Cytosine Binding in the Novel Organoplatinum(II) Complex [(COD)PtMe(cytosine)](SbF$_6$)†

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Received September 19, 2006

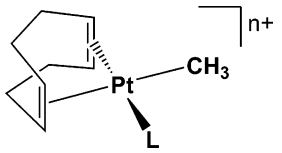
The organoplatinum fragment [(COD)PtMe] (COD = 1,5-cyclooctadiene) binds to cytosine mainly via the N(3) atom in the water-stable organoplatinum complex [(COD)PtMe(cytosine)]$^+$. This is evident from detailed NMR investigations and a crystal structure determination of [(COD)PtMe(cytosine)](SbF$_6$)·0.5H$_2$O. In solution the *N3* and *N1* stereoisomers are observed in a ratio of 1:0.2. Both species were fully characterized from detailed NMR spectroscopy and reveal marked differences from their non-organometallic counterparts.

Introduction

Organoplatinum(II) complexes [(COD)PtR(L)] (R = alkyl, alkynyl, aryl; L = other ligands) with COD (1,5-cyclooctadiene) as an easily exchangeable ligand have been known for decades and used as precursors for mono- and polynuclear organometallic platinum(II) compounds[1−3] with applications in the field of catalysis[4] or chemical vapor deposition (CVD) of platinum.[5] Their use as antitumor agents was initially proposed by Komiya et al. some years ago.[6] The series of complexes [(COD)PtMe(Nuc)](NO$_3$) (Nuc = guanosine, cytosine, adenosine nucleosides) have been synthesized and examined by ^{1}H and ^{13}C NMR spectroscopy, and the preference of platinum binding to guanosine was shown by exchange reactions using the three nucleosides. Furthermore, preliminary cell tests using P388 leukemia cells have shown "considerable cytotoxic activities".[6] Unfortunately, these studies were neither continued nor driven to a conclusive end. The reason seems to be the presence of the hydrophobic COD ligand, which is not very suitable to deliver into a cell. On the other hand, we have recently shown the suitability of the [(COD)PtMe] fragment to coordinate various ligands.[7] This moiety allows detailed insight into the binding properties of the ligands to platinum by ^{1}H NMR spectroscopy or molecular structure determination.[7] Most importantly, the concept of introducing bio-relevant ligands in platinum anticancer drugs[8] makes complexes of the type [(COD)PtR(L)]$^{n+}$ (R = alkyl, alkynyl, aryl; L = bioligand) very interesting precursor molecules.

Hence, we started an investigation with the aim of testing various bio-relevant ligands in the system [(COD)PtMe(L)]$^{n+}$

Chart 1



(L = bioligand; Chart 1), focusing on their binding properties (bond strength or binding options—if they were ambident). As a first example we present a thorough investigation of the water-soluble and water-stable organoplatinum complex [(COD)PtMe(cytosine)](SbF$_6$), including its crystal and molecular structure and detailed NMR spectroscopic investigations.

Cytosine can exist in various tautomers, as depicted in Chart 2. For isolated cytosine molecules (gas phase or calculations) the aminohydroxo forms III and IV slightly exceed the aminooxo forms I and II.[9−11] In solutions and in the solid state I and II are more relevant, with I exceeding II by a factor of $10^{2.9}$.[9,11]

The formation of corresponding platinum complexes from these tautomers has been studied recently by Lippert et al. with methylamine (CH_3NH_2),[11,12] diethylenetriamine (dien),[13] chloro,[14] or chloro and ammine (NH_3)[15] as coligands showing mainly coordination to the N(3) atom. Coordination to N(1) in 1:1 complexes is of minor importance[11−13] but can be enhanced by base pairing.[12] Furthermore, binuclear or trinuclear complexes with bridging N(3), N(1) coordination have been studied.[11,13,14]

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† Dedicated to Prof. Dr. Josef Hahn on the occasion of his retirement.

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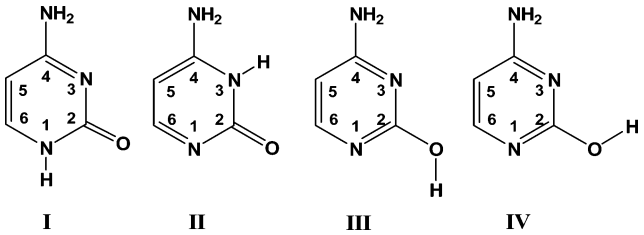
10.1021/om060856y CCC: $37.00
Publication on Web 12/05/2006

Chart 2



I II III IV

All of these studies were carried out in aqueous solution, owing to solubility reasons. Due to the organometallic nature of our system, we have been able to perform our studies in organic solvents, which is of great advantage for spectroscopic characterization and which might also have a strong impact on the binding preferences of the cytosine ligand.

Results and Discussion

Synthesis. The novel complex [(COD)PtMe(cytosine)](SbF$_6$) was synthesized from [(COD)PtMeCl] and cytosine in acetone solution, using AgSbF$_6$ to abstract the chloride ligand (see Experimental Section), as reported recently for a number of related complexes.[7] The colorless complex is not very soluble in water, with 33 mg in 100 mL $= 4 \times 10^{-4}$ mol L^{-1}, which lies far below the value of cisplatin (0.83×10^{-2} mol L^{-1}), but we are confident that the use of counterions such as Cl$^-$ and NO$_3^-$ will lead to improved solubility. More importantly, the compound is water-stable for at least 2 months in acetone/water (10:1) solution, as monitored by NMR spectroscopy. It can also be dissolved in organic solvents such as dichloromethane, THF, acetone, acetonitrile, DMSO, and DMF.

NMR Spectroscopy. In the ^{1}H NMR spectrum of the product we found two sets of signals, both corresponding to the expected composition. From ^{1}H,^{195}Pt correlation experiments a major species at -3593 ppm (A) and a minor species at -3553 ppm (B) in a 5:1 ratio could be discriminated unequivocally. ^{1}H,^{1}H COSY, ^{1}H,^{1}H NOESY, ^{1}H,^{1}H TOCSY, and ^{1}H,^{13}C NOESY experiments proved that the two molecules in solution correspond to two stereoisomers (A and B, see Table 1) with varying cytosine coordination. Figure 1 shows spectra of the isomeric mixture at high and low concentrations and at various temperatures. Table 1 gives selected data for the assignments of the isomers.

The NMR spectroscopy of the major isomer, which we assume to be the *N3*-coordinated species, differs markedly in a number of points from the already mentioned non-organometallic derivatives. The HC(5) proton signal shows a coupling to the ^{195}Pt isotope ($I = {}^1/_2$, 33.8% natural abundance) of about 18 Hz; previously, only values of below 10 Hz have been assumed from so far unresolved lines.[11,13,14] Only for N(1)-methyl-substituted analogues have higher coupling constants of about 15 Hz been reported.[14,16] For the HC(6) proton the usual coupling to HC(5) of 7.2 Hz is visible, as well as the coupling to the HN(1) proton (~6 Hz) (Figure 1, lowest trace), creating a complex signal pattern of an AB system and supporting strongly the assignment of the cytosine ligand to the tautomer I in Chart 2. Upon dilution the coupling to the HN(1) proton is lost, leaving a doublet signal (Figure 1, upper trace). Since the rest of the spectrum remains unchanged and we do not see any signal due to an −OH group, we can discard the tautomeric forms III and IV as being responsible for this change.

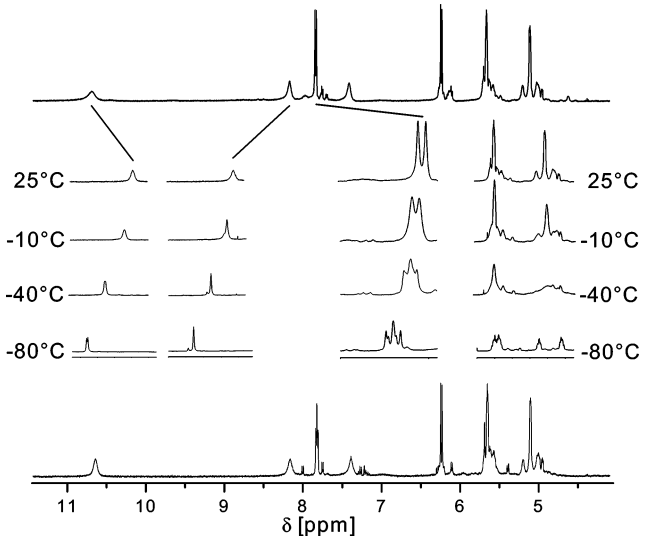


Figure 1. Expansions of ^{1}H NMR spectra of [(COD)PtMe(cytosine)]$^+$ in acetone-d_6 at various temperatures: (top and right) spectra measured on a diluted sample; (bottom and left) spectra measured on a concentrated sample.

The HC(6) and HC(5) signals are markedly shifted to higher frequency compared to those of the free cytosine ligand. All of these findings point to a stronger binding of the cytosine ligand in the organometallic system compared to that in the non-organometallic derivatives. This is supported by the ^2J(HC$_{trans}$−Pt) coupling, which was found to be quite indicative of the ligand−metal bond strength.[7] The observed coupling constant of 75 Hz places the *N3*-bound cytosine ligand in the group of medium-strong ligands such as Cl$^-$ (74.3 Hz), OH$^-$ (73.7 Hz), and pyridine (72.1 Hz),[7] far higher than H$_2$O (89.3 Hz). In terms of bond strength this means that cytosine might be replaced by Cl$^-$ or OH$^-$ in solution but the complex is stable toward hydrolysis, which confirms our corresponding experiments. Also, in contrast to the hitherto reported NMR data for cytosine complexes, our measurements in acetone solution allow the observation of the HN(1) proton at 10.67 ppm and markedly separated signals for the HN(4) protons at 8.14 and 7.34 ppm. Either the proximity of the platinum atom or hindered rotation around the C−N(4) bond due to some double-bond character[11] is the reason for the strong dissimilarity of these two protons.

At low temperatures the doublet signal for the HC(6) proton in dilute solutions evolves to a multiplet due to the coupling to HN(1) (Figure 1, middle traces), while the HN(1) signal sharpens to a doublet. Also, the HN(4) proton resonances become reasonably sharpened to singlets. The coupling between the two protons can thus be estimated to be smaller than 3 Hz. Even under these conditions a signal for the HO(2) proton could not be observed, which supports our assignment to the tautomer I (not III or IV).

Furthermore, at low temperatures we observed a splitting of the resonances for the olefinic protons into four distinct signals (Figure 1, right traces). This means that the coordination plane as defined by the platinum atom, N$_{cytosine}$, C$_{methyl}$, and the centers of the C═C bonds is no longer a mirror plane. This is very probably due to the now frozen toggling motion of the CH$_2$-CH$_2$ backbone of the COD ligand. A comparable behavior has been observed for solid-state NMR spectra of [(COD)PtMeCl][17] and can be seen in the molecular structures of crystalline samples.[7]

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Table 1. Selected NMR Data for the Two Isomeric Complexes [(COD)PtMe(cytosine)]$^{+}$ [a]

	$\delta(^1H)$, ppm (J_{Pt}, in Hz)									
species	H_3C	HC^{cis}═	HC^{trans}═	HC(6)	HC(5)	HN(4) (a)	HN(4) (b)	HN(1)	HN(3)	$\delta(^{195}Pt)$, ppm
A	0.78 (69)	5.59 (31)	5.03 (74)	7.81 (<3)	6.19 (18.5)	8.14	7.37	10.67		−3593
B	0.73 (71)	5.52 (31)	4.88 (66.5)	7.73 (49)	6.06 (<6)	7.83[b]	6.96[b]		10.8[b]	−3553
cytosine				7.43	5.52	*c*	*c*	*c*		

[a] Measured in acetone-d_6. [b] Detected only at −70 °C. [c] Not detected due to poor solubility combined with signal broadening.

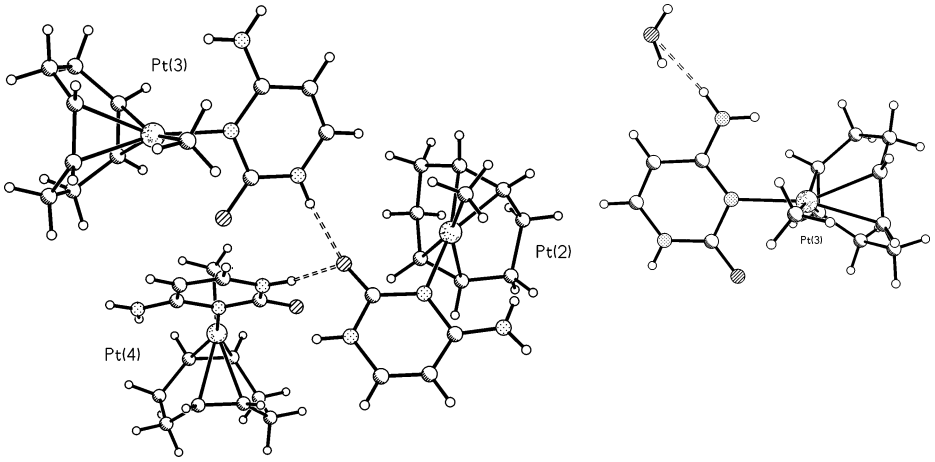

Figure 2. Section of the crystal structure of [(COD)PtMe(cytosine)](SbF_6)·0.25H_2O showing H-bridging interactions.

For the second species (B in Table 1) measured at 25 °C, resonances for HN or HO protons are missing. At low temperatures relatively sharp signals for the HN(4) protons were found at 7.83 and 6.96 ppm, together with a broad resonance at 10.8 ppm. The HN(4) proton signals were shifted markedly to lower frequency from those of the *N3* isomer (full data are given in the Supporting Information). The broad signal at 10.8 ppm is due either to the HN(3) proton, expected for the tautomer I, or to HO(2) for the forms III and IV. However the ^{13}C shift for the C(2) atom is almost the same as in the *N3* isomer; therefore, tautomers III and IV can be ruled out. Also, the anionic form of the cytosine ligand (N(1) *and* N(3) deprotonated) is very unlikely, since a change in the overall charge of the complex would lead to marked effects in coupling constants and chemical shifts for nuclei close to the platinum atom. Therefore, the 10.8 ppm signal in the ^1H spectrum is assigned to the HN(3) proton. Furthermore, $^2J(HC_{trans}-Pt)$ coupling indicative of the ligand strength shows a value of 66.5 Hz, which is fully in line with the higher basicity of the N(1) nitrogen atom ($pK_a = 12.15$) compared to N(3) ($pK_a = 4.58$).[13,18] This coupling constant lies higher than those found for ligands such as H_2O (89.2 Hz) and Cl^- (74.3 Hz), which implies a strong bonding to N(1).

Thus, the B isomer can be unequivocally assigned to the *N1*-bound isomer corresponding to tautomer II. The found *N1* to *N3* ratio of 1:5 exceeds by far the natural ratio of 1:1000 and is close to the corresponding relations found in the platinum complexes [$(CH_3NH_2)_2$Pt(cytosine)$_2$] (1:20 ratio)[11,12] and [(dien)-Pt(cytosine)] (dien = diethylenetriamine; 1:10 ratio).[13] The higher steric hindrance at the N(3) position might be the main reason for the observed promotion of the *N1* isomer.[13] Furthermore from $^1H,^1H$ NOESY and $^1H,^1H$ TOCSY spectra we can say that there is a dynamic equilibrium of the two species in solution. The way the exchange occurs will be subject of further studies.

Crystal and Molecular Structure. From the title compound a suitable crystal was obtained by slow evaporation of the solution of the complex in acetone. [(COD)PtMe(*N3*-cytosine)]-(SbF_6)·0.5H_2O was found to crystallize in the triclinic space group $P\bar{1}$; crystallographic data are summarized in Table 2. Four independent molecules were present in the unit cell, along with two water molecules. The crystal structure reveals numerous intermolecular contacts; some of them are depicted in Figure 2. The shortest intermolecular distances were found between the cytosine ligands of neighboring complexes, e.g., N(2)−H···O(1) (d(H···O)/N−H−O: 1.9158(13) Å/147.42(14)°; 1.9588-(12) Å/160.61(14)°; 1.9805(12) Å/172.60(14)°; 2.0030(12) Å/158.84(14)°) and N(3)−H···O(1) (1.9185(13) Å/177.83(15)°) and between the cocrystallized water molecule and cytosine N(3)−H (2.0754(12) Å/170.607(14)°). These H bridges can be considered to be of medium strength with mainly electrostatic character.[19] An impact on the crystal structure and molecular structure is very likely in such cases (see below).

The molecular structure of [(COD)PtMe(cytosine)]$^+$ (Figure 3) reveals that the cytosine ligand binds via the N(3) atom. This was expected from other platinum cytosine complexes.[10,11,14,15] *N1* coordination has been observed in crystal structures, when the HN(3) protonation (tautomer II) is favored by strong H bonding to other nucleobases[12] or if the *N1* position is deprotonated and cytosine bridges two platinum centers.[11] The cytosine ligand is oriented almost perpendicular to the platinum binding plane, although the tilt angles of the four molecules vary from 91.8 to 98.8°, which is due to the H-bridging interactions described above. The metal to ligand distances are in the range of what has been observed for related [(COD)-PtMe(L)] complexes[7] and platinum(II) cytosine complexes.[11−15]

Conclusions

In the novel complex cation [(COD)PtMe(cytosine)]$^+$ the organoplatinum fragment [(COD)PtMe] binds to the ambivalent ligand cytosine, forming the *N3* and *N1* stereoisomers in a ratio

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Table 2. Crystallographic and Structure Refinement Data and Selected Bond Distances (Å) and Bond Angles (deg) of [(COD)PtMe(cytosine)](SbF$_6$)·0.25H$_2$O

Crystallographic Data	
empirical formula	$C_{13}H_{20.5}N_3O_{1.25}PtSbF_6$
formula wt	669.66
cryst syst/space group	triclinic/$P\bar{1}$
unit cell dimensions	
a	12.697(3) Å
b	12.709(3) Å
c	25.614(5) Å
α	66.42(3)°
β	88.08(3)°
γ	86.84(3)°
V/*Z*	3782.1(13) Å^3/8
calcd density	2.352 g cm^{-3}
abs coeff/*F*(000)	8.882 mm^{-1}/2500
limiting indices	$-13 < h < 13$, $-14 < k < 16$, $0 < l < 32$
no of rflns coll/indep	13 281/13 281
no. of data/restraints/params	13 281/3/916
goodness of fit on F^2	1.427 ($R_{int} = 0.0960$)
final *R* indices ($I > 2\sigma(I)$)	R1 = 0.0766, wR2 = 0.1368
R indices (all data)	R1 = 0.1282, wR2 = 0.1513
largest diff peak and hole	5.276 and −5.285 e·Å^{-3}

Distances[a]

Pt−N(3)	2.091(13)	Pt−C(12)	2.309(17)
Pt−C(1)	2.052(17)	Pt−C(15)	2.134(17)
Pt−C(11)	2.275(18)	Pt−C(16)	2.156(18)

Angles[a]

C(1)−Pt−N(3)	87.6(6)	C(1)−Pt−X(1)	178.3(6)
N(1)−Pt−X(1)	93.6(7)	N(3)−Pt−X(2)	175.6(7)
X(1)−Pt−X(2)	86.1(7)	∑ around Pt	360.0
X(2)−Pt−C(1)	92.7(6)		

Tilt Angles[a]

X(1)X(2)Pt/NCPt	4.5	X(1)X(2)CNPt/aryl	95.1

[a] Averaged values from four independent molecules. X(1) is the centroid for the C(11)═C(12) coordination site, and X(2) represents the C(15)═C(16) coordination.

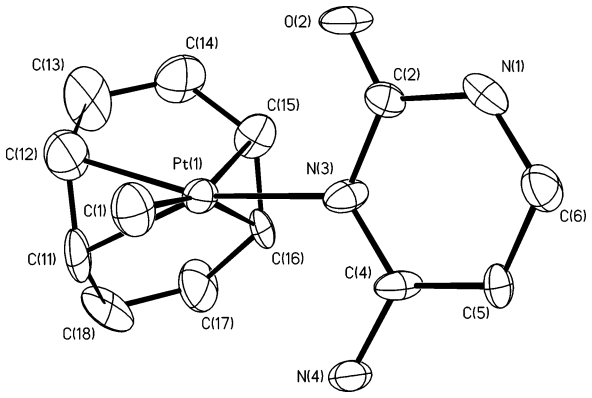

Figure 3. Molecular structure of [(COD)PtMe(cytosine)]$^+$ (molecule 1) with full numbering, in the crystal structure of [(COD)-PtMe(cytosine)](SbF$_6$)·0.25H$_2$O. Thermal ellipsoids are given at the 30% probability level; H atoms, water molecules, and SbF$_6^-$ counterions are omitted for clarity.

of 5:1. The organometallic approach (organometal binding to cytosine) allows a very detailed spectroscopic and structural characterization of the complex, due to the solubility in almost any organic solvent; this reveals, for example, the strength of the *N3* (biologically important) or *N1* binding in comparison to that of other ligands such as H$_2$O, OH$^-$ or Cl$^-$. Other properties such as, for example, the 5:1 preference of the *N3* over the *N1* coordination and essential binding parameters in the structure of [(COD)PtMe(cytosine)](SbF$_6$)·0.5H$_2$O are similar to those of related non-organometallic species, confirming the biological relevance of our results.

Experimental Section

General Procedures. All reagents were of commercial quality, solvents were degassed prior to use, and all reactions and manipulations were carried out under an atmosphere of argon. The precursor complex [(COD)PtMeCl] was prepared according to the procedures by Clark and Manzer.[1] The NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz; ^{195}Pt, 86,01 MHz) using a triple-resonance ^{1}H, ^{19}F, BB inverse probehead. The broadband coil was tuned to either the carbon or the platinum frequency and the detection coil to the proton frequency, resulting in 90° pulses of 11.9 μs for ^{13}C, 12.5 μs for ^{195}Pt, and 12.4 μs for ^{1}H. The unambiguous assignment of the ^{1}H, ^{13}C, and ^{195}Pt resonances was obtained from ^{1}H TOCSY, ^{1}H COSY, gradient-selected ^{1}H,^{13}C HSQC and HMBC, and gradient-selected ^{1}H,^{195}Pt HMBC experiments. Chemical exchange of the isomers was derived from a two-dimensional ^{1}H NOESY spectrum (mixing time 1 s). All 2D NMR experiments were performed using standard pulse sequences from the Bruker pulse program library. Chemical shifts were relative to TMS for ^{1}H and ^{13}C and Na$_2$[PtCl$_6$] in D$_2$O for ^{195}Pt.

All 2D NMR spectra were detected on a sample of the product dissolved in acetone-d_6 at 25 °C. Additionally, proton NMR spectra at varying temperatures between 25 and −70 °C were recorded.

Crystal Structure. The data collection was performed at T = 173(2) K on a Siemens P4 diffractometer with Mo Kα radiation (λ = 0.710 73 Å) employing the $\omega-2\theta$ scan technique. The structure was solved by direct methods using the SHELXTL package, and refinement was carried out with SHELXL97 employing full-matrix least-squares methods on F^2 with $F_o^2 \geq 2\sigma(F_o^2)$ with the results shown in Table 1 (and the Supporting Information). All non-hydrogen atoms were treated anisotropically, and hydrogen atoms were included by using appropriate riding models. CCDC 617240 contains the full crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax, + 44-1223-336-033; e-mail, deposit@ccdc.cam.ac.uk).

[(COD)PtMe(cytosine)](SbF$_6$). To a stirred solution of [(COD)-PtMeCl] (280 mg, 0.791 mmol) in acetone (20 mL) was added AgSbF$_6$ (271 mg, 0.791 mmol). After 30 min the colorless precipitate was filtered off, and to the colorless solution cytosine (89 mg, 0.801 mmol), suspended in acetone (6 mL), was added. After 30 min the solvent was removed and the resulting off-white solid was washed with small portions of water before complete drying in vacuo. Yield of the colorless complex: 97.5% (512 mg, 0.77 mmol). Anal. Found (calcd for PtSbF$_6$ON$_3$C$_{13}$H$_{20}$): C, 23.43 (23.47); H, 3.09 (3.03); N, 6.36 (6.32). ^{1}H NMR (acetone-d_6): *N3* isomer, δ 10.67 (br s, 1H, HN1), 8.14 (br s, 1H, H^{a}N4), 7.81 (s, 1H, HC6), 7.37 (br s, 1H, H^{b}N4), 6.19 (s, 1H, HC5), 5.59 (s, 2H, HC^{cis}═), 5.09 (s, 2 H, HC^{trans}═), 2.75−2.4 (m, 8H, −CH$_2$−), 0.78 (s, 3H, PtCH$_3$); *N1* isomer, δ 7.73 (s, 1H, HC6), 6.06 (s, 1H, HC5), 5.52 (s, 2H, HC^{cis}═), 4.88 (s, 2H, HC^{trans}═), 2.6−2.4 (m, 8H, −CH$_2$−), 0.73 (s, 3H, PtCH$_3$). ^{195}Pt NMR (acetone-d_6): *N3* isomer, δ −3593; *N1* isomer, δ −3553.

Acknowledgment. We gratefully acknowledge Johnson Matthey PLC ("JM") for a loan of K$_2$PtCl$_4$.

Supporting Information Available: CIF files and tables giving full XRD data for [(COD)PtMe(cytosine)]SbF$_6$·0.25H$_2$O, together with two figures representing the molecules in the unit cell and packing in the unit cell, and a table giving complete ^{1}H, ^{13}C, and ^{195}Pt NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

OM060856Y