Contribution from the Fachbereich Chemie,
Universität Dortmund, 4600 Dortmund, Germany

Platinum(II) Coordination to N1 and N7,N1 of Guanine: *cis*-DDP Model Cross-Links in the Interior and Simultaneous Cross-Links at the Periphery and the Interior of DNA

Gudrun Frommer, Ilpo Mutikainen,[1] Ferdinand J. Pesch, Edda C. Hillgeris, Hans Preut, and Bernhard Lippert*

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The preparation and characterization of a series of mono-, di-, and trinuclear Pt(II) complexes of 9-methylguanine (9-MeGH) are reported. The compounds contain the guanine heterocycle monoplatinated at N1 and/or diplatinated at N1 and N7. The route to these compounds involves a primary fixation of a (dien)Pt(II) entity to the N7 position, fixation of a second Pt(II) at N1, and subsequent removal of the N7-bound Pt(II) by cyanide. The crystal structure via X-ray diffraction of a representative example, (en)Pt(9-MeG-N^1)$_2$·3H$_2$O (**4a**) is reported: tetragonal system, space group $I4_1/a$, a = 16.003 (2) Å, c = 32.247 (6) Å, V = 8258 (2) Å^3, Z = 16.

The preferred cross-links of the antitumor agent *cis*-diamminedichloroplatinum(II), *cis*-DDP, with DNA involve binding to the N7 sites of the purine bases guanine (G) and adenine (A), specifically intrastrand adducts of types GG, AG, and GXG.[2] These cross-links account for more than 90% of all *cis*-DDP-bound DNA. Among the minor cross-links (≈1%), two are presently known: the GG interstrand adduct and G–protein adducts. Little is known about their possible biological significance and about the nature of any other minor cross-links.[3] Considering the various unusual DNA secondary structures that are emerging[4] and their suspected role in gene regulation, *cis*-DPP binding patterns other than those at the purine N7 positions can be envisaged and therefore should be considered. In fact, there are several reports, e.g., on low *cis*-DDP affinity for oligoG sequences,[5] on the effect of a second DNA binder on the platination pattern,[5] or on a sequence dependency of a AG platination reaction,[6] which somewhat modify the picture of preferential reaction with purine N7 sites. Although not directly related to the topic discussed here, a recent finding on the switch of *trans*-DPP from *GCG* to *CGCG* in a dodecamer oligonucleotide[7] may very well be relevant to *cis*-DDP interactions with DNA as well. At least with tRNA, *cis*-DDP binding to a G and a C has been reported,[8] and substantial binding of *trans*-DDP to cytosines both in single- and double-stranded DNA appears to be established now.[9]

In our laboratory, we have prepared and studied a great number of model cross-links of *cis*- and *trans*-DDP with isolated nucleobases.[10] In continuation of this work and specifically of a previous paper on two Pt(II) complexes containing N7,N1-bridging 9-methylguaninato ligands,[11] we herewith report on a series of compounds containing 9-methylguanine ligands platinated exclusively at N1 or simultaneously at N1 and N7. Some of the compounds prepared represent DNA cross-linking models with concurrent *cis*-DDP binding at the periphery and in the interior, both in inter- and intrastrand fashion.

Experimental Section

Starting Materials. *cis*-(NH$_3$)$_2$PtCl$_2$,[13] *cis*-[N(CH$_3$)$_2$H]$_2$PtCl$_2$,[14] (en)PtCl$_2$,[15] [(dien)PtI]I,[16] *cis*-(NH$_3$)$_2$Pt(1-MeU)Cl·H$_2$O,[17] *cis*-[(NH$_3$)$_2$Pt(1-MeC)Cl]Cl,[18] [(dien)Pt(9-MeGH-N^7)](ClO$_4$)$_2$,[11] {[(dien)Pt]$_2$(9-MeGH-N^7,N^1)}(ClO$_4$)$_3$·2H$_2$O (**1**),[11] *cis*-[(NH$_3$)$_2$Pt(1-MeU)(9-MeGH-N^1,N^7)Pt(dien)](ClO$_4$)$_2$·2.5H$_2$O (**2**),[11] 1-methylcytosine,[19] and 1-methyluracil[20] were prepared as described. 9-MeGH was purchased from Chemogen (Konstanz, Germany).

cis-{[N(CH$_3$)$_2$H]$_2$Pt(9-MeGH-N^7)Cl}ClO$_4$ was prepared from *cis*-[N(CH$_3$)$_2$H]$_2$PtCl$_2$ (1 mmol), NaCl (2 mmol), and 9-MeGH (1 mmol) in H$_2$O (200 mL). After 3 d at 40 °C, the clear solution was concentrated to a 4-mL volume, filtered from the Pt starting compound, and passed over a cation-exchange column (CM Sepharose Fast Flow; NaCl gradient). To the fraction containing the desired compound was added NaClO$_4$ (1 mmol). Upon crystallization, the compound was obtained as pale yellow cubes in 41% yield. Anal. Calcd (found) for C$_{10}$H$_{20}$N$_7$O$_5$Cl$_2$Pt: C, 20.5 (20.6); H, 3.6 (3.6); N, 16.8 (16.9).

Preparation of Compounds. *cis*-(NH$_3$)$_2$Pt(1-MeU)(9-MeG-N^1)·4.5H$_2$O (**2a**) was obtained in 55% yield by reaction of **2** (0.2 mmol) with NaCN (1.6 mmol) in water (20 mL) for 2 h at 20 °C, concentration to a 6-mL volume and crystallization at 4 °C. Anal. Calcd (found) for C$_{11}$H$_{26}$N$_9$O$_{7.5}$Pt: C, 22.0 (22.1); H, 4.4 (4.5); N 21.0 (21.0).

cis-[(NH$_3$)$_2$Pt(1-MeU)(9-MeGH-N^1)]ClO$_4$·3.5H$_2$O (**2g**) was isolated in 28% yield as colorless crystals on slow-evaporation of a solution of **2a** (0.037 mmol) in H$_2$O (2 mL), which had been brought to pH 3 by means of 0.1 N HClO$_4$. Anal. Calcd (found) for C$_{11}$H$_{25}$N$_9$O$_{10.5}$ClPt: C, 19.7 (19.3); H, 3.8 (3.6); N, 18.8 (18.9).

cis,cis-[(NH$_3$)$_2$(1-MeU)Pt(9-MeG-N^1,N^7)Pt(1-MeC)(NH$_3$)$_2$](ClO$_4$)$_2$·5H$_2$O (**2e**) and *cis,cis*-{(NH$_3$)$_2$(1-MeU)Pt(9-MeG-N^1,N^7)Pt(9-MeGH-N^7)[N(CH$_3$)$_2$H]$_2$}(ClO$_4$)$_2$·H$_2$O (**2f**) were prepared as follows. *cis*-[(NH$_3$)$_2$Pt(1-MeC)Cl]Cl (0.04 mmol) and AgClO$_4$ (0.078 mmol) and analogously *cis*-{[N(CH$_3$)$_2$H]$_2$Pt(9-MeGH-N^7)Cl}ClO$_4$ (0.04 mmol) and AgClO$_4$ (0.039 mmol) were stirred in H$_2$O (10 mL) for 3 d at 20 °C. After filtration of AgCl, **2a** (0.035 mmol) was added to the respective solutions and the reaction mixture was allowed to slowly evaporate. Colorless crystals of **2e** (57% yield) and of **2f** (51% yield) were obtained in this manner. Anal. Calcd (found) for C$_{16}$H$_{40}$N$_{14}$O$_{17}$Cl$_2$Pt$_2$

(1) Permanent address; Department of Chemistry, University of Helsinki, Finnland.
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(**2e**): C, 16.5 (16.4); H, 3.5 (3.5); N, 16.9 (17.0). Anal. Calcd (found) for $C_{21}H_{40}N_{16}O_{13}Cl_2Pt_2$ (**2f**): C, 21.3 (20.9); H, 3.4 (3.1); N, 18.9 (18.9).

$[(NH_3)_2Pt(1\text{-}MeC)(9\text{-}MeG\text{-}N^1,N^7)Pt(dien)](ClO_4)_3\cdot 2H_2O$ (**3**) was prepared by mixing an aqueous suspension of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)Cl]Cl$ (0.75 mmol in 100 mL of H_2O) with an aqueous solution of $AgClO_4$ (1.48 mmol in 8 mL of H_2O) and stirring it for 48 h at 20 °C in the dark. After filtration of AgCl, $[(dien)Pt(9\text{-}MeGH\text{-}N^7)](ClO_4)_2$ (0.5 mmol) was added (pH 4) and the mixture brought to pH 8 by means of 0.1 N NaOH. After 3 d at 70 °C, the solution was allowed to evaporate to a 10-mL volume and a small amount of *ht-cis*-$[(NH_3)_2Pt(1\text{-}MeC^-)]_2(ClO_4)_2$[21] was removed. The filtrate was passed over a Sephacryl S100 HR column and colorless cubes of **3** crystallized from the middle fractions (14% yield). Anal. Calcd (found) for $C_{15}H_{36}N_{13}O_{16}Cl_3Pt_2$: C, 15.7 (15.5); H, 3.2 (3.2); N, 15.8 (15.5).

$\{(en)Pt[(9\text{-}MeG\text{-}N^1,N^7)Pt(dien)]_2\}(ClO_4)_4\cdot 2H_2O$ (**4**) was prepared as follows: $[(dien)Pt(9\text{-}MeGH\text{-}N^7)](ClO_4)_2$ (2.0 mmol) was added to an aqueous solution of $[(en)Pt(H_2O)_2](ClO_4)_2$ (1 mmol in 40 mL of H_2O; prepared from $enPtCl_2$ and $AgClO_4$), the pH adjusted to 8 by means of NaOH and the mixture stirred for 4 d at 60 °C. The solution was then concentrated to a 6-mL volume and passed over Sephadex G10. **4** was isolated in 17% yield as a colorless powder from the final fractions. Anal. Calcd (found) for $C_{22}H_{50}N_{18}O_{20}Cl_4Pt_3$: C, 16.5 (16.5); H, 3.1 (3.1); N, 15.7 (15.7); Cl, 8.8 (8.8).

$(en)Pt(9\text{-}MeG\text{-}N^1)_2\cdot 3H_2O$ (**4a**) was obtained from **4** (0.25 mmol in 4 mL of H_2O) and NaCN (2.50 mmol) after 1 h of reaction time at 20 °C. It was separated from unreacted NaCN, $NaClO_4$, and $Na_2Pt(CN)_4$ by size exclusion chromatography (Sephacryl S100 HR) and isolated as colorless cubes in 50% yield. Anal. Calcd (found) for $C_{14}H_{26}N_{12}O_5Pt$: C, 26.4 (26.5); H, 4.1 (4.0); N, 26.4 (26.4).

cis,cis-$\{(en)Pt[(9\text{-}MeG\text{-}N^1,N^7)Pt(1\text{-}MeC)(NH_3)_2]_2\}(ClO_4)_4\cdot 9H_2O$ (**4b**) was obtained in 28% yield upon slow evaporation (30 °C) of a mixture of **4** (0.04 mmol) and *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)](ClO_4)_2$ (0.08 mmol in 10 mL of H_2O, obtained from $[(NH_3)_2Pt(1\text{-}MeC)Cl]Cl$ and $AgClO_4$). Anal. Calcd (found) for $C_{24}H_{64}N_{22}O_{29}Cl_4Pt_3$: C, 15.6 (15.5); H, 3.5 (3.2); N, 16.6 (16.1).

Solution Studies. Reaction of **2a** (0.01 mmol in 0.5 mL of D_2O) with a mixture of *cis*-$[(NH_3)_2Pt(D_2O)_2]^{2+}$ and *cis*-$(NH_3)_2PtCl_2$ (prepared from 0,01 mmol of *cis*-$(NH_3)_2PtCl_2$ and ca. 0.018 mmol of $AgNO_3$ in 0.1 mL of D_2O) led to rapid formation of three products which, on the basis of pD dependent ^1H NMR spectroscopy, were assigned to *cis,cis*-$[(NH_3)_2(1\text{-}MeU)Pt(9\text{-}MeG\text{-}N^1,N^7)Pt(NH_3)_2(D_2O)](ClO_4)_2$ (**2b**), *cis,cis*-$[(NH_3)_2(1\text{-}MeU)Pt(9\text{-}MeG\text{-}N^1,N^7)Pt(NH_3)_2Cl]ClO_4$ (**2c**), and *cis,cis,cis*-$\{[(NH_3)_2(1\text{-}MeU)Pt(9\text{-}MeG\text{-}N^1,N^7)]_2Pt(NH_3)_2\}(ClO_4)_2$ (**2d**). Addition of excess NaCl to the mixture converted **2b** quantitatively to **2c**.

cis-$[(NH_3)_2Pt(1\text{-}MeC)(9\text{-}MeG\text{-}N^1)]ClO_4$ (**3a**) was prepared by reaction of **3** (0.01 mmol) in 0.55 mL of D_2O) with NaCN (0.08 mmol) within 1 h at 20 °C in 100% yield but later decomposed in the presence of excess CN^-.

Spectra. IR spectra were recorded on a Perkin-Elmer 580 B instrument on KBr pellets and Nujol mulls. ^1H NMR spectra were taken on a Bruker AC 200 instrument for complexes in D_2O with TSP and/or $[NMe_4]^+$ (3.19 ppm downfield from TSP) as internal reference. δ values are given relative to TSP. Occasionally, e.g., with **2f** and **4b**, TSP (3-(trimethylsilyl)-1-propanesulfonate, Na^+ salt) proved an unreliable internal reference, in contrast to $[NMe_4]^+$. pH-dependent NMR shifts were determined using uncorrected pH* values.

Crystallography. A crystal of **4a** (0.5 × 0.2 × 0.15 mm) was mounted in a Lindemann glass capillary. Intensity data were collected at T = 291(1) K with $\omega/2\theta$ scans, variable scan speed 2.5–15.0° min^{-1} in θ, and scan width 1.2° + dispersion. A Nicolet R3m/V diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) was used for preliminary examinations and data collection. The lattice parameters were determined from a symmetry-constrained least-squares fit of 25 reflections with $2\theta_{max}$ = 19.35°. Crystal data are as follows: $C_{14}H_{26}N_{12}O_5Pt$, fw = 637.53, tetragonal system, space group $I4_1/a$, a = 16.003 (2) Å, c = 32.247 (6) Å, V = 8258 (2) Å^3, Z = 16, d_{calcd} = 2.051 g cm^{-3}. ω scans of low-order reflections along the three crystal axes showed acceptable mosaicity. Six standard reflections (5,–2,5; –5,2–5; 1,–6,2; –1,6–2; 0,0,12; 0,0,–12) were recorded every 300 reflections, only random deviations were detected during 448.12 h of X-ray exposure; 25 792 reflections with 1.0° ≤ 2θ ≤ 50.0°, –20 ≤ h ≤ 20, –20 ≤ k ≤10, and –39 ≤ l ≤ 39 were measured. The data were corrected for Lorentz–polarization but not for absorption effects (μ = 6.9 mm^{-1}) and averaged (R_{int} = 0.033) to 3661 unique reflections, 2937 of which had $F \geq 4.0\sigma(F)$. The systematic absences (hkl) $h + k + l$ = 2n + 1, ($hk0$) h = 2n + 1, and ($00l$) l = 4n + 1, l = 4n + 2, and = 4n + 3 conform to space group $I4_1/a$.

Table I. Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2 × 10^4) of $(en)Pt(9\text{-}MeG\text{-}N^1)_2\cdot 3H_2O$ (**4a**)[a]

	x	y	z	U_{eq}
Pt	0.28956 (1)	0.53964 (1)	0.04763 (1)	225
N(1)	0.2321 (3)	0.4676 (3)	0.0923 (1)	249
N(2)	0.2889 (3)	0.3444 (3)	0.0660 (1)	365
N(3)	0.1996 (3)	0.3320 (3)	0.1199 (1)	294
N(7)	0.0944 (3)	0.4783 (3)	0.1855 (1)	295
N(9)	0.1080 (3)	0.3397 (3)	0.1794 (1)	310
N(11)	0.2234 (3)	0.4804 (3)	0.0020 (1)	230
N(12)	0.1011 (3)	0.5441 (3)	0.0258 (1)	331
N(13)	0.0877 (3)	0.4532 (3)	–0.0283 (1)	264
N(17)	0.2364 (3)	0.3388 (3)	–0.0896 (1)	342
N(19)	0.0971 (3)	0.3605 (3)	–0.0875 (1)	289
N(20)	0.3541 (3)	0.6084 (3)	0.0904 (1)	342
N(21)	0.3460 (3)	0.6192 (3)	0.0066 (1)	298
O(6)	0.1768 (2)	0.5896 (2)	0.1183 (1)	355
O(16)	0.3443 (2)	0.4219 (3)	–0.0225 (1)	345
O(30)	0.2640 (3)	0.6950 (3)	0.1678 (1)	519
O(40)	0.5181 (3)	0.5929 (3)	–0.0253 (1)	514
O(50)	0.506 (6)	0.244 (6)	0.0616 (3)	1074
C(2)	0.2389 (3)	0.3817 (3)	0.0936 (2)	275
C(4)	0.1536 (3)	0.3746 (3)	0.1477 (2)	250
C(5)	0.1446 (3)	0.4604 (3)	0.1516 (2)	255
C(6)	0.1837 (3)	0.5110 (4)	0.1214 (2)	265
C(8)	0.0745 (3)	0.4054 (4)	0.2007 (2)	332
C(9)	0.1067 (4)	0.2513 (4)	0.1890 (2)	456
C(12)	0.1386 (3)	0.4905 (3)	–0.0006 (2)	257
C(14)	0.1312 (3)	0.4053 (3)	–0.0551 (2)	250
C(15)	0.2159 (3)	0.3915 (3)	–0.0563 (2)	262
C(16)	0.2664 (3)	0.4304 (3)	–0.0260 (2)	262
C(18)	0.1636 (4)	0.3223 (4)	–0.1063 (2)	368
C(19)	0.0104 (4)	0.3614 (4)	–0.1003 (2)	450
C(20)	0.4079 (4)	0.6711 (4)	0.0697 (2)	394
C(21)	0.3666 (4)	0.6970 (4)	0.0306 (2)	383

[a] $U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i\cdot\mathbf{a}_j$.

The structure was solved via a Patterson function and $\Delta\rho$ maps. It was refined (on F) using full-matrix least-squares methods with anisotropic displacement parameters for all non-H atoms and a common isotropic displacement parameter for the H atoms, which were placed in geometrically calculated positions (C–H = 0.96 Å; N–H = 0.90 Å). A total of 289 parameters were refined. Weights $w = 1.0/(\sigma^2(F) + (0.00002F^2))$ led to a featureless analysis of variance in terms of sin θ and F_o. The refinement converged to S = 1.27, R = 0.027, R_w = 0.022, $(\Delta/\sigma)_{max}$ = 0.07 (except for atom O(50) which had 0.05 ≤ (Δ/σ) ≤ 1.2) (no extinction correction). The correctness of the space group choice was checked by using MISSYM.[22] The largest peaks in final $\Delta\rho$ map were ±0.7 (3) e Å^{-3}. Atomic scattering factors for neutral atoms and real and imaginary dispersion terms were taken from ref 23. The programs used were PARST,[24] SHELXTL PLUS,[25] PLATON,[26] and MISSYM.[22] Positional parameters and the equivalent values of the anisotropic displacement parameters for the non-H atoms are given in Table I.

Results and Discussion

Method of Preparation of Compounds. The preparation of N1 or N7,N1 platinated 9-methylguanine complexes is schematically outlined in Figure 1. The starting material in all cases was $[(dien)Pt(9\text{-}MeGH\text{-}N^7)]^{2+}$,[11] which was reacted at neutral or slightly alkaline pH with a second Pt electrophile such as the monofunctional $[(dien)Pt(H_2O)]^{2+}$, *cis*-$[(NH_3)_2Pt(1\text{-}MeU\text{-}N^3)(H_2O)]^+$, and *cis*-$[(NH_3)_2Pt(1\text{-}MeC\text{-}N^3)(H_2O)]^{2+}$ or the bifunctional $[(en)Pt(H_2O)_2]^{2+}$ to give the di- and trinuclear species $[(dien)Pt(N^1\text{-}9\text{-}MeG\text{-}N^7)Pt(dien)]^{3+}$, **1**, *cis*-$[(NH_3)_2(1\text{-}MeU\text{-}N^3)Pt(N^1\text{-}9\text{-}MeG\text{-}N^7)Pt(dien)]^{2+}$, **2**, *cis*-$[(NH_3)_2(1\text{-}MeC\text{-}N^3)\text{-}Pt(N^1\text{-}9\text{-}MeG\text{-}N^7)Pt(dien)]^{3+}$, **3**, or $\{(en)Pt[(N^1\text{-}9\text{-}MeG\text{-}N^7)Pt\text{-}$

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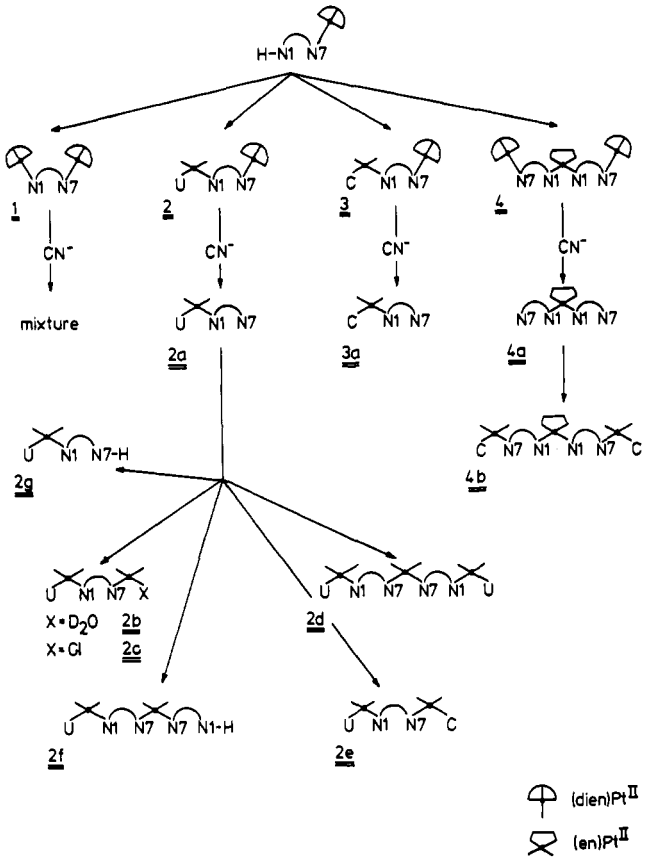

Figure 1. Schematic outline of the method of preparation of the compounds described. The guanine ligand is represented as N1⌒N7, indicating the two principle donor sites which can be protonated or platinated. Pt entities are abbreviated as shown in the figure.

$(dien)]_2]^{4+}$, **4**, respectively. Details of the preparations and X-ray structure of **1** and **2** have already been published.[11]

In a second step, the N7,N1-bridged complexes were treated with excess CN^- (8–10 equiv) at pH ≈ 11, 20 °C. It was the aim of this procedure to selectively cleave the (9-MeG-N^7)Pt(dien) bond in order to prepare 9-methylguanine species platinated exclusively at the N1 position. The rationale behind this reaction was previous findings on a kinetic inertness of Pt–N bonds toward CN^- when properly shielded by exocyclic groups of nucleobases adjacent to the metal binding site.[27] As expected, selectivity was poor in the case of **1** with all three decomposition products, namely free 9-MeGH, $[(dien)Pt(9\text{-}MeGH\text{-}N^7)]^{2+}$, and $[(dien)Pt(9\text{-}MeG\text{-}N^1)]^+$, detectable in the reaction mixture. According to ^1H NMR spectroscopy, reaction **3** → **3a** is complete within 1 h at 20 °C, but after 24 h, partial displacement of all Pt ligands has started. From a preparative point a view, reactions **4** → **4a** and **2** → **2a** were most satisfactory because of a pronounced inertness of the product even toward a 20-fold excess of cyanide. While not unexpected for the mixed uracil, guaninato adduct **2a**,[27] the inertness of the bis(guaninato) complex **4a** suggested to us that the two guanine rings were in a head–tail orientation with the two O6 oxygens shielding the Pt center.

The third reaction step involved fixation of a mono- or bifunctional Pt entity again to the N7 position, thereby generating novel N1,N7-diplatinated guanine species. Reactions were remarkably fast and usually complete within minutes. For example, if one started with **4a** and reacted it with *cis*-$[(NH_3)_2Pt(1\text{-}MeC\text{-}N^3)(H_2O)]^{2+}$, the trinuclear compound **4b** could be prepared.

(27) (a) Raudaschl-Sieber, G.; Lippert, B. *Inorg. Chem.* **1985**, *24*, 2426. (b) Frommer, G.; Lippert, B. *Inorg. Chem.* **1990**, *29*, 3259. (c) Lippert, B.; Frommer, G.; Renn, O.; Krizanovic, O.; Dieter, I.; Krumm, M.; Trötscher, G.; Pesch, F.; Schwarz, F.; Menzer, S.; Hillgeris, E. C. In *Proceedings of the 6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Howell, S. B., Ed.; Plenum Publ. Corp.: New York, 1991, p 25.

Table II. Chemical Shifts of 9-Methylguanine (9-Methylguaninato) Resonances in the Pt Complexes

	pD	H8	CH_3	rotation about Pt–N7
	Pt(9-MeGH-N^7)			
$[dienPt(9\text{-}MeGH\text{-}N^7)]^{2+}$	2–7	8.12	3.70	
2f	2–7	8.23	3.64	medium
	Pt(9-MeG-N^7,N^1)Pt			
1	3–10	7.96	3.67	
2	3–10	7.96	3.66	
2b	5	8.00	3.64	
2c	3–10	7.97	3.63	
2d	3–10	7.79	3.54	slow
2e	3–10	7.85	3.62	slow
2f	3–10	7.95	3.57	medium
3	3–10	7.98	3.65	
4	3–10	7.95	3.64	
4b[a]	3–10	7.87	3.61	
		7.86	3.60	slow
		7.84	3.59	
	Pt(9-MeG-N^1)			
2a	>6	7.55	3.54	
3a	>6	7.66	3.61	
4a	>6	7.52	3.47	
	Pt(9-MeGH-N^1)			
2g	<3	8.63	3.77	

[a] Three sets of resonances due to rotamers.

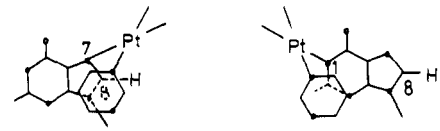

Figure 2. Different base overlap in mixed purine, pyrimidine complexes of *cis*-a_2Pt^{II} with purine-N^7 binding (a) and purine-N^1 binding (b) and different effects on the purine H8 proton.

2a was reacted with the Pt electrophiles *cis*-$[(NH_3)_2Pt(D_2O)_2]^{2+}$, *cis*-$[(NH_3)_2Pt(D_2O)Cl]^+$, *cis*-$[(NH_3)_2Pt(1\text{-}MeC\text{-}N^3)(D_2O)]^{2+}$, and *cis*-$\{[(CH_3)_2NH]_2Pt(9\text{-}MeGH)(D_2O)\}^{2+}$ to give the corresponding complexes **2b–2f**.

In the following section some selected details of the various compounds will be discussed in more detail.

Characterization of Compounds. With the exception of **2b–2d** and **3a**, all compounds reported have been isolated on a preparative scale. Compounds **1** and **2** have previously been studied by X-ray analysis.[11]

^1H NMR chemical shifts of the N3-platinated pyrimidine nucleobases 1-MeU and 1-MeC are close to those reported elsewhere.[17,28] Shifts of the 9-MeG(H) resonances (Table II) are consistent with consideration of electron densities in the heterocyclic ring(s) and follow the sequence Pt(9-MeG-N^1), Pt_2(9-MeG-N^1,N^7), Pt(9-MeGH-N^7), and Pt(9-MeGH-N^1). As is evident from Table II, any second nucleobase coordinated to Pt at N1 of the guanine (in a cis orientation) does not strongly influence the guanine resonances H8 and CH_3(9). This situation is in contrast to bis(nucleobase) complexes with *cis*-$(NH_3)_2Pt^{II}$ bound to guanine through N7 (Figure 2). There, stacking between the imidazole moiety of the guanine ring and the second nucleobase causes an upfield shift of the guanine resonances.

N7,N1-bridged 9-methylguanine is neither protonated nor deprotonated in the pH range 3–10. Only in strongly acidic medium is there protonation; e.g., the pK_a of protonated **2** is ca. 1.0, probably facilitated by the 1-MeU ligand.[29] Compounds with 9-methylguanine bound to Pt exclusively via N1 display a strong pH dependence in their H8 and CH_3 resonances due to the

(28) See, e.g.: (a) Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1982**, *21*, 3210. (b) Beyerle-Pfnür, R.; Brown, B.; Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1985**, *24*, 4001.

(29) Schöllhorn, H.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1989**, *111*, 7213.

proximity of the N7 site. The pK_a determined for *cis*-$[(NH_3)_2Pt(1\text{-MeU})(9\text{-MeGH-}N^1)]^+$ (**2g**) is 5, in agreement with findings by van der Veer et al.[30] The difference between N1-platinated 9-MeG and N1,N7-diplatinated 9-MeG toward H^+ provided also conclusive evidence for the formation of the bridged complexes **2b–d** from **2a** (supplementary material). Reaction of the *cis*-$(NH_3)_2Pt^{II}$ moiety via O4 of 1-MeU O6 of 9-MeG in **2a** was considered possible, yet the fact that 1-MeU resonances are hardly affected when going from **2a** to **2b–2d** clearly ruled against such a possibility. We note, however, that upon long reaction times (days), further ^1H NMR changes occur which cannot be interpreted at present.

Integration of nucleobase and amine ligand (dien, $NH(CH_3)_2$) resonances of the compounds in all cases is consistent with the proposed composition. As far as isolated complexes are concerned, ^1H NMR spectra established the absence of any impurities such as free nucleobase(s) or unreacted starting materials. ^1H NMR spectra of all compounds not characterized by X-ray analysis are given in the supplementary material. Occasionally resonances are split or display temperature-dependent behavior. Undoubtedly this is a consequence of multiple rotamers being possible and present in solution. As demonstrated by Marzilli et al.[31] and supported by the molecular mechanics calculations of Hambley,[32] the rotation of nucleobases in bis(nucleobase) complexes of *cis*-$(NH_3)_2Pt^{II}$ is strongly affected by the nature and number of exocyclic groups adjacent to the metal binding site. In particular, unfavorable interactions between the NH_3 groups at Pt and exocyclic amino groups of nucleobases are responsible for a hindered rotation. For example, ^1H NMR spectra of **3**, **3a**, **4**, and **4a** display sharp, single sets of nucleobase resonances which we attribute to the presence of single rotamers as a consequence of steric hindrance about the Pt–N3 cytosine and/or Pt–N1 guanine bonds rather than to fast interconversion of rotamers. A head–tail arrangement of the two bases, as observed for **4a** in the solid state (vide infra), probably is favored in all cases because it allows a weak H bonding interaction between an exocyclic NH_2 of one base and an exocyclic O of the other one. It is also realized in *cis*-$[(NH_3)_2Pt(1\text{-MeC})_2]^{2+}$.[28a,33]

1-MeU resonances in **2–2f** are broad and ill-resolved at ambient temperature, but sharpen at higher temperatures. This behavior indicates the beginning of fast rotation of the uracil rings at increasing temperatures (see supplementary material).

IR spectroscopy proved to be of limited usefulness in the characterization of the compounds (cf. also discussion in ref 11). While the disappearance of bands due to anions, e.g., during processes **2** → **2a** or **4** → **4a** or their reappearance (**2a** → **2g**), were helpful in recognizing acid/base reactions, superpositions of bands in mixed nucleobase complexes were severe. As to guanine absorptions in the double bond stretching region, it was surprising to find how minor the spectroscopic changes were once the N1 position was deprotonated and platinated. Thus the position of the intense bands in the 1600–1700-cm^{-1} region are very insensitive to second platination at N7 or even protonation at that site.

Reactivity of Compounds. The N7 position of neutral guanine nucleobases displays a long-established kinetic preference for soft metal ions such as Pt^{II}.[34,35] Reaction between the N1-deprotonated guanine and Pt^{II} electrophiles is slow because of simultaneous formation of kinetically inert $Pt^{II}(OH)$ species, even though prolonged reaction times afford N1-platinated compounds.[30] Reaction at the N1 position is reasonably fast once the N7 site is platinated, and as a consequence of the latter, the N(1)H becomes more acidic.[11,36–38]

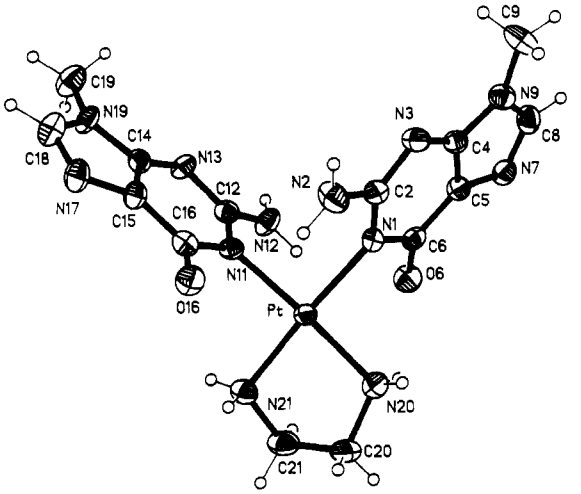

Figure 3. General view and atom-numbering scheme of the title compound **4a**. Anisotropic ellipsoids represent 50% probability boundaries. Water molecules are omitted.

Table III. Selected Interatomic Distances (Å) and Angles (deg) in **4a**

Pt(1)–N(1)	2.061 (4)	N(13)–C(12)	1.347 (7)
Pt(1)–N(11)	2.045 (4)	N(13)–C(14)	1.348 (7)
Pt(1)–N(20)	2.043 (5)	N(17)–C(15)	1.403 (7)
Pt(1)–N(21)	2.047 (4)	N(17)–C(18)	1.311 (8)
N(1)–C(2)	1.381 (7)	N(19)–C(14)	1.378 (7)
N(1)–C(6)	1.401 (7)	N(19)–C(18)	1.370 (7)
N(2)–C(2)	1.338 (7)	N(19)–C(19)	1.448 (7)
N(3)–C(2)	1.320 (7)	N(20)–C(20)	1.481 (8)
N(3)–C(4)	1.346 (7)	N(21)–C(21)	1.501 (7)
N(7)–C(5)	1.386 (7)	O(6)–C(6)	1.266 (7)
N(7)–C(8)	1.305 (7)	O(16)–C(16)	1.259 (7)
N(9)–C(4)	1.375 (7)	C(4)–C(5)	1.386 (8)
N(9)–C(8)	1.365 (7)	C(5)–C(6)	1.412 (7)
N(9)–C(9)	1.449 (8)	C(14)–C(15)	1.373 (8)
N(11)–C(12)	1.369 (7)	C(15)–C(16)	1.414 (8)
N(11)–C(16)	1.389 (7)	C(20)–C(21)	1.485 (8)
N(12)–C(12)	1.350 (7)		
N(20)–Pt(1)–N(21)	83.0 (2)	N(1)–C(2)–N(2)	118.1 (5)
N(11)–Pt(1)–N(21)	93.0 (2)	N(3)–C(4)–N(9)	125.5 (5)
N(11)–Pt(1)–N(20)	174.9 (2)	N(9)–C(4)–C(5)	106.2 (5)
N(1)–Pt(1)–N(21)	175.3 (2)	N(3)–C(4)–C(5)	128.3 (5)
N(1)–Pt(1)–N(20)	93.2 (2)	N(7)–C(5)–C(4)	109.7 (5)
N(1)–Pt(1)–N(11)	90.7 (2)	C(4)–C(5)–C(6)	117.3 (5)
Pt(1)–N(1)–C(6)	116.0 (3)	N(7)–C(5)–C(6)	133.0 (5)
Pt(1)–N(1)–C(2)	122.9 (3)	O(6)–C(6)–C(5)	125.8 (5)
C(2)–N(1)–C(6)	121.1 (4)	N(1)–C(6)–C(5)	115.0 (5)
C(2)–N(3)–C(4)	112.5 (5)	N(1)–C(6)–O(6)	119.1 (5)
C(5)–N(7)–C(8)	104.7 (5)	N(7)–C(8)–N(9)	113.7 (5)
C(8)–N(9)–C(9)	129.7 (5)	N(9)–C(8)–H(8a)	123.0 (7)
C(4)–N(9)–C(9)	124.3 (5)	N(11)–C(12)–N(13)	126.0 (5)
C(4)–N(9)–C(8)	105.7 (5)	N(11)–C(12)–N(12)	118.3 (5)
Pt(1)–N(11)–C(16)	118.5 (3)	N(13)–C(14)–N(19)	125.1 (5)
Pt(1)–N(11)–C(12)	120.3 (3)	N(19)–C(14)–C(15)	106.6 (4)
C(12)–N(11)–C(16)	121.2 (4)	N(13)–C(14)–C(15)	128.2 (5)
C(12)–N(13)–C(14)	111.4 (4)	N(17)–C(15)–C(14)	110.4 (5)
C(15)–N(17)–C(18)	103.2 (5)	C(14)–C(15)–C(16)	118.3 (5)
C(18)–N(19)–C(19)	128.5 (5)	N(17)–C(15)–C(16)	131.3 (5)
C(14)–N(19)–C(19)	126.2 (5)	O(16)–C(16)–C(15)	125.4 (5)
C(14)–N(19)–C(18)	105.1 (4)	N(11)–C(16)–C(15)	114.9 (5)
Pt(1)–N(20)–C(20)	110.9 (3)	N(11)–C(16)–O(16)	119.7 (5)
Pt(1)–N(21)–C(21)	106.2 (3)	N(17)–C(18)–N(19)	114.6 (5)
N(2)–C(2)–N(3)	116.4 (5)	N(20)–C(20)–C(21)	108.1 (5)
N(1)–C(2)–N(3)	125.6 (5)	N(21)–C(21)–C(20)	107.8 (5)

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(31) (a) Reily, M. D.; Wilkowski, K.; Shinozuka, K.; Marzilli, L. G. *Inorg. Chem.* **1985**, *24*, 37. (b) Reily, M. D.; Marzilli, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 6785.
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(36) Raudaschl-Sieber, G.; Marzilli, L. G.; Lippert, B.; Shinozuka, K. *Inorg. Chem.* **1985**, *24*, 989.

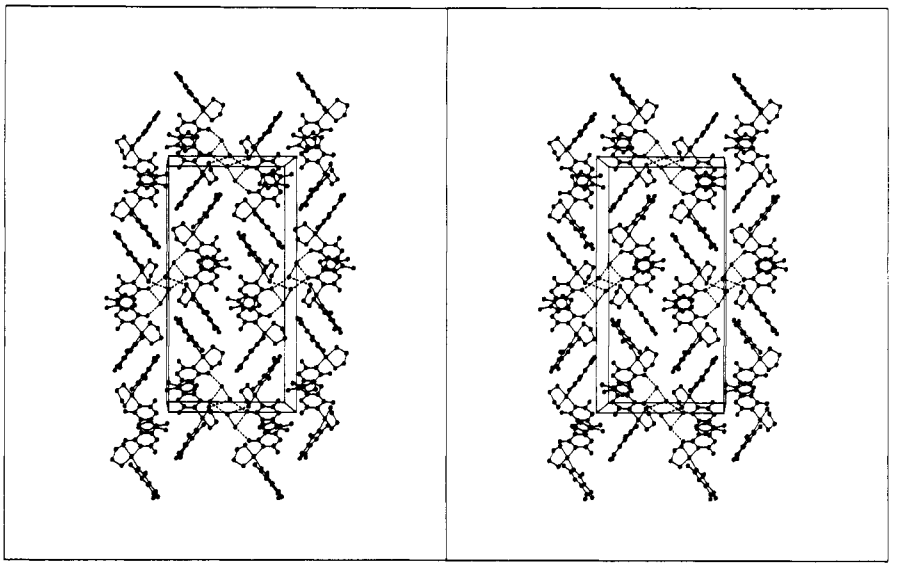

Figure 4. Stereoscopic view of the unit cell of **4a** with H bonds involving H_2O molecules indicated.

As now demonstrated by the behavior of complexes containing N1-bound Pt^{II} (**2a**, **3a**, **4a**) toward other Pt electrophiles, reactions at N7 become very fast and are complete within minutes, once the N1 position is platinated. This is a consequence of the fact that Pt bound to the deprotonated N1 site does not neutralize the negative charge but effectively increases the basicity of the ring as compared to the neutral ligand. Formation of a trinuclear (N7, N1, N3) Pt^{II} complex[37] as well as a 2:2 compound between 5'-IMP and Cu^{II} with metal binding through N1, O6, and N7[39] is rationalized on the same basis, as is formation of di- and multinuclear thymine and uracil complexes described in large numbers.[10,40]

As expected, reaction of *cis*-$(NH_3)_2Pt(1\text{-MeU})(9\text{-MeG-}N^1)$ (**2a**) with Cu^{II} is very fast. However, coordination of Cu^{II} does not take place via N7 but rather through O6 of 9-MeG in conjunction with O4 of 1-MeU. A trinuclear, reddish-brown complex of composition *cis*-$\{[(NH_3)_2Pt(1\text{-MeU})(9\text{-MeG-}N^1,O^6)]_2Cu\}^{2+}$ has been isolated in crystalline form.[41] In this centrosymmetric compound, the Pt–Cu distance is very short, 2.649 (1) Å.

X-ray Structure of (en)Pt(9-MeG-N^1)$_2$·3H$_2$O (4a). Figure 3 gives a view of (en)Pt(9-MeG-N^1)$_2$·3H_2O (**4a**) and Table III lists selected interatomic distances and angles. Pt adopts a normal square-planar coordination geometry without unusual features. The two CH_2 groups of the en ligand are symmetrically distributed about the PtN_4 plane with normal bond distances and angles.[42] The two nucleobases are coordinated to Pt via the N1 positions and are arranged head-to-tail. As compared to N1,N7-diplatinated compounds,[11] there are no significant differences in the geometries of the two purine rings. Dihedral angles between the pyrimidine and the imidazole part of the purine rings are very small, 1.6 (1) and 0.9 (2)°. Distances between the Pt and O6 sites (3.08 (1) and 3.01 (1) Å) are similar to those observed in the related 7,9-dimethylhypoxanthine[43] complex of $(en)Pt^{II}$ and the 7,9-dimethylguanine[44] complex of *trans*-$(NH_3)_2Pt^{II}$, where Pt also binds to the N1 positions. They are also similar to those found in *cis*-$[(NH_3)_2Pt(1\text{-MeC-}N^3)_2]^{2+}$ with the cytosine providing a coordination sphere similar to that of the two guanines in **4a**.[28a,33] Dihedral angles in **4a** were determined according to the convention of Kistenmacher et al.[45] and are as follows: PtN_4/9-MeG, 121.0 (1) and 112.7 (1)° (average); 9-MeG/9-MeG, 77.2 (2)°.

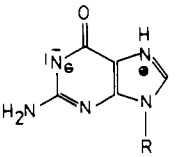

Figure 5. Unusual tautomeric structure of a 9-substituted guanine. In **2g** the N1 position is platinated.

Figure 4 provides a stereoscopic view of the unit cell. As can be seen, there is extensive base overlap with each guanine ring stacked with a guanine of an adjacent molecule. Hydrogen-bonding interactions are numerous, but with two exceptions longer than 3 Å. Intramolecular H bonds are between the $NH_2(2)$ and O6 sites of the two guanine rings (N(2)–O(16), 3.232 (6) Å; N(12)–O(6), 3.297 (6) Å) and between the O6 sites and the two NH_2 groups of the en chelate (O(6)–N(20), 2.991 (6) Å; O(16)–N21, 3.293 (6) Å). The water molecules are also involved in H bonding (e.g. O(30)–N(20), 3.198 (6) Å or O(40)–N(21), 2.969 (6) Å). Additional intermolecular H bonds are given in the supplementary material.

A Platinated Rare Guanine Tautomer. Compound **2a**, *cis*-$(NH_3)_2Pt(1\text{-MeU})(9\text{-MeG-}N^1)$, undergoes protonation to give *cis*-$[(NH_3)_2Pt(1\text{-MeU})(9\text{-MeGH-}N^1)]^+$ (**2g**) upon addition of acid. The pK_a for **2g** $\rightleftharpoons$ **2a** + H^+ is 5, in agreement with data reported by van der Veer et al. for N1-platinated 9-ethylguanine compounds.[30] From pH-dependent ^1H NMR spectra it is concluded that protonation occurs preferentially at N7 of the guanine ligand, since H8 undergoes a 1 ppm downfield shift on protonation, while the uracil resonances hardly are affected. Formally, the neutral guanine ligand in **2g** is present in an unusual tautomeric structure (Figure 5), stabilized by a metal at N1. Similar metal-stabilized rare nucleobases have been prepared and studied in our laboratory for 1-MeUH,[29] 1-MeTH,[46] and 1-MeC.[47] Considering the similarity in pK_a for protonated cytosine and the well-established fact of protonated cytosine occurring under

(37) Raudaschl-Sieber, G.; Schöllhorn, H.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1985**, *107*, 3591.
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physiological pH conditions,[48] or the occurrence of a mismatch base pair between cytosine and protonated adenine,[49] with the pK_a of adeninium again in the same range,[48] a N1-metalated guanine species should be potentially mutagenic. Mispairing could, in theory, occur, with the guanine and a second nucleobase interacting in a Hoogsteen-like fashion.

While heating at 80 °C has been reported to lead to an isomerization of N1-bound guanine to N7-bound guanine,[30] *H* especially in acidic medium, we found no evidence for any substantial metal migration at room temperature in the case of **2a** (**2g**) or **4a**.

Summary

With this report we continue our studies on possible cross-linking models of *cis*-a_2Pt^{II} (a = NH_3 and $N(CH_3)_2H$ or a_2 = en) with nucleobases, specifically those involving both N7 and N1 sites as well as exclusively the N1 site of guanine. Ready formation of N7,N1-diplatinated guanine species, as previously observed for $Pt^{11,30,34,36-38,50}$ and also for Pd,[51] is confirmed. In line with a long-standing suggestion,[52] we feel that N7,N1-diplatinated guanines might be formed in partially denatured DNA and/or on high platination levels. As outlined above, a multiplicity of reaction products are feasible, including trinuclear species. Cross-linking of nucleobases could occur in intra- or interstrand fashion or a combination of both.[27c]

Compound **4a**, (en)Pt(9-MeG-N^1)$_2$, is a model for a hypothetical adduct of *cis*-a_2Pt^{II} with two purine-N^1 sites. It further extends the list of X-ray structurally characterized adducts of types (i) purine-N^7, purine-N^7, (ii) pyrimidine-N^3, pyrimidine-N^3, (iii) purine-N^7, pyrimidine-N^3, and (iv) purine-N^1, pyrimidine-N^3.[11] The formation of a bis(purine-N^1) adduct with pu = guanine in duplex DNA must be considered unlikely because of the kinetic preference of Pt and N7 and the involvement of N(1)H in Watson-Crick base pairing. Binding to N1 of guanine is possible in principle, however, in single-stranded DNA or in double-stranded DNA with guanine in a syn orientation engaged in Hoogsteen base pairing. This situation is known to occur in G = (HC^+) base pairs,[53] as verified by X-ray crystal structure of a d(GCGTACGC) duplex with intercalated triostin A,[54] and it has also been proposed to occur in a mismatch between G_{syn} and protonated adenine (AH^+_{anti}) in a DNA dodecamer.[55] In all these cases, N1 is quite accessible in the major groove of duplex DNA, ready to interact with a $Pt^{II}OH$ entity.

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Registry No. **2**, 126255-36-5; **2a**, 141221-38-7; **2b**, 141221-51-4; **2c**, 141221-53-6; **2d**, 141221-55-8; **2e**, 141221-42-3; **2f**, 141221-44-5; **2g**, 141221-40-1; **3**, 141247-86-1; **3a**, 141221-57-0; **4**, 141247-88-3; **4a**, 141221-45-6; **4b**, 141221-47-8; *cis*-{$[N(CH_3)_2H]_2Pt$(9-MeGH-N^7)Cl}-ClO_4, 141221-37-6; *cis*-$[N(CH_3)_2H]_2PtCl_2$, 27928-80-9; *cis*-$[(NH_3)_2Pt$(1-MeC)Cl]Cl, 75659-46-0; $[$(dien)Pt(9-MeGH-N^7)$]$$(ClO_4)_2$, 126217-15-0; *ht-cis*-$[(NH_3)_2Pt$(1-MeC$^-$)$]_2(ClO_4)_2$, 141315-71-1; $[$(en)-$Pt(H_2O)_2](ClO_4)_2$, 33728-67-5; $(en)PtCl_2$, 14096-51-6; $Na_2Pt(CN)_4$, 15321-27-4; *cis*-$[(NH_3)_2Pt$(1-MeC)$(H_2O)](ClO_4)_2$, 98874-75-0; *cis*-$[(NH_3)_2Pt(D_2O)_2](NO_3)_2$, 141221-49-0; *cis*-$(NH_3)_2PtCl_2$, 15663-27-1.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters, anisotropic thermal parameters and close contacts, equation of planes, and dihedral angles for **4a** and figures depicting ^1H NMR spectra of **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **3**, **3a**, **4**, and **4b** (15 pages); a table of observed and calculated structure factors of **4a** (14 pages). Ordering information is given on any current masthead page.

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Contribution from the Fachbereich Chemie, Universität Dortmund, 4600 Dortmund, Germany, and Istituto Chimico Farmaceutico della Università di Milano, 20131 Milano, Italy

Diplatinum and Heteronuclear Complexes Derived from (tmeda)Pt(1-MeU)$_2$ (tmeda = *N,N,N',N'*-Tetramethylethylenediamine, 1-MeU = 1-Methyluracilate-N^3). Steric Effect of the tmeda Ligand on the Orientation of the Second Metal

Gudrun Frommer,[1a] Francesca Lianza,[1b] Alberto Albinati,*[,1b] and Bernhard Lippert*[,1a]

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The reaction of (tmeda)Pt(1-MeU)$_2$ (tmeda = *N,N,N',N'*-tetramethylethylenediamine, 1-MeU = 1-methyluracilate-N^3) toward several electrophiles (H^+, Ag^+, Cu^{2+}, $PdCl_4^{2-}$, *cis*-$(NH_3)_2Pt^{II}$, (dien)Pt^{II}, enPdCl_2) has been studied using ^1H NMR spectroscopy (H^+, Ag^+, Pd^{II}, Pt^{II}) and X-ray structure crystallography (Cu^{2+}). (tmeda)Pt (1-MeU)$_2$ exists in solution in two rotamers (head-head and head-tail) which exhibit two separate acid-base equilibria between the neutral and monoprotonated species. Ag^+, Cu^{2+}, and $PdCl_4^{2-}$ bind to (tmeda)Pt(1-MeU)$_2$ via the exocyclic O4 oxygens in the well-known fashion with metals facing each other. In contrast, amine-containing species (*cis*-$NH_3)_2Pt^{II}$, (dien)Pt^{II}, (en)Pd^{II}) bind to (tmeda)Pt(1-MeU)$_2$ via a single O4 oxygen in a face-back fashion, which leads to a short contact between the entering second metal and H5 of the bridging 1-MeU. This situation is reflected in a large downfield shift (Pt, 1.64 ppm; Pd, 1.13-1.28 ppm) of this resonance in the ^1H NMR spectrum. The X-ray structure of $\{[$(tmeda)Pt(1-MeU)$_2]_2Cu\}(ClO_4)_2$ is reported. As a consequence of the steric bulk of the tmeda ligand, the tilt between the metal coordintaion planes (32.3°) and the Pt-Cu separation (2.9843 (1) Å) are considerably larger than in related compounds derived from *cis*-$(NH_3)_2Pt^{II}$.

Introduction

Principles of the formation of diplatinum(II), dipalladium(II), or mixed-metal (Pt_xM_y) complexes derived from *cis*-$(NH_3)_2Pt^{II}$ and containing the deprotonated model nucleobases 1-methyluracil (1-MeU, $C_5H_5N_2O_2$) and 1-methylthymine (1-MeT, $C_6H_7N_2O_2$) or related ligands are reasonably well understood.[2,3] Unlike for

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