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*-{[$N(CH_3)_2H$]$_2$Pt(9-MeGH-N^7)Cl}ClO_4, 141221-37-6; *cis*-[$N(CH_3)_2H$]$_2PtCl_2$, 27928-80-9; *cis*-[$(NH_3)_2$Pt(1-MeC)Cl]Cl, 75659-46-0; [(dien)Pt(9-MeGH-N^7)]$(ClO_4)_2$, 126217-15-0; *ht-cis*-[$(NH_3)_2$Pt(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*-[$(NH_3)_2$Pt(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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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

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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}, en$PdCl_2$) 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)$_2$]$_2$Cu}$(ClO_4)_2$ 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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Table I. Experimental Data for the X-ray Diffraction Study of {[(tmeda)Pt(1-MeU)$_2$]$_2$Cu}(ClO$_4$)$_2$ (**2**)

chem formula	$C_{32}H_{52}Cl_2CuN_{12}O_{16}Pt_2$
mol wt	1385.45
space group	$P\bar{1}$ (No. 2)
a, Å	10.127 (1)
b, Å	10.816 (2)
c, Å	12.317 (2)
α, deg	68.54 (1)
β, deg	65.75 (1)
γ, deg	89.52 (2)
Z	1
V, Å^3	1128.8 (2)
ρ(calcd), g cm^{-3}	2.037
μ, cm^{-1}	69.08
T, °C	RT
λ, Å	0.710 69 (graphite monochromated, Mo Kα)
transmission coeff	0.8360–0.9987
R^a	0.021
$R_w{}^b$	0.031

[a] $R = \sum||F_o| - (1/k)|F_o|| / \sum|F_o|$. [b] $R_w = [\sum w(|F_o| - (1/k)|F_c|)^2 / \sum w|F_o|^2]^{1/2}$ where $w = [\sigma^2(F_o)]^{-1}$ and $\sigma(F_o) = [\sigma^2(F_o{}^2) + f^2(F_o{}^2)^2]^{1/2}/2F_o$ with $f = 0.060$.

Table II. Final Positional Parameters and Equivalent Thermal Factors for **2**[a]

atom	x	y	z	B, Å^2
Pt	0.257 02 (1)	0.030 55 (1)	0.225 15 (1)	2.009 (2)
Cu	0.500	0.000	0.000	2.76 (1)
Cl	0.8329 (1)	0.510 71 (9)	0.3028 (1)	4.66 (2)
O1	0.8477 (5)	0.3793 (4)	0.3675 (4)	8.0 (1)
O2	0.2329 (3)	0.2730 (3)	0.2967 (3)	4.56 (7)
O2a	0.2593 (3)	−0.0143 (3)	0.4832 (2)	3.63 (5)
O3	0.9664 (6)	0.5827 (6)	0.1936 (5)	10.5 (2)
O4	0.4000 (3)	−0.1302 (2)	−0.0254 (2)	3.48 (5)
O4a	0.5035 (3)	−0.1442 (2)	0.1486 (2)	3.49 (5)
O5	0.7967 (5)	0.5800 (4)	0.3875 (4)	8.0 (1)
O7	0.7192 (4)	0.5059 (4)	0.2641 (3)	8.1 (1)
N1	0.4595 (3)	0.3997 (3)	0.1816 (2)	3.43 (6)
N1a	0.4246 (3)	−0.1538 (3)	0.4978 (2)	3.07 (6)
N3	0.4067 (3)	0.2009 (2)	0.1560 (2)	2.55 (5)
N3a	0.3798 (3)	−0.0734 (2)	0.3119 (2)	2.42 (5)
N11	0.1035 (3)	−0.1413 (3)	0.3044 (2)	2.69 (5)
N12	0.1191 (3)	0.1246 (3)	0.1421 (2)	2.94 (6)
C1	0.4057 (6)	0.4944 (4)	0.2425 (4)	5.1 (1)
C1a	0.3859 (4)	−0.1658 (4)	0.6304 (3)	3.97 (8)
C2	0.3570 (4)	0.2896 (3)	0.2170 (3)	3.09 (7)
C2a	0.3491 (3)	−0.0767 (3)	0.4341 (3)	2.64 (6)
C4	0.5514 (3)	0.2143 (3)	0.0745 (3)	2.82 (6)
C4a	0.4795 (3)	−0.1446 (3)	0.2583 (3)	3.00 (7)
C5	0.6511 (5)	0.3284 (4)	0.0451 (3)	3.74 (8)
C5a	0.5524 (4)	−0.2242 (4)	0.3284 (4)	4.13 (9)
C6	0.6025 (4)	0.4151 (4)	0.0995 (3)	3.86 (8)
C6a	0.5208 (4)	−0.2268 (4)	0.4459 (4)	4.11 (9)
C11	0.0140 (4)	−0.1117 (4)	0.2290 (4)	4.57 (9)
C12′	0.063 (2)	0.012 (2)	0.124 (2)	4.5 (3)*
C12	−0.0198 (5)	0.0243 (5)	0.2058 (4)	3.6 (1)
C13	0.1652 (4)	−0.2656 (3)	0.2984 (3)	3.65 (8)
C14	0.0077 (4)	−0.1714 (4)	0.4435 (3)	3.69 (8)
C15′	0.207 (2)	0.235 (2)	0.015 (2)	4.6 (3)*
C15	0.1845 (5)	0.1578 (7)	0.0008 (4)	4.7 (1)
C16′	0.012 (2)	0.179 (2)	0.224 (1)	4.3 (3)*
C16	0.0714 (6)	0.2510 (5)	0.1612 (5)	4.5 (1)

[a] Values marked with an asterisk are for atoms that were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$. Atoms C12, C15, and C16 were refined with an occupancy factor of 0.75, the primed atoms with an occupancy of 0.25.

similar compounds of *trans*-(NH$_3$)$_2$Pt^{II}, for which we recently have observed several unusual features (trans → cis isomerization,[4] Pt → Pd dative bond formation and loss of NH$_3$,[5] and severe distortions in metal coordination geometries[6]) and which are attributed to steric effects (unfavorable short NH$_3$···NH$_3$ separations and ligand bite distance), substitution of the ammonias in *cis*-(NH$_3$)$_2$Pt^{II} by chelating diamines (ethylenediamine[7,8] and 2,2′-bipyridine[9]) appears not to drastically change the basic structural patterns. However, as we now found, more severe steric crowding about the Pt metal, e.g., by introduction of the bulky *N,N,N′,N′*-tetramethylethylenediamine (tmeda) ligand, can lead to profound deviations from the previously observed binding pattern of the second metal if the latter carries an amine ligand.

Experimental Section

Preparations. (tmeda)Pt(1-MeU)$_2$·2NaNO$_3$ (**1**) and (tmeda)Pt(1-MeU)$_2$·0.25NaNO$_3$·2H$_2$O (**1a**) were prepared as follows: To an aqueous suspension of (tmeda)PtI$_2$ (4 mmol in 200 mL of H$_2$O), which was obtained according to a modified Dhara method,[10] was added AgNO$_3$ (8 mmol), and the mixture was stirred at 50 °C for 12 h. AgI was filtered off, and 1-MeUH[11] (12 mmol) and NaOH (8 mmol) were added. After 3 days at 65 °C, the mixture was evaporated to dryness and treated with excess MeOH to remove unreacted 1-MeUH. The residue was recrystallized from water to give a white powder of **1** in 47% yield. Anal. Calcd for $C_{16}H_{26}N_8O_{10}PtNa_2$ (found): C, 26.27 (26.0); H, 3.58 (3.6); N, 15.32 (15.4). The IR spectrum of **1** confirmed the presence of NO$_3^-$. NaNO$_3$ was incompletely removed from **1** by exclusion chromatography (Sephadex G10) to give **1a**. Anal. Calcd for $C_{16}H_{30}N_{6.25}O_{6.75}PtNa_{0.25}$ (found): C, 31.06 (31.1); H, 4.89 (4.4); N, 14.14 (13.9).

{[(tmeda)Pt(1-MeU)$_2$]$_2$Cu}(ClO$_4$)$_2$ (**2**) was prepared by adding Cu(ClO$_4$)$_2$(aq) (0.10 mmol) to a solution of **1** (0.08 mmol in 2 mL of H$_2$O). Upon slow evaporation of the resulting green solution, **2** was isolated as bright green single crystals in 87% yield. Anal. Calcd for $C_{32}H_{52}N_{12}O_{16}Cl_2Pt_2Cu$ (found): C, 27.74 (27.8); H, 3.78 (3.8); N, 12.13 (12.2).

Spectra. ^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer using D$_2$O as solvent and TSP as internal reference. Quoted chemical shifts (δ scale) are relative to TMS. pD values were measured with a glass electrode. For the determination of the pK_a values, the pH meter readings were not corrected.

X-ray Crystallography. A prismatic, bright green crystal was mounted on a glass fiber at a random orientation on an Enraf-Nonius CAD4 diffractometer for the unit cell and space group determination and for the data collection. Unit cell dimensions were obtained by a least-squares fit of the 2θ values of 25 high-order angle reflections (9.9° < ϑ < 16.8°) using the CAD4 centering routines. Crystallographic and other experimental data are listed in Table I and supplementary Table S1.

Data were measured with variable scan speed to ensure constant statistical precision on the collected intensities. Three standard reflections were used to check the stability of the crystal and of the experimental conditions and measured every hour; no significant variation was detected. The orientation of the crystal was checked by measuring three reflections every 300 measurements. Data have been corrected for Lorentz and polarization factors and for decay (correction factors in the range 1.149–0.960), using the data reduction programs of the CAD4-SDP package.[12] An empirical absorption correction was applied by using azimuthal (ψ) scans of five "high-χ" angle reflections (χ > 87°; 13.0° < ϑ < 23.5°). A total of 5437 independent reflections were collected of which 4955 were considered as observed having $|F_o|^2 > 2.5\sigma|F|^2$, and used for the solution and refinement of the structure. A $F_o = 0.0$ was given to those reflections having negative net intensities. The standard deviations on intensities were calculated in terms of statistics alone while those on F_o were calculated as reported in Table I.

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Table III. Selected Interatomic Distances (Å) and Angles (deg) of **2**

Pt-Cu	2.9843 (1)	N3-Pt-N3a	87.1 (1)
Pt-N11	2.073 (3)	N11-Pt-N12	84.2 (1)
Pt-N12	2.102 (3)	N11-Pt-N3	177.0 (1)
Pt-N3	2.063 (3)	N11-Pt-N3a	91.6 (1)
Pt-N3a	2.034 (3)	N12-Pt-N3a	175.8 (1)
		N12-Pt-N3	97.1 (1)
Cu-O4	1.927 (3)	O4-Cu-O4a	88.9 (1)
Cu-O4a	1.936 (2)	O3-Cu-O4a′	91.1 (1)

Uracil

		a			*a*
N1-C1	1.458 (6)	1.469 (5)	C6-N1-C2	121.9 (3)	121.4 (3)
N1-C2	1.398 (5)	1.378 (5)	N1-C2-N3	116.8 (6)	117.2 (3)
			N1-C6-C5	121.2 (4)	122.1 (4)
N1-C6	1.351 (4)	1.352 (5)	C2-N3-C4	121.4 (3)	121.2 (3)
N3-C2	1.395 (5)	1.392 (4)	N3-C4-C5	118.3 (3)	119.5 (3)
N3-C4	1.365 (4)	1.364 (4)	C1-N1-C2	116.6 (3)	117.8 (3)
O2-C2	1.199 (4)	1.218 (4)	C1-N1-C6	121.4 (4)	120.4 (3)
O4-C4	1.259 (5)	1.268 (5)	O2-C2-N1	120.9 (3)	121.0 (3)
C4-C5	1.438 (5)	1.414 (6)	O2-C2-N3	122.3 (3)	121.8 (3)
C5-C6	1.322 (6)	1.337 (7)	O4-C4-N3	122.4 (3)	120.8 (3)
			O4-C4-C5	119.3 (3)	119.7 (3)
			C4-C5-C6	120.0 (3)	118.4 (4)

The structure was solved by a combination of Patterson and Fourier methods and refined by full matrix least squares[12] (the function minimized was $\sum w(|F_o| - (1/k)|F_c|)^2$). No extinction correction was found necessary.

The tmeda ligand was found to be disordered between two different conformations. The positional parameters of the atoms in both conformations were refined together with their occupancy; the factors found for the disordered atoms are 0.75 and 0.25, respectively (imposing the equal occupancy for all atoms of the same moiety). It should be noted, however, that the atoms with occupancy 0.25 are determined less precisely (e.g., see values in Tables II and III).

The scattering factors used, corrected for the real and the imaginary parts of the anamalous dispersion, were taken from ref 13. Anisotropic temperature factors were used for all refined atoms except for the carbon atoms of the tmeda having 25% occupancy. The contribution of the hydrogen atoms in their idealized position (C-H = 0.95 Å, B_{iso} = 5.0 Å^2) was taken into account but not refined.

Upon convergence (no parameter to shift >0.14$\sigma(p)$) the Fourier difference map showed no significant feature. Final atomic coordinates and equivalent isotropic thermal factors are given in Table II.

Results and Discussion

Basicity of Exocyclic Oxygens in (tmeda)Pt(1-MeU)$_2$ (1). The ^{1}H NMR spectrum of **1** in D_2O displays two sets of H5 and H6 resonances of the 1-MeU ligand of an approximately 1:1 intensity ratio in the pD range 1–4. The two sets are attributed to two rotamers with head–head (hh) and head–tail (ht) arranged 1-MeU rings. pH-dependent spectra reveal that the two sets are affected differently by protonation (Figure 1), giving pK_a values of 2.9 and 2.5, respectively. The magnitude of H5 and H6 downfield shifts (ca. 0.45 ppm) when going from pD 10 to pD 1 is consistent with a single protonation process for both rotamers, hence formation of [(tmeda)Pt(1-MeUH)(1-MeU)]$^+$ in an acidic medium.[14] We assume that O4 is the most basic site and therefore is protonated preferentially (Figure 2), consistent with present evidence for H$^+$ binding[14] and metal binding[1] in related *cis*-$(NH_3)_2Pt^{II}$ compounds. The observed pK_a values are more positive by 1.5 and 1.1 log units as compared to *cis*-[$(NH_3)_2$Pt(1-MeUH)(1-MeU)]$^+$.[14] Whether this is primarily a consequence of a weaker Pt-N(uracil) bond due to steric crowding about the Pt or a consequence of an inductive effect of the tmeda ligand is unknown. However, the pK_a of *cis*-[$(cpa)_2$Pt(1-MeTH)(1-MeT)]$^+$ (cpa = cyclopropylamine) of 3.0,[15] which is higher than that of the analogous *cis*-$(NH_3)_2Pt^{II}$ compound (2.0[16]), seems to favor the second possibility. As in all related 1-MeU (1-MeT) compounds, the 1-MeUH ligand is displaced according to

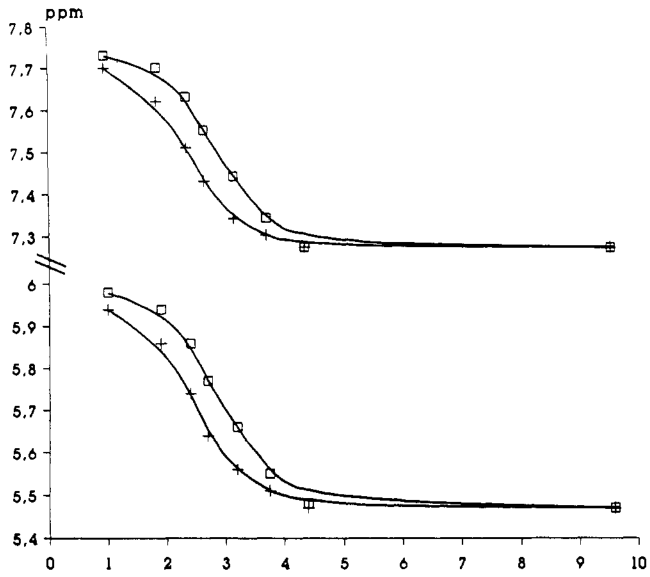

Figure 1. pH* dependence of H6 (top) and H5 (bottom) resonances of 1-MeU ligands in (tmeda)Pt(1-MeU)$_2$.

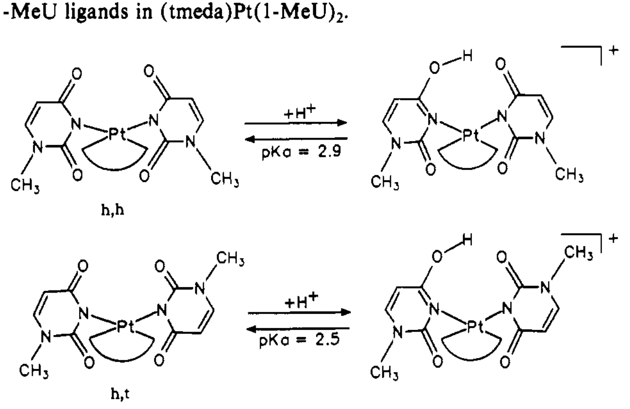

Figure 2. Two possible rotamers of [(tmeda)Pt(1-MeU)(1-MeUH)]$^+$ with head–head and head–tail arrangement of the two nucleobases.

$$[(\text{tmeda})\text{Pt}(1\text{-MeUH})(1\text{-MeU})]^+ + H_2O \rightarrow [(\text{tmeda})\text{Pt}(1\text{-MeU})(H_2O)]^+ + 1\text{-MeUH}$$

At pD 3.3 and 22 °C, the half-life of [(tmeda)Pt(1-MeUH)(1-MeU)]$^+$ is approximately 4 h. This pronounced lability of the 1-MeUH ligand is in marked contrast to the complete inertness of **1**[17] and its *cis*-$(NH_3)_2Pt^{II}$ analogue[18] toward excess cyanide, which raises the question of the mechanism of substitution of 1-MeUH by H_2O.

Heterometal Adducts of 1. **1** was obtained from the reaction mixture in the form of a bis(sodium nitrate) adduct. The $NaNO_3$ is not readily removed, not even by exclusion chromatography. It probably is the consequence of the high basicity of the O4 sites in the platinated uracil rings.

Addition of increasing amounts of $AgNO_3$ to an aqueous solution of **1** causes small downfield shifts of both sets of H5 and H6 resonances, consistent with the formation of mixed $PtAg_x$ complexes.[19] Interestingly, the tmeda resonances are, unlike during the protonation process of **1**, also affected by Ag$^+$

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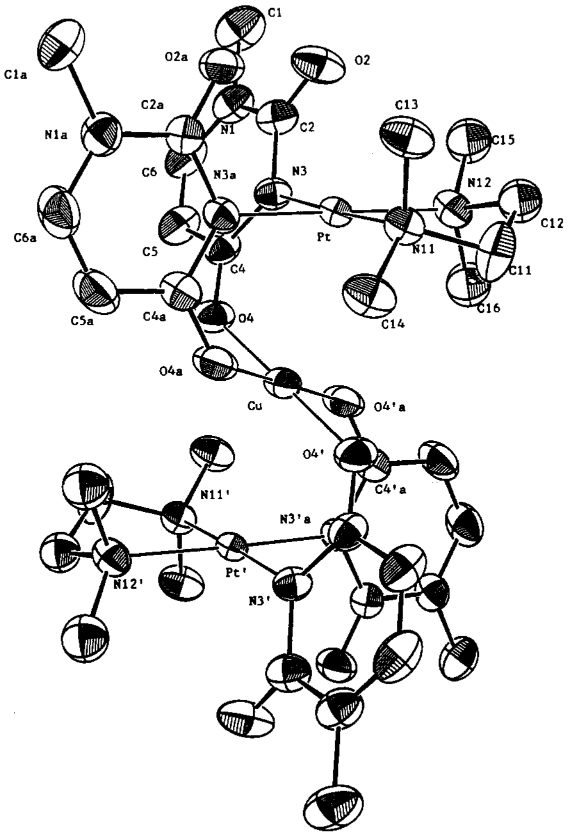

Figure 3. View of the trinuclear cation of **2**. For clarity, only a single conformation of the tmeda chelate ring is shown.

(downfield shift), which suggests that the coordinated Ag$^+$ is facing the tmeda ligand. It thus appears that the well-known metal binding pattern for *cis*-(NH$_3$)$_2$Pt^{II} analogues is also adopted in the case of Ag$^+$ binding to **1**.

This assumption is further supported by the results of the X-ray structure determination of [(tmeda)Pt(1-MeU)$_2$Cu(1-MeU)$_2$Pt(tmeda)](ClO$_4$)$_2$ (**2**), a bright green compound obtained on slow crystallization of **1** in the presence of Cu(ClO$_4$)$_2$. Figure 3 gives a perspective view of the cation of **2**. Selected interatomic distances and angles are listed in Table III. In the trinuclear cation, two (tmeda)Pt(1-MeU-N^3)$_2$ entities are connected via four O$_4$ positions to a Cu^{II}, which sits on an inversion center. All three metals exhibit square-planar coordination geometries with a slight nonplanarity in the case of Pt (supplementary material) and a somewhat compressed N11-Pt-N12 angle (84.2 (1)°) about the Pt ions. Pt-N3 and Pt-N3a as well as Pt-N11 and Pt-N12 distances differ slightly (Table III).

There are no unusual features about the 1-MeU rings, which are arranged head-head. Since **2** is isolated in high yield (almost 90%), yet in aqueous solutions of **1** only 50% occur in hh form, a slow rotation of one of the 1-MeU ligands from ht to hh, hence a shift of the ht $\rightleftharpoons$ hh equilibrium toward hh, must have taken place during the crystallization process.

Distances and angles of the tmeda chelates are normal.[20,21] In the tmeda chelates C12 as well as C15 and C16 show some disorder, which can be explained by a 25:75 distribution of two differently puckered conformers (Figure 4). Cu and Pt ions are arranged in a face-face manner. The Pt-Cu distance of 2.9843 (1) Å and the tilt angle τ between the PtN$_4$ and CuO$_4$ planes of 32.3° are considerably larger than in previously reported mixed Pt-Cu complexes[22-24] containing the *cis*-(NH$_3$)$_2$Pt^{II} instead of (tmeda)Pt^{II} (Table IV). Undoubtedly this is a consequence of the steric bulk caused by the CH$_3$ groups of the tmeda ligands.

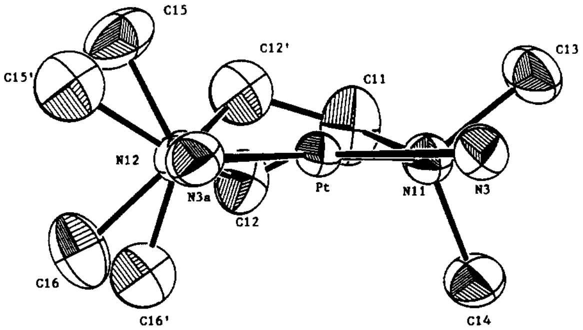

Figure 4. Superposition of the two different puckerings of the tmeda chelates at Pt. The arrangement with approximal C_{2v} symmetry (C11 and C12 at opposite sides of the PtN$_4$ plane) is favored by 3:1 over the alternative arrangement (C11 or C12' on same side of Pt plane).

Table IV. Comparison of Intermetallic Distances and Tilt Angles of Metal Planes in Mixed Pt-Cu Complexes

	Pt-Cu, Å	τ, deg	ref
cis-(NH$_3$)$_2$Pt(1-MeU)$_2$Cu(H$_2$O)$_2$$^{2+}$	2.765 (3)	25.8	22
cis-[(NH$_3$)$_2$Pt(1-MeU)$_2$]$_2$Cu^{2+}	2.684 (1)	15.7	23
cis-[(NH$_3$)$_2$Pt(1-MeU)(1-MeC)]$_2$Cu^{4+}	2.681 (1)	17.8	24
2	2.9843 (1)	32.2	*a*

[a] This work.

Reaction of **1** with 2 equiv of K$_2$PdCl$_4$ in D$_2$O at pD 5 rapidly (15 min) leads to a main product (60%) with ^{1}H NMR shifts downfield relative to those of **1** (H5, 0.30 ppm; H6, 0.13 ppm; CH$_3$, 0.09 ppm; tmeda,[25] 0.26 and 0.29 ppm). The magnitude of the downfield shifts of the 1-MeU resonances and the different effects on H5 and H6 are consistent with Pd binding to two O4 oxygens of the two 1-MeU rings.[8] The appearance of a single set of 1-MeU resonances in the product indicates a head-head orientation of the two uracils, as further supported by the fact that the ratio between hh and ht rotamers in unreacted material has diminished to 1:3. The downfield shift of the tmeda resonances suggests a face-face arrangement of Pt and Pd as discussed above for Pt-Ag and realized in many related examples.[8,26] We propose that the product formed initially is [(tmeda)Pt(1-MeU-N^3,O^4)$_2$PdX$_2$]$^{n+}$ with X = Cl (n = 0) *or*, more likely, X = H$_2$O (n = 2). A mixed chloro-aqua (hydroxo) complex is less likely since it should give rise to two sets of 1-MeU resonances. Within 90 min at 22 °C, two additional sets of 1-MeU resonances of unequal intensities are observed, both of which occur further downfield from the initial product. Possibly they are of Pt$_2$Pd[26] or PtPd$_2$ composition with hh arranged uracil rings. The latter species could form from PtPd upon addition of another Pd to the still available O2 sites, very much like PtPtAg.[27] After 24 h the spectrum consists of a large number of uracil resonances, including those of free 1-MeUH.

^{1}H NMR spectroscopic changes upon reaction of **1** with *cis*-[(NH$_3$)$_2$Pt(D$_2$O)$_2$]$^{2+}$ (1 or 2 equiv, pD 4) are given in Figure 5. Certainly the most unusual features, and never observed in Pt uracil chemistry before, are the two signal sets at 7.1 and 7.7 ppm which, by 2D COSY ^{1}H NMR spectroscopy, have been correlated and assigned to H5 and H6 1-MeU resonances, respectively. The remaining resonances (5.6-5.8 ppm; 7.4-7.6 ppm) are in the "normal" range for Pt^{II}-1-MeU resonances. The concentration of the unusual product peaks after ca. 4 h, even then it represents a minor component only. The other products formed are 1-MeUH, [(tmeda)Pt(1-MeU)(D$_2$O)]$^+$, and/or *cis*-[(NH$_3$)$_2$Pt(1-

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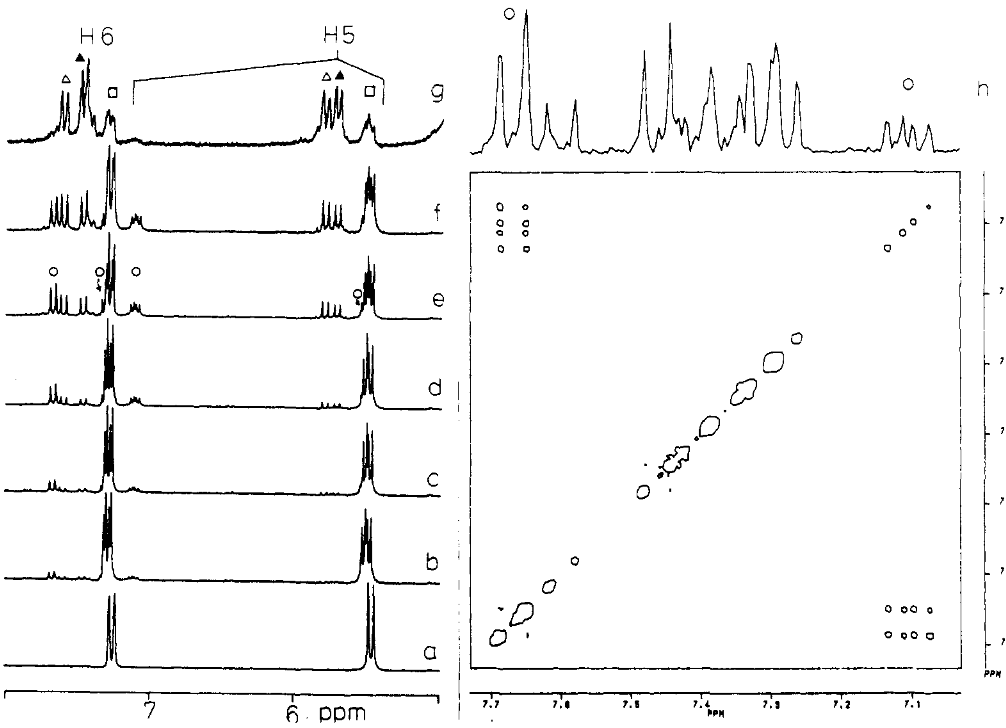

Figure 5. Low-field portion of ^1H NMR spectrum (D_2O, 200 MHz) of reaction mixtures of **1a** with *cis*-$[(NH_3)_2Pt(D_2O)_2]^{2+}$ (2 equiv): (a) **1a** prior to addition of *cis*-$(NH_3)_2Pt^{II}$ (pD 8.0); (b) 10 min after addition (pD 4.1); (c) after 25 min; (d) after 40 min; (e) after 2.5 h; (f) after 5 h; (g) after 24 h; (h) 2D COSY ^1H NMR spectrum after 4 h in the 7–7.7 ppm range. Triangles denote H5 and H6 resonances of free 1-MeUH, filled triangles those of $[(tmeda)Pt(1\text{-}MeU)D_2O)]^+$ and/or *cis*-$[(NH_3)_2Pt(1\text{-}MeU)D_2O]^+$, and squares those of **1a**. Additional unmarked resonances (e.g., around 7.4 ppm) are not assigned. H5 and H6 resonances of the product with face–back orientation of the two metals are marked by circles. Only those resonances are well separated from **1a** resonances that experience the vicinity of the O4-bound Pt^{II}.

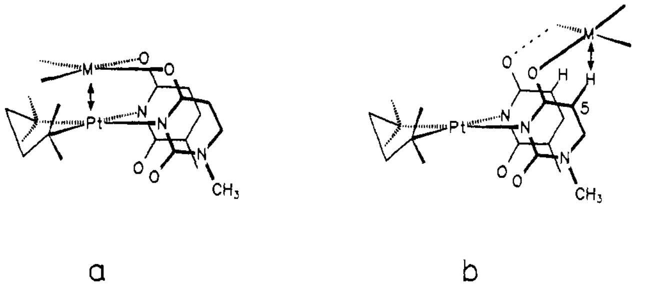

Figure 6. (a) "Normal" face–face orientation of $(tmeda)Pt^{II}$ and M (e.g., Ag^+) as observed in many related complexes of *cis*-$(NH_3)_2Pt^{II}$. (b) Proposed face–back orientation of $(tmeda)Pt^{II}$ and M (*cis*-$(NH_3)_2Pt^{II}$) with short contact between M and H5 of bridging 1-MeU. Only one of two possible rotamers is shown. A possible H-bonding interaction is indicated.

$MeU)(D_2O)]^+$, possibly also $[a_2(1\text{-}MeU)Pt\text{–}OH\text{–}Pt(1\text{-}MeU)a_2]^+$ (a_2 = $(NH_3)_2$ or tmeda).[28] The reaction carried out at pD ~6 is somewhat slower but essentially leads to a very similar product distribution. We assign the "unusual" compounds to the two rotamers (1:1 ratio) obtained by monofunctional coordination of a *cis*-$[(NH_3)_2Pt(D_2O)_2]^{2+}$ entity to O4 of a single nucleobase in **1** (Figure 6). Contrary to the situation with Ag^+ and PdX_2 described above, the orientation of the second metal entity (*cis*-$(NH_3)_2Pt^{II}$) is such that it is pointing away from the first metal ($(tmeda)Pt^{II}$). In doing so, the second Pt is getting very close to H5 of 1-MeU (estimated 2.5–3 Å), with the d_{z^2} orbital of the metal pointing toward H5. From model building it is evident that this arrangement can be stabilized by H bond formation between H_2O or NH_3 of the second Pt and O4 (hh rotamer) or O2 (ht rotamer) of the other 1-MeU ring. This interpretation is supported by the following arguments: (i) Chemical shift of H5. The downfield shift of H5 relative to the starting compound is 1.64 ppm, compared to only 0.36 for H6. This compares with a shift of ca. 0.3 ppm for H5 and ca. 0.1–0.2 ppm for H6 in dinuclear Pt_2 uracil compounds with the two metals facing each other.[8,28] Low-field shifts of similar magnitude have been observed in a number of cases with X-ray structurally confirmed short C–H···Pt contacts of 2.3–2.9 Å[29] and are indicative of a weak Pt–H interaction. While observation of $^{195}Pt\text{–}^1H5$ coupling would make this argument even stronger, the low concentration of the product did not allow detection of *J*, not even with a spectrometer of sufficiently low magnetic field strength. (ii) Behavior of $(dien)Pt^{II}$ toward **1**. $[(dien)Pt(D_2O)]^{2+}$ (dien = diethylenetriamine) behaves virtually in the same manner as does *cis*-$[(NH_3)_2Pt(D_2O)_2]^{2+}$, thereby confirming monodentate binding of the latter. While binding of two $(dien)Pt^{II}$ or two *cis*-$(NH_3)_2Pt^{II}$ entities to **1** is sterically possible (in particular for the ht isomer), it is probably the resulting +4 charge that appears to prevent its formation in detectable amounts. (iii) Decomposition. The release of 1-MeUH from **1** as a consequence of protonation of O4 of 1-MeU is not expected to occur to an appreciable extent at pD 6. The observation of formation of 1-MeUH in the reaction of **1** with added platinum amine species points toward a "proton-like" effect, hence bond weakening of (tmeda)Pt–1-MeU-*N*^{3} by an additional electrophile. This behavior is in marked contrast to the situation with hh or ht dinuclear Pt_2 complexes with a face–face arrangement of the two metals. These species show *no* signs of release of 1-MeUH.

$(en)PdCl_2$ reacts with **1** in a way similar to that of *cis*-$(NH_3)_2Pt^{II}$ and $(dien)Pt^{II}$, as evident from the large downfield shifts of H5 resonances (1.28 and 1.13 ppm for the two rotamers) of the bridging 1-MeU. H6 resonances are affected less, with shifts being 0.42 and 0.40 ppm downfield.

Summary

Coordination of metal aqua cations to $(tmeda)Pt(1\text{-}MeU)_2$ occurs in very much the same fashion as seen for a series of

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compounds obtained from *cis*-$(NH_3)_2Pt(1\text{-}MeU)_2$, namely, in a face–face fashion with the filled d_{z^2} orbital of Pt "interacting" with the second metal. As shown for the mixed Pt_2Cu compound **2**, the steric bulk of the tmeda ligand causes a stronger tilting of the Cu coordination plane with respect to the Pt plane and a longer Pt–Cu separation as compared to similar compounds derived from *cis*-$(NH_3)_2Pt^{II}$, which is hardly surprising, however. With metal amine (amine = $(NH_3)_2$, en, dien) species, the interaction between CH_3 protons of tmeda and NH protons of the amine apparently becomes so unfavorable that a face–face orientation of the two metals is avoided. As a consequence, a face–back arrangement with monofunctional binding of the entering metal amine entity is realized that leads to short contacts between the metal and H5 of the bridging 1-MeU ring and large downfield shifts in the ^1H NMR spectra.

The proposed structure could be relevant with regard to C5–H activation of 1-MeU and subsequent covalent metal binding to C5. Such binding has been reported for both Pt[30] and Hg,[31] but the mechanism of formation of these organometallic compounds has not been established as yet.

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Supplementary Material Available: Tables of crystallographic and experimental details, anisotropic displacement parameters of heavy atoms, calculated positional parameters of H atoms, bond distances and angles, least-squares plane equations, and dihedral angles between planes (13 pages); listing of observed and calculated structure factors for **2** (50 pages). Ordering information is given on any current masthead page.

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Hydroxyl Radical Induced Decarboxylation and Deamination of 2-Methylalanine Catalyzed by Copper Ions

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Using the pulse radiolysis technique, the rate constants of the reactions of $^{\bullet}CH_2C(CH_3)(NH_3^+)COO^-$ (the radical derived via H-abstraction from 2-methylalanine) with Cu^{2+}_{aq} and Cu^{+}_{aq} to form unstable intermediates with a copper–carbon σ-bond have been determined to be $(1.3 \pm 0.3) \times 10^7$ and $(1.3 \pm 0.2) \times 10^9$ M^{-1} s^{-1}, respectively. In the case of cupric ions, the transient decomposes via a β-carboxyl elimination reaction yielding Cu^{+}_{aq}, CH_3COCH_3, and CO_2, whereas in the case of cuprous ions it decomposes via a β-amine elimination reaction yielding Cu^{2+}_{aq}, $CH_2{=}C(CH_3)COO^-$, and NH_3. A reaction mechanism for aliphatic radical induced amino acid damage catalyzed by copper ions in different oxidation states is suggested. This mechanism describes a plausible new pathway for biological damage induced by free radicals.

Introduction

Aliphatic free radicals react with many Cu^{II} and Cu^{I} complexes through a mechanism involving the formation of an organometallic intermediate with a metal–carbon σ-bond.[1-9]

$$Cu^{2+}_{aq} + R^{\bullet} \rightarrow (Cu^{III}\text{–}R)^{2+} \qquad (1)$$

$$Cu^{+}_{aq} + R^{\bullet} \rightarrow (Cu^{II}\text{–}R)^{+} \qquad (2)$$

The mechanisms of decomposition of these intermediates depend on the nature of the aliphatic radical and the nonparticipating ligands of the copper ion.

Until recently, most of the decomposition processes of $(Cu^{III}\text{–}R)^{2+}$ were described by

$$(Cu^{III}\text{–}R)^{2+} \rightarrow Cu^{+} + R^{+} \qquad (3)$$

where R^+ is the oxidized form of the radical. We have recently demonstrated for the first time that Cu^{2+}_{aq} induces a β-carboxyl elimination reaction when it reacts with $^{\bullet}CH_2C(CH_3)_2COO^-$ via $[Cu^{III}\text{–}CH_2C(CH_3)_2COO^-]^{2+}$ as a transient.[7] $^{\bullet}CH_2C(CH_3)_2COO^-$ reacts also with Cu^{+}_{aq} to form a complex with a metal–carbon σ-bond, which decomposes both via homolysis and by a reaction with Cu^{2+}_{aq} to form $2Cu^{+}_{aq}$ and $(CH_3)_3CCOO^-$. We have also shown[9] that the complexes formed between $^{\bullet}CH_2C(CH_3)_2NH_3^+$ and Cu^{+}_{aq} and Cr^{2+}_{aq} decompose via β-elimination of NH_3 to yield 2-methylpropene, ammonia, and Cu^{2+}_{aq} or Cr^{3+}_{aq}. The rates of these β-elimination reactions were considerably slower than those of the analogous β-hydroxyl elimination reactions. It was suggested that the rates of the β-elimination processes are correlated to the C–O and C–N bond strength, which are cleaved in these reactions.[9]

In order to continue the research on the effects of different substituents on the β-elimination process of transients with a copper–carbon σ-bond, we have decided to investigate the mechanism of the decomposition of transients with a metal–carbon σ-bond containing both an amine and a carboxylate group at the β position to the carbon-centered free radical formed.

Free radicals are responsible for many deleterious effects in biological systems.[10] It has been well established that transition

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