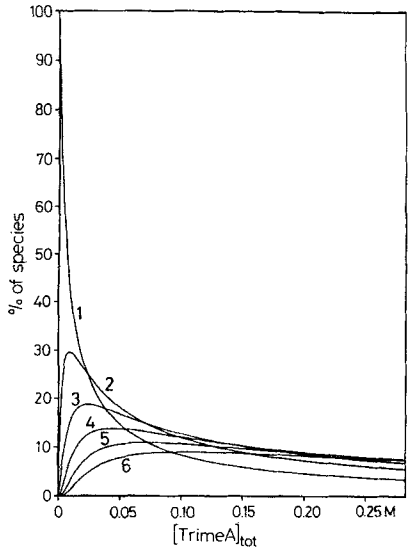

Figure 4. Computer-calculated species distribution (monomer, dimer, trimer, ...) of the neutral TrimeA as a function of concentration in aqueous solution with $K = 85\,M^{-1}$ (see Table 2).

Specifically, stacking of TrimeA reduces the basicity of the nucleobase to accept a proton.

At ambient temperature and neutral pH or pD values, the resonance due to the N6 methyl protons in D_2O consists of a rather broad singlet. At pD values ≤ 3 this singlet splits into two signals, separated by about 116 Hz. This behavior indicates that rotation of the $N6(CH_3)_2$ entity about the C6–N6 bond is slow at ambient temperature and frozen out upon protonation at N1. The slowing down of this rotation probably is due to an increase in the C6–N6 double-bond character as a consequence of nucleobase protonation. NMR spectra of the neutral nucleobase recorded at low temperature in [D_7]DMF permit an estimation of the $\Delta G^{\neq}$ value for this process [ca. 56 kJ mol^{-1}].[34] This value compares very well with data reported for 1,4′,4′-trimethylcytosine.[35]

Formation and NMR spectroscopic characterization of M^{II}(dien) (M = Pt, Pd) complexes: The formation of [Pd(dien)(TrimeA-N^3)]$^{2+}$ (**1**) and [Pt(dien)(TrimeA-N^3)]$^{2+}$ (**2**) from the adenine nucleobase and the respective [M(dien)(D_2O)]$^{2+}$ species was monitored initially by ^1H NMR spectroscopy in D_2O. Complex formation was evident from downfield shifts of the adenine resonances ($\Delta\delta(H2) \approx 1$, $\Delta\delta(H8) \approx 0.5$, $\Delta\delta(N9(CH_3)) \approx 1.3$ ppm). Both complexes are inert on the NMR time scale; in each case separate sets of resonances were observed for the complexes and the free nucleobase. Complex **1** was isolated on a preparative scale as its ClO_4^- salt **1a**, complex **2** as the ClO_4^- salt **2a** and the NO_3^- salt **2b**. As expected, different counterions in **2a** and **2b** have no effect on the solution spectra.

Pt^{II} binding to the adenine nucleobase in **2** is confirmed by ^{195}Pt NMR spectroscopy ($\delta = -2825$ in D_2O, pD 6.1; $\delta = -2527$ in [D_6]DMSO); the chemical shift observed is consistent with a PtN_4 coordination sphere.[36] The ^1H NMR resonances of the isolated compounds in D_2O are identical with those of the species formed upon mixing the starting materials. In [D_6]DMSO the resonances for H2, H8, and $N9(CH_3)$ are split into two components each in a ratio of about 2:1, in D_2O

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this is true for H2 and N9(CH_3) (see below). Resonances arising from the dien ligand are very complex[37] and are superimposed with the N6(CH_3)$_2$ resonances. They were not further analyzed. Relative to the neutral nucleobase, H2, H8, and N9(CH_3) resonances have shifted downfield as a consequence of Pt binding. The effect is most dramatic for the N9(CH_3) signals, which are shifted by about 1.3 ppm (D_2O) and about 1.0 ppm ([D_6]DMSO). Since these signals in D_2O are close to that of residual water at $\delta = 4.75$, detection is difficult, in particular, if the resonance signal for water is suppressed by presaturation. The large shift is a consequence of the close proximity between Pt at N3 and the protons of the methyl group at N9, as seen in the crystal structure analyses of **1a** and **2a**. Since the methyl group can still rotate, the observed shift is reduced due to signal averaging. The downfield shifts are comparable to that of the CH_2 quartet of the ethyl group of 9-EtG in its triply platinated complex.[22] However, through-space $^{195}Pt,^{1}H$ coupling is not observed in either case.

The above-mentioned splitting of adenine resonances probably is due to differences in the folding of the dien ligand ($\lambda\delta$ or $\delta\lambda$ conformation). The splitting is absent in the case of *trans*-(NH_3)$_2$Pt^{II} binding to N3 (see below) and disappears above 70 °C–80 °C ([D_6]DMSO), but is consistently observed when M(dien) (M = Pt^{II} or Pd^{II}) is bound to N3 of a guanine nucleobase (5′-dGMP or 9-MeG).[38]

The ^{1}H NMR spectrum of **1** in D_2O is very similar to that of **2**, both in terms of the resonance splitting and the chemical shifts of protons. However, compound **1** is less stable than **2**; even at pH 6 traces of free nucleobase are detectable, which increase in intensity as the pH value is reduced. At pD ≈ 3.3, 50% of **1** is decomposed, and at pD = 1.2 only free, protonated ligand is observed in the ^{1}H NMR spectrum. This behavior suggests that, unlike with **2** (see below), a protonated derivative of **1**, that is H[Pd(dien)(TrimeA)]$^{3+}$, is not stable in aqueous solution. Since DNO_3 was used in this experiment we can exclude the possibility that coordination of an anion (of the acid used) is responsible for the removal of Pd^{II} from the complex.

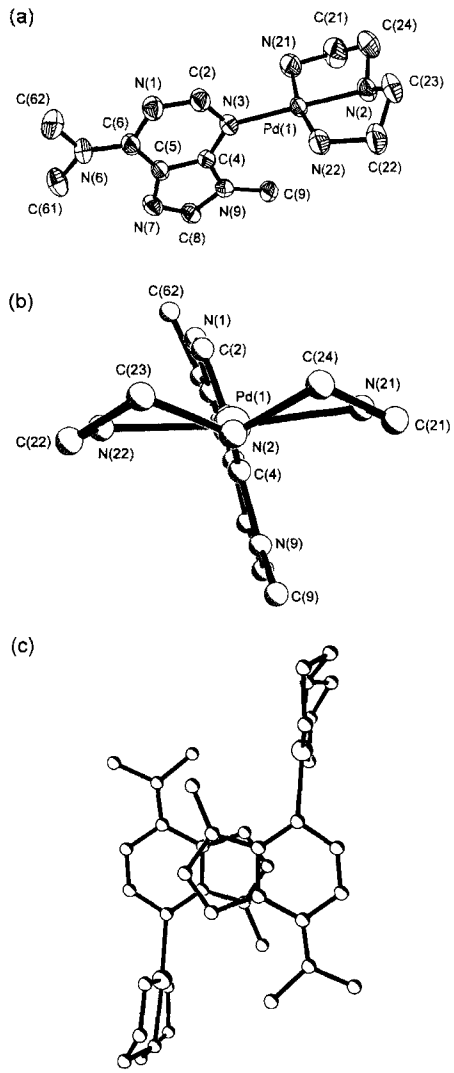

Figure 5. a) View of the cation **1** with atom numbering scheme; b) view of the cation **1** along the N2-Pd-N3 vector; c) view perpendicular to the TrimeA planes of two adjacent cations of **1a**.

Crystal structure analysis of 1a: Figure 5 depicts the cation **1**, and provides two additional views, along the N2-Pd-N3 vector, and perpendicular to the adenine plane. Crystal data and experimental details of the data collection, solution of the structure, and refinement are summarized in Table 3 and in the Experimental Section. Selected structural features are compiled in Table 4.

The molecular structure of the cation **1** confirms N3 metal coordination of Pd^{II} to the trimethyladenine. The dien ligand adopts a sting-ray like folding (Figure 5b), very much like that in many related M(dien)X compounds (M = Pt^{II},[37, 39, 40] Pd^{II}[41]). Like in these compounds, the angles of the metal coordination sphere deviate from ideal square-planar, but the Pd–N distances are normal, including the one to the nucleobase. The dihedral angle between the Pd coordination plane and the adenine nucleobase is 78.2°. Comparison of structural details of the trimethyladenine ring in **1** with that in 9-substituted adenines[42] or in 9-methyladenine (9-MeA) in particular[43] reveals a number of interesting details. For example, the external ring angle C(4)-N(9)-C(9) (130.3(4)° in **1**) is clearly larger than that in 9-MeA (126.1(1)°), while the reverse is true for the angle C(8)-N(9)-C(9) (124.0(5)° in **1**, 128.4(1)° in 9-MeA), suggesting that the 9-methyl group and the Pd at N3 are mutually pushing away each other. This interpretation is supported by the considerable differences in external ring angles at N3 of complex **1** (C(4)-N(3)-Pd(1) 128.4(3)°; C(2)-N(3)-Pd(1) 118.7(3)°). The internal ring angle at N3 (112.7(4)° in **1**) is larger than that found in 9-MeA (110.0(1)°, 6σ[44]), as expected for Pd binding to the lone pair of electrons at N3. Although protons were not located in the structure determination, from the intracomplex distance between Pd(1) and C(9) (3.30 Å) the shortest possible separation between a C9 proton and Pd can be estimated to be around 2.4 Å.[45] Thus the proton is virtually in an axial position relative to the Pd center. This feature is undoubtedly responsible for the observed downfield shift of the CH_3 protons at N9. Similar short metal-H-C contacts have been reported for a number of Pt^{II} complexes.[46]

Crystal structure analysis of 2a: Pertinent crystal structure data of [Pt(dien)(TrimeA-N^3)](ClO$_4$)$_2$·1.5 H_2O (**2a**) are included in Table 3 and in the Experimental Section. Selected bond lengths

Table 3. Crystal structure data of **1a**, **2a**, and **3**.

	1a	**2a**	**3**
formula	$C_{12}H_{24}N_8O_8Cl_2Pd$	$C_{12}H_{24}N_8O_8Cl_2Pt\cdot 1.5H_2O$	$C_8H_{17}N_7O_4Cl_2Pt$
M_r	585.69	701.41	541.28
system	triclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P2(1)/c$	$P\bar{1}$
a (Å)	9.233(2)	15.218(3)	8.746(2)
b (Å)	10.513(2)	21.546(4)	12.128(2)
c (Å)	11.627(2)	14.634(3)	16.792(3)
α ( )	84.85(3)	90	105.88(3)
β ( )	88.14(3)	106.12(3)	98.39(3)
γ ( )	71.64(3)	90	104.33(3)
V (Å^3)	1066.8(4)	4609.6(16)	1615.7(5)
Z	2	8	4
ρ_{calcd} (Mgm^{-3})	1.823	2.021	2.225
absorb. coeff. (1 mm^{-1})	1.178	6.383	9.043
cryst. size (mm)	1.2 × 0.5 × 0.5	0.42 × 0.23 × 0.22	0.33 × 0.14 × 0.13
no. meas. refl.	3619	4811	7817
no. unique refl.	3482	4679	7466
no. obs. refl.	3232	4629	4720
criterion for obs.	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
T_{min}, T_{max}	0.764, 0.969	0.045, 0.081	0.059, 0.108
variation obs. stand.	−5.20%	−3.08%	−5.01%
decay correction	linear	linear	linear
refinement type	on F_o^2	on F_o^2	on F_o^2
R (obs. data) [a]	0.0412	0.0600	0.0354
R_w (obs. data) [b]	0.1170 [d]	0.1072 [e]	0.0703 [f]
GooF (= S) [c]	1.130	1.097	0.980
no. refined param.	284	593	410
$(\Delta\rho)_{min}$ (e Å^{-3})	−0.985	−0.738	−1.340
$(\Delta/\rho)_{max}$ (e Å^{-3})	0.714	1.155	1.047

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$. [c] GooF $= S = [\sigma[w(F_o^2 - F_c^2)^2]/(n - p)]^{1/2}$. n = number of reflections, p = number of parameters refined. [d] $w = 1/[\sigma^2(F_o^2) + 0.0699P^2 + 1.97P]$. $P = [\max(F_o^2,0) + 2F_c^2]/3$. [e] $w = 1/[\sigma^2(F_o^2) + 0.0505P^2 + 4.72P]$. $P = [\max(F_o^2,0) + 2F_c^2]/3$. [f] $w = 1/[\sigma^2(F_o^2) + 0.0343P^2 + 0.00P]$. $P = [\max(F_o^2,0) + 2F_c^2]/3$.

Table 4. Selected interatomic distances [Å] and angles [°] of **1a** with estimated deviations in parentheses.

Pd(1)–N(2)	2.007(5)	N(2)-Pd(1)-N(22)	84.4(2)
Pd(1)–N(22)	2.045(5)	N(2)-Pd(1)-N(3)	177.8(2)
Pd(1)–N(3)	2.047(4)	N(22)-Pd(1)-N(3)	93.7(2)
Pd(1)–N(21)	2.057(5)	N(2)-Pd(1)-N(21)	85.0(2)
		N(22)-Pd(1)-N(21)	167.1(2)
		N(3)-Pd(1)-N(21)	96.7(2)
Pd(1)–C(9)	3.294(5)	C(4)-N(9)-C(9)	130.3(4)
		C(8)-N(9)-C(9)	124.0(5)
		C(4)-N(3)-Pd(1)	128.4(3)
		C(2)-N(3)-Pd(1)	118.7(3)
		C(2)-N(3)-C(4)	112.7(4)

Table 5. Selected interatomic distances [Å] and angles [°] of **2a** with estimated deviations in parentheses.

	Cation 1	Cation 2
Pt–N(3)	2.066(11)	2.049(13)
Pt–N(11)	2.026(14)	2.045(12)
Pt–N(12)	1.988(12)	1.994(12)
Pt–N(13)	2.046(13)	2.054(11)
Pt–C(9)	3.270(18)	3.340(18)
N(3)-Pt-N(11)	93.6(5)	95.0(5)
N(11)-Pt-N(12)	84.2(6)	84.7(5)
N(12)-Pt-N(13)	84.8(7)	83.8(5)
N(13)-Pt-N(3)	97.0(6)	96.1(5)
N(3)-Pt-N(12)	176.8(6)	176.6(5)
N(11)-Pt-N(13)	166.5(6)	166.9(5)
C(4)-N(9)-C(9)	129.8(13)	126.4(13)
C(8)-N(9)-C(9)	126.0(13)	127.8(14)
C(4)-N(3)-Pt	128.4(11)	127.7(11)
C(2)-N(3)-Pt	117.9(11)	117.6(11)
C(2)-N(3)-C(4)	112.7(13)	114.8(14)

and angles are listed in Table 5. The compound crystallizes with two crystallographically independent units (Pt(1), Pt(2)), which differ only slightly. Both cations are very similar to **1** and are therefore not shown. Similarities include the folding of the dien ligand, the angles at N3 and N9, and the Pt(1)–C(9) (3.27(2) Å) and Pt(2)–C(9′) (3.34(2) Å) separations. Dihedral angles between the PtN_4 coordination planes and the adenine nucleobase are almost identical (89.8(5)° at Pt(1) and 89.0(4)° at Pt(2)). A difference exists in terms of the arrangement of pairs of identical cations in the solid state (Figure 6). Thus, two Pt(1) cations are oriented head-to-tail; the adenine rings are stacked (3.41 Å), and two H bonds form between N(7) of TrimeA and N(11) [N(11)···N(7a) and N(7)···N(11a)] of the dien ring (3.11(2) Å). Pairs of Pt(2) cations are likewise oriented head-to-tail; the adenine rings are parallel, and stacked (3.25 Å), but in this case the H bonding is indirect and occurs through a water molecule (N(7)–O(w3), 3.00(2) Å; O(w3)–N(11), 2.88(2) Å).

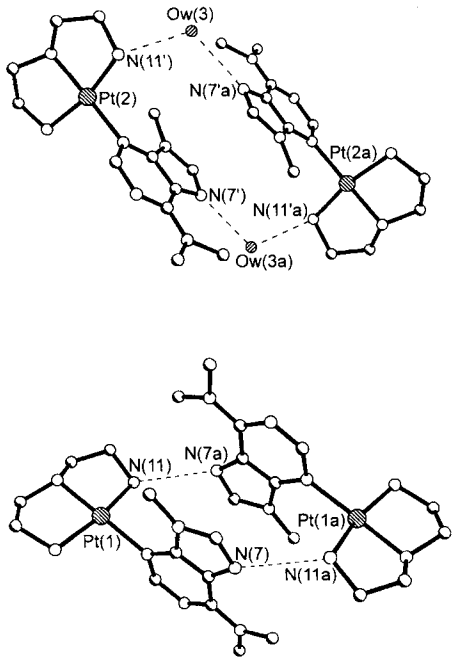

Figure 6. View of H bonding schemes of two independent cations of [Pt(dien)(TrimeA-N^3)](ClO$_4$)$_2\cdot 1.5H_2O$ (**2a**).

NMR spectra and crystal structure analysis of *trans*-[Pt(NH$_3$)$_2$(TrimeA-N^3)Cl]ClO$_4$ (3): Reaction of *trans*-[Pt(NH$_3$)$_2$Cl(H$_2$O)]$^+$ with TrimeA yields **3**. The ^{195}Pt NMR spectrum ($\delta = -2276$, D_2O) is consistent with a PtN_3Cl coordination sphere. Unlike with **1** and **2**, H2 and H8 resonances of the TrimeA ligand in **3** display single resonances. H2 occurs downfield from H8 and undergoes partial H/D exchange in D_2O. The N9(CH$_3$) reso-

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nance is located close to the water resonance ($\delta = 4.9$) and not observed if the water resonance is suppressed. The N6(CH_3)$_2$ signals appear as two broad singlets or as a single, broad resonance at about $\delta = 3.5$. pD-dependent ^{1}H NMR spectra indicate protonation of the adenine ligand ($pK_a \approx 0.8$ in D_2O and 0.3 in H_2O[29]), most likely at N7, since the downfield shift of H8 upon protonation ($\Delta\delta \approx 0.8$ ppm) is larger than that of H2 ($\Delta\delta \approx 0.5$ ppm).

The X-ray structure determination of **3** confirms Pt binding to the N3 position of adenine. The compound crystallizes with two independent cations. Crystallographic data and selected geometrical features are given in Tables 3 and 6. One of the two independent cations is depicted in Figure 7a. The Pt coordination spheres in both cations are not unusual in terms of the bond lengths.[47] A comparison of Pt–N3 bond lengths in **2a** and **3** reveals no crystallographically significant differences. The angles about Pt, although close to 90°, do show some alternation in both cations that appears to be related to a mutual repulsion of C9(CH_3)/C9′(CH_3) and the ammonia ligand closest to this group (N(11) and N(22), respectively), for example N(3′)-Pt(2)-N(22) 92.9(2)°, but N(22)-Pt(2)-Cl(2) 87.4(2)°. Pt–C9(CH_3) separations are 3.35(1) and 3.39(1) Å for the Pt(1) and the Pt(2) cation, respectively, very similar to the values in **1a** and **2a**. The changes in ring angles at N3 and N9 relative to the free adenine nucleobases, as discussed for **1a** and **2a**, also apply to **3**. The major difference between the two crystallographically independent cations of **3** refers to the dihedral angles between Pt coordination planes and the adenine base (Figure 7b). While in the Pt(1) cation these two planes are practically perpendicular (dihedral angle 89.3(2)°), they form an angle of 68.2(2)° in the Pt(2) cation. The latter appears to be attributed to the presence of an oxygen atom (O(32)) of a ClO_4^- counterion, which, located exactly above the PtN_3Cl plane, forms a short contact (3.43 Å) with Pt(2). At the opposite side of the Pt plane, the mentioned short contact to CH_3(9) exists, thus making Pt^{II} essentially (4 + 2) coordinate.

Table 6. Selected interatomic distances [Å] and angles [°] of **3** with estimated deviations in parentheses.

	Cation 3	Cation 4
Pt–N(3)	2.038(6)	2.048(5)
Pt–N(11)/N(21)	2.055(6)	2.047(6)
Pt–N(12)/N(22)	2.056(6)	2.043(6)
Pt–Cl	2.283(2)	2.278(2)
Pt–C(9)	3.352(10)	3.390(9)
N(3)-Pt-N(11)/N(21)	91.9(2)	90.3(3)
N(11)/N(21)-Pt-Cl	87.9(2)	89.3(2)
Cl-Pt-N(12)/N(22)	89.4(2)	87.4(2)
N(12)/N(22)-Pt-N(3)	90.9(3)	92.9(2)
N(3)-Pt-Cl	178.3(2)	176.1(2)
N(11)/N(21)-Pt-N(12)/N(22)	177.0(3)	176.6(3)
C(4)-N(9)-C(9)	130.2(6)	130.8(6)
C(8)-N(9)-C(9)	124.1(7)	124.0(6)
C(4)-N(3)-Pt	128.5(5)	128.1(5)
C(2)-N(3)-Pt	120.1(5)	117.1(5)
C(2)-N(3)-C(4)	111.2(6)	114.8(6)

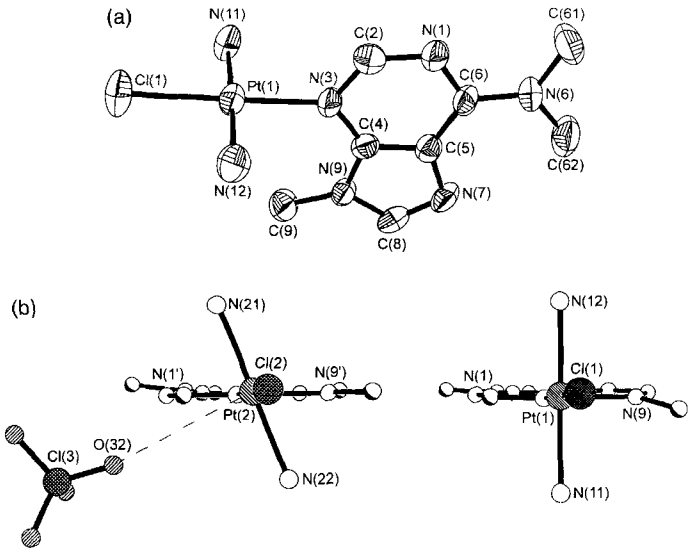

Figure 7. a) View of one of two independent cations of *trans*-[Pt(NH_3)$_2$(TrimeA-N^3)Cl]ClO_4 (**3**); b) different orientations of PtN_3Cl planes with respect to the adenine planes in the two cations of **3**. The close contact (3.43 Å) between Pt(2) and a perchlorate oxygen atom is shown.

Guanine derivative of 3: A mixed nucleobase complex, *trans*-[Pt(NH_3)$_2$(TrimeA-N^3)(9-EtGH-N^7)](NO_3)(ClO_4)·H_2O (**4**) has also been prepared. Pt binding sites at the two nucleobases are straightforward on the basis of pD-dependent ^{1}H NMR spectra (Figure 8): Guanine deprotonation at the N1 site occurs with a

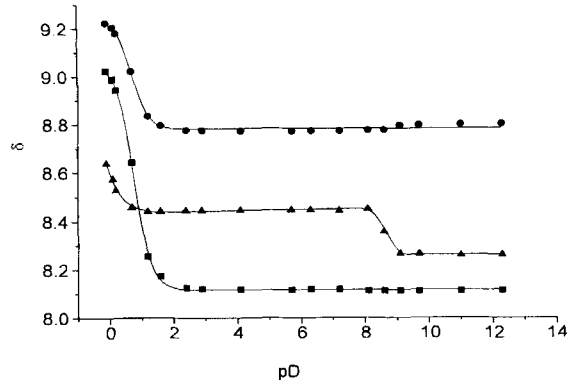

Figure 8. Dependence of aromatic CH resonances of TrimeA and 9-EtGH of **3** on the pD value. ● H$_2$(TrimeA); ▲ H8(9-EtGH); ■ H8(TrimeA).

$pK_a \approx 8.6$ in D_2O and 8.0 in H_2O,[29] consistent with N7 platination,[48] and TrimeA deprotonation at the H^+(N7) site occurs with a $pK_a \approx 0.7$ in D_2O and 0.2 in H_2O. The site assignments are in agreement with the extents of the proton downfield shifts. The ^{195}Pt NMR resonance at $\delta = -2418$ (D_2O) is consistent with Pt^{II} being surrounded by four nitrogen donors. Compound **4** can be considered as an example of a metal-modified base pair[49] between two noncomplementary bases, adenine and guanine. We have recently reported on another adenine, guanine adduct of *trans*-a$_2$Pt^{II}, in which the N7 positions of both bases are cross-linked.[49a] With a single exception,[50] all bis- or mixed-nucleobase complexes of *trans*-a$_2$Pt^{II} studied thus far by X-ray crystallographic methods have the two bases almost parallel to each other as a consequence of the presence of the two amine ligands at the Pt center. In principle, two orientations of the two bases are feasible (Figure 9); the C9(CH_3) group of TrimeA and O6 of 9-EtGH are either next to each other (a) or

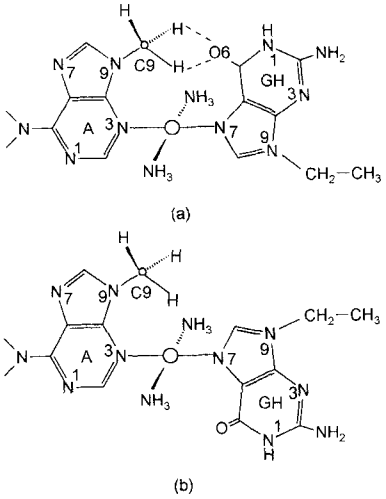

Figure 9. Schematic views of two posssible orientations (a), (b) of the two purine nucleobases in **4**. On the basis of ^{1}H NMR spectroscopy, arrangement (b) appears to be favored in water.

well separated (b). In principle, in the arrangement (a) O6 and two of the N9(CH_3) protons could form a hydrogen bond. The ^{1}H NMR spectrum (D_2O) rules out such a possibility, however, since the N9(CH_3) resonance is hardly affected when going from **3** to **4** (**3**: $\delta = 4.82$; **4**: $\delta = 4.93$). Therefore, arrangement (b) in which the two components are more separated is more likely to represent the preferred nucleobase orientation in water.

Acid–base equilibria of [Pt(dien)(TrimeA-N^3)]$^{2+}$ (2): In order to see if the N3-coordinated $[Pt(dien)]^{2+}$ ion still allows the acceptance of protons at the nucleobase, we measured the chemical shifts of H2, H8, and N9(CH_3) of TrimeA as well as of ^{195}Pt as a function of the pD value for **2b**. The individual results for the dependence of the various chemical shifts on the pD value, and the shifts for the protonated and free complex, are summarized in Table 7. The weighted mean of the individual results gives $pK^{D}_{D[Pt(dien)(TrimeA)]} = 0.65 \pm 0.13\,(3\sigma)$ (20 °C; $I \approx 0.5$ M). Transformation of the pK_a value valid for D_2O gives for water (H_2O) as solvent[29] (see also the section on solution behavior of TrimeA) $pK^{H}_{H[Pt(dien)(TrimeA)]} = 0.20 \pm 0.13$. This value is most reasonable, especially as it refers to the deprotonation of the H^+(N7) site in the complex, as follows from the extent of the chemical shifts summarized in Table 7. The downfield shift that occurs upon protonation is more pronounced for H8 ($\Delta\delta = 1.0$ ppm), which neighbors N7, than for H2 ($\Delta\delta = 0.6$ ppm).

The above pK_a value for H[Pt(dien)(TrimeA)]$^{3+}$ was checked independently by spectrophotometric measurements. Evaluations at 242 and 290 nm, where isosbestic points are observed, and where the additional spectral change is due to the equilibrium (c), as well as to the absorption difference at these two wavelengths, that is $\Delta A = A_{290} - A_{242}$, furnished three values for $pK^{H}_{H[Pt(dien)(TrimeA)]}$. The averaged result of two independent experiments is $pK^{H}_{H[Pt(dien)(TrimeA)]} = 0.30 \pm 0.14\,(3\sigma)$ (25 °C; $I \approx 0.5$ M), which is in excellent agreement with the result of the NMR measurements.

$$H[Pt(dien)(TrimeA)]^{3+} \rightleftharpoons [Pt(dien)(TrimeA)]^{2+} + H^+ \qquad (c)$$

Table 7. Acidity constant pK_a of H[Pt(dien)(TrimeA-N^3)]$^{3+}$ (= HL) in D_2O (20 °C; $I \approx 0.5$ M) [a] as determined by ^{1}H and ^{195}Pt NMR shift experiments, and the chemical shifts [δ] of the protonated and deprotonated species as well as the resulting shift difference $\Delta\delta$ [b]. $pK_{a/av} = 0.65 \pm 0.13\,(3\sigma)$.

NMR signal	pK_a [b]	δ(HL) [c]	δ(L) [c]	$\Delta\delta = \delta(HL) - \delta(L)$ [d]
H2(A)	0.663 ± 0.052	9.240 ± 0.071	8.642 ± 0.022	0.598 ± 0.074
H2(B)	0.620 ± 0.045	9.124 ± 0.072	8.507 ± 0.021	0.617 ± 0.075
H8	0.845 ± 0.081	9.059 ± 0.145	8.077 ± 0.053	0.982 ± 0.154
N9(CH_3)(A)	0.522 ± 0.131	4.998 ± 0.037	4.774 ± 0.013	0.224 ± 0.039
N9(CH_3)(B)	0.625 ± 0.051	4.967 ± 0.028	4.734 ± 0.008	0.233 ± 0.029
^{195}Pt	0.995 ± 0.448	−2835.4 ± 3.4	−2826.8 ± 1.6	−8.6 ± 3.8

[a] This is the ionic strength close to the measured pK_a; in the whole experiment I varied between about 0.15 and 1.3 M. [b] The error limits given in the second column for the pK_a values are 1σ; $pK_{a/av}$ is the weighted mean of the individual shift evaluations; with the latter value 3σ are given. [c] The chemical shifts given in the third and fourth columns were calculated by applying $pK_{a/av}$ to the experimental data points and by calculating the best fit; the error limits given here are 3σ. [d] Shift difference; the error limit was calculated according to the error propagation after Gauss (3σ).

Examples of the evaluations at 242 and 290 nm as well as of $\Delta A = A_{290} - A_{242}$ are shown in Figure 10, in which A (or ΔA) is plotted against the pH value. Figure 10 also shows the absorptions at 245, 280, and 295 nm as a function of the pH value.

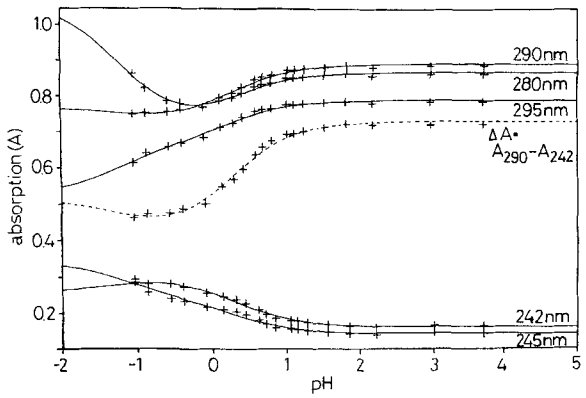

Figure 10. Evaluation of the dependence of the UV absorption of [Pt(dien)(TrimeA-N^3)]$^{2+}$ at various wavelengths as well as for the absorption difference $\Delta A = A_{290} - A_{242}$ on the pH value in aqueous solution (see Experimental Section). The solid curves, as well as the broken one, are the computer-calculated best fits through the experimental data points with $pK_{a/1} = -1.2$ and $pK_{a,2} = 0.30$.

From the alterations that take place at these three wavelengths, especially at 280 nm, it is evident that an additional acid–base reaction occurs. Unfortunately, this reaction is not completely reversible; that is, if a strongly acidic $H_n[Pt(dien)(TrimeA)]^{(2+n)+}$ solution (e.g. in 6 M $HClO_4$) is neutralized again, the absorption spectrum no longer completely matches that expected for $[Pt(dien)(TrimeA)]^{2+}$ at a pH value of about 3. We interpret this observation as a decomposition of the Pt^{2+} complex; as in H[Pt(dien)(TrimeA)]$^{3+}$ N7 is protonated, the only other basic site that remains in the complex is N1, and apparently protonation of N1 labilizes in part the Pt^{2+} coordinated at N3. For this reason the lower pK_a value could only be estimated; that is, for the deprotonation of the H^+(N1) site in $H_2[Pt(dien)(TrimeA)]^{4+}$ we obtain $pK^{H}_{H_2[Pt(dien)(TrimeA)]} \approx -1.2 \pm 0.3$ (25 °C; $I \approx 10$ M, $HClO_4$). The error limit is also an estimate and is based on the reasonableness of the extrapolated spectral alterations

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associated with the formation of the $H_2[Pt(dien)(TrimeA)]^{4+}$ species (see also Figure 10). Figure 10 shows the experimental data points for *one* series of the two independent measurements we carried out. The solid curves in this figure are the computer-calculated best fits of the experimental data points based on $pK_{a/1} = -1.2$ and $pK_{a/2} = 0.30$. It is evident that the various fits are excellent, which confirms the conclusions drawn.

Effects of Pt^{II} and Pd^{II} on the acid–base properties of TrimeA: At the end of the preceding section we described that the N3-coordinated $[Pt(dien)]^{2+}$ is labilized in its $[Pt(dien)(TrimeA\text{-}N^3)]^{2+}$ complex when in addition to N7 also N1 is protonated. This observation corroborates those made with $[Pd(dien)(TrimeA\text{-}N^3)]^{2+}$; as described in an earlier section, this complex decomposes rapidly upon protonation, showing at $pH \approx 1$ only the monoprotonated ligand $H(TrimeA)^+$ in the NMR spectrum. However, as the ^1H NMR spectra of $[Pt(dien)(TrimeA)]^{2+}$ and $[Pd(dien)(TrimeA)]^{2+}$ are very similar in terms of the chemical shifts of the protons and also the resonance splittings, this indicates that the electron distribution in the two complexes is also very similar; consequently, one may suggest that the acidity constants described above for protonated $[Pt(dien)(TrimeA)]^{2+}$ hold to a first approximation also for the corresponding Pd^{2+} complex.

Important observations in this context are those made for $H[trans\text{-}Pt(NH_3)_2(TrimeA\text{-}N^3)Cl]^{2+}$ and $H[trans\text{-}Pt(NH_3)_2(TrimeA\text{-}N^3)(9\text{-}EtGH\text{-}N^7)]^{3+}$, the cations of **3** and **4**, which have pK_a values of 0.3 and 0.2, respectively, as estimated by NMR spectroscopy (see previous sections). These two acidity constants are within the error limits identical with the pK_a value of 0.20 ± 0.13 determined for $H[Pt(dien)(TrimeA\text{-}N^3)]^{3+}$. This result suggests that N3-bound Pt affects the basicity of N7 of the coordinated adenine nucleobase to about the same extent, regardless of the kind of ligands that occupy the other three Pt^{2+} sites, and their arrangement.

As far as the effect of N3-coordinated Pt^{2+} on N7 is concerned, the following comparisons, including the results given in the first part of the Results and Discussion section, are of interest. If there is a proton at N1 and at N7, as is the case in $H_2(TrimeA)^{2+}$, deprotonation of the $H^+(N7)$ site occurs first with $pK^H_{H_2(TrimeA)} = -0.75 \pm 0.20$; that is, the difference between the two pK_a values involved is given by Equation (d). The

$$\begin{aligned}\Delta pK_{a/TrimeA} &= pK^H_{H(TrimeA)} - pK^H_{H_2(TrimeA)} \\ &= (4.15 \pm 0.05) - (-0.75 \pm 0.20) \\ &= 4.9 \pm 0.2.\end{aligned} \quad (d)$$

analogous comparisons for twofold protonated adenine [Eq. (e)][25] and adenosine [Eq. (f)][25b, 26] give, within the error limits, the same result.

$$\begin{aligned}\Delta pK_{a/Ade} &= pK^H_{H(Ade)} - pK^H_{H_2(Ade)} \\ &= 4.2 - (-0.4) \\ &= 4.6\end{aligned} \quad (e)$$

$$\begin{aligned}\Delta pK_{a/Ado} &= pK^H_{H(Ado)} - pK^H_{H_2(Ado)} \\ &= 3.6 - (-1.5) \\ &= 5.1\end{aligned} \quad (f)$$

If there is a $[Pt(dien)]^{2+}$ unit at N3, the *sequence of adenine protonation is reversed* in comparison with that of the free adenine nucleobase: N7 is protonated first, followed by N1. Deprotonation of the $H^+(N7)$ site occurs with $pK^H_{H[Pt(dien)(TrimeA)]} = 0.30 \pm 0.14$; that is, the release of the proton from the $H^+(N7)$ sites may be compared in $H_2(TrimeA)^{2+}$ and in $H[Pt(dien)(TrimeA)]^{3+}$ [Eq. (g)].

$$\begin{aligned}\Delta pK_{a/Pt(TrimeA)} &= pK^H_{H[Pt(dien)(TrimeA)]} - pK^H_{H_2(TrimeA)} \\ &= (0.30 \pm 0.14) - (-0.75 \pm 0.2) \\ &= 1.1 \pm 0.25\end{aligned} \quad (g)$$

This result means that $[Pt(dien)]^{2+}$ at N3 with $\Delta pK_a \approx 1.1$ is considerably less effective in acidifying the $H^+(N7)$ site of TrimeA than the proton at N1; this is despite the fact that the distances between N1 and N7 or between N3 and N7 in a purine moiety are about the same, that is there are three bonds in between in each case. This observation may at first sight appear somewhat surprising because the platinum unit carries a charge of 2+, whereas the proton carries only a single charge. The explanation probably is that Pt^{2+} is "soft" and not only able to accept electrons in a σ bond but also to transmit d electrons into the π system of the purine; consequently, its acidification power should be somewhat less pronounced than that of H^+, which is in accord with the present observation. The corresponding properties are also expected for Pd^{2+}. In any case, these results demonstrate that N7 of a purine system, to which a Pt^{2+} unit is coordinated through N3, still possesses basic properties allowing this N7 to participate in hydrogen bonding and possibly even in metal ion binding.

Conclusions

The possible involvement of the N3 position of adenine in metal ion binding has been a long-standing question. This site is located in the minor groove of DNA and is generally disfavored relative to the N7 position, which is in the major groove and usually well accessible. Metal ion binding to N3 could, in principle, be relevant to species with a general affinity for the minor groove, for example complexes with large π ligands, or whenever the N7 or N6 positions are blocked, for example upon single methylation of adenine-N6 during gene inactivation.[51] As we have shown in the present study, artificial blockage of N1 and N7 (and at the same time, of course, of N6′) by twofold methylation of the exocyclic amino group directs Pt^{II} and Pd^{II} entities to the N3 position. Methylation of the exocyclic amino group has a relatively minor effect on the basicity of the adenine ring; that is TrimeA follows the behavior of 9-MeA and adenosine as far as its role as base is concerned. Therefore, the analogy between a putative N3 metal complex of an unmethylated or singly methylated (at N6′) adenine nucleobase in a DNA duplex and our N3-metalated TrimeA model compounds is justified. There are two important consequences of N3 metalation: First, the overall basicity of the adenine ring drops by about 4 log units. Second, relative basicities of N1 and N7 are reversed; N7 is thus more basic than N1. With N7-platinated adenine nucleobases, the basicity of the N1 position also is reduced, albeit to a considerably smaller extent.[21] In terms of base pair-

ing properties of a N3-metalated adenine (M = Pt^{II}, Pd^{II}), the dramatic decrease in basicity of the N1 position is noteworthy, since it is expected to cause a substantial weakening of the Watson–Crick pair with thymine.

Experimental Section

Materials: TrimeA was obtained from Chemogen, Konstanz, Germany. [Pt(dien)I]I,[52] [Pd(dien)I]I,[53] and *trans*-$[Pt(NH_3)_2Cl_2]$[54] were prepared from K_2PtCl_4 and K_2PdCl_4 (Degussa) as reported. For the syntheses of the other complexes see below. All other materials (pro analysi) used in the experiments, including potassium hydrogen phthalate, HNO_3, $NaNO_3$, $HClO_4$, $NaClO_4$, and NaOH (Titrisol) were purchased from Merck AG, Darmstadt, Germany. All solutions were prepared with distilled CO_2-free water.

Instrumentation: ^1H and ^{195}Pt NMR spectra were recorded on a Bruker AC 200 instrument. Chemical shifts are referenced to internal TSP (^1H) and external Na_2PtCl_6 (^{195}Pt). pD values were obtained by adding 0.40 to the pH meter (Metrohm 6321) reading.[55] The potentiometric pH titrations were carried out with a Metrohm E536 potentiograph equipped with an E665 dosimat and a 6.0202.100(NB) combined macro glass electrode. The buffer solutions (pH 4.00, 7.00, 9.00, based on the NBS scale, now US National Institute of Standard and Technology (NIST)) used for calibration were also from Metrohm. The direct pH-meter readings were used to calculate the acidity constants; that is, these constants ($pK_a > 2$) are so-called practical, mixed, or Brønsted constants. Their negative logarithms given for aqueous solutions at $I = 0.1$ M ($NaNO_3$) and 25 °C may be converted into the corresponding concentration constants by subtracting 0.02 log units.[56] This conversion term contains the junction potential of the glass electrode and the hydrogen ion activity.[56, 57] The acidity constants $pK_a < 2$ are given as concentration constants (see below). The spectrophotometric experiments were carried out with a Perkin Elmer Lambda 2 UV/Vis spectrophotometer connected with an IBM compatible computer with a Pentium processor, a Brother M-1509 printer, and a Graphtec MP3100 xy plotter.

Potentiometric pH titrations: The titer of the NaOH used for the titrations was established with potassium hydrogen phthalate. The aqueous stock solutions of TrimeA were freshly prepared daily and the exact concentration was newly determined each time. The acidity constant $K^H_{H(TrimeA)}$ of $H(TrimeA)^-$ was determined by titrating 25 mL of aqueous 3 mM HNO_3 and $NaNO_3$ ($I = 0.1$ M; 25 °C) in the presence and absence of TrimeA (0.46 mM) under N_2 with NaOH (0.03 M, 2.5 mL). The experimental data were evaluated with an IBM compatible computer with an 80486 processor (connected with an Epson Stylus 1000 printer and a Hewlett–Packard 7475A plotter) by a curve-fit procedure using a Newton–Gauss nonlinear least-squares program within the pH range 3.0 to 6.2, which corresponds to about 6% and 99% neutralization for the equilibrium $H(TrimeA)^+$/TrimeA. The result given in the first part of the Results and Discussion section is the average of four independent pairs of titrations.

Spectrophotometric measurements: The spectra were recorded in aqueous solution ([TrimeA] or $[[Pt(dien)(TrimeA\text{-}N^3)]^{2+}] = 0.050$ to 0.056 mM) with 1-cm quartz cells from 190 to 350 nm (the data were collected by the computer every 0.1 nm) at 25 °C; at pH values > 1 I was adjusted to 0.1 M with $NaClO_4$; at pH values < 1 I varied, that is, up to 10 M $HClO_4$. At pH values < 1 the exact pH of the solutions was calculated from the known concentration of $HClO_4$ (which was established by titration with standarized NaOH), and at pH values > 1 the pH value was measured with a Metrohm 605 digital pH-meter using a Metrohm 6.0216.100(PC) glass electrode. This pH-meter was calibrated with the buffer solutions 4.00, 7.00 (from Metrohm), and 1.00 (from Merck AG). The spectrophotometric data were analyzed with the above-mentioned IBM-compatible computer by a curve-fit procedure using a Newton–Gauss nonlinear least-squares program.

For TrimeA three series of independent experiments were carried out in the pH range from about −1 to 6.5. The concentration of TrimeA in a given series was kept constant, and only the concentration of $HClO_4$ was varied. From the dependence of the UV spectra on the pH value, it is evident that there are two deprotonation steps in the pH range of −1 to 6, and that at 271 and 284 nm partial isosbestic points are observed. At 271 nm the absorption A increases in the pH range from about −1 to 1 (due to $pK^H_{H_2(TrimeA)}$), and at 284 nm it also increases in the pH range from about 2.5 to 6 (due to $pK^H_{H(TrimeA)}$); at 278 nm the absorption increases with increasing pH throughout the range from −1 to 6, whereas at 291 nm the absorption first decreases (pH −1 to 1) and then increases again (pH 2.5 to 6). At the mentioned wavelengths the spectral alterations are large and therefore they were chosen for the calculation of the acidity constants. Figure 3 shows an example for the evaluation of one of the series of measurements of the dependence of the UV absorption of TrimeA on the pH value at 271, 278, 284, and 291 nm (from top to bottom) by plotting the absorption A versus pH. The solid curves represent the computer-calculated best fits of the experimental data points at pH values of −1.02, −0.90, −0.70, −0.50, −0.40, −0.30, 0.00, 0.50, 1.01, 1.47, 1.94, 2.43, 2.98, 3.30, 3.49, 3.76, 3.96, 4.09, 4.26, 4.49, 4.58, 4.77, 5.07, 5.43, 6.07, and 6.70 (from left to right), which leads for this experimental series to $pK^H_{H_2(TrimeA)} = -0.75 \pm 0.12 (1\sigma)$, -0.81 ± 0.12, and -0.76 ± 0.11 for the evaluations at 271, 278, and 291 nm, respectively, and to $pK^H_{H(TrimeA)} = 4.18 \pm 0.05 (1\sigma)$, 4.19 ± 0.02, and 4.18 ± 0.04 for the evaluations at 278, 284, and 291 nm, respectively. Because the spectral dependence on pH has isosbestic points at 284 and 271 nm for the first and second deprotonation steps, respectively, as mentioned above, at these two wavelengths only a value for $pK^H_{H(TrimeA)}$ (284 nm) and $pK^H_{H_2(TrimeA)}$ (271 nm) can be calculated; that is, each series furnishes three values for each pK_a constant. Consequently, the final results given in first part of the Results and Discussion section for $pK^H_{H_2(TrimeA)}$ and $pK^H_{H(TrimeA)}$ are the averages of three independent series of experiments with a total of nine values for each constant.

The acid–base properties of $[Pt(dien)(TrimeA\text{-}N^3)]^{2+}$ were determined in two series of experiments in the pH range of about −1 to 3.8. There are also two deprotonation steps in the mentioned pH range, and two partial isosbestic points exist at 242 and 290 nm. At 242 nm the absorption A decreases from a pH value of about −0.5 to 3.8, and at 290 nm it increases in the same pH range; at 245 nm A decreases with increasing pH in the range of −1 to 3.8, and at 295 nm the absorption increases with increasing pH in the same pH range, whereas at 280 nm the absorption first decreases (pH −1 to about −0.3) and then increases again (pH about −0.3 to 3.8; see also Figure 10). The evaluation of such experiments at 242, 245, 280, 290, and 295 nm as well as of the difference in the UV absorptions $\Delta A = A_{290} - A_{242}$ is shown in Figure 10 in which the absorption A is plotted against the pH value. Because the spectral dependence on pH has isosbestic points at 242 nm and 290 nm for the first deprotonation step, at these two wavelengths and also at their difference, $\Delta A = A_{290} - A_{242}$, values for $pK^H_{H[Pt(dien)(TrimeA)]}$ can be calculated; from these three evaluations in two independent series of experiments the average value, that is $pK^H_{H[Pt(dien)(TrimeA)]} = 0.30 \pm 0.14 (3\sigma)$ was obtained. For $pK^H_{H_2[Pt(dien)(TrimeA)]}$ only a rough estimate (-1.2 ± 0.3) could be made based on the evaluations at 245, 280, and 295 nm in the two independent experiments (see also the text in the corresponding section of the Results and Discussion). The curves shown in Figure 10 are the calculated best fits through the experimental data points at pH values of −1.02, −0.85, −0.55, −0.37, −0.07, 0.15, 0.33, 0.45, 0.63, 0.73, 0.85, 1.06, 1.15, 1.28, 1.57, 1.86, 2.22, 3.01, and 3.73 (from left to right) of one of the two mentioned experiments by using $pK^H_{H_2[Pt(dien)(TrimeA)]} = -1.2$ and $pK^H_{H[Pt(dien)(TrimeA)]} = 0.30$. The pK_a value of −1.2 (as well as its error limit of ±0.3) is an estimate, because in the experiments with $[HClO_4] > 3$ M the spectra were not completely reversible any more within the time used for the measurements; that is, adjustment of a pH value close to 3 of such a solution gave a spectrum that was not completely equal any more to that of a solution originally adjusted only to this pH. This indicates that the twofold protonated $H_2[Pt(dien)(TrimeA)]^{4+}$ complex is unstable and decomposes (see also the corresponding part in the Results and Discussion section).

Self-association of TrimeA: The ^1H NMR chemical shifts of H2 and H8 vary depending on the concentration; that is, the signals are shifted upfield with increasing concentration (pD = 7.3). This, and the extent of the observed upfield shifts (see Table 2) demonstrate that the self-association occurs by stacking, in agreement with previous studies of adenine derivatives.[26, 28, 31] Twelve measurements were made in the concentration range between 0.28 and 280 mM; their plots of chemical shift (δ) versus concentration are similar to previous ones[26, 31d] and therefore are not shown. All the experimental data can be interpreted in terms of the isodesmic model of indefinite noncooperative self-association.[31] The calculations were carried out exactly as before.[26, 31c] The individual results are listed in Table 2, and Figure 4 shows the computer-calculated distribution of the various species as a function of the concentration; the distribution shown in this figure is analogous to previous ones.[26, 28, 31]

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Determination of acidity constants by NMR spectroscopy: The ^{1}H NMR spectra of TrimeA (0.13 M) and [Pt(dien)(TrimeA)]$^{2+}$ (0.05 M) in D_2O were recorded as a function of the pD value. All the experimental data were analyzed with the above-mentioned IBM compatible computer and a Newton–Gauss nonlinear least-squares program; this curve-fit program is based on the general equation [Eq. (4)] published previously in ref. [26]. The detailed results concerning the acidity constant $K^{D}_{D(TrimeA)}$ of D(TrimeA)$^+$ in D_2O are summarized in Table 1. It is important to note that the acidity constant given there is an apparent constant because the self-association is large under the experimental conditions ([TrimeA] = 0.13 M; see also the first part of the Results and Discussion section). The chemical shifts of the protons of [Pt(dien)(TrimeA)]$^{2+}$ in its protonated and free state are listed in Table 7, which also includes the corresponding shifts of the ^{195}Pt signal. It should be emphasized that due to the positive charges of H[Pt(dien)(TrimeA)]$^{3+}$ and [Pt(dien)(TrimeA)]$^{2+}$ no self-association by the adenine residue is expected, despite the fact that in these experiments a concentration of 0.05 M was used. Indeed, this assumption is confirmed by the excellent agreement of the acidity constants obtained by NMR spectroscopy and spectrophotometry (cf. the corresponding section in the Results and Discussion) because in the latter experiments the concentration of the complex was only 5×10^{-5} M.

[D$_8$]TrimeA: 8-deuterated TrimeA was obtained by dissolving TrimeA (300 mg, 1.69 mmol) in D_2O (1.5 mL), and stirring the solution at 60 °C for 2 d (pD 3.6); white powder; ^{1}H NMR (D_2O, pD 4.2): δ = 3.1–3.4 (N6(CH_3)$_2$), 3.67 (s, N9(CH_3)), 7.85 (s, H2).

[Pd(dien)(TrimeA-*N*^{3})](ClO$_4$)$_2$ (1a): Complex **1** was prepared by the reaction of [Pd(dien)I]I (259.5 mg, 0.56 mmol) and $AgNO_3$ (186.9 mg, 1.1 mmol) (15 min in ultrasonic bath), followed by filtration of AgI, and addition of TrimeA. Afterwards the mixture (pH 4.6) was stirred at 40 °C for 3 d in a stoppered flask. The solution was then concentrated by rotary evaporation at 30 °C to a volume of 5 mL, and $NaClO_4 \cdot H_2O$ (450 mg, 3.2 mmol) was added. A pale yellow precipitate was isolated; ^{1}H NMR spectroscopy revealed that this precipitate was a mixture of **1a** and unconverted TrimeA. The powder was dissolved in a minimum amount of water (1 mL), and yellow crystals of **1a** were obtained on slow evaporation at 4 °C (77%). **1a**: ^{1}H NMR (D_2O, pD 3.8): δ = 2.8–3.7 (m, N6(CH_3)$_2$, dien-CH), 4.76 (s, N9-CH_3), 8.08 (s, H8), 8.48, 8.61 (s, H2, 4:1).

[Pt(dien)(TrimeA-*N*^{3})](ClO$_4$)$_2$ (2a) and **[Pt(dien)(TrimeA-*N*^{3})](NO$_3$)$_2$ (2b)**: Compound **2a** was prepared by the reaction of [Pt(dien)I]I (1.54 g, 2.8 mmol) with 1.98 equiv of $AgNO_3$ (934.3 mg, 5.5 mmol) and TrimeA (500 mg, 2.8 mmol). The solution was stirred 15 min at 60 °C and 3 d at 40 °C in a stoppered flask under the exclusion of light. AgI was filtered off and the solution (pH 5) was then concentrated to a volume of 5 mL. After addition of $NaClO_4 \cdot H_2O$ (6.1 g, 43.6 mmol), **2a** was obtained as a pale yellow powder (1.1 g, 58%). The ClO_4^- salt **2a** was passed over an anion exchange column to give the NO_3^- salt **2b** (73%). **2a**: pale yellow powder; ^{1}H NMR (D_2O, pD 2.7): δ = 2.9–3.8 (m, N6(CH_3)$_2$, dien-CH), 4.80 (s, N9(CH_3), 8.14 (s, H8), 8.55, 8.68 (s, H2, 3:1); $C_{12}H_{24}N_8O_8Cl_2Pt$ (674.4): calcd: C 21.3, H 3.6, N 16.6; found: C 21.0, H 3.7, N 16.6. Crystals suitable for X-ray crystallography were grown by dissolving **2a** in warm water and allowing the solution to stand at 4 °C for several days. Crystals obtained by this route proved to be the trihydrate of **2a** (X-ray structure analysis). **2b**: pale yellow powder; $C_{12}H_{24}N_{10}O_6Pt \cdot 2.5H_2O$ (644.5): calcd: C 22.3, H 4.5, N 21.7; found: C 22.1; H 4.4, N 21.7.

***trans*-[Pt(NH$_3$)$_2$(TrimeA)Cl]ClO$_4$ (3)**: Compound **3** was prepared by reaction (4 h, 60 °C, light exclusion) of *trans*-Pt(NH_3)$_2$Cl$_2$ (253.6 mg, 0.85 mmol) with $AgNO_3$ (143.6 mg, 0.85 mmol), followed by filtration of AgCl, and addition of TrimeA (150 mg, 0.85 mmol). The clear solution (pH 5.1) was stirred at 40 °C for 2 d. The reaction mixture was then evaporated to a volume of 5 mL and $NaClO_4 \cdot H_2O$ (1.3 g, 9.3 mmol) was added. A pale yellow powder was obtained (205 mg, 34%). **3**: ^{1}H NMR (D_2O, pD 6.4): δ = 3.3–3.75 (N6(CH_3)$_2$), 4.82 (s, N9(CH_3)), 8.08 (s, H8), 8.70 (s, H2); $C_8H_{17}N_7O_4Cl_2Pt \cdot 0.5NaClO_4$ (602.5): calcd: C 16.0, H 2.8, N 16.3; found: C 16.3, H 3.0, N 16.4. The presence of Na^+ was confirmed by scanning electron microscopy. Single crystals of **3** were prepared by recrystallizing the powder from water (40 °C, then cooled to 4 °C).

***trans*-[Pt(NH$_3$)$_2$(TrimeA)(9-EtGH)](NO$_3$)(ClO$_4$) (4)**: **3** (200 mg, 0.33 mmol) was dissolved in H_2O (20 mL), and $AgNO_3$ (56.0 mg, 0.33 mmol) was added. The reaction mixture was stirred for 4.5 h at 60 °C. After filtration of AgCl, 9-EtGH (58.8 mg, 0.33 mmol) was added, and the solution was kept for 2 d at 40 °C. Then the solution (pH 3.9) was concentrated by rotary evaporation to a volume of 5 mL and allowed to stand at 4 °C. After 2 d (at 4 °C) **4** was obtained as a white powder in 62% yield (175 mg). **4**: ^{1}H NMR (D_2O, pD = 3.2): δ = 1.51 (t, CH_2CH_3), 3.3–3.7 (N6(CH_3)$_2$), 4.23 (q, CH_2CH_3), 4.93 (s, N9(CH_3)), 8.13 (s, H8 (TrimeA)), 8.45 (s, H8 (9-EtGH)), 8.78 (s, H2 (TrimeA)); $C_{15}H_{26}N_{13}O_8ClPt \cdot H_2O$ (765.0): calcd: C 23.6, H 3.7, N 23.8; found: C 23.7, H 3.3, N 23.8.

X-ray diffraction studies: X-ray data of **1a** were collected on a Nicolet R3m/V single crystal diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Unit cell parameters were obtained from a least-squares fit of 50 randomly selected reflections in the range $15.01 \le 2\theta \le 28.71°$. Intensity data were collected by the $\omega/2\theta$ scan technique to a maximum 2θ value of 50°. Data collection for **2a** and **3** was performed on a Siemens P4 four-circle diffractometer with the same radiation using the ω-scan technique to a maximum 2θ value of 55°. Unit cell parameters were obtained from a least-squares fit of 15 reflections ($5.0 \le 2\theta \le 26.4°$ (**2a**) and $5.0 \le 2\theta \le 26.8°$ (**3**)). The intensities of six (**1a**) and three (**2a**, **3**) representative reflections were measured every 300 (**1a**) and 100 data points (**2a**, **3**), and a linear correction applied to account for the intensity decay. All data were collected at room temperature with variable scan speed and have been corrected for absorption, Lorentz, and polarization effects by using the data reduction program XDISK.[61] An empirical absorption correction was carried out by azimuth (ψ) scans ($\chi > 67°$). For **3** DIFABS[62] was also applied. All structures were solved by standard Patterson and difference Fourier methods.[58] The scattering factors were those given in ref. [59] (taken from ref. [60]). The positions and anisotropic thermal parameters of all non-hydrogen atoms were refined satisfactorily by full-matrix least-squares calculations (SHELXL-93 program[59]), except those of the three evidently disordered perchlorate oxygen atoms in **2a**, which occupy six (molecule 2 and 4) and seven (molecule 3) positions, respectively. The hydrogen atoms were placed in geometrically calculated positions and refined with a common isotropic temperature factor (for **1a**: $U_{iso(all)}$ 0.071(4) Å^2; for **2a**: $U_{iso(methyl)}$ = 0.111(17), $U_{iso(methylene)}$ = 0.068(13), $U_{iso(aryl)}$ = 0.020(15), $U_{iso(amino)}$ = 0.058(18), $U_{iso(imino)}$ = 0.053(34) Å^2; for **3**: $U_{iso(methyl)}$ = 0.103(8), $U_{iso(aryl)}$ = 0.046(11), $U_{iso(amino)}$ = 0.094(10) Å^2). The final cycle of refinement gave for structure **1a** R_1 = 0.0412 and wR_2 = 0.1170 for the observed data [$I > 2\sigma(I)$] and 284 parameters and R_1 = 0.0443 and wR_2 = 0.1201 for all data, and for **2a** R_1 = 0.0600 and wR_2 = 0.1072, based on 4720 observed reflections and 410 variable parameters, and R_1 = 0.0648 and wR_2 = 0.1408 for all data. For compound **3** refinement converged at R_1 = 0.0354 and wR_2 = 0.0703 for the observed data and 593 parameters and R_1 = 0.0651 and wR_2 = 0.0758 for all data. Crystallographic data and experimental details are reported in Table 3, bond lengths and angles are listed in Tables 4, 5, and 6 respectively. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100019. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Telefax: Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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