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The Uracil C(5) Position as a Metal Binding Site: Solution and X-ray Crystal Structure Studies of Pt^{II} and Hg^{II} Compounds

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1,3-Dimethyluracil (1,3-DimeU) reacts with *trans*-$[(CH_3NH_2)_2Pt(H_2O)_2]^+$ to give *trans*-$[(CH_3NH_2)_2Pt$(1,3-DimeU-*C5*)$(H_2O)]X$ (X = NO_3^-, **1a**, ClO_4^-, **1b**) and subsequently with NaCl to give *trans*-$(CH_3NH_2)_2Pt$(1,3-DimeU-*C5*)Cl (**2**) or with NH_3 to yield *trans*-$[(CH_3NH_2)_2Pt$(1,3-DimeU-*C5*)$(NH_3)]ClO_4$ (**3**). In a similar way, (dien)Pt^{II} forms [dienPt(1,3-DimeU-*C5*)]$^+$ (**4**). Reactions leading to formation of **1** and **4** are slow, taking days. In contrast, $Hg(CH_3COO)_2$ reacts fast with 1,3-DimeU to give (1,3-DimeU-*C5*)$Hg(CH_3COO)$ (**5**). Both 1-methyluracil (1-MeUH) and uridine (urdH) react with (dien)Pt^{II} initially at N(3) and subsequently with either (dien)Pt^{II} or $Hg(CH_3COO)_2$ also at C(5) to give the diplatinated species **7** and **9** or the mixed PtHg complex **8**. C(5) binding of either Pt^{II} or Hg^{II} is evident from coupling of uracil-H(6) with either ^{195}Pt or ^{199}Hg nuclei and ^3J values of 47−74 Hz (for Pt compounds) and 185−197 Hz (for Hg compounds). J values of Pt compounds are influenced both by the ligands *trans* to the uracil C(5) position and by the number of metal entities bound to a uracil ring. Both **2** and **5** were X-ray structurally characterized. **2**: monoclinic system, space group $P2_1/c$, $a = 15.736(6)$ Å, $b = 11.481(6)$ Å, $c = 25.655$ (10) Å, $\beta = 145.55(3)°$, $V = 2621.9(28)$ Å^3, $Z = 4$. **5**: monoclinic system, space group $P2_1/c$, $a = 4.905(2)$ Å, $b = 18.451(6)$ Å, $c = 11.801(5)$ Å, $\beta = 94.47(3)°$, $V = 1064.77(72)$ Å^3, $Z = 4$.

Introduction

Metal binding to isolated nucleobases usually occurs via endocyclic N or exocyclic O and N donor atoms.[1] There are few exceptions to this rule and these include (i) binding to a ring C atom (with deprotonation) or (ii) μ^2 coordination to a C=C bond. As to (i), the earliest findings of covalent mercury binding to C(5) sites of cytosine and uracil as well as C(7) of 7-deazaadenine are from 1973 and 1975, respectively,[2,3] followed by scattered reports on C(8) metalation of 1,3,7-trimethylxanthosine by Ru(III),[4] Os(III),[5] and Hg(II)[6] or C(5) metalation of 1-methyluracil by Pt(III).[7] Binding pattern (ii) has been reported both for cationic $(NH_3)_5Ru^{II}$ and $(NH_3)_5Os^{II}$[8] as well as the anionic $[Ru^{II}(hedta)]^-$ (hedta = *N*-(hydroxyethyl)-ethylenediaminetriacetate)[9] for a number of cytosine and uracil ligands. With the exception of a diplatinum(III) complex containing both N(3),O(4) bridged and terminal and C(5)-bound 1-methyluracil ligands,[7] none of the uracil compounds mentioned have been X-ray structurally examined. Here we report the synthesis and characterization of a series of complexes of Pt(II) and Hg(II) with 1,3-dimethyluracil as well as other uracil ligands and the X-ray single-crystal structure determinations of two examples.

The compounds described here represent bioorganometallic species in the strict sense, containing M−C bonds with a biomolecule. They therefore differ from a class of compounds commonly also termed "bioorganometallic" but containing an organometallic fragment bound to a biomolecule in a coordinative fashion.[10]

Experimental Section

Preparation of Starting Compounds. The starting materials *trans*-$(CH_3NH_2)_2PtCl_2$,[11] *trans*-$[(CH_3NH_2)_2Pt(H_2O)_2]^{2+}$,[12] [(dien)PtI]I,[13] and 1-methyluracil (1-MeUH)[14] were prepared as previously described. 1,3-Dimethyluracil (1,3-DimeU), uridine (urdH) and 5′-UMP were purchased from Sigma and $Hg(CH_3COO)_2$ from Fluka.[15] *trans*-$(CH_3NH_2)_2Pt$(1-MeU-*N3*)$_2$·$3H_2O$, **11**, was prepared by reacting *trans*-$[(CH_3NH_2)_2Pt(H_2O)_2](NO_3)_2$ with 2 equiv of 1-MeUH at pH 8.2 (pH repeatedly adjusted by means of NaOH) for 4 d at 60 °C and subsequent slow evaporation. The yield of the white compound was 62%. Anal. Calcd (found) for $C_{12}H_{26}N_6O_7Pt$: C, 25.7 (25.3); N, 15.0 (15.0); H, 4.7 (4.8). The purity of the compound was confirmed by ^1H NMR spectroscopy.

Preparation of the C(5)-Bonded Metal Compounds. *trans*-$[(CH_3NH_2)_2Pt$(1,3-DimeU-*C5*)$(H_2O)](NO_3)$, **1a**, was prepared by the reaction

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(15) Abbreviations used: 1,3-DimeU = free base; 1,3-DimeU-*C5* = 1,3-dimethyluracil deprotonated at C5 and metalated at this site; 1-MeUH = free base; 1-MeU-*N3* = monoanion, coordinated to metal via N(3); 1-MeU-*N3,C5* = dianion, metalated at N(3) and C(5) and possibly a monoanion at low pH (protonated at O(4) or O(2)).

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of the diaqua species (NO_3 salt) of *trans*-$(CH_3NH_2)_2PtCl_2$ with 2 equiv of 1,3-DimeU (stirred at 65 °C for 23 d in stoppered flask, pH = 3−4). The brown suspension was then concentrated to an oil by rotary evaporation at 30 °C. After repeated extraction of the oil with 30 mL-portions of $CHCl_3$ or CH_3OH, **1a** was obtained as a pale brown powder. Although isolated yields were only 10−12%, according to ^1H NMR spectroscopy the product is formed in 60−70% yield. Anal. Calcd (found) for $C_8H_{19}N_5O_6Pt$: C, 20.2 (21.0); N, 14.7 (15.0); H, 4.0 (3.7).

The perchlorate salt **1b** was obtained analogously.

trans-$(CH_3NH_2)_2$Pt(1,3-DimeU-*C5*)Cl, **2**, was obtained as pale yellow cubes by addition of an excess of NaCl to a concentrated aqueous solution of **1a** after 1 h at 4 °C (yield 60%). Anal. Calcd (found) for $C_8H_{17}N_4O_2ClPt$: C, 22.2 (22.0); N, 13.0 (13.2); H, 4.0 (3.9).

trans-[$(CH_3NH_2)_2$Pt(1,3-DimeU-*C5*)(NH_3)]ClO_4, **3**, was prepared by reacting a solution of *trans*-[$(CH_3NH_2)_2$Pt(1,3-DimeU-*C5*)(H_2O)]ClO_4, **1b**, with aqueous NH_3 (1 N, stirred at 22 °C for 6 h in a stoppered flask). After concentration to an oil and extraction with $CHCl_3$, the crude product was recrystallized from water and **3** isolated as colorless cubes. Due to very low yields, **3** was characterized by NMR spectroscopy (^1H, ^{195}Pt, $^{195}Pt-^1H$ HMQC) only.

(1,3-DimeU-*C5*)Hg(CH_3COO), **5**, was prepared as follows: to a solution of 1,3-DimeU (1.06 mmol in 60 mL of water) was added Hg($CH_3COO)_2$ (1.06 mmol) and the mixture stirred at 50 °C for 16 h. The solution (pH 3.5) was then concentrated to 3 mL. After 5 d at room temperature, colorless needles of **5** were removed from the aqueous solution. Yield: 53%. Anal. Calcd (found) for $C_8H_{10}N_2O_4Hg$: C, 24.1 (24.2); N, 7.0 (7.1); H, 2.5 (2.6).

[dienPt(1-MeU-*N3*)]$NO_3 \cdot H_2O$, **6**, was obtained by reaction of [dienPt(H_2O)]$(NO_3)_2$ (1 mmol in 100 mL of water; obtained from [dienPtI]I and $AgNO_3$) with 1 equiv of 1-MeUH and 1 equiv of NaOH. After 2 d at 60 °C the mixture was evaporated to 4 mL. After several hours at 4 °C a white powder was filtered and then treated with excess MeOH to remove unreacted 1-MeUH. The residue was finally recrystallized from water to give a white powder of **6** in 74% yield. Anal. Calcd for $C_9H_{20}N_6O_6Pt$ (found): C, 21.5 (21.7); N, 16.7 (16.7); H, 4.0 (4.1).

Identification of C(5)-Bonded Metal Compounds by NMR Spectroscopy. A number of compounds were prepared on an ^1H NMR scale only and identified by ^1H NMR spectroscopy, yet were not isolated, e.g. [dienPt(1,3-DimeU-*C5*)]$^+$, **4**, [dienPt(*N3*-(1-MeU)-*C5*)Ptdien]$^{2+}$, **7**, [dienPt(*N3*-(1-MeU)-*C5*)Hg(CH_3COO)]$^+$, **8**, and [dienPt-(*N3*-(urd)-*C5*)Ptdien]$^{2+}$, **9** (cf. Results and Discussion).

Instrumentation. IR spectra (KBr pellets) were recorded on a Perkin-Elmer 580 B spectrometer. ^1H, ^{195}Pt, and ^{199}Hg NMR spectra (200.13, 42.95, and 35.79 MHz) were recorded on a Bruker AC 200 instrument. Chemical shifts are given in ppm and are referenced to internal TSP (^1H), external Na_2PtCl_6 (^{195}Pt), and external Me_2Hg (^{199}Hg), respectively. Assignment of the metal−nuclei satellites in proton NMR spectra was made by 2D $^1H-^{195}Pt$ HMQC experiments, without decoupling during acquisition. The sequence was optimized to $^3J(^{195}Pt-^1H)$ = 61−74 Hz. With help of a nondecoupled ^{199}Hg NMR spectrum of **2**, the $^3J(^{195}Pt-^1H)$ was determined as 197 Hz.

X-ray Crystallography. X-ray data of compounds **2** and **5** were collected on a Nicolet R3m/V single-crystal diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Unit cell parameters were obtained from least squares fit to 23 (**2**) and 24 (**5**) randomly selected reflections in the range $15 \leq 2\theta \leq 30°$ as follows: **2**, a = 15.736(6) Å, b = 11.481(6) Å, c = 25.655(10) Å, and β = 145.55(3)° and **5**, a = 4.905(2) Å, b = 18.451(6) Å, c = 11.801(5) Å, and β = 94.47(3)°. Intensity data were collected at room temperature at variable scan speeds ($\omega/2\theta$ scan). An empirical absorption correction via ψ-scans was applied for **5**. No correction was made for extinction.

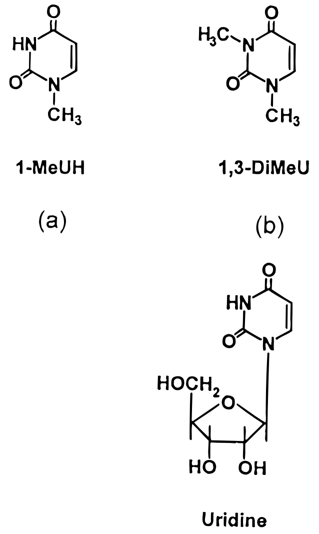
The structures were solved by conventional Patterson and Fourier methods and refined by full-matrix least squares to R = 5.2% (**2**) and R = 4.3% (**5**) using the SHELXTL PLUS and SHELX-93 systems of crystallographic computer programs.[16] For **2**, two crystallographically independent molecules were found. The hydrogen atoms were not determined. The scattering factors were those given in the SHELXTL PLUS program. Attempts to obtain a better data collection with lower standard deviations for **2** at low temperature were unsuccessful as the crystals undergo a phase transition at low temperature.

Table 1. Crystallographic Data and Experimental Details of the X-ray Studies

	2	5
formula	$C_8H_{17}ClN_4O_2Pt$	$C_8H_{10}N_2O_4Hg$
fw	431.784	398.768
cryst dimens, mm	0.35 × 0.3 × 0.25	0.2 × 0.3 × 0.2
cryst syst	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/n$
a, Å	15.736(6)	4.905(2)
b, Å	11.481(6)	18.451(6)
c, Å	25.655(10)	11.801(5)
β, deg	145.55(3)	94.47(3)
V, Å^3	2621.9(28)	1064.77(72)
d(calcd), g cm^{-3}	2.188	2.488
Z	4	4
μ(Mo Kα), mm^{-1}	11.01	14.45
F(000)	1632	736
2θ max, deg	50	50
no. of reflcns measd	3849	2147
no. of indep reflcns ($F > 4\sigma(F)$)	1123	707
no. of variables	144	86
final R, R_w[a]	R_1 = 5.3%	R_1 = 5.4%
	R_{w2} = 13.8%	R_{w2} = 6.5%

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $R_{w1} = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{0.5}$; $R_{w2} = (\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{0.5}$.

Chart 1



Crystallographic data and experimental details are reported in Table 1 and Supporting Information Tables S1 and S2, final positional and equivalent isotropic thermal parameters are listed in Tables 2 and 3.

Results and Discussion

The Ligands. The uracil nucleobases applied in this study are presented in Chart 1. They include 1-methyluracil, 1-MeUH (a), 1,3-dimethyluracil, 1,3-DimeU (b), and uridine, urdH (c). Metal binding patterns of these compounds have been reviewed.[17−20] In the majority of cases, metal binding to 1-MeUH and uridine is via N(3), following deprotonation of

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Table 2. Atomic Positional Parameters and Equivalent Isotropic Displacement Coefficients ($Å^2$) for **2**

atom	x	y	z	$U_{eq}{}^{a}$
Pt(1)	0.7592(1)	−0.0117(1)	0.22112(1)	0.028(1)[b]
Pt(2)	0.1601(1)	−0.0089(1)	0.19280(1)	0.029(1)[b]
Cl(1)	0.7453(4)	−0.0385(4)	0.12160(4)	0.049(1)
Cl(2)	−0.0766(4)	−0.0407(5)	0.03217(4)	0.058(4)[b]
C(11)	0.8429(27)	0.2544(24)	0.4411(24)	0.097(9)
C(12)	0.8000(16)	0.0398(18)	0.4326(17)	0.048(5)
C(13)	0.7377(29)	−0.1719(28)	0.4118(28)	0.116(11)
C(14)	0.7580(16)	−0.0880(16)	0.3330(17)	0.047(5)
C(15)	0.7751(14)	0.0137(14)	0.3018(14)	0.038(4)
C(16)	0.8024(20)	0.1189(21)	0.3396(20)	0.073(7)
C(23)	0.7001(16)	−0.1508(16)	0.5491(16)	0.050(5)
C(25)	0.3633(13)	0.0141(14)	0.3283(13)	0.034(4)
C(26)	0.4041(13)	0.1249(12)	0.3653(13)	0.028(4)
C(100)	0.4407(16)	0.0596(17)	0.09990(16)	0.050(5)
C(110)	0.9538(16)	−0.2231(16)	0.3139(16)	0.046(5)
C(210)	0.3874(17)	0.0118(17)	0.2122(17)	0.056(5)
N(11)	0.8121(13)	0.1305(14)	0.3995(14)	0.049(4)
N(13)	0.7609(13)	−0.0708(14)	0.3899(13)	0.050(4)
N(100)	0.5599(11)	0.0722(12)	0.11791(12)	0.039(4)
N(110)	0.9629(11)	−0.0950(11)	0.32407(12)	0.037(3)
N(200)	0.0701(11)	−0.0791(12)	0.21628(12)	0.037(3)
N(210)	0.2379(13)	0.0678(14)	0.16055(13)	0.055(4)
O(12)	0.7989(13)	0.0618(15)	0.4754(13)	0.076(5)
O(14)	0.7243(16)	−0.1866(16)	0.3002(16)	0.098(6)
O(22)	0.7659(10)	0.0699(10)	0.6027(10)	0.043(3)
O(24)	0.4231(11)	−0.1843(11)	0.3646(11)	0.052(3)
N(21)	0.5452(12)	0.1449(12)	0.4601(12)	0.041(4)
N(23)	0.5899(11)	−0.0512(12)	0.4800(11)	0.040(4)
C(21)	0.6008(17)	0.2649(16)	0.4969(15)	0.048(5)
C(22)	0.6449(11)	0.0537(11)	0.5180(11)	0.017(3)
C(24)	0.4462(14)	−0.0792(15)	0.3848(15)	0.040(4)
C(200)	0.0479(19)	−0.2147(18)	0.2016(18)	0.064(6)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. [b] Anisotropically refined.

Table 3. Atomic Positional Parameters and Equivalent Isotropic Displacement Coefficients ($Å^2$) for **5**

atom	x	y	z	$U_{eq}{}^{a}$
Hg(1)	0.0148(2)	0.0973(1)	0.0824(1)	0.045(1)[b]
C(1)	−0.6312(86)	0.2774(12)	0.3249(29)	0.072(13)[b]
C(2)	−0.2890(69)	0.1939(13)	0.4277(27)	0.062(7)
C(3)	0.0173(121)	0.1146(17)	0.5422(31)	0.126(27)[b]
C(4)	−0.0081(64)	0.1108(11)	0.3397(26)	0.051(6)
C(5)	−0.1314(64)	0.1377(11)	0.2298(23)	0.047(10)[b]
C(6)	−0.3249(56)	0.1891(11)	0.2252(22)	0.045(5)
C(10)	0.4734(72)	0.0498(14)	−0.2030(29)	0.068(7)
C(20)	0.3698(71)	0.0768(12)	−0.0881(27)	0.049(5)
N(1)	−0.4019(56)	0.2184(11)	0.3219(22)	0.060(5)
N(3)	−0.1096(59)	0.1422(11)	0.4341(22)	0.060(5)
O(2)	−0.3900(53)	0.2216(10)	0.52307(21)	0.079(5)
O(4)	0.1736(54)	0.0662(11)	0.3460(22)	0.082(6)
O(10)	0.1466(46)	0.0548(9)	−0.0702(19)	0.061(4)
O(20)	0.5018(52)	0.1198(11)	−0.0302(22)	0.083(10)[b]

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. [b] Anisotropically refined.

this site (p$K_a \approx 9.8$), or simultaneously via N(3),O(4) or N(3),O-(4),O(2).[17,20] However, there is also clear evidence for exclusive metal binding via exocyclic oxygens of the neutral bases,[21−23] and that is why, at least for 1,3-DimeU, exclusive metal binding via one of two exocyclic oxygens could have been anticipated also in our studies. On the other hand, theoretical calculations on the electron density distribution in uracils have revealed similar electron densities at the N(3) and the C(5) ring positions,[24] and susceptibility of the 5-position for substitution reactions is well-known.[25]

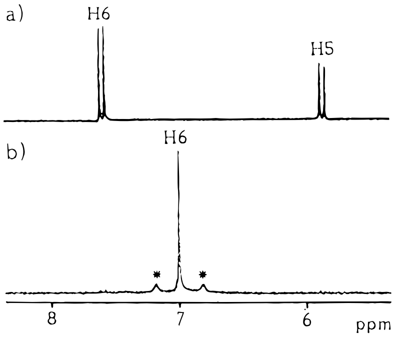

Figure 1. ^1H NMR spectra (200 MHz, D_2O, pD, 3.8; aromatic region only) of (a) 1,3-DimeU and (b) **1a** with ^{195}Pt satellites indicated (*).

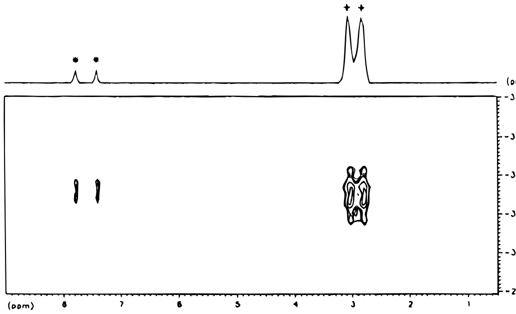

Figure 2. $^{195}Pt-^1H$ HMQC spectrum (D_2O) of **1a** with ^{195}Pt satellites of H6 (*) and of the CH_3ND_2 proton (+).

Table 4. NMR Data (D_2O) for *trans*-$[(CH_3NH_2)_2Pt(1,3\text{-DimeU-C5})X]^{n+}$ Compounds

compd	X	$\delta(^{195}Pt)^a$	$\delta(H6)^b$	$3J(^{195}Pt-H6)^c$	pD
1	H_2O	−3126	6.98	74	3.8
2	Cl	−3181	7.08	72	8
3	NH_3	−3251	7.10	61	9.5

[a] ppm relative to $[PtCl_6]^{2-}$. [b] ppm relative to TSP. [c] Hz.

Reaction of *trans*-$[(CH_3NH_2)_2Pt(H_2O)]^{2+}$ with 1,3-DimeU. *trans*-$[(CH_3NH_2)_2Pt(1,3\text{-DimeU-}C5)(H_2O)]X$ ($X = NO_3$, **1a**; ClO_4, **1b**) was prepared in aqueous solution (pH 3−4) from *trans*-$[(CH_3NH_2)_2Pt(H_2O)_2]^{2+}$ and 1,3-DimeU. Formation of a C(5)-bound uracil species was first detected by us using ^1H NMR spectroscopy. Addition of NaCl to aqueous solutions (pH 4) of **1a** or **1b** afforded pale yellow *trans*-$(CH_3NH_2)_2(1,3\text{-DimeU-}C5)Cl$, **2**, and reaction of NH_3 with **1b** gave colorless *trans*-$[(CH_3NH_2)_2Pt(1,3\text{-DimeU-}C5)(NH_3)]ClO_4$, **3**.

In all cases, ^1H NMR spectroscopy indicates a 1:1 stoichiometry between Pt and 1,3-DimeU (relative intensities of CH_3 resonances of 1,3-DimeU and methylamine), and $^{195}Pt-^1H$-NMR correlations reveal the existence of Pt−C bonds. Typically, the H(6) proton of 1,3-DimeU is shifted upfield by ca. 0.5−0.6 ppm upon metalation and displays ^{195}Pt satellites of 61−74 Hz, depending on the ligand *trans* to C(5). CH_3 protons of 1,3-DimeU are hardly affected upon Pt binding (upfield shifts of 0.02−0.04 ppm), and CH_3ND_2 groups display ^{195}Pt satellites of 47−51 Hz. ^{195}Pt resonances are between −3126 (**1a**) and −3251 ppm (**3**), in a range expected for Pt^{II} aryl complexes.[26] In Figures 1 and 2 examples are given, and Table 4 lists selected NMR data. $^3J(^{195}Pt-^1H(6))$ coupling values qualitatively agree with expectations according to which in nucleobase complexes they inversely correlate with the *trans*-influence of the X ligand *trans* to C(5), viz. O > Cl > N.[27]

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(24) Pullman, B.; Pullmann, A. *Prog. Nucl. Acid Res. Mol. Biol.* **1968**, *9*, 342.
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(26) Pregosin, P. S. *Annu. Rep. NMR Spectrosc.* **1986**, *17*, 172.

Table 5. Selected Bond Lengths (Å) and Bond Angles (deg) for **2**

molecule A		molecule B	
Pt(1)−Cl(1)	2.40(1)	Pt(2)−Cl(2)	2.38(5)
Pt(1)−C(15)	1.90(4)	Pt(2)−C(25)	2.01(2)
Pt(1)−N(100)	2.02(1)	Pt(2)−N(200)	2.10(3)
Pt(1)−N(110)	2.05(1)	Pt(2)−N(210)	2.15(4)
N(110)−Pt(1)−C(15)	90.4(9)	N(210)−Pt(2)−C(25)	90.8(9)
N(100)−Pt(1)−C(15)	91.3(10)	N(200)−Pt(2)−C(25)	92.4(8)
N(100)−Pt(1)−N(110)	178.1(9)	N(200)−Pt(2)−N(210)	176.3(7)
Cl(1)−Pt(1)−C(15)	178.0(6)	Cl(2)−Pt(2)−C(25)	178.0(6)
Cl(1)−Pt(1)−N(110)	89.2(7)	Cl(2)−Pt(2)−N(210)	88.4(6)
Cl(1)−Pt(1)−N(100)	89.2(5)	Cl(2)−Pt(2)−N(200)	88.6(6)
Pt(1)−C(15)−C(14)	121.6(14)	Pt(2)−C(25)−C(24)	120.1(13)
Pt(1)−C(15)−C(16)	126.1(20)	Pt(2)−C(25)−C(26)	118.8(13)
C(14)−C(15)−C(16)	112.4(24)	C(26)−C(25)−C(24)	120.0(17)
C(15)−C(16)−N(11)	122.5(21)	C(25)−C(26)−N(21)	120.7(14)

When redissolved in D_2O, **2** always gives rise to an additional minor species (few percent of major species), which can be assigned to the aqua complex **1** as a consequence of Cl hydrolysis. This interpretation is supported by the fact that addition of Ag^+ (and AgCl precipitation) leads to an increase in intensity of this resonance and the appearance of the corresponding ^{195}Pt satellites. Cl hydrolysis appears to be considerably more pronounced than in related Cl, nucleobase-*N* complexes of *trans*-(diamine)platinum(II). We assume that this is a direct consequence of the high *trans*-effect of C(5) as opposed to a N donor typically found in nucleobase complexes.

X-ray Analysis of 2. The X-ray crystal structure analysis of **2** has been performed. Salient structural features are listed in Table 5 and a view of the two crystallographically independent molecules is given in Figure 3. Despite the poor crystal quality and the relatively high standard deviations, the structure fully confirms the binding mode as determined from NMR spectroscopy. A packing diagram (supplementary material) reveals intermolecular H bonding between the carbonly oxygens of the nucleobase and the amine ligands (Table 6). The crystal lattice is built up of layers in such away that the pyrimidine rings of molecules *A* and *B* are stacked, respectively.

(dien)Pt^{II} Binding to 1,3-DimeU. In a slow reaction, $[dienPt(D_2O)]^{2+}$ (and $[dienPt(OH)]^+$, respectively, pK_a = 6.3[28]) reacts with 1,3-DimeU at pD 7.5 to give [dienPt(1,3-DimeU-*C5*)]$^+$, **4**. As a consequence of Pt binding and release of H^+, the pD drops to ca. 5.0. Although the product was not isolated, C(5) binding in **4** is evident from the H(6) upfield shift (6.88 ppm) and ^{195}Pt coupling (54 Hz). The ^{195}Pt NMR resonance of **4** is observed at −3294 ppm. Parallel to formation of **4**, isotopic H/D exchange at the 5-position takes place, leading to a simplification of the spectrum (Supporting Information). In addition, a minor, unidentified species (H(6), 7.20 ppm) forms.

Hg(II) Binding to 1,3-DimeU. Colorless needles of (1,3-DimeU-*C5*)Hg(CH_3COO), **5** were obtained from aqueous solution by reaction of 1,3-DimeU with $Hg(CH_3COO)_2$ at pH = 3.5. ^{1}H NMR spectroscopy permits an unambiguous assignment of the composition of **5**. The uracil H(6) resonance in **5** is shifted upfield and displays ^{199}Hg satellites (^3J) of 197 Hz (Figure 4). In the ^{199}Hg NMR spectrum, a doublet, arising from coupling with ^{1}H(6) and centered at −2668.5 ppm, is seen.

Crystal Structure of 5. The molecule with atom numbering scheme is shown in Figure 5, and selected interatomic distances and angles are presented in Table 7.

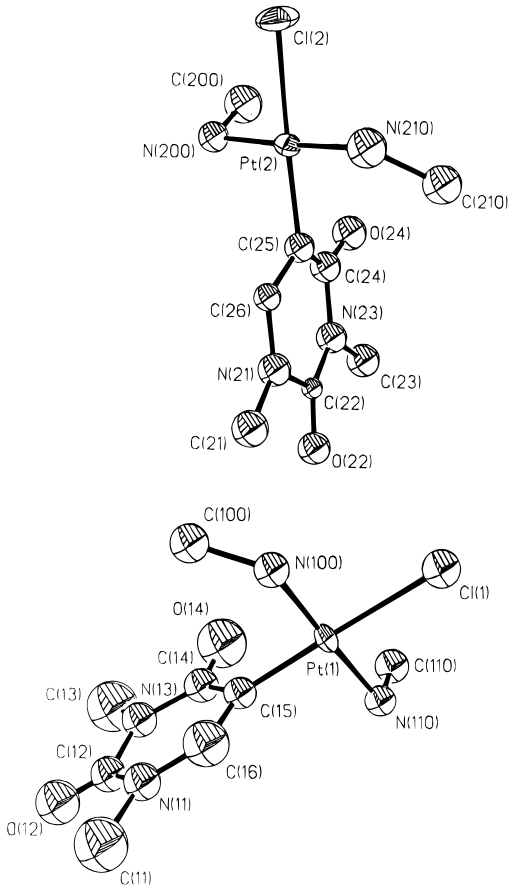

Figure 3. View of the two crystallographically independent molecules of *trans*-$(CH_3NH_2)_2$Pt(1,3-DimeU-*C5*)Cl (**2**) with the atom numbering scheme.

Table 6. Possible Hydrogen-Bonding Interactions in **2**^{a}

Cl(2)−N(210)^a	3.21(3)	N(100)−O(24)^d	2.81(2)
N(110)−O(12)^b	2.98(3)	N(110)−O(22)^b	2.93(3)
N(200)−O(22)^c	2.91(4)	N(210)−O(14)^d	2.89(3)
Cl(2)−N(210)−C(210)^a	89.3(19)	C(100)−N(100)−O(24)^d	94.1(12)
N(100)−O(24)−C(24)^d	159.8(20)	C(110)−N(110)−O(12)^b	103.8(15)
N(110)−O(12)−C(12)^b	134.3(13)	C(110)−N(110)−O(22)^b	95.3(16)
N(110)−O(22)−C(22)^b	116.9(19)	C(200)−N(200)−O(22)^c	98.0(18)
N(200)−O(22)−C(22)^c	148.9(19)	C(210)−N(210)−O(14)^d	114.04(11)
N(210)−O(14)−C(14)^d	144.5(27)		

^{a} Symmetry operations: (a) $-x, -y, -z$; (b) $-x + 2, -y, -z + 1$; (c) $-x + 1, -y, -z + 1$; (d) $-x + 1, y + {}^1/_2, -z + {}^1/_2$.

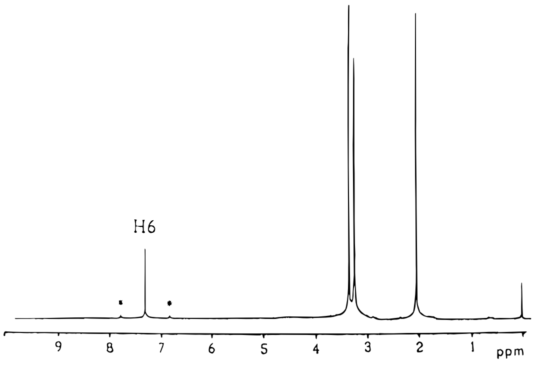

Figure 4. ^{1}H NMR spectrum (200 MHz, D_2O, pD 4.5) of **5** with ^{199}Hg satellites indicated (*).

Hg is bound to the nucleobase through C(5) and to the acetate oxygen O(10). The Hg−C(5) distance of 2.07(3) Å is in the range of Hg−N bond lengths typically found in Hg nucleobase complexes[29] and also compares well with values observed in

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(27) Raudaschl, G.; Lippert, B. *Inorg. Chim. Acta* **1983**, *80*, L 49 and references cited therein.

(28) pK_a of H_2O in $[(dien)Pt(H_2O)]^{2+}$ ca. 6.3, cf.: (a) Appleton, T. G.; Hall, J. R.; Ralph, S. F.; Thompson, C. S. M. *Inorg. Chem.* **1989**, *28*, 1989. (b) Arpalahti, J.; Lehikoinen, P. *Inorg. Chem.* **1990**, *29*, 2564.

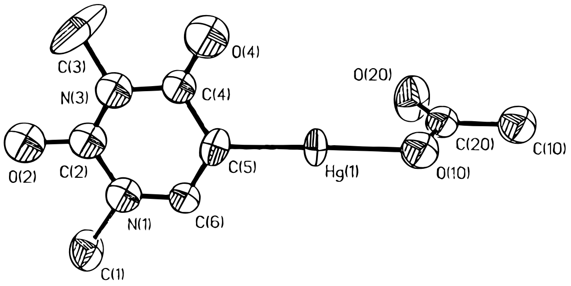

Figure 5. View of Hg(1,3-DimeU-*C5*)(CH_3COO), **5**, with atom numbering scheme.

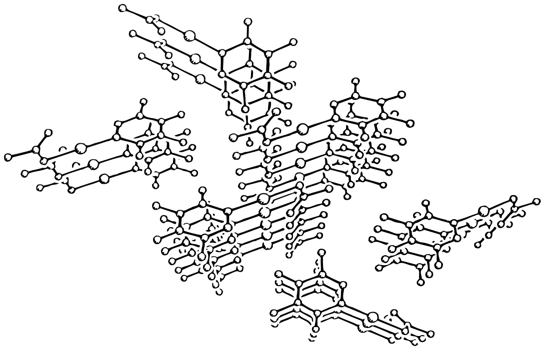

Figure 6. Packing of **5** with view along the *y* axis.

Table 7. Selected Bond Lengths (Å) and Bond Angles (deg) for **5**

Hg−C(5)	2.07(3)	Hg−O(10)	2.11(2)
C(4)−C(5)	1.48(4)	C(6)−C(5)	1.34(4)
O(10)−C(20)	1.20(4)		
Hg−C(5)−C(4)	118.2(17)	Hg−C(5)−C(6)	120.7(20)
Hg−O(10)−C(20)	111.6(18)	O(10)−Hg−C(5)	177.6(18)
C(6)−C(5)−C(4)	121.0(23)	N(1)−C(6)−C(5)	119.7(24)
N(3)−C(4)−C(5)	114.8(22)	O(10)−C(20)−O(20)	125.5(32)

Hg organyl compounds. The Hg−O(10) bond distance of 2.11(2) Å is also in the normal range. The pyrimidine ring and acetate ligand are planar within the standard deviations, and Hg does not deviate significantly from the mean planes through the ligands. The coordination geometry of Hg is essentially linear, with the O(10)−Hg−C(5) angle being 177.6(18)°. The Hg−O(4) distance of 3.19(2) Å clearly rules out additional interactions between the metal and the exocyclic oxygen of 1,3-DimeU. Bonding interactions between Hg and the acetate oxygen O(20) (2.88(3) Å) can likewise be excluded. The nucleobase and the acetate ligand form a dihedral angle of 75.4(8)°.

The packing of the molecules in the crystal is depicted in Figure 6. The crystal lattice is built up of layers parallel to the crystallographic a plane and the nucleobases are stacked along the y-axis. Short contacts are observed between Hg and O(10) at $-x$, $-y$, $-z$ (2.91(2) Å) and between Hg and O(20) at $x - 1$, y, z (2.75(2) Å).

IR Spectra of 1−3 and 5. Characteristic IR spectroscopic changes of 1-MeUH upon N(3) deprotonation and subsequent metal binding to this site as well as O(4) have been described.[30,31] Similarly, the effects of metal binding to O(4) of a neutral 1,3-DimeU ligand on the ring vibrations have been reported.[22,23] Displacement of the H(5) proton in 1,3-DimeU by a metal electrophile causes characteristic alterations in the IR spectra, which are useful for diagnostic purposes. The most characteristic changes are observed in the double-bond stretching modes. Thus, in 1,3-DimeU two intense bands at 1705 and around 1650 cm^{-1} are observed, which are due to ν(C=O) and ν(C=C) modes.[32] The two bands are characteristically shifted to lower energies, to 1670 and 1600 cm^{-1}, respectively (Figure 7). These changes are primarily a consequence of nucleobase deprotonation. In **5**, the acetate modes are superimposed with the lower energy mode. A second characteristic feature in the IR spectra occurs in the 750−820 cm^{-1} range. The two intense and sharp bands at 755 and 815 cm^{-1}, assigned to δ_{oop} CH(6) and δ_{oop} CH(5) modes,[33] are lost and replaced by weaker bands at 755 and 775 cm^{-1} (Pt compounds) and 750 and 765, 770 cm^{-1} (**5**).

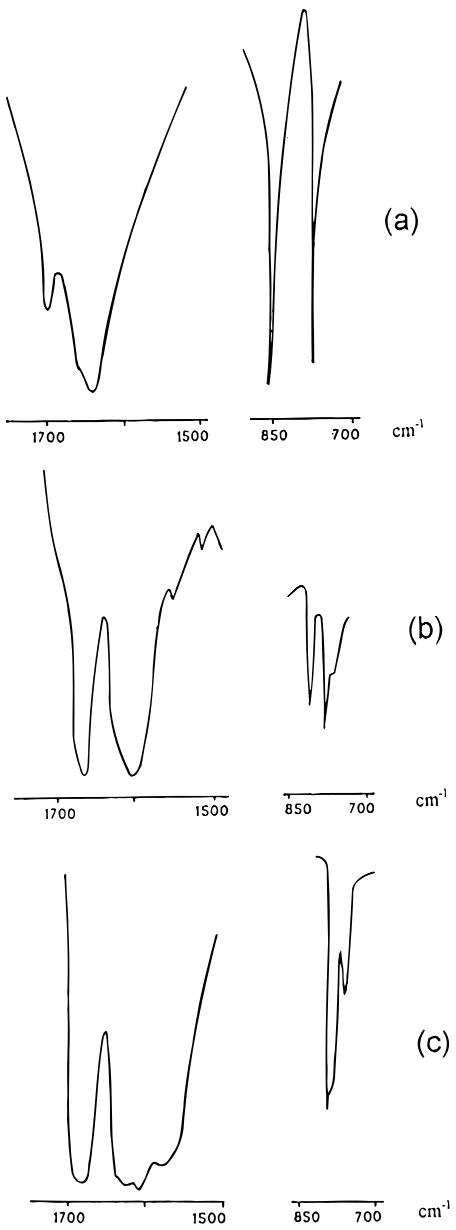

Figure 7. Sections of IR spectra of (a) 1,3-DimeU, (b) **2**, and (c) **5**.

2-fold Platination at N3 and C5. When [dienPt(1-MeU-*N3*)]$^{+}$ (**6**) is treated with a 2-fold excess of [dienPt(D_2O)]$^{2+}$ at

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(29) See, e.g.: (a) Kosturko, L. D.; Folzer, C.; Stewart, R. F. *Biochemistry* **1974**, *13*, 3949. (b) Poojary, M. D.; Manohar, H. *Inorg. Chim. Acta* **1984**, *93*, 153 and references cited therein. (c) Menzer, S.; Hillgeris, E. C.; Lippert, B. *Inorg. Chim. Acta* **1993**, *211*, 221.

(30) Lippert, B.; Neugebauer, D. *Inorg. Chim. Acta* **1980**, *46*, 171.

(31) Guay, F.; Beauchamp, A. L.; Gilbert, C.; Savoie, R. *Can. J. Spectrosc.* **1983**, *28*, 13.

(32) (a) Wierzchowski, K. L.; Litonska, E.; Shugar, D. *J. Am. Chem. Soc.* **1965**, *87*, 4621. (b) Bandekar, J.; Zundel, G. *Spectrochim. Acta* **1983**, *39 A*, 337.

(33) Bandekar, J.; Zundel, G. *Spectrochim. Acta* **1982**, *38 A*, 815.

Scheme 1

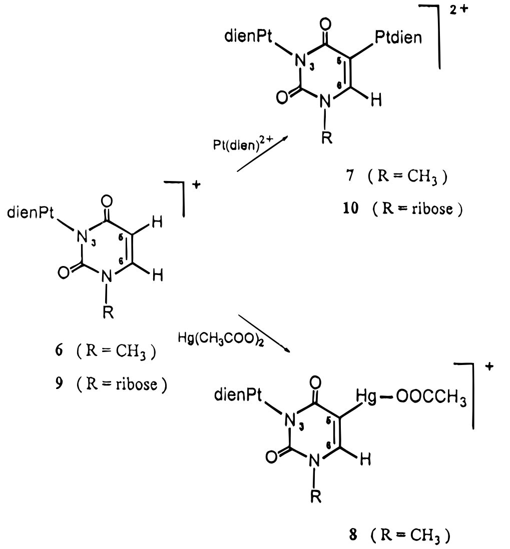

Table 8. NMR Data (D_2O) of (1-MeU-*N3*)/(urd-*N3*) and (1-MeU-*N3*,*C5*)/(urd-*N3*,*C5*) Compounds

compd	δ(H5)[a]	δ(H6)[a]	δ(^{195}Pt)[b]	3J(^{195}Pt−H6)[c]	3J(^{199}Hg−H6)[c]	pD
6	5.68[d]	7.42[d]	−2840			7.1
7		6.75	−2818 −3301	53		5.6
8		7.28	−2830		185	5.9
9	5.76[d]	7.67[d]	nr[e]			7.2
10		6.89	nr[e]	47		7.2

[a] ppm relative to TSP. [b] ppm relative to $[PtCl_6]^{2-}$. [c] Hz. [d] Doublets each, ^3J(H5-H6) ≈ 7.5 Hz. [e] Not recorded.

65 °C for several days and the reaction followed by ^{1}H NMR spectroscopy, the appearance of a new H(6) singlet at 6.75 ppm displaying ^{195}Pt satellites of 53 Hz indicates formation of a C(5) platinated species (Scheme 1). The assignment of the new species [(dienPt)$_2$(1-MeU-*N3*,*C5*)]$^{2+}$ (**7**) to a diplatinated species rather than a monoplatinated C(5) compound is on the following grounds: First, the chemical shift of H(6) is substantially upfield from that of the triamine complex **3** (7.10 ppm, cf. Table 4). Second, the ^3J coupling is significantly reduced, from 61 Hz in **3** to 53 Hz in **7**. Third, the ^{195}Pt NMR spectrum displays two resonances in a 1:1 ratio at −3301 and −2818 ppm that could be assigned to C(5) and N(3) Pt binding, respectively. Resonances due to unreacted dienPt^{II} and [dienPt(1-MeU-*N3*)]$^+$ (**6**) occur at −2420 and −2840 ppm in the ^{195}Pt NMR spectrum. The reaction leading to **7** is slow: Within 10 d, approximately only one-third of **6** has reacted to give **7**. During this time, isotopic H/D exchange at the 5-position of the 1-MeU of **6** is extensive (Supporting Information). Relevant NMR data are compiled in Table 8.

In an analogous way, uridine (urdH) was treated with a 3-fold excess of [dienPt(D_2O)]$^{2+}$ at 65 °C and pD ≈ 7 and the reaction studied by ^{1}H NMR spectroscopy. Initially formation of the N(3) bound product [(dien)Pt(urd-*N3*)]$^+$ (**9**) is observed, followed by formation of the N(3),C(5) diplatinated species **10**. The latter has its H(6) resonance at 6.89 ppm (with ^3J ^{195}Pt−^{1}H(6) coupling of 47 Hz) and H1′ at 5.87 ppm (pD 7.15).

Mixed Pt−N3, Hg−C5 Binding. Reaction of **6** with Hg(CH_3COO)$_2$ (D_2O, pD 5, 40- 50 °C) leads to a fast (2 h) and almost quantitative formation of a new species **8** (Scheme 1). It is assigned to [dienPt(*N3*-(1-MeU)-*C5*)Hg(CH_3COO)]$^+$ on the basis of ^{199}Hg coupling with H(6) of 1-methyluracil (7.28 ppm; ^3J = 185 Hz) as well as ^{195}Pt NMR spectroscopy: The ^{195}Pt NMR resonance of **6** (-2840 ppm) is slightly shifted upon addition of 1 equiv of Hg(CH_3COO)$_2$ to −2801 ppm, and appears at −2830 ppm in **8**. The Pt entity clearly reamains bonded to the uracil ring initially. Only with longer reaction times (> 4 h at 45 °C), **8** undergoes changes which result, among others, in a displacement of dienPt^{II}. Thus, in the ^{195}Pt NMR spectrum a new resonance at −2500 ppm grows in (Supporting Information), which can be assigned to [dienPt(CH_3COO)]$^+$. The signal/noise ratio of the ^{195}Pt NMR resonances does not change during this process, strongly suggesting that all Pt remains dissolved. At the same time, the ^{1}H NMR resonances of the nucleobase decrease in intensity and a colorless precipitate starts to form. The identity of this precipitate is as yet unclear, but we can rule out that it is Hg(1-MeU-*N3*)$_2$.[34] Finally, during these changes, a new ^{1}H NMR resonance close to the methyl resonance of the original acetate develops, which is due to acetate coordinated to dienPt^{II}.[35]

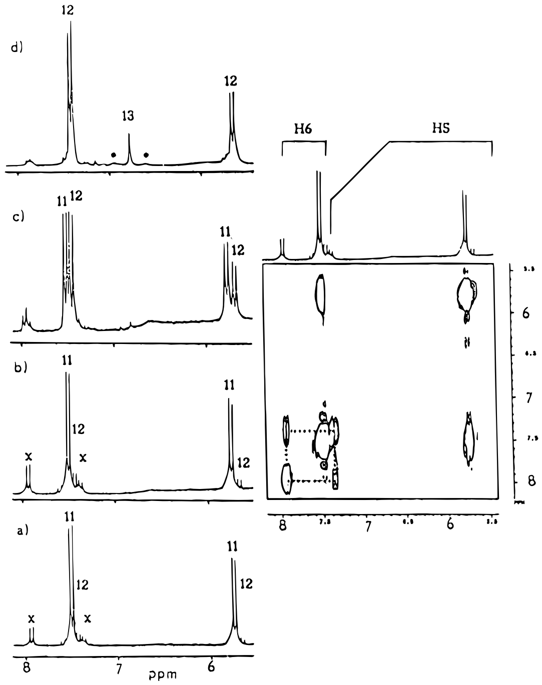

Figure 8. ^{1}H NMR spectra (200 MHz, D_2O, pD ≈ 4; aromatic region only) of reaction of *trans*-(CH_3NH_2)$_2$Pt(1-MeU-*N3*)$_2$, **11**, with excess *trans*-[(CH_3NH_2)$_2$Pt(D_2O)$_2$]$^{2+}$: (a) after 40 min; (b) after 3 h; (c) after 5 d; (d) after 11 d. The insert shows a 2D-COSY-^{1}H-NMR spectrum of solution a with the two unusually shifted 1-MeU doublets X.

Speculations on the Formation of the Metal-C Bond. Displacement of H(5) and formation of the metal−carbon bond is feasible as a result of an electrophilic attack of the metal entity on the heteroaromat. Alternatively, η^2 binding of the metal entitiy to the C(5)−C(6) double bond might activate the C(5)−H bond prior to σ bond formation, as found for many arenes[36] and even for the reaction of (NH_3)$_5$Os^{II} with 2,6-lutidine[37] and its protonated form, respectively.[38] While we cannot contribute anything with regard to the mechanism of formation of compounds **1** and **5** at this stage, we made an interesting observation during the reaction of *trans*-(CH_3NH_2)$_2$-

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(34) An authentic sample was prepared and analyzed in analogy to the corresponding 1-methylthymine complex reported by: Kosturko, L. D.; Folzer, C.; Stewart, R. F. *Biochemistry* **1974**, *13*, 3949.

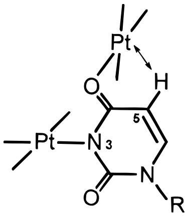
(35) Confirmed by reaction of [dienPtI]I with 2 equiv of Ag(CH_3COO): CH_3-resonance of ionic acetate at 2.1 ppm, of coordinated acetate at 2.0 ppm (D_2O, pD 5−6).

(36) Parshall, G. W. *Homogeneous Catalysis*; Wiley-Interscience: New York, 1980; Chapter 7.

(37) Cordone, R.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 8101.

(38) Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 2896.

Pt(1-MeU-*N3*)$_2$, **11**, with *trans*-[(CH$_3$NH$_2$)$_2$Pt(D$_2$O)$_2$]$^{2+}$ (pD 4). This reaction eventually leads to *trans*-[(CH$_3$NH$_2$)$_2$Pt(1-MeU-*N3*)(D$_2$O)]$^+$, **12**, as the major product as well as to *trans*-[(CH$_3$NH$_2$)$_2$Pt(1-MeU-*C5*)(D$_2$O)]$^+$, **13**, as a minor one. Assignment of **13**, is based on the chemical shift of its H(6) resonance (6.80 ppm) and its ^3J coupling constant with ^{195}Pt (72 Hz), which is close to that of **1**, yet considerably larger than the 53 Hz observed for diplatinated (*N3,C5*) **7**. At an early stage of the reaction, a set of uracil H(5) and H(6) doublets is observed which has undergone a dramatic *downfield* shift as compared to free 1-MeUH or Pt(1-MeU-*N3*), by ca. 1.6 ppm for H(5) and ca. 0.5 ppm for H(6) (Figure 8). We have only once seen a similar phenomenon and assigned it to a "face−back" arrangement of two Pt^{II} entities bound to N(3) and O(4) of 1-MeU.[39] In this orientation, the filled d$_{z^2}$ orbital (and the empty 6 p$_z$ orbital) of the O(4) bound Pt^{II} are pointing toward H(5). In the present case, these unusual resonances are visible throughout the reaction. Since they appear prior to formation of the C(5)-bound species **13**, we propose that binding of the "back-oriented" Pt entity at O(4) precedes C(5) binding (structure **I**). We favor this view over one that implies a η^2-bound precursor at the C(5)−C(6) double bond since the latter should produce significant upfield shifts of the olefinic protons as a consequence of π-back-bonding: For example, (NH$_3$)$_5$-Os^{II} typically causes upfield shifts >2 ppm for the adjacent protons,[36,37] and for Ru^{II} species binding in a η^2 fashion (C(5),C(6)) to uracils, upfield shifts of 0.7−1.4 ppm for H(5) are common.[9]



Summary

In this work we have established basic features of the formation, structure and NMR spectroscopy of uracil nucleobases containing Pt^{II} or Hg^{II} covalently attached to the C(5) position of these ligands. Our result extend the pioneering work of Dale et al.[2] on mercuration reactions of cytosine and uracil nucleobases as well as limited own work on C(5)-platinated uracil[7] and add a structural component to this work. The fact that synthetic routes to the important class of antiviral 5-substituted pyrimidine nucleoside analogues frequently involve C(5)-metalated intermediates[40] and recent suggestions on the possible role of 5-substituted uracils for the transition from the RNA to the DNA-protein world[41] makes this research interesting also from a mechanistic point of view. We plan to continue this work and in particular to study reactivity aspects of these compounds.

Acknowledgment. This work has been supported by the Deutsche Forschungsgemeinschaft (DFG), the Fonds der Chemischen Industrie (FCI), and Asta Medica.

Supporting Information Available: Tables of complete crystallographic data, complete bond lengths and angles, and anisotropic displacement coefficients of **2** and **5**, Figures showing the packing of **2** and ^{1}H NMR and ^{195}Pt NMR spectra (12 pages). Ordering information is given on any current masthead page.

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(39) Frommer, G.; Lianza, F.; Albinati, A.; Lippert, B. *Inorg. Chem.* **1992**, *31*, 2434.

(40) See, e.g.: (a) Bergstrom, D. E.; Ruth, J. L.; Warwick, P. *J. Org. Chem.* **1981**, *46*, 1432. (b) Bergstrom, D.; Beal, P.; Husain, A.; Lind, R.; Jensen, J. *J. Am. Chem. Soc.* **1989**, *111*, 374. (c) Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1991**, *28*, 1629.

(41) Robertson, M. P.; Miller, S. L. *Science* **1995**, *268*, 702.