Affinity of the Iminooxo Tautomer Anion of 1-Methylcytosine in *trans*-$[Pt(NH_3)_2(1\text{-}MeC\text{-}N4)_2]^{2+}$ for Heterometals**

Jens Müller, Ennio Zangrando, Norbert Pahlke, Eva Freisinger, Lucio Randaccio,* and Bernhard Lippert*

Abstract: Reaction of a Pt^{II} complex containing two 1-methylcytosine (1-MeC) nucleobases bound through the exocyclic amino group N4, *trans*-$[Pt(NH_3)_2(1\text{-}MeC\text{-}N4)_2](NO_3)_2$ (**1**), with the heterometal species $[(dien)Pd]^{2+}$ or Hg^{2+} gives *trans*-$[(NH_3)_2Pt\{(N4\text{-}1\text{-}MeC^-\text{-}N3)Pd(dien)\}_2](ClO_4)_4 \cdot 2H_2O$ (**3**) and *trans*-$[(NH_3)_2Pt(N4\text{-}1\text{-}MeC^-\text{-}N3)_2Hg](NO_3)_2 \cdot 2H_2O$ (**4**), respectively. The heterometal(s) is (are) bound through the N3 positions of the two cytosine rings. Compound **1** contains the nucleobase in the form of its rare iminooxo tautomer. In the solid-state structure of **1**, the two nucleobases display a *syn* orientation between Pt and the endocyclic N3 position, whereas in compound **3** they adopt an *anti* conformation. In both compounds the cytosine bases are in a head-to-tail orientation. In the bimetallic complex **4** however, the 1-methylcytosine ligands are head-to-head and *syn* with the two nucleobases acting as chelating ligands. The Pt–Hg distance in **4** is quite short (2.7498(6) Å), suggesting a weak bonding interaction. In the case of **3** the Pt–Pd distance (5.13 Å) is too long for any interaction. While H-bond formation between the iminooxo tautomer of 1-MeC in **1** with free 1-MeC and likewise between the deprotonated form *trans*-$[Pt(NH_3)_2(1\text{-}MeC^-\text{-}N4)_2]$ (**2**) and free 9-ethylguanine (9-EtGH) is possible only if the cytosine bases are in an *anti* orientation, there is no indication for such H-bonding patterns from ^1H NMR studies.

Keywords: cytosine · metal–metal interactions · nucleobases · platinum · tautomerism

Introduction

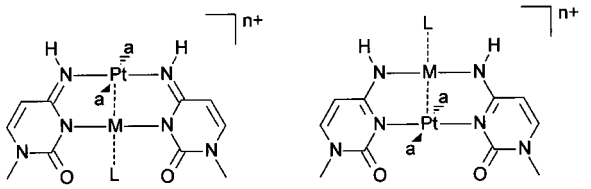
There are many possible ways that can lead to the formation of mismatched DNA base pairs,[1] one of which includes a tautomeric shift of one of the nucleobases involved in hydrogen bonding.[2–5] A rare tautomer may be generated spontaneously or its formation may be induced by a chemical modification of a base, for example the coordination of a metal entity to the base. As a consequence the hydrogen-bonding behaviour of the nucleobase is altered. In the course of our attempts to study metallated forms of rare nucleobases (metal-stabilised rare tautomers)[6–11] we have recently reported the platinum(II) complex *trans*-$[Pt(NH_3)_2(1\text{-}MeC\text{-}N4)_2]^{2+}$ (**1**) in which the model nucleobase 1-methylcytosine exists in its rare iminooxo form.[11] This compound represents only the second example[7] of a metal complex containing a neutral cytosine nucleobase bound to N4 (hence the rare tautomer) that has been characterised by X-ray crystallography. In several other cases in which the metal binds to the exocyclic N4 position,[12] the cytosine base is in its N3 deprotonated state. As far as the base-pairing behaviour of N4-metallated cytosines is concerned, we have pointed out[11] that an *anti* orientation[13] of the N4-metallated cytosine is necessary to avoid steric interference with other ligands at the metal, unless the metal ions were to cross-link to another base.

It occurred to us that compound **1** might be an ideal starting material for the synthesis of heteronuclear Pt/M complexes I of the composition *trans*-$[(NH_3)_2Pt(N4\text{-}1\text{-}MeC^-\text{-}N3)_2ML_x]^{2+}$ ($1\text{-}MeC^-$ = anion of 1-MeC, L = additional ligand in the coordination sphere of M, M = heterometal ion). These compounds I would then represent the inverse of the class of compounds II, which we have recently described and which were obtained from *trans*-$[Pt(NH_3)_2(1\text{-}MeC\text{-}N3)_2]^{2+}$ upon reaction with heterometal ions M.[14–19] Type II compounds reveal metal–metal dative bonds for M^{n+} with d^8 and d^9

[*] Prof. Dr. B. Lippert, Dipl.-Chem. E. Freisinger, Dipl.-Chem. J. Müller, Dipl.-Chem. N. Pahlke
Fachbereich Chemie, Universität Dortmund
Otto-Hahn-Strasse 8, D-44221 Dortmund (Germany)
Fax: Int. code + (49) 231 755-3797
e-mail: lippert@pop.uni-dortmund.de
Prof. Dr. L. Randaccio, Dr. E. Zangrando
Dipartimento di Scienze Chimiche, Università di Trieste
Via Giorgieri 1, I-34127 Trieste (Italy)
Fax: Int. code + (39) 40 676-3903
e-mail: randaccio@univ.trieste.it

[**] Metal-Stabilised Rare Tautomers of Nucleobases, Part 7. Part 6: F. Zamora, M. Kunsman, M. Sabat, B. Lippert, *Inorg. Chem.* **1997**, *36*, 1583–1587.

  0947-6539/98/0403-0397 $ 17.50+.25/0



I II

electron configurations or a weak bonding interaction with metal ions with a d^{10} electron configuration; this was deduced from short Pt–M distances and supported by theoretical calculations[17] as well as NMR evidence.[16] Formation of type II compounds requires a head-to-head orientation of the two nucleobases, but in solution this rotamer coexists with the head-to-tail form.[20] However, depending on the conditions of the crystallisation process, both rotamers can be isolated.[20] Similarly, the two nucleobases in type I compounds also require a head-to-head orientation, but as has already been pointed by us,[11] in solution an equilibrium between various rotamers of the N4-coordinated species exists. This stems from the fact that in I rotation is feasible not only about the Pt–N bond, but also about the N4–C4 bond in the nucleobase. As a result of this complexity we thought that formation of the heteronuclear species from *trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2]^{2+}$ might be more complicated than in the case of II.

Abstract in German: *Der Pt^{II}-Komplex trans-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2](NO_3)_2$ (**1**), in welchem die beiden 1-Methylcytosin-Nucleobasen (1-MeC) über die exocyclische Aminogruppe N4 gebunden sind, wurde mit den Heterometallspezies $[(dien)Pd]^{2+}$ und Hg^{2+} zu trans-$[(NH_3)_2Pt\{(N4\text{-}1\text{-}MeC^{-}\text{-}N3)Pd(dien)\}_2](ClO_4)_4\cdot 2H_2O$ (**3**) und trans-$[(NH_3)_2Pt(N4\text{-}1\text{-}MeC^{-}\text{-}N3)_2Hg](NO_3)_2\cdot 2H_2O$ (**4**) umgesetzt. Die Heterometalle sind über die N3-Positionen der zwei Cytosinringe koordiniert. Verbindung **1** enthält die Nucleobase in Form ihres seltenen Iminooxo-Tautomers. Im Festkörper von **1** liegen die zwei Nucleobasen in einer syn-Anordnung von Pt und endocyclischen N3-Positionen vor, während sie in **3** eine anti-Konformation einnehmen. In beiden Verbindungen befinden sich die Cytosinbasen in einer Kopf-Schwanz-Anordnung. Im Dimetallkomplex **4** hingegen nehmen die 1-Methylcytosin-Liganden eine Kopf–Kopf-Anordnung mit syn-Orientierung ein, wobei sie als chelatisierende Liganden fungieren. Der relativ kurze Pt–Hg-Abstand in **4** (2.7498(6) Å) deutet auf eine schwache bindende Wechselwirkung hin. Der im Falle von **3** bestimmte Pt–Pd-Abstand (5.13 Å) ist zu groß für jegliche Art einer Wechselwirkung. Eine Bildung von H-Brücken zwischen dem Iminooxo-Tautomer von 1-MeC in **1** mit freiem 1-MeC und ebenso zwischen der deprotonierten Form trans-$[Pt(NH_3)_2(1\text{-}MeC^{-}\text{-}N4)_2]$ (**2**) und freiem 9-Ethylguanin (9-EtGH) ist nur dann möglich, wenn sich die Cytosinbasen in einer anti-Anordnung befinden. ^{1}H-NMR-Untersuchungen ergaben allerdings keinerlei Hinweise auf ein solches Wasserstoffbrückenbindungsmuster.*

Results and Discussion

Improved synthesis of *trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2]^{2+}$ (1): Compound **1** was prepared from *trans*-$[Pt(NH_3)_2(1\text{-MeC-}N3)_2]^{2+}$ by means of the redox-assisted metal-migration process previously described,[11] with the reduction of the Pt^{IV} complex *trans,trans,trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2(OH)_2]^{2+}$ with hydrogen as the final step [Eq. (1)].

$$trans,trans,trans\text{-}[Pt(NH_3)_2(1\text{-MeC-}N4)_2(OH)_2]^{2+} + H_2 \rightarrow trans\text{-}[Pt(NH_3)_2(1\text{-MeC-}N4)_2]^{2+} + 2H_2O \quad (1)$$

This step of the original synthesis of **1** (3 d reaction time, 31 % yield) has been improved, which now leads to an almost quantitative yield of the desired product. This was achieved by exploiting the observation that the presence of elemental Pt in the reaction mixture (generated unintentionally) led to a higher yield of **1**. Deliberate addition of a small amount of finely dispersed Pt (obtained by pyrolysis of Magnus green salt, $[Pt(NH_3)_4][PtCl_4]$) during the reduction process increased the yield to 96 %. Furthermore, addition of Pt^0 shortened the reaction time noticeably. The temperature was also varied and the optimum was found to be 50 °C, resulting in a virtually complete reduction within $3^1/_2$ h. Given that in the pH region relevant for the reduction process (pH 4–6) the starting material *trans,trans,trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2(OH)_2]^{2+}$ and product **1** have pK_a values (deprotonation of the 1-MeC ligand at N3) that differ by nearly three log units (5.8 and 8.4,[21] respectively), we thought that it would be possible to control the progress of the reaction simply by monitoring the pH of the solution. In fact, we found that the change in pH with time (rise of pH, sigmoidal curve) was a convenient way to follow the reaction.

Crystal structure analysis of *trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2](NO_3)_2$ (1): The cation of **1** is depicted in Figure 1. As in the corresponding ClO_4 salt,[11] the two bases are orientated head-to-tail, with N4 nitrogen atoms representing the Pt binding sites. Selected structural details are included in Table 1. The Pt coordination geometry is not unusual.

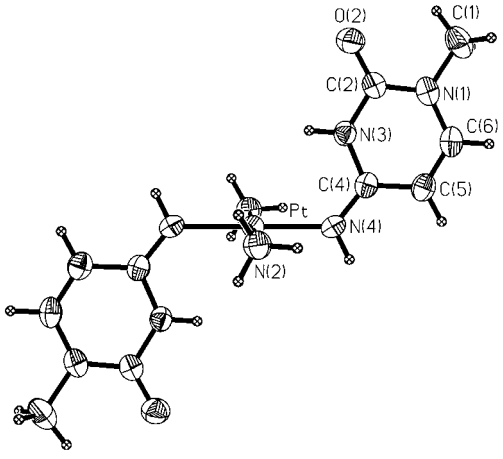


Figure 1. X-ray structure of the cation of *trans*-$[Pt(NH_3)_2(1\text{-MeC-}N4)_2](NO_3)_2$ (**1**).

0947-6539/98/0403-0398 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 3

Table 1. Selected structural data of **1** and **3** compared with those of 1-MeC (bond lengths in Å, angles in °).

	1	**3**	1-MeC [35]
N1 – C6	1.377(9)	1.296(13)	1.357(2)
C2 – N3	1.387(7)	1.332(13)	1.358(2)
N3 – C4	1.382(9)	1.375(13)	1.332(2)
C4 – N4	1.309(7)	1.296(13)	1.336(2)
C2-N3-C4	125.2(5)	122.8(10)	120.0(1)
N3-C4-N4	118.5(5)	122.9(11)	117.8(1)
N3-C4-C5	115.3(5)	115.3(9)	121.8(1)
N4-C4-C5	126.2(6)	121.7(10)	120.4(1)
H_3N-Pt-N4	88.5(3)	89.5(4)	–
Pt-N4-C4	128.3(5)	131.0(8)	–
Pt – N4	1.986(5)	2.001(8)	–
Pt – NH_3	2.032(8)	2.046(10)	–
Pd – N3	–	2.047(8)	–
Pt – H5	–	3.00(1)	–
Pt-H5-C5	–	106.4(2)	–

Features previously outlined for the rare cytosine tautomer ligand[11] hold up for compound **1** as well. The reason for carrying out an X-ray structure analysis with the NO_3 salt was to verify our previous observation with the ClO_4 salt that the Pt – N4 bond length (1.993(9) Å) tends to be shorter than in the Pt^{IV} starting compound (2.022(4) and 2.028(3) Å)[7] and in *trans*-$[Pt\,a_2(1\text{-MeC-}N3)_2]^{2+}$ with $a = NH_3$ (2.023(8) Å)[23] or CH_3NH_2 (2.010(7), 2.03(2) and 2.10(3) Å).[20] Indeed, the Pt – N4 bond in **1** (1.986(5) Å) is significantly shorter than in the mentioned X-ray structures with a comparable resolution. We considered the question of the strength of this bond relevant in view of the rotational behaviour of the 1-MeC-*N*4 ligand in solution. It is noted that this bond length is at the lower end of the range typically seen for Pt^{II} complexes containing anionic pyrimidine nucleobases.[24] It is difficult to say whether or not this feature implies some π back-bonding from a filled d orbital of Pt (e.g. d_{xy}) to an antibonding orbital of the heterocycle (with N4 involved in the π system) and therefore leads to an increase in the Pt – N bond order,[25] or if it is simply a result of the reduction in coordination number (from Pt^{IV} to Pt^{II} species) and differences in steric pressure (N3 vs N4 in Pt^{II} compounds). We note, however, that for nucleobases binding to Pt^{II} through endocyclic nitrogen atoms—a situation that should favour π back-bonding more than in **1**—this phenomenon has never been implicated. Despite the relatively short Pt – H3 contact of 2.74 Å in the solid state, in solution a pregostic interaction[26] probably can be excluded; this is mainly a result of the nonexistence of a $^1J(^{195}Pt,^1H)$ coupling in the NMR spectra.[27] However, it should be mentioned that the solution conformation may of course be different from the one present in the solid state.

Ligand rotation in 1: Because of possible rotation about both the C4 – N4 and the Pt – N4 bonds, a total of six rotamers is feasible for **1** (Figure 2). For simplification purposes, a denomination according to the stereochemistry (*hh* for a head-to-head and *ht* for a head-to-tail arrangement of the nucleobases, *a* for *anti* and *s* for *syn* orientation between N(3)H and Pt) will be used.[11,13] The number of NMR resonances for H5 and H6 cytosine protons indicates the existence of at least four different rotamers in both D_2O and $[D_6]$DMSO (Tables 2 and 3). A complete assignment of the

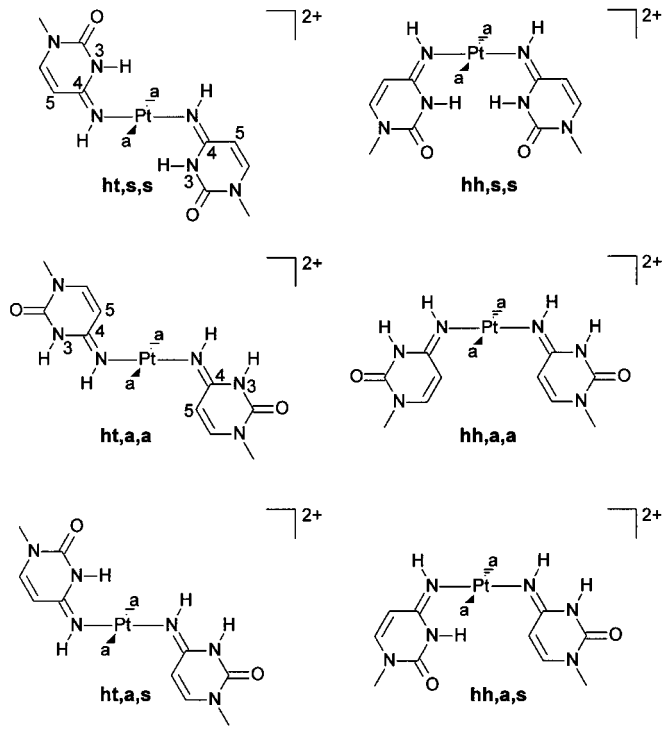


Figure 2. The six possible rotamers of **1**. The denomination was selected according to the stereochemistry (*hh* for a head-to-head and *ht* for a head-to-tail arrangement of the nucleobases, *a* for *anti* and *s* for *syn* orientation between N(3)H and Pt).

Table 2. Chemical shifts of cytosine H5 and H6 doublets and ^{195}Pt resonance of **1** (D_2O, pD 5.4).

	δ_{H5}	δ_{H6}	δ_{Pt}
(*ht*,*s*,*s*)	5.98	7.12	– 2607
(*hh*,*s*,*s*)	5.98	7.13	– 2607
(*ht*,*a*,*a*)	6.68	7.49	– 2578
(*hh*,*a*,*a*)	6.71	7.50	– 2578

Table 3. Selected ^1H chemical shifts and ^{195}Pt resonance of **1** ($[D_6]$DMSO).

	δ_{H5}	δ_{H6}	$\delta_{N4(H)}$	$\delta_{N3(H)}$	δ_{Pt}
(*s*,*s*)	5.93	7.26	7.55	11.71	– 2564
(*ht*,*a*,*a*) or (*hh*,*a*,*a*)	6.39	7.69	8.34	10.66	– 2541
(*hh*,*a*,*a*) or (*ht*,*a*,*a*)	6.61	7.71	8.34	10.66	– 2541

H5/H6 signals in D_2O (Table 2) was possible on the basis of an experiment which resulted in the removal of Pd from a heteronuclear $PtPd_2$ derivative of **1** and generation of **1** in its (*ht*,*a*,*a*) rotamer form (vide infra). The H6 doublets at $\delta = 7.50$ and 7.49 (the latter sometimes appears only as a shoulder of the former) as well as the H5 doublets at $\delta = 6.71$ and 6.68 can easily be assigned to those of the *anti* rotamers. Their significant downfield shift compared with that of the other rotamers can be explained by the magnetic anisotropy of the d^8 Pt^{II} atom in a square planar arrangement, which deshields protons situated directly above or below the coordination plane.[28] The same effect is observed for the N(3)H proton of the *syn* conformers in $[D_6]$DMSO ($\delta = 11.71$ compared with

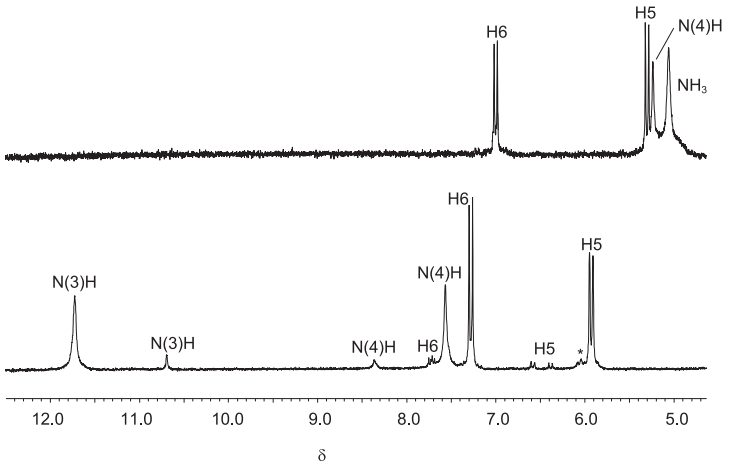
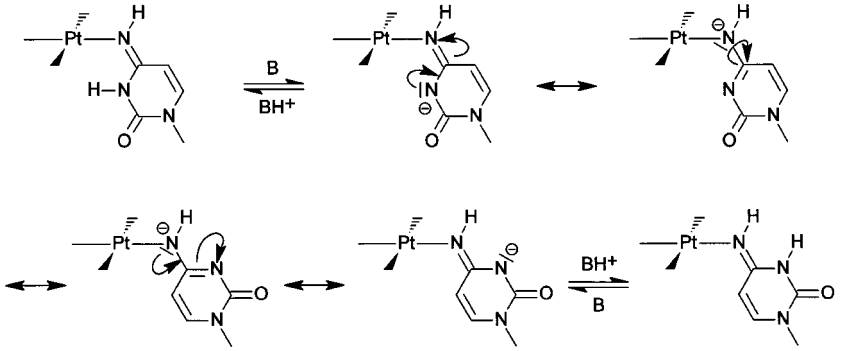


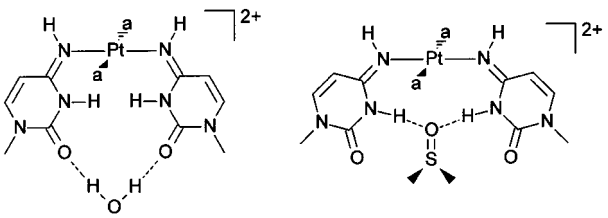
Figure 3. Comparison of the ^{1}H NMR spectra of deprotonated compound **2** (top) and starting material **1** (bottom) in [D_6]DMSO (* denotes an unknown impurity that is always present in low concentrations after the reduction process).

10.66 for the *anti* rotamers), confirming the above assignment (Figure 3). The rotameric forms (*ht*,*a*,*s*) and (*hh*,*a*,*s*) are not detected in the NMR spectra most probably because the chemical shifts of the protons on one ligand are practically independent of the conformation of the other ligand, which results in NMR signals for (*a*,*s*) overlapping with those of (*s*,*s*) and (*a*,*a*). ^{195}Pt NMR spectra show only two resonances, which are assigned to the head-to-head and the head-to-tail forms on the basis of relative intensities of ^{1}H NMR resonances. Here a distinction between *syn* and *anti* conformers is not possible. A striking difference between the D_2O and the [D_6]DMSO solution is the ratio *r* between the *syn* and the *anti* conformers of $r = 4.3$ (D_2O) and $r = 13$ ([D_6]DMSO), which points to differences in the stabilisation of the various rotamers by the solvent (Scheme 1). Since in the solid state, **1** exists in its (*ht*,*s*,*s*) rotameric form only, an equilibration of the rotamers should be observed when dissolving **1** in D_2O. Similar studies of *trans*-[$Pt(CH_3NH_2)_2$(1-MeC-*N*3)$_2$]$^{2+}$ have shown that the equilibrium is reached within about 450 min.[20] As a result of the partial double bond of C4–N4 and the possibility of a bond order larger than 1 for the Pt–N4 bond in **1**, a slower equilibration was considered possible in this case. On the other hand, ligand rotation in **1** is expected to be less restricted from a steric point of view (two exocyclic groups adjacent to Pt binding sites in *trans*-[$Pt(CH_3NH_2)_2$(1-MeC-*N*3)$_2$]$^{2+}$). However, ^{1}H NMR studies show that within 5 min after dissolution of **1** the solution is equilibrated. A possible explanation for this finding is given in Scheme 2. This implies a mechanism consisting of a base catalysed rotation of the nucleobase about the C4–N4 axis. This proposal is supported by the fact that in temperature-dependent ^{1}H NMR spectra of **1** (20–95 °C), in a basic medium only (pD 8.5) (not in weakly acidic solution, pD 6), a general signal broadening with increasing temperature is observed.

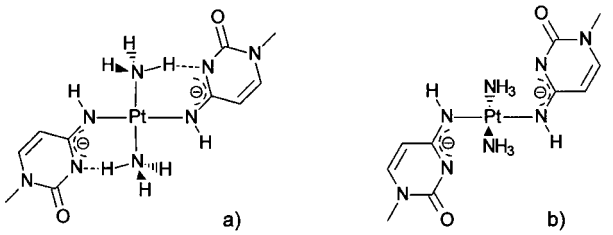
Deprotonation of 1: Upon deprotonation of the N3 nitrogen atoms of **1**, a neutral complex *trans*-[$Pt(NH_3)_2$(1-MeC$^-$-*N*4)$_2$]·3H_2O (**2**) is generated. A singly deprotonated *trans*-[$Pt(NH_3)_2$(1-MeC-*N*4)(1-MeC$^-$-*N*4)](NO$_3$) can be excluded on the basis of its IR spectrum, since it does not reveal any nitrate bands. Furthermore, the elemental analysis of **2** gives a C:N ratio of 10:8, which is only consistent with a neutral product. For **2**, two fundamentally different structures are feasible depending on the dihedral angle between the square planar coordination of Pt^{II} and the plane of the 1-MeC$^-$ ligand (Scheme 3). If the nucleobases lie in the coordination plane of the Pt atom an intramolecular stabilisation is feasible between the lone pair at N3 and one or two of the protons of the ammine ligand. Compared with **1**, the ^{1}H NMR resonances for H5, H6, N(4)H and CH_3 of **2** undergo large shifts towards higher field in [D_6]DMSO, by 0.63, 0.28, 2.34 and 0.29 ppm, respectively, whereas the NH_3 signal is shifted 1.16 ppm downfield. A signal for N(3)H is no longer



Scheme 2. Base-catalysed rotation of 1-MeC about the C4–N4 axis: a possible explanation for the fast equilibration of the rotamers.



Scheme 1. Possible differential stabilisation of **1** by the solvents H_2O and DMSO.

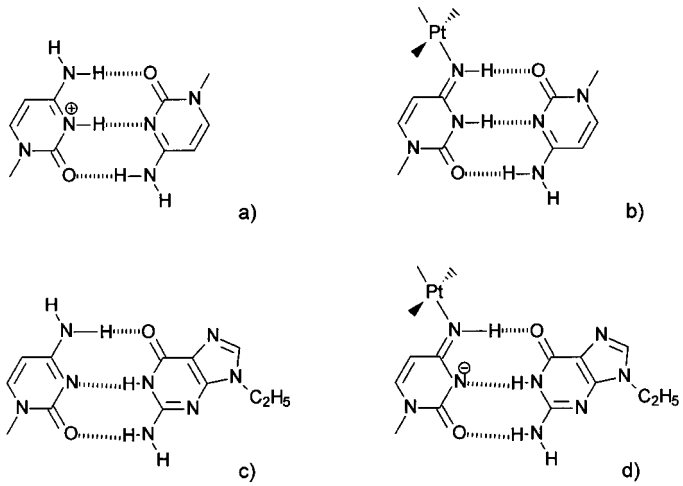


Scheme 3. Structures feasible for deprotonated **2**: a) nucleobase coplanar with PtN_4 plane; b) nucleobase perpendicular to PtN_4 plane.

0947-6539/98/0403-0400 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 3

observed (Figure 3). These findings are consistent with cytosine deprotonation at N3, resulting in an increase in electron density in the aromatic system. The downfield shift of the ammine signal in **2** is best explained by intramolecular H-bonding between NH_3 protons and N3. Rotation about the Pt–NH_3 bond is still sufficiently fast on the NMR timescale to lead to a single, averaged NH_3 resonance. We are confident that base-flipping as a consequence of nucleobase deprotonation of **1** takes place. Similar findings with *trans,trans,trans*-$[Pt(NH_3)_2(OH)_2(1\text{-}MeC^-\text{-}N4)_2]$, characterised by X-ray crystallography,[29] and a structurally related complex[30] support this view. H-bonding between a Ru–NH_3 group and N3 of cytosine is likewise observed in $[Ru(NH_3)_5(1\text{-}MeC^-\text{-}N4)]^{2+}$.[12c,13] The fact that within several days at room temperature (even faster upon warming) weak resonances due to free 1-MeC begin to emerge when $[D_6]$DMSO is used as the solvent might be a result of the planar structure, which should facilitate the attack of nucleophiles through the axial positions of Pt.

Probing hydrogen bonding of 1 and 2 in solution: With respect to the biologically relevant question of the base-pairing behaviour of a N4-metallated iminooxo tautomer form of cytosine and factors influencing the rotational equilibrium, we also studied the effects of the free nucleobases 1-MeC and 9-EtGH on the solution structures of **1** and **2**. The rationale was that the rare cytosine tautomer in **1** could feasibly undergo pairing with neutral 1-MeC to give the equivalent of a hemiprotonated cytosine pair[31] and that the deprotonated cytosine ligand in **2** could pair with neutral 9-EtGH (or likewise **1** with deprotonated guanine, 9-EtG) in what would then be an analogue of the Watson–Crick G,C pair. In either case the N4-metallated cytosine bases need to be in an *anti* orientation (Scheme 4). Neither pairing scheme is possible for



Scheme 4. a) Hemiprotonated cytosine base pair; b) **1**·1-MeC base pair; c) Watson–Crick G,C base pair; d) **2**·9-EtGH or **1**·9-EtG.

the *syn* rotamers as in both cases three hydrogen bonds are involved. The ^1H NMR spectroscopic findings are as follows: 1) addition of increasing amounts of 1-MeC to a solution of **1** in $[D_6]$DMSO neither reveals any downfield shifts of N(3)H and N(4)H resonances assigned to the *anti* rotamers nor does it have any effect on the relative populations of the *syn* and *anti* rotamers. Moreover, a dilution experiment (concentration range 62–1 mmol L^{-1} for **1**, concentration of 1-MeC higher by a factor of 2) does not have any effect either. The observed exchange broadening of the N(3)H resonance of **1** is not unexpected, nor necessarily an indication of base-pair formation.[32] Likewise, if D_2O is used as the solvent, free 1-MeC (2 equiv per molecule of **1**) has no effect on the rotamer distribution. 2) Addition of 9-EtGH to an aqueous solution of **1**, with pD adjusted to 8.9 (either **1** or 9-EtGH partially deprotonated) has no effect on the rotamer equilibrium. Because of severe solubility problems, spectra of **2** in the presence of 9-EtGH could only be recorded in $[D_6]$DMSO at a single concentration. However, no changes that could have been interpreted in terms of H-bonding were detected. We conclude from these findings that there appears to be neither appreciable hydrogen bonding between N4 platinated cytosine in **1** and neutral cytosine nor between the deprotonated cytosine ligand in **2** and guanine in $[D_6]$DMSO solution. Whether or not these features are inherent properties of **1** and **2** (alternation of electronic complementarity on account of metal binding) or a consequence of competition for H-bonding sites in **1** and **2** between the added free base and water present in $[D_6]$DMSO, is difficult to judge. In the case of **2** it is feasible that yet another property, favourable intramolecular H-bonding (vide supra) that prevents the *anti* orientation of the cytosine nucleobases, impairs H-bond formation with guanine. Thus, the two requirements for Watson–Crick pairing between N4-metallated cytosine and free guanine, *anti* orientation of cytosine and N3 deprotonation, seem to be mutually exclusive. In principle, H-bonding according to the Hoogsteen pattern between the neutral cytosine (with the metal in *anti* orientation) and guanine is feasible, but there is no way to prove the existence of this type of H-bonding in DMSO.

At least one additional aspect should be noted here: Even if Watson–Crick pairing was possible, the considerable increase in basicity of the N3 position of N4-metallated cytosine (4–5 log units) could make such a pair prone to proton transfer and result in either a pair containing deprotonated guanine and a neutral metallated cytosine or a pair consisting of a guanine tautomer and yet another rare cytosine tautomer, after a concerted transfer of two protons (Löwdin mechanism).[33] Provided the lifetimes of these forms exceed the time required for base-pair opening ($\approx 10^{-10}$ s), the chances of mispair formation should be high. While none of our findings can prove or disprove any of these possibilities, the likelihood of a substantial mutagenic potential of N4-metallated cytosine in DNA should not be overlooked.[25a]

Heteronuclear $PtPd_2$ derivative 3: If **1** is treated with a monofunctional heterometal complex carrying a bulky ligand, the formation of a type I complex of composition *trans*-$[(NH_3)_2Pt(N4\text{-}1\text{-}MeC^-\text{-}N3)_2ML_x]^{2+}$ with both nucleobases in a *syn* orientation is not possible. However, the formation of a trinuclear compound *trans*-$[(NH_3)_2Pt\{(N4\text{-}1\text{-}MeC^-\text{-}N3)\text{-}ML_x\}_2]^{n+}$, among others, is feasible. In fact, reaction of **1** with $[(dien)Pd(H_2O)]^{2+}$ (dien = diethylenetriamine) yields the $PtPd_2$ complex *trans*-$[(NH_3)_2Pt\{(N4\text{-}1\text{-}MeC^-\text{-}N3)Pd\text{-}$

(dien)}$_2$](ClO$_4$)$_4$ · 2 H$_2$O (**3**). The X-ray structure analysis of **3** (Figure 4) shows an (*ht*,*a*,*a*) arrangement of the two nucleobases. The Pd atoms coordinate to the two endocyclic N3 atoms and thus stabilise the *anti* conformation of the two

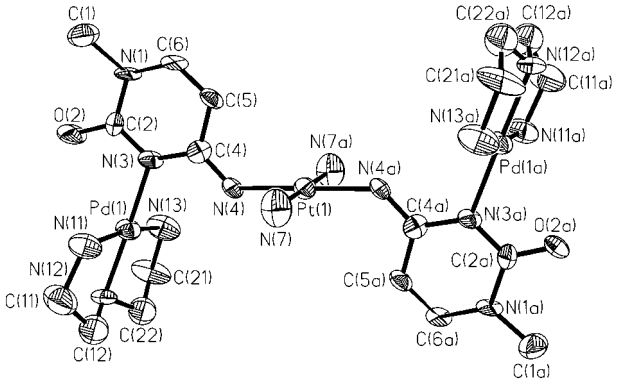
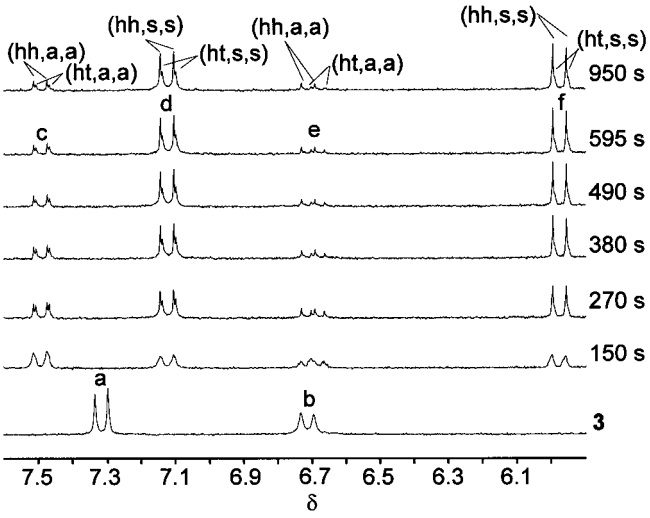


Figure 4. X-ray structure of the cation of the PtPd$_2$ derivative **3**.

nucleobases. Pt–N and Pd–N bond lengths are normal (Table 1). The dien ligands adopt the typical sting-ray folding pattern,[34] but there is a 0.6:0.4 disorder over two possible orientations that affects the C(12) and C(22) atoms. The nucleobases are almost perpendicular to the Pt coordination plane (88.2(4)°). A comparison of structural details of the cytosine nucleobases in **1** and **3** displays significant differences in the two external ring angles of the C4 atom. Thus, in **3** the N3-C4-N4 angle opens up while N4-C4-C5 decreases by 4.4–4.7° (4σ). The distance between H5 (calculated) and Pt is 3.00(1) Å, with a C5-H5-Pt angle of 106.4(2)°. This distance is of some interest because it is considerably longer than the Pt–H3 distance in **1** (2.74 Å). The fact that the N4-C4-C5 angle decreases as a consequence of Pd coordination at N3, thereby allowing the Pt and H5 atoms to approach each other, tentatively suggests that in the *anti* conformers of **1** Pt and H5 might even be further apart. Two molecules of water of crystallisation are observed per PtPd$_2$ unit. One water molecule connects the dien ligands of two PtPd$_2$ units through hydrogen bonds (O2w–N11 3.22(2) and O2w–N12 2.90(2) Å) and furthermore shows an extraordinarily short contact to the keto function of the nucleobase (O2w–O2 2.45(2) Å). The other water molecule has hydrogen bonds to the ammine ligands of one PtPd$_2$ unit as well as to one of the dien ligands of the same unit (O1w–N4 3.32(2), O1w–N7 3.08(2) and O1w–N13 2.96(3) Å).

Both ^{195}Pt NMR ($\delta = -2542$) and ^{1}H NMR spectra show the existence of only one rotamer in solution. In the ^{1}H NMR spectrum of **3**, the H6 resonance ($\delta = 7.32$) is found upfield with respect to the corresponding *anti* and downfield from the *syn* resonance in **1** ($\delta = 7.5$ and 7.1, respectively). As substitution of the proton at N3 by a metal ion leads to a shielding effect, the signals are expected to be shifted upfield. This confirms the *anti* conformation of **3** in solution. On account of the steric bulk of the Pd(dien) moieties and the fact that even immediately after dissolution only one rotamer is observed in solution, it is assigned as the (*ht*,*a*,*a*) rotamer. This interpretation was further confirmed by the following experiment: DCl (pD 2.6) was added to an aqueous solution of **3** (pD 8.3) in order to cleave the (dien)Pd–N3 bonds and the appearance of resonances resulting from the formation of **1** was followed with respect to time (Figure 5). Within 10 min (ambient temperature) a spectrum was obtained which was identical



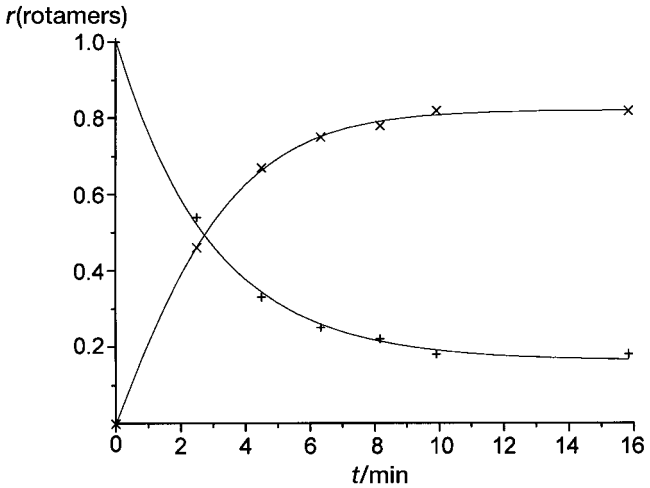


Figure 5. Top: ^{1}H NMR spectra recorded during the decomposition of **3** by DCl (pD 2.6); a: H6 of **3**, b: H5 of **3**, c: H6 of **1** *anti* rotamers, d: H6 of **1** *syn* rotamers, e: H5 of **1** *anti* rotamers, f: H5 of **1** *syn* rotamers; bottom: time dependence of the rotameric ratio r; × : *syn* rotamers, + : *anti* rotamers.

with that of solid **1** dissolved in D$_2$O. During the initial phase of the DCl decomposition reaction (*ht*) and (*hh*) forms could clearly be differentiated, because at the very beginning **1** was present exclusively in the (*ht*,*a*,*a*) conformation, with the (*hh*) species only forming with time. The complete assignments of resonances are summarised in Table 2.

Heteronuclear PtHg derivative 4: The heteronuclear derivative *trans*-[(NH$_3$)$_2$Pt(*N*4-1-MeC$^-$-*N*3)$_2$Hg](NO$_3$)$_2$ · 2 H$_2$O (**4**) was synthesised by an analogous method to that of its structural isomer and was obtained as colourless crystals. Figure 6 depicts the cation of **4**. Selected coordination bond lengths and angles are reported in Table 4. The metals are

0947-6539/98/0403-0402 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 3

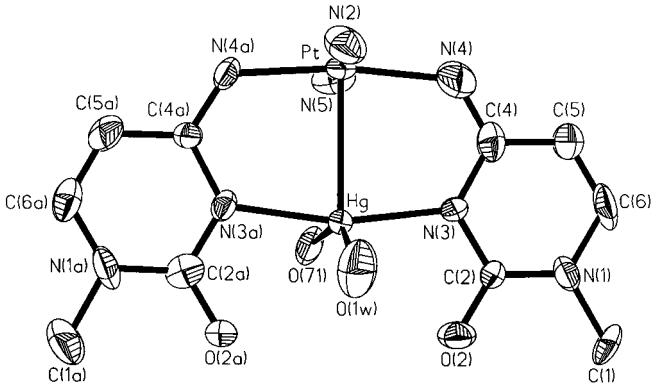


Figure 6. X-ray structure of the cation of the PtHg derivative **4** including the coordination sphere of Hg.

Table 4. Selected structural data of **4** (bond lengths in Å, angles in°).

Pt – N4	2.085(14)	N4-Pt-N4a	171.3(5)
Pt – N4a	2.031(10)	N2-Pt-N5	174.9(5)
Pt – N2	2.026(12)	N2-Pt-N4	91.6(6)
Pt – N5	2.056(12)	N2-Pt-N4a	88.8(5)
Pt – Hg	2.7498(6)	N4-Pt-N5	90.6(6)
Hg – N3	2.066(10)	N4a-Pt-N5	89.7(5)
Hg – N3a	2.080(10)	N4-Pt-Hg	85.2(3)
Hg – O1w	2.606(13)	N4a-Pt-Hg	86.2(3)
Hg – O71	2.873(11)	N2-Pt-Hg	94.0(4)
N3 – C4	1.39(2)	N5-Pt-Hg	90.8(3)
N3a – C4a	1.396(13)	N3-Hg-N3a	165.9(4)
C4 – N4	1.27(2)	N3-Pt-Hg	83.2(3)
C4a – N4a	1.301(14)	N3a-Pt-Hg	82.7(3)
		O1w-Hg-O71	107.1(3)
		N4-C4-C5	118.7(13)
		N4a-C4a-C5a	120.6(11)
		Pt-N4-C4	124.7(10)
		Pt-N4a-C4a	125.1(8)

bridged by two almost coplanar cytosine bases (dihedral angle 1.6(8)°) in the (*hh*,*s*,*s*) arrangement through the deprotonated amino groups N4 and N4a (coordinated to Pt) and the endocyclic nitrogen N3 and N3a (bound to Hg). The coordination sphere of Pt is completed by two ammonia ligands and by the heterometal in the apical position. The Pt – N distances are normal, but the N4-Pt-N4a angle (171.3(5)°) deviates markedly from 180°. The Hg – N3 distances are in agreement with those found in other PtHg complexes.[16] The N3-Hg-N3a angle is also significantly bent (165.9(4)°). A molecule of water (O1w) and a nitrate anion (O71) complete the coordination of Hg with long Hg – O distances (2.606(13) and 2.873(11) Å, respectively). The Pt – Hg distance of 2.7498(6) Å is slightly shorter than those detected in the *trans*-[$(NH_3)_2$Pt(*N*3-1-MeC$^-$-*N*4)$_2$Hg]$^{2+}$ structural isomers (2.765 – 2.835 Å).[16] The cations in the crystal are connected through weak hydrogen bonds between oxygens O2, O2a and ammine ligands N2, N5 of adjacent cations (O2 – N5 2.924, O2 – N2 3.005 and O2a – N2 2.991 Å). Moreover, the water molecule O1w has short contacts with nitrate oxygen atoms O62 (2.68 Å) and O71 (2.76 Å, unit at x, $0.5-y$, $0.5+z$). Furthermore, O2w is involved in hydrogen bonding with O2a (2.75 Å, unit at $x-0.5$, y, $0.5-z$), nitrate oxygen O63 (2.87 Å) as well as N2 (2.90 Å). The geometries of the N3-Hg-N3a and N4-Pt-N4a fragments are not significantly different from those found in the other structurally characterised PtHg complexes.[15] The problem of too close an approach between Pt and Hg is avoided by elongation of the Pt – N4 and Pt – N4a bonds, with respect to those of **1**.

The ^{195}Pt NMR spectrum of **4** shows one singlet at $\delta = -2284$, 323 ppm downfield of **1**. This shift cannot be explained by additional metal binding to the endocyclic N3 atom only, as a comparison with **3**, where no metal – metal interactions are possible, reveals that the signal is shifted only 36 ppm downfield. Therefore, this finding, in accordance with theoretical calculations,[17] suggests a weak bonding Pt – Hg interaction in **4**. Interestingly, the structural isomer *trans*-[$(NH_3)_2$Pt(*N*3-1-MeC$^-$-*N*4)$_2$Hg]$^{2+}$ exhibits a remarkable $^1J(^{199}\mathrm{Hg},^{195}\mathrm{Pt})$ coupling of 2783 Hz.[16] No such coupling is observed with **4**, possibly owing to the fact that **4** is poorly soluble, with the satellites of the NMR signal being buried in the noise. Also, despite several attempts, a ^{199}Hg NMR spectrum could not be obtained as in the cases of the structural isomer and a molecular hexagon derived from it.[36] We assume that the unfavourable relaxation behaviour of Hg^{II} in the N-Hg-N environment is responsible for this. The H5 and H6 signals in the ^{1}H NMR spectrum of **4** in D_2O each show heteronuclear couplings of $^4J(^{199}\mathrm{Hg},^1\mathrm{H5}) = 78$ Hz and $^5J(^{195}\mathrm{Pt},^1\mathrm{H6}) = 7$ Hz. It is interesting to compare this with the structural isomer (Pt at N3, Hg at N4) in which $^5J(^{199}\mathrm{Hg},^1\mathrm{H6}) = 20$ Hz, whereas $^4J(^{195}\mathrm{Pt},^1\mathrm{H5})$ is not resolved. A summary of the coupling constants observed in **4** and related N3,N4-bimetallated 1-MeC complexes is given in Table 5.

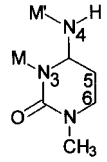


Table 5. Comparison of heteronuclear couplings in bimetallated 1-MeC$^-$ complexes as shown in Scheme 5.

M	M′	^4J(M,H5)	^5J(M′,H6)	Ref.
Hg	Pt	78	7	this paper
Pt	Hg	n.o.[a]	20	[16]
Pt	Pt	15.4	7.6	[37]
Hg	Hg	n.o.	n.o.	[38]

[a] n.o. = not observed.

Experimental Section

Materials: *trans*-[Pt$(NH_3)_2Cl_2$][39] and [Pd(dien)I]I[40] (from K_2PtCl_4 and K_2PdCl_4), 1-MeC[31] and *trans,trans,trans*-[Pt$(NH_3)_2$(1-MeC-*N*4)$_2$(OH)$_2$]-$(NO_3)_2$[7] were synthesised according to the literature. For the synthesis of the other complexes see below. All other materials (pro analysis) used in the experiments were purchased from Merck, Darmstadt (Germany). All solutions were prepared with distilled CO_2-free water.

Instrumentation: ^{1}H and ^{195}Pt spectra were recorded at ambient temperature on a Bruker AC200 instrument. Chemical shifts were measured with internal reference to sodium-3-(trimethylsilyl)propanesulfonate (^{1}H, D_2O) or tetramethylsilane (^{1}H, [D_6]DMSO) and external to Na_2PtCl_6 (^{195}Pt). Chemical shifts of **4** were measured with reference to internal tetramethylammonium tetrafluoroborate (^{1}H, $\delta = 3.19$). pD values were obtained by adding 0.4 to the pH meter reading (Metrohm 632).[41] For the determi-

Table 6. Crystal data and details of structure refinement for **1**, **3** and **4**.

	1	**3**	**4**
Formula	$C_{10}H_{20}N_{10}O_8Pt$	$C_{18}H_{48}N_{14}O_{20}Cl_4PtPd_2$	$C_{10}H_{22}N_{10}O_{10}PtHg$
M_r	603.42	1330.39	838.06
crystal system	triclinic	orthorhombic	orthorhombic
space group	$P\bar{1}$	*Pbca*	*Pbca*
a /Å	6.872(3)	10.451(3)	13.423(1)
b /Å	6.952(3)	14.908(6)	23.506(5)
c /Å	10.734(5)	27.904(4)	13.738(3)
α /°	89.79(3)		
β /°	105.25(2)		
γ /°	108.22(2)		
V /Å^3	468.1(4)	4347(2)	4335(1)
Z	1	4	8
ρ_{calcd} /g cm^{-3}	2.14	2.03	2.57
μ /mm^{-1}	$Mo_{K\alpha}$ 7.63	$Ag_{K\alpha}$ 4.36	$Mo_{K\alpha}$ 13.59
F(000)	292	2608	3120
crystal size /mm	$0.30 \times 0.24 \times 0.20$	$0.19 \times 0.15 \times 0.13$	$0.40 \times 0.20 \times 0.10$
$2\theta_{max}$ for data collection	60	36	56
index ranges	$-11 \le h \le 11,\ -11 \le k \le 11,\ 0 \le l \le 16$	$0 \le h \le 9,\ 0 \le k \le 17,\ 0 \le l \le 33$	$0 \le h \le 17,\ 0 \le k \le 31,\ -18 \le l \le 0$
reflns collected	2856	3341	5785
independent reflns	2720	3341	5785
reflns observed	2540 (3σ)	1678 (2σ)	2847 (2σ)
refinement method	full-matrix least-squares on F	full-matrix least-squares on F^2	
parameters refined	134	267	311
goodness-of-fit	1.381 (F_o)	0.935 (F^2)	0.937 (F^2)
R_1[a]	0.0414	0.0537	0.0546
wR_2[b]	0.0487	0.1018	0.1295
residuals /e Å^{-3}	1.66 / −2.04	1.05 / −1.63	2.36 / −1.96

[a] $R_1 = (\Sigma \mid F_o \mid - \mid F_c \mid)/\Sigma \mid F_o \mid$. [b] $wR_2 = \sqrt{[(\Sigma w(\mid F_o \mid - \mid F_c \mid)^2/\Sigma w(F_o)^2]}$ for **1**; $wR_2 = \sqrt{[(\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]}$ for **3** and **4**.

nation of pK_a values, uncorrected (pH*) values were plotted against chemical shifts. Elemental analyses were carried out on a LECO Elemental Analyzer CHNS-932 and a Carlo Strumentazione 1106 instrument.

X-ray diffraction studies: Diffraction data of **1**, **3** and **4** were collected at room temperature on an Enraf–Nonius CAD4 diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å) (**3**: $Ag_{K\alpha}$ radiation, $\lambda = 0.56083$ Å). Intensities of three standard reflections measured during data collections did not show any significant variation and a linear correction was applied to the data. Reflections were corrected for Lorentz-polarisation effects and an absorption correction, based on empirical ψ-scan, was applied to the structures of **1** and **4**. Structures were determined by conventional Patterson method and subsequent Fourier syntheses. The final refinements on F_o^2 for **3** and **4** (SHELXL 93 program)[42] and on F_o for **1** (MolEN package)[43] were carried out with anisotropical thermal parameters for all non-H atoms except for the four disordered ClO_4 oxygen atoms in **3**, which have occupation factors of 0.68/0.32 (O11A/B), 0.77/0.23 (O13A/B) and 0.5 (O22A/B, O23A/B). The dien ligands were found to be disordered in **3**, with C12 and C22 in two conformations with occupancy factors of 0.40(1) and 0.60(1). Hydrogen atoms at calculated positions were introduced in final cycles of refinement as fixed contributions, except those of water molecules and of the disordered methylene groups in the dien ligands of **3**. The final weighting schemes were unity for **1**, $1/[\sigma^2(F_o^2) + (0.0643P)^2]$ for **3** and $1/[\sigma^2(F_o^2) + (0.1681P)^2 + 21.53P]$ for **4** where $P = (F_o^2 + 2F_c^2)/3$. Crystallographic data and experimental details are reported in Table 6. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100598. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code + (44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

Preparation of *trans*-[Pt(NH$_3$)$_2$(1-MeC-*N*4)$_2$](NO$_3$)$_2$ · 2H$_2$O (1): Hydrogen was bubbled through a solution of *trans*,*trans*,*trans*-[Pt(NH$_3$)$_2$(1-MeC-*N*4)$_2$(OH)$_2$](NO$_3$)$_2$ (70.0 mg, 0.104 mmol) in H_2O (20 mL) at 50 °C for 3^3/$_4$ h. The pH of the solution was monitored and found to rise from 4.1 at the beginning to 6.3 at the end. The reaction apparatus consisted of a heated glass tube (34 cm length, 1.2 cm diameter) with a porous frit and a gas inlet at the bottom. Some finely dispersed Pt^0 (obtained by pyrolysis of Magnus green salt $[Pt(NH_3)_4][PtCl_4]$) was added to accelerate the reaction. When a constant pH was reached, colourless crystals of **1** (60.1 mg, 96 %) were obtained upon slow crystallisation in a N_2 flow. They were washed with H_2O (1 mL) and dried (1 d, 40 °C). **1**: $C_{10}H_{20}N_{10}O_8Pt$ (603.4): calcd C 19.9, H 3.3, N 23.2; found C 20.0, H 3.7, N 23.6.

Preparation of *trans*-[Pt(NH$_3$)$_2$(1-MeC$^-$-*N*4)$_2$] · 3H$_2$O (2): The pH of a solution of **1** (32 mg, 53 μmol) in H_2O (5 mL) was raised from 5.2 to 12.4 with a solution of NaOH (1 M, 0.2 mL). After 12 h at 4 °C under the exclusion of air, the white precipitate of **2** (24 mg, 85 %) was filtered off, washed with H_2O (10 mL) and dried (1 d, 40 °C). ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.00$ (H6), 5.30 (H5), 5.23 (N(4)H), 5.06 (NH_3), 3.05 (CH_3); $C_{10}H_{24}N_8O_5Pt$ (531.4): calcd C 22.6, H 4.6, N 21.1; found C 22.6, H 4.3, N 20.9.

Preparation of *trans*-[(NH$_3$)$_2$Pt{(*N*4-1-MeC$^-$-*N*3)Pd(dien)}$_2$](ClO$_4$)$_4$ · 2H$_2$O (3): Complex **3** was prepared by the reaction of [Pd(dien)I]I (153.6 mg, 0.3315 mmol) and $AgNO_3$ (110.4 mg, 0.6499 mmol, 1.96 equiv) in H_2O (10 mL). After 15 min at ambient temperature, AgI was filtered off and **1** (100.0 mg, 0.1657 mmol), dissolved in H_2O (15 mL), was added. After another 15 min at 25 °C the pH was adjusted stepwise from 3.0 to 6.4 with a solution of NaOH (1 M, 275 μL). Upon concentration in a stream of N_2 the yellow solution turned orange. After the addition of $NaClO_4$ (0.663 mmol) pale yellow crystals appeared and were recrystallised from H_2O (25 mL) to yield **3** (54.1 mg, 24 %). ^{1}H NMR (D_2O, pD 8.3): $\delta = 7.32$ (H6), 6.72 (H5), 3.30 (CH_3), 3.25–2.75 (dien); ^{195}Pt NMR (D_2O, pD 8.3): $\delta = -2542$; $C_{18}H_{48}N_{14}O_{20}PtPd_2Cl$ (1330.4): calcd C 16.3, H 3.6, N 14.7; found C 16.1, H 3.5, N 14.8.

Preparation of *trans*-[(NH$_3$)$_2$Pt(*N*4-1-MeC$^-$-*N*3)$_2$Hg](NO$_3$)$_2$ · 2H$_2$O (4): Compound **4** was prepared from a solution of **1** (60.3 mg, 0.100 mmol) and $Hg(OOCCF_3)_2$ (42.3 mg, 0.099 mmol, 0.99 equiv) in H_2O (10 mL). After 10 min of stirring at 25 °C, the pH was raised from 1.8 to 2.9 with a solution of NaOH (1 M, 180 μL). Upon slow crystallisation, colourless rhombic crystals of **4** (35.1 mg, 42 %) were obtained and subsequently washed with H_2O (0.5 mL) and dried (1 d, 40 °C). ^{1}H NMR (D_2O, pD 4.8): $\delta = 7.10$ ($^5J(^{195}Pt,^1H) = 7$ Hz, H6), 6.0 ($^4J(^{199}Hg,^1H) = 78$ Hz, H5), 3.38 (CH_3); ^{195}Pt NMR (D_2O, pD 4.8): $\delta = -2284$; $C_{10}H_{22}N_{10}O_{10}PtHg$ (838.0): calcd C 14.3, H 2.6, N 16.7; found C 14.4, H 2.8, N 16.7.

Received: September 1, 1997 [F812]

[1] T. Brown, W. N. Hunter, *Biopolymers* **1997**, *44*, 91–103.
[2] J. D. Watson, F. H. C. Crick, *Nature* **1953**, *171*, 737–738.
[3] M. D. Topal, J. R. Fresco, *Nature* **1976**, *263*, 289–293.
[4] L. A. Loeb, R. A. Zakour, in *Nucleic Acid-Metal Ion Interactions* (Ed.: T. G. Spiro), Wiley, New York, **1980**, pp. 115–144.
[5] K. M. Downey, A. G. So, *Met. Ions Biol. Syst.* **1989**, *25*, 1–30.
[6] B. Lippert, *Inorg. Chim. Acta* **1981**, *55*, 5–14.
[7] B. Lippert, H. Schöllhorn, U. Thewalt, *J. Am. Chem. Soc.* **1986**, *108*, 6616–6621.
[8] H. Schöllhorn, U. Thewalt, B. Lippert, *J. Am. Chem. Soc.* **1989**, *111*, 7213–7221.
[9] O. Renn, B. Lippert, A. Albinati, *Inorg. Chim. Acta* **1991**, *190*, 285–289.
[10] B. Lippert, H. Schöllhorn, U. Thewalt, *Inorg. Chim. Acta* **1992**, *198–200*, 723–732.
[11] F. Pichierri, D. Holthenrich, E. Zangrando, B. Lippert, L. Randaccio, *J. Biol. Inorg. Chem.* **1996**, *1*, 439–445.
[12] a) S. Mansy, J. P. Frick, R. S. Tobias, *Biochim. Biophys. Acta* **1975**, *378*, 319–332; b) M. J. Clarke, *J. Am. Chem. Soc.* **1978**, *100*, 5068–5075; c) B. J. Graves, D. J. Hodgson, *ibid.* **1979**, *101*, 5608–5612; d) S. E. Taylor, E. Buncel, A. R. Norris, *Inorg. Biochem.* **1981**, *15*, 131–141.
[13] Definition of *anti* as in ref. [11], with Pt pointing away from N3. This corresponds to the *Z* rotamer definition used by V. M. Rodriguez-Bailey and M. J. Clarke, *Inorg. Chem.* **1997**, *36*, 1611–1618. Similarly, our *syn* definition corresponds to the *E* definition used by these authors.
[14] M. Krumm, B. Lippert, L. Randaccio, E. Zangrando, *J. Am. Chem. Soc.* **1991**, *113*, 5129–5130.
[15] M. Krumm, E. Zangrando, L. Randaccio, S. Menzer, B. Lippert, *Inorg. Chem.* **1993**, *22*, 700–712.
[16] M. Krumm, E. Zangrando, L. Randaccio, S. Menzer, A. Danzmann, D. Holthenrich, B. Lippert, *Inorg. Chem.* **1993**, *22*, 2183–2189.
[17] C. Mealli, F. Pichierri, L. Randaccio, E. Zangrando, M. Krumm, D. Holthenrich, B. Lippert, *Inorg. Chem.* **1995**, *34*, 3418–3424.
[18] D. Holthenrich, M. Krumm, E. Zangrando, F. Pichierri, L. Randaccio, B. Lippert, *J. Chem. Soc. Dalton Trans.* **1995**, 3275–3279.
[19] G. Fusch, E. C. Fusch, A. Erxleben, J. Hüttermann, H.-J. Scholl, B. Lippert, *Inorg. Chim. Acta* **1996**, *252*, 167–178.
[20] D. Holthenrich, I. Sóvágó, G. Fusch, A. Erxleben, E. C. Fusch, I. Rombeck, B. Lippert, *Z. Naturforsch. B* **1995**, *50*, 1767–1775.
[21] The pK_a of 8.4 for deprotonation of the N(3)H groups of **1** was determined by pH*-dependent ^{1}H NMR spectra. It differs from the one determined in ref. [11], but seems to be the more accurate one because of the larger number of data points and the use of four sets of resonances instead of only the two most intensive ones. As a matter of fact, the *syn* and *anti* rotamers showed slightly, but not significantly, different pK_a values of 8.37 and 8.47, respectively. Similar findings have been reported in ref. [13] for $[Ru(NH_3)_5(1\text{-}MeC^-\text{-}N4)]^{2+}$, where the p$K_a$ values were found to be 2.6 and 5.3. This difference can most probably be attributed to the higher charge of the metal.
[22] H. Schöllhorn, R. Beyerle-Pfnür, U. Thewalt, B. Lippert, *J. Am. Chem. Soc.* **1986**, *108*, 3680–3688.
[23] B. Lippert, C. J. L. Lock, R. A. Speranzini, *Inorg. Chem.* **1981**, *20*, 808–813.
[24] E. Zangrando, F. Pichierri, L. Randaccio, B. Lippert, *Coord. Chem. Rev.* **1996**, *156*, 275–332.
[25] a) M. J. Clarke, *Inorg. Chem.* **1980**, *19*, 1103–1104; b) D. Mansuy, M. Drême, J.-C. Chottard, J.-P. Girault, J. Guilhem, *J. Am. Chem. Soc.* **1980**, *102*, 844–845; c) V. Y. Kukushkin, V. K. Belsky, E. A. Aleksandrova, V. E. Konovalov, G. A. Kirakosyan, *Inorg. Chem.* **1992**, *31*, 3836–3840; d) C. Navarro-Ranninger, I. López-Solera, A. Alvarez-Valdéz, J. H. Rodríguez-Ramos, J. R. Masaguer, J. L. García-Ruano, *Organometallics* **1993**, *12*, 4104–4111.
[26] a) M. Bortolin, U. E. Bucher, H. Rüegger, L. M. Venanzi, A. Albinati, F. Lianza, S. Trofimenko, *Organometallics* **1992**, *11*, 2514–2521; b) W. Yao, O. Eisenstein, R. H. Crabtree, *Inorg. Chim. Acta* **1997**, *254*, 105–111.
[27] a) J. M. Casas, L. R. Falvello, J. Forniés, A. Martín, A. J. Welch, *Inorg. Chem.* **1996**, *35*, 6009–6014; b) T. K. Kawamoto, I. Nagasawa, H. Kuma, Y. Kushi, *ibid.* **1996**, *35*, 2427–2432; c) W. I. Sundquist, D. P. Bancroft, S. J. Lippard, *J. Am. Chem. Soc.* **1990**, *112*, 1590–1596; d) A. Albinati, F. Lianza, P. S. Pregosin, B. Müller, *Inorg. Chem.* **1994**, *33*, 2522–2526.
[28] a) A. D. Buckingham, P. J. Stephens, *J. Chem. Soc.* **1964**, 4583–4587; b) R. G. Miller, R. D. Stauffer, D. R. Fahey, D. R. Parnell, *J. Am. Chem. Soc.* **1970**, *92*, 1511–1521.
[29] L. Randaccio, E. Zangrando, A. Cesàro, D. Holthenrich, B. Lippert, *J. Mol. Struct.* **1998**, *440*, 221–226
[30] F. P. Intini, M. Lanfranchi, G. Natile, C. Pacifico, A. Tiripicchio, *Inorg. Chem.* **1996**, *35*, 1715–1717.
[31] T. J. Kistenmacher, M. Rossi, J. P. Caradonna, L. G. Marzilli, *Adv. Mol. Relax. Interact. Processes* **1979**, *15*, 119–133.
[32] L. G. Marzilli, C.-H. Chang, J. P. Caradonna, T. J. Kistenmacher, *Adv. Mol. Relax. Interact. Processes* **1979**, *15*, 85–101.
[33] J. Florián, J. Leszczynski, *J. Am. Chem. Soc.* **1996**, *118*, 3010–3017.
[34] J. F. Britten, C. J. L. Lock, W. M. C. Pratt, *Acta Crystallogr. Sect. B* **1982**, *38*, 2148–2155, and references therein.
[35] M. Rossi, T. J. Kistenmacher, *Acta. Crystallogr.* **1977**, *B33*, 3962–3965.
[36] H. Rauter, J. Mutikainen, M. Blomberg, C. J. L. Lock, P. Amo-Ochoa, E. Freisinger, L. Randaccio, E. Zangrando, E. Chiarparin, B. Lippert, *Angew. Chem.* **1997**, *109*, 1353–1357; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1296–1301.
[37] B. Lippert, *Gazz. Chim. Ital.* **1988**, *118*, 153–165.
[38] L. Prizant, R. Rivest, A. L. Beauchamp, *Can. J. Chem.* **1981**, *59*, 2290–2297.
[39] G. B. Kauffman, D. O. Cowan, *Inorg. Synth.* **1963**, *7*, 239–245.
[40] F. Basolo, H. B. Gray, R. G. Pearson, *J. Am. Chem. Soc.* **1960**, *82*, 4200–4203.
[41] R. B. Martin, *Science* **1963**, *139*, 1198–1203.
[42] G. M. Sheldrick, SHELXL 93, Program for crystal structure refinement, Universität Göttingen, **1993**.
[43] C. K. Fair, MolEN, An Interactive Intelligent System for Crystal Structure Analysis, Enraf–Nonius, Delft (The Netherlands) **1990**.