Effects of Six-Membered-Ring Conformation on the Rotamer Distribution and Rate of Atropisomerization in Platinum(II)−Guanine Compounds: 2,4-Bis(methylamino)pentane Complexes

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NMR and CD spectroscopy and molecular mechanics and dynamics (MMD) calculations were used to characterize $(Me_2DAP)Pt(G)_2$ complexes (G = N9-substituted guanine derivative; Me_2DAP = 2,4-bis(methylamino)pentane with N, C, C, and N stereochemistries of *S,R,S,R*, *S,R,R,R*, and *R,R,R,R*). NMR and MMD results indicated that the favored Me_2DAP chelate ring conformations were chair. There are two possible head-to-tail rotamers (ΔHT and ΛHT) and, depending on the Me_2DAP stereochemistry, one or two head-to-head (HH) rotamers. Rotation of the G bases around the Pt−N7 bond was found to be rapid on the NMR time scale for all compounds in D_2O at room temperature; in contrast, slow rotation was reported for $(Me_2DAB)Pt(G)_2$ (Me_2DAB = 2,3-bis-(methylamino)butane by Xu et al.) Because of the additional flexibility of the six-membered chelate ring in the Me_2DAP systems versus the five-membered ring in Me_2DAB, the *N*-methyl groups of Me_2DAP can occupy more pronounced axial positions, allowing a low-energy path to rotation as suggested by MMD calculations. The fast rotation necessitated that the rotamer preference be assessed by CD spectroscopy. For the *S,R,S,R* complexes, the G N9 substituent strongly influenced which HT rotamer was preferred. The ΛHT rotamer was favored for the *R,R,R,R* complexes at pH 3 regardless of the G used. MMD calculations on the $[(R,R,R,R)\text{-}(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complex suggested amine-O6 hydrogen bonding in the ΛHT rotamer and indicated an unfavorable nonbonded interaction between the G O6 and an axial cis *C*-methyl group in the ΔHT rotamer. This nonbonded interaction was also observed in calculated structures of the $[(S,R,R,R)\text{-}(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complex, for which experimental data showed a preference for the ΛHT rotamer as well. Thus, the orientations of the *N*- and *C*-methyl groups appear to be important in determining both the rate of rotation and the rotamer preference of the $(Me_2DAP)Pt(G)_2$ systems.

Introduction

Compounds of the general type *cis*-PtX_2A_2, where X_2 represents two unidentate or one bidentate leaving group and A_2 represents two unidentate or one bidentate amine, show anticancer activity against certain types of tumors.[1,2] These platinum compounds preferentially bind to the N7 of purine residues of DNA, with the N7 of guanine more favored over N7 of adenine (Figure 1).[2] The major adduct formed by platinum anticancer compounds is a 1,2-intrastrand cross-link to guanine residues, and this cross-link is thought to be responsible for the anticancer activity. Other adducts that are formed by platinum complexes include interstrand cross-links, 1,3-intrastand cross-links, and DNA−protein cross-links.

In *cis*-$Pt(A)_2(G)_2$ complexes (G = N9-substituted guanine derivative), the G bases can be oriented in a head-to-head (HH) arrangement, in which both H8 atoms lie on the same side of the coordination plane, or in a head-to-tail (HT) arrangement with the H8 atoms on opposite sides of the coordination plane (Figure 2). The two possible HT atropisomers are designated as Δ and Λ. When the complexes are viewed from the nucleotide side of the coordination plane, a line connecting the O6 atoms will be rotated (by an angle <90°) clockwise (ΛHT) or counterclockwise (ΔHT) in order to be aligned with the perpendicular to the coordination plane. Either one or two HH atropisomers are possible, depending on the presence or absence of C_2 symmetry, respectively. The HH orientation is generally found for intrastrand cross-links,[3,4] whereas the HT orientation is often observed for interstrand cross-links.[5−7] When the G bases are not joined by a phosphodiester linkage, HT conformers are favored both in solution[8−10] and in crystal structures.[11,12]

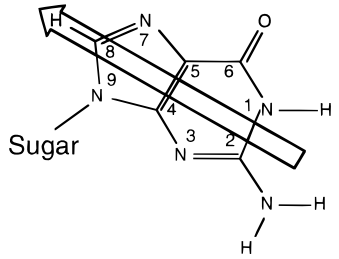

Figure 1. Representation of the guanine base showing the atom-numbering scheme and arrow used in Figure 2.

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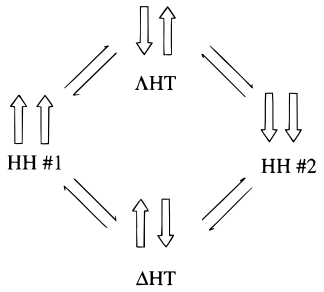

Figure 2. Representations of the HH, ΛHT, and ΔHT atropisomers when viewed from the nucleobase side of the coordination plane. The arrow points in the direction of the guanine H8. In the case in which two HH atropisomers exist, HH #1 is used to designate the one that has the H8 atoms on the same side of the coordination plane as the *N*-Me groups of Me_2DAP. The exception is for *R,R,S,R*/*S,R,S,S*, in which HH #1 designates the HH with the H8 atoms on the same side of the coordination plane as the *C*-Me groups of Me_2DAP.

G bases coordinated to platinum complexes with nonbulky amine groups exhibit rapid rotation around the Pt−N7 bond on the NMR time scale.[13−15] Therefore, only one set of G resonances is seen in the NMR spectra of these complexes. However, for the platinum complex with the bulky diamine group *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, two sets of guanosine resonances were observed due to slow rotation around the Pt−N7 bond.[16] The two sets of resonances were reasoned to be HT atropisomers by assuming that the HH atropisomer would be sterically unfavorable. On the basis of the chemical shift difference of the H1′ resonances, the rotation barrier was determined to be >86 kJ/mol. Slow rotation around the Pt−N7 bond has been observed for a number of other bulky amine platinum complexes.[8−10,13,14]

Studies of C_2-symmetrical $(Me_2DAB)Pt(5'\text{-GMP})_2$ complexes (Me_2DAB = 2,3-bis(methylamino)butane) gave the first evidence of an HH atropisomer in solution, although one HT atropisomer was favored.[9] When the stereochemistry of the chiral centers was changed from *S,R,R,S* to *R,S,S,R*, the other HT atropisomer was favored. The subsequent finding that the N9 substituent did not change which atropisomer was favored indicated that the amine stereochemistry controlled the favored atropisomer.[17]

$(Bip)Pt(G)_2$ complexes (Bip = 2,2′-bipiperidine) were designed to concentrate amine bulk in the Pt coordination plane.[18] Rotation around the Pt−N7 bond was found to be very slow on the NMR time scale, with no magnetization transfer even at 80 °C. Thus, the atropisomer distribution at early stages in the reaction could be determined by NMR spectroscopy. The reaction of $(Bip)Pt(NO_3)_2$ with 5′-GMP was monitored over time by both NMR and CD spectroscopy, and the HH atropisomer was found to be the kinetically favored rotamer. One HT atropisomer becomes favored over time, indicating that it is the thermodynamically favored product. The CD signals of the ((*S,R,R,S*)-Bip)- and ((*R,S,S,R*)-Bip)PtG_2 complexes were found to be similar in shape but opposite in sign. This result strongly suggests that CD spectroscopy can be used to determine which HT rotamer is favored in solutions of other *cis*-PtA_2G_2 complexes, even when rotation around the Pt−N7 bond is rapid on the NMR time scale.

Previously we studied the solution-state conformations for $PtCl_2(Me_2DAP)$ complexes (Me_2DAP = 2,4-bis(methylamino)-pentane) (Figure 3).[19] The six-membered chelate ring can assume several conformations, including two chair and six skew conformations; however, the two most likely skew conformations have the three ring carbons (C^2-C^4) and the metal center coplanar. In these two skew conformations, there is a true helicity of the ring pucker. The pucker is defined as λ and δ. When the complexes are viewed from the diamine side of the coordination plane, a line connecting two atoms of the carbon chain bridging the two nitrogens will be rotated (by an angle <90°) clockwise (λ) or counterclockwise (δ) in order to be aligned with the axis connecting the two nitrogens. For the chair conformations, there is no true helicity; therefore, we designate the ring puckers by choosing one carbon bond of the bridging chain (namely C^2-C^3) to define a pseudo-helicity λ and δ, according to the rules given above. The favored conformations of the Me_2DAP ring were determined by NMR spectroscopy to be fluxional skew for *S,R,S,R*, λ-skew for *R,R,R,R*, and δ-chair for *S,R,R,R*. However, the favored conformation of a chelate ring has been shown previously to be affected by the other groups on the platinum.[20] Therefore, the conformations of $(Me_2DAP)Pt(G)_2$ complexes could differ from those of the corresponding dichloro compound. We have studied the $(Me_2DAP)Pt(G)_2$ complexes using NMR and CD spectroscopy and MMD calculations.

Experimental Section

Materials. Commercial reagent grade chemicals were used without further purification.

$PtCl_2(Me_2DAP)$. The synthesis, separation, and characterization of $PtCl_2(Me_2DAP)$ isomers has been described previously.[19]

Methods. An ~10 mM solution of $PtCl_2(Me_2DAP)$ in D_2O was treated with 2 equiv of G (guanosine 5′-monophosphate (5′-GMP), guanosine 3′-monophosphate (3′-GMP), guanosine (Guo), or 9-ethylguanine (9-EtG)). Deuterated nitric acid was added to adjust the pH (uncorrected) to 3 to prevent hydroxide ion catalyzed isomerization at the nitrogen centers. Platination reactions were monitored by ^1H NMR spectroscopy on a GE QE-300 or a GE GN-500 spectrometer using a presaturation pulse sequence. The residual HDO peak was used as a reference (4.8 ppm).

Variable-temperature studies in the 5−45 °C range were performed on a GE GN-Omega 600 spectrometer using D_2O as solvent. The

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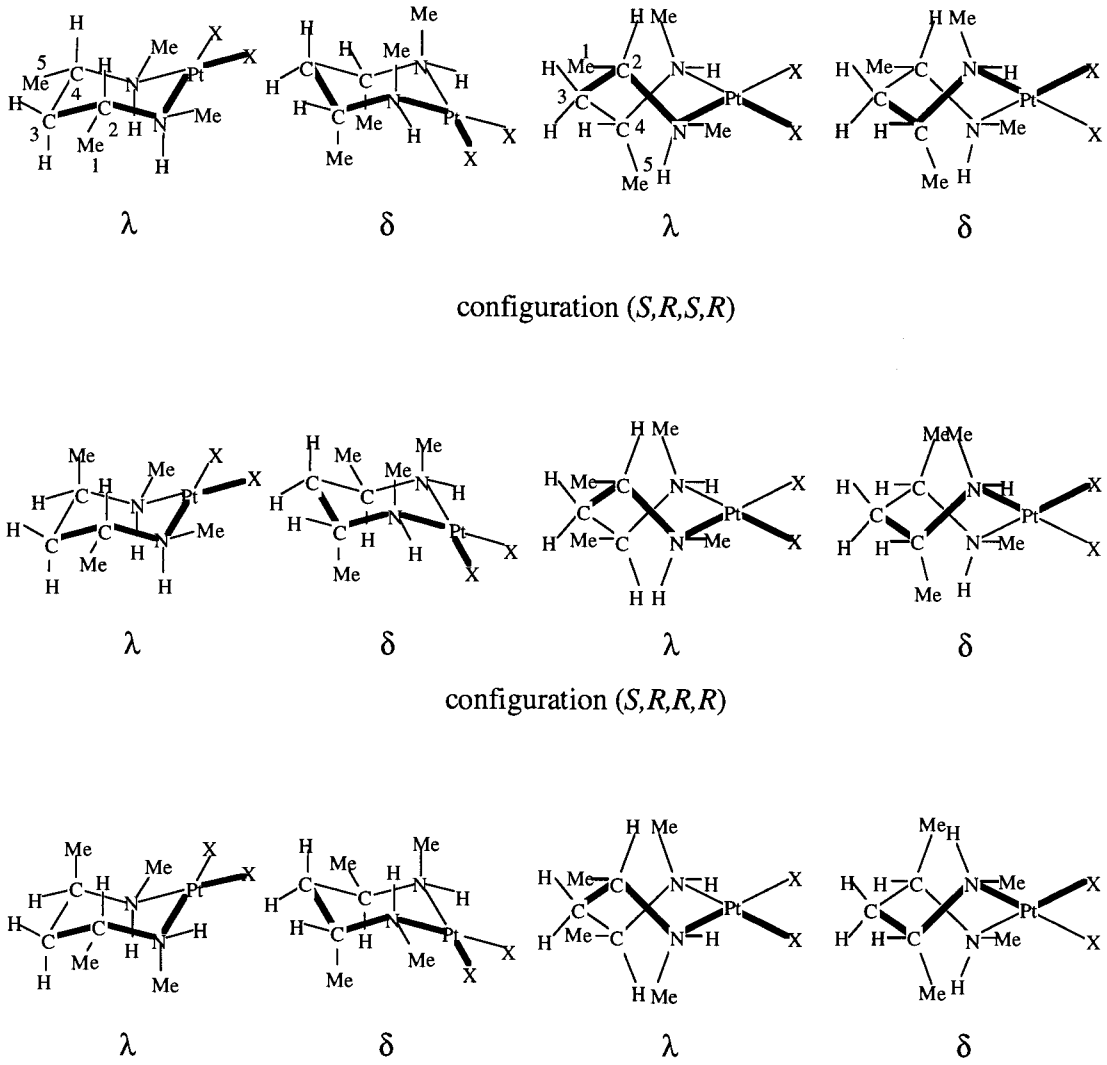

Figure 3. Schematic drawings of possible $PtX_2(Me_2DAP)$ configurations in the chair (left two) and the skew (right two) conformations. The numbering scheme for the six-membered ring is shown for the *λ*-chair and *λ*-skew conformations of the isomer with the *S,R,S,R* configuration.

chemical shift of the residual HDO peak, adjusted for the effect of temperature, was used as a secondary reference relative to TSP.[21] Spectra at −20 °C were taken on samples in a 2:1 D_2O:CD_3OD mixture using TSP as a reference. The spectra were processed using Felix 2.3 from Biosym Inc. on a Silicon Graphics Personal Iris or INDY workstation. To measure the line widths of the peaks accurately, no baseline correction or apodization function was used in the data processing. Line widths were measured using manual optimization within the peakpick module of Felix. The error in line width measurements was assumed to be equal to the digital resolution, which was 0.63 Hz.

$^{31}P\{^1H\}$ NMR spectra were recorded on a GE GN-500 spectrometer in 90% H_2O/10% D_2O with NaCl added to give an ionic strength of 0.1 M. Trimethyl phosphate (TMP) was used as an external reference.

The pK_a of each phosphate group was determined by curve fitting the following equation on a Macintosh computer using KaleidaGraph (Abelbeck Software):

$$\delta = (\delta_A[H^+] + \delta_B K_a)/([H^+] + K_a)$$

where δ is the ^{31}P chemical shift at a given pH, δ_A is the ^{31}P chemical shift of the phosphate group when protonated, δ_B is the ^{31}P chemical shift of the phosphate group when deprotonated, and K_a is the acidity constant.

CD spectra were recorded at 25 °C on a Jasco J-600 CD spectropolarimeter. Samples were diluted to ∼60 μm in H_2O with NaCl added to give an ionic strength of 0.1 M. The pH was adjusted using dilute H_2SO_4 and NaOH.

Molecular mechanics and dynamics (MMD) calculations were performed on a Silicon Graphics INDY workstation using the InsightII package version 95.0 from Biosym, Inc. A modified version of the AMBER force field[22] was used in the minimization calculations. The charges were determined as described previously.[22] The preferred conformation of the Me_2DAP ligand was determined by fixing the nucleobases and using dynamics to simulate heating to 1800 K for 500 ps; 500 structures were generated and subsequently minimized fully. Minimization procedure consisted of a steepest descents minimization for 100 iterations followed by a conjugate gradients minimization for 5000 iterations or until the Δ(rms) gradient was < 0.001 kcal/(mol Å). To determine the relative energies of the Δ and Λ atropisomers, MMD calculations were used to simulate heating the molecule to 300 K in steps of 20 K (at a simulated temperature of 300 K the Me_2DAP ligand does not interchange between conformations on the picosecond time scale); 500 structures were generated and minimized as above for each atropisomer.

The theoretical relative populations of the $[((R,S)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ and $[((R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ species were calculated

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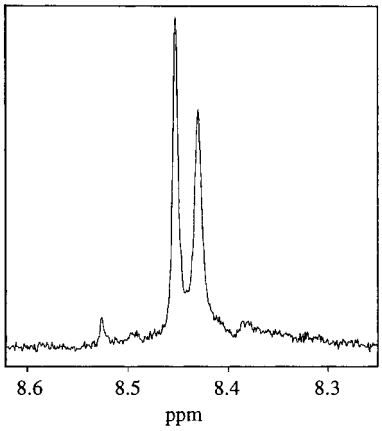

Figure 4. H8 region of the final ^{1}H NMR spectrum of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ at pH 3.3 and room temperature. The small peak at 8.52 ppm is due to a mono product.

by assuming a Boltzmann distribution of states at 298 K. Only calculated structures that were within 1.0 kcal/mol of the minimum energy structure for the configuration were included in the calculations.

Energy barriers to rotation about the Pt−N7 bond were calculated for $[(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes. A C5−N7−Pt−*cis*-N torsion angle was rotated in increments of 1°, and each rotation was followed by an energy minimization subroutine. A force constant of 20 000 kcal/rad^2 was used to maintain the desired C5−N7−Pt−*cis*-N torsion angle during minimization.

Results

Formation of $(Me_2DAP)Pt(G)_2$ Complexes. The reactions of $PtCl_2(Me_2DAP)$ complexes with G derivatives in D_2O were monitored by ^{1}H NMR spectroscopy. After ∼30 min, new resonances corresponding to $(Me_2DAP)PtX(G)$ (X = Cl, H_2O) and $(Me_2DAP)Pt(G)_2$ were observed. The reactions were typically completed in ∼2−3 days, with $(Me_2DAP)Pt(G)_2$ as the final product. For $PtCl_2$((*S*,*R*,*R*,*R*)-Me_2DAP), a complex with an unsymmetrical diamine, addition of 9-EtG to one coordination site was favored over addition to the other site.

^{1}H NMR Results. *S*,*R*,*S*,*R* Complexes. The ^{1}H NMR spectrum of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ at pH 3 had two peaks in the H8 region (Figure 4); up to eight H8 signals would be expected for this complex if restricted rotation around the Pt−N7 bond were observed.[10] At 25 °C and pH 3.2, the downfield peak had a line width of 0.7 Hz, while the upfield peak had a line width of 1.0 Hz. Complexes of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(3′-GMP)$_2$ and ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(Guo)$_2$ also had two H8 signals each. The presence of only two H8 signals in the spectra of these ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(G)$_2$ complexes suggests that the G bases either are locked into one orientation (i.e. no rotation) or are in fast rotation.

The effect of temperature on the H8 signals of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ at pH 3 was studied to assess the rate of G rotation, which should increase with temperature. If the G bases of the 5′-GMPs were locked into one orientation, the H8 signals would broaden. If the 5′-GMPs were actually in fast rotation, the H8 signals would sharpen. As the temperature was increased from 25 to 45 °C, both H8 signals sharpened to a line width of 0.5 Hz, suggesting that the 5′-GMPs are in the fast rotation rate regime on the NMR time scale at room temperature. Consistent with this interpretation, the H8 signals became broader as the temperature was lowered from 25 to 5 °C. The downfield signal broadened from 0.7 to 2.7 Hz, while the upfield signal broadened from 1.0 to 3.7 Hz. The broadening of these signals indicated that the rotation rate was slowing as the temperature was lowered. However, there was no evidence for a new set of H8 resonances, indicating that the rate of rotation was still relatively fast on the NMR time scale.

Only one set of Me_2DAP resonances was observed for the ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ complex from 5 to 45 °C (Supporting Information); thus, either the diamine had one conformation, or it was rapidly interchanging between multiple conformations of similar energy. The boat conformations of the Me_2DAP ligand were sterically unfavorable in $PtCl_2(Me_2$-DAP) complexes;[19] therefore, only the skew and chair conformations can reasonably explain the results. Although the Me_2DAP resonances of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ were broad at room temperature, this region of the spectrum was sharp at 45 °C. The methine signals of the Me_2DAP ligand showed moderately strong coupling to the downfield methylene proton resonance (∼9 Hz) but weak coupling to the upfield resonance (<3 Hz). This type of coupling rules out a predominant δ-chair, which would have weak coupling for both methylene signals. The λ-chair would be expected to have very strong coupling (∼15 Hz) between one methylene signal and the methine signals. Fast interconversion between the two skew conformations, which are unsymmetrical and similar in energy, would be expected to give the observed coupling pattern. It is to be noted, however, that interconversion between two skew conformations requires passing through either a boat transition state or a chair intermediate with two half-chair transition states.[23] Therefore, if fluxional skew conformations are favored, participation of a chair conformation might need to be considered. Another possible explanation for the coupling would be fluxional chair conformations with a contribution by an intermediate skew conformation, but the two chair conformations must be of comparable energy and be more stable than the skew conformations. Experimental data (coupling pattern and line width as a function of temperature) do not help distinguish between the alternatives, but a choice can be made on the basis of the MMD calculations, as will be discussed later.

As the pH was raised, different behavior was observed for the H8 signals of each of the ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(G)$_2$ complexes. The H8 signals of the Guo complex shifted upfield by 0.1 ppm as the pH was raised from 6 to 9 (N1H deprotonation). The H8 signals of the 3′-GMP complex shifted downfield slightly from pH 3 to 7 (phosphate group deprotonation) and then shifted upfield by 0.2 ppm from pH 7 to 9. The H8 signals of the 5′-GMP complex showed no appreciable change in chemical shift from pH 3 to 9. For each complex the increase in line widths of the H8 signals as the pH increased suggested that the rotation rate could be slower at high pH. The line widths throughout the pH range of 3−9 were greatest for the 5′-GMP complex and smallest for the guanosine complex, indicating that the rotation rates for the complexes follow the order 5′-GMP < 3′-GMP < Guo.

***S*,*R*,*R*,*R* Complexes.** Eight H8 signals would be expected for ((*S*,*R*,*R*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ for slow nucleotide rotation, while two H8 signals would be expected for fast rotation. At pH 3, two H8 signals were observed at 8.39 and 8.25 ppm, suggesting that the ((*S*,*R*,*R*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ complex has relatively fast rotation on the NMR time scale. The H8 signals had line widths of 2.0 and 3.0 Hz, respectively. Only one set of Me_2DAP resonances is observed for these complexes as well.

***R*,*R*,*R*,*R* Complexes.** Because the diamine Pt moiety has local C_2 symmetry, only four H8 resonances are possible for ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ if the 5′-GMP rotation around

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the Pt−N7 bond is slow on the NMR time scale. Only one sharp resonance would be observed for fast G rotation.[9,10] Only one broad H8 resonance was seen at pH 3; raising the pH from 3.1 to 7.2 did not affect the line width. At pH 3, the observed H8 signal sharpened from 7.0 to 2.4 Hz as the temperature was raised from 25 to 45 °C, indicating that these complexes are in moderately fast rotation at room temperature.

As the temperature was lowered from 25 to 15 °C, the H8 signal broadened to 11.7 Hz. However, when the temperature was lowered to 5 °C, the line width decreased to 7.7 Hz, and a very broad resonance appeared downfield of the original H8 signal. After addition of deuterated methanol (1:2 $CD_3OD:D_2O$) to the ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ sample, the temperature was lowered to −20 °C. Four H8 signals were observed at this temperature, indicating slow exchange either between rotamers or between conformations of the Me_2DAP ring (Supporting Information).

Even at 45 °C, the Me_2DAP signals were broad; however, $^3J_{C^{2,4}H,\ C^3H}$ (see Figure 3 for labeling scheme) was 5.8 Hz, which is in accord with fluxional chair conformations with a contribution from the most stable skew conformation.[19] The other explanation is fluxional skew conformations with a possible contribution by the chair conformations, but this requires that the skew conformations be of similar energy and be more stable than the chair conformations. Again, experimental data (coupling pattern and line width as a function of temperature) do not help distinguish between the two alternatives, and a choice must be made on the basis of the MMD calculations discussed below. In contrast, the diamine in $PtCl_2$((*R*,*R*,*R*,*R*)-Me_2DAP) was found to be in the λ-skew conformation, which has both *C*-methyl groups equatorial and both *N*-methyl groups axial.[19] In the chloro compounds, severe interligand interactions between equatorial *N*-methyl groups and the cis chloro ligand were observed in the MMD structures; these interactions destabilized all structures with equatorial *N*-methyl groups. Such interligand interactions may be less severe for a cis 5′-GMP than for a cis chloro group.

Isomerization of [(Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ Species. To determine the relative thermodynamic stabilities of the [(Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ species, we raised the pH of the acidic solutions of [((*R*,*R*,*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ and of [((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ to 10.4 and monitored their NMR spectra for several days. Equilibrium was established between the various ((*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$ or ((*R*,*S*)-Me_2DAP)Pt(9-EtG)$_2$ species (Figure 5) within 24 h (results equivalent to those for the *R*,*R* species would be obtained for the *S*,*S* species because of the lack of chirality in 9-EtG). The H8 region of the spectrum of the equilibrated ((*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$ solution at pH 10.4 showed four peaks, two of which are of equal intensity and must therefore correspond to the unsymmetrical ((*S*,*R*,*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$. This assignment was confirmed by comparison to the spectrum of ((*S*,*R*,*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$ at a similar pH. One of the remaining two peaks could be identified easily as the starting material, ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$. Thus, all three species could be assigned; the relative ratios determined by integration were 4:2:1 for *S*,*R*,*R*,*R*:*R*,*R*,*R*,*R*:*S*,*R*,*R*,*S*. The H8 region of equilibrated ((*R*,*S*)-Me_2DAP)Pt(9-EtG)$_2$] at pH 10.4 also showed four peaks, one of which was the starting material, ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(9-EtG)$_2$. Two of the remaining peaks were of equal intensity and were assigned to the unsymmetrical species (*S*,*R*,*S*,*S* and *R*,*R*,*S*,*R* are considered to be one species since they are enantiomeric for a G derivative lacking asymmetric centers such as 9-EtG). The final peak must therefore correspond to ((*R*,*R*,*S*,*S*)-Me_2DAP)Pt(9-EtG)$_2$. The relative ratios were 2.4:1.5:1 for *S*,*R*,*S*,*S*/*R*,*R*,*S*,*R*:*S*,*R*,*S*,*R*:*R*,*R*,*S*,*S*.

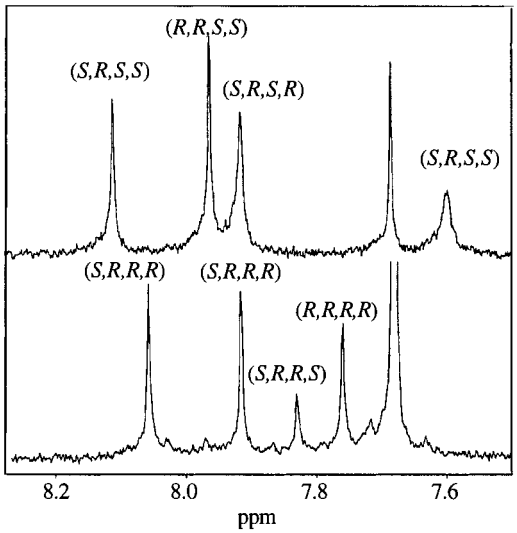

Figure 5. ^{1}H NMR spectra of equilibrated isomers of ((*R*,*S*)-Me_2DAP)-Pt(9-EtG)$_2$ (top) and of ((*R*,*R*)-Me_2DAP)Pt(9-EtG)$_2$ (bottom) at pH 10.4 after 2−3 days. The unlabeled peak in each spectrum is due to an excess of 9-EtG.

^{31}P NMR Results. At pH 3.7 ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ had two ^{31}P NMR signals, at −2.58 and −2.62 ppm; as the pH was raised to 7.8, the signals shifted downfield to 0.74 ppm and broadened into one signal. The ^{31}P NMR spectrum of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(3′-GMP)$_2$ at pH 3.1 showed two signals at −3.21 and −3.22 ppm, which shifted downfield and broadened into one signal at 0.31 ppm by pH 7.1.

The presence of two phosphate group signals allowed us to determine the pK_a values separately in 90% H_2O/10% D_2O. In both of these complexes the phosphate groups deprotonate with equal probability (i.e. have the same pK_a). Because of the lack of symmetry in these complexes, the two phosphate groups are in nonequivalent environments. Thus, concomitant deprotonation is contrary to what is expected if only one of the phosphate groups accepted a hydrogen bond from an amine hydrogen.

The pK_a value of 6.01 for the phosphate groups of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ is similar to the value of 5.94 we determined for *cis*-Pt(NH_3)$_2$(5′-GMP)$_2$. The pK_a value of unplatinated 5′-GMP was determined to be 6.23 in a separate experiment. The pK_a of 5.55 for ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(3′-GMP)$_2$ is similar to the value of 5.52 that we found for *cis*-Pt(NH_3)$_2$(3′-GMP)$_2$. The pK_a of unplatinated 3′-GMP was determined to be 5.88. Thus, platination of 5′-GMP caused the pK_a of the phosphate group to decrease by 0.22 unit, while platination of 3′-GMP caused a decrease of 0.36 unit. Because 3′-GMP cannot form a hydrogen bond to an amine hydrogen, the decrease in pK_a in the 3′-GMP complex cannot be due to amine−phosphate hydrogen bonding. The decrease must be due either to the influence of the positively charged platinum center or to hydrogen bonding between the phosphate group of one 3′-GMP and the N1H or exocyclic NH_2 group of the other 3′-GMP.

CD Results. *S*,*R*,*S*,*R* Complexes. The CD spectra of ((*S*,*R*,*S*,*R*)-Me_2DAP)Pt(5′-GMP)$_2$ in the pH range of 3.5−7.3 have positive ∼285 and 225 nm and negative ∼250 and 205 nm features (Figure 6). These spectra are similar to those of *cis*-Pt(NH_3)$_2$(5′-GMP)$_2$ in this pH range,[24] although the Me_2-DAP complex gave signals of slightly greater intensity. Spectra

(24) Williams, K. M.; Marzilli, L. G. Unpublished results, 1998.

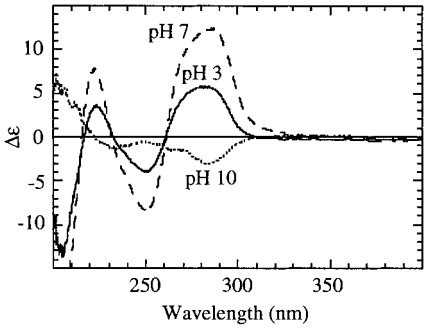

Figure 6. CD spectra of ((*S,R,S,R*)-Me_2DAP)Pt(5′-GMP)$_2$ (60 μM) at pH 3 (solid line), pH 7 (dashed line), and pH 10 (dotted line) collected at room temperature.

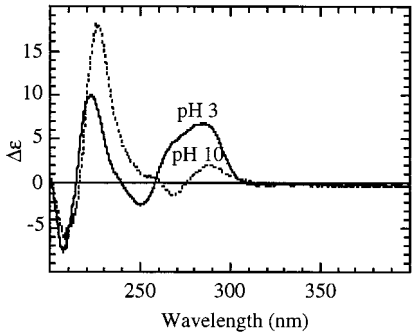

Figure 7. CD spectra of [((*R,R,R,R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ (60 μM) at pH 3 (solid line) and pH 10 (dotted line) collected at room temperature.

similar to these have been found for complexes in which ΛHT is the dominant solution atropisomer as determined by NMR;[17] therefore, this type of signal with positive ∼285 and 225 nm and negative ∼250 and 205 nm features has been designated as Λ. The sign of the signal of ((*S,R,S,R*)-Me_2DAP)Pt(5′-GMP)$_2$ inverted as the pH was raised from 7.3 to 11.5, with the inversion occurring at pH ∼9.5 (Supporting Information). The high-pH spectra were collected immediately after raising the pH to minimize the degree of isomerization of the nitrogen centers of the Me_2DAP ligand. The changes observed at high pH were not due to isomerization, as the original spectrum was obtained when the pH was lowered to 3.5.

MMD calculations suggested that, in the ΔHT rotamer, the phosphate groups in 5′-GMP complexes are close to the platinum, where an electrostatic attraction is possible. Also, hydrogen bonding between one phosphate group and the cis amine hydrogen is possible in this rotamer. However, this rotamer is not favored in solution, suggesting that these interactions, if present, are weak. In the ΛHT rotamer, the phosphate groups are close enough to the N1H of the other 5′-GMP to form phosphate−N1H hydrogen bonds. At pH 7, the phosphate groups are deprotonated, and this phosphate−N1H hydrogen bonding would be more likely. Therefore, the increase in intensity of the CD signal upon raising the pH from 3 to 7 could be due to an increase in the ΛHT population favored by phosphate−N1H hydrogen bond interactions. Upon N1H deprotonation, phosphate−N1H hydrogen bonding becomes impossible; the loss of such hydrogen bonding could explain the decrease in the CD signal intensity from pH 7 to 10.

The CD spectrum of ((*S,R,S,R*)-Me_2DAP)Pt(3′-GMP)$_2$ had positive features at 255 and 210 nm and negative features at 290 and 225 nm in the pH range 3.0−7.1. This spectrum is similar to but weaker than that of *cis*-Pt(NH_3)$_2$(3′-GMP)$_2$.[24] This type of signal is designated as Δ, since complexes that give a similar signal have been found by NMR to have a dominant ΔHT atropisomer.[17] Inversion of the signals of ((*S,R,S,R*)-Me_2DAP)Pt(3′-GMP)$_2$, which occurred above pH 10, was found to be reversible.

Modeling studies indicated that 3′-GMP complexes have the phosphate groups located away from the platinum and cis amine groups in both HT rotamers. However, the calculations suggested that 3′-GMP complexes can form internucleotide phosphate−N1H hydrogen bonds in the ΔHT atropisomer, explaining the preference of ((*S,R,S,R*)-Me_2DAP)Pt(3′-GMP)$_2$ for the ΔHT rotamer. At pH 10, the N1H will deprotonate and phosphate-N1H hydrogen bonding will be impossible. Therefore, the preference of ((*S,R,S,R*)-Me_2DAP)Pt(3′-GMP)$_2$ for the ΛHT atropisomer at high pH agrees with the phosphate−N1H hydrogen bonding hypothesis.

***R,R,R,R* Complexes.** The CD signal of ((*R,R,R,R*)-Me_2DAP)Pt(5′-GMP)$_2$ was Λ at pH 3.5 with a broad feature from 290 to 270 nm (Supporting Information). As the pH was raised to 6.9, the signal became more intense, and the broad feature was resolved into a peak at 290 nm and a shoulder at 270 nm. At pH 9.8, the signal had decreased in intensity but was still Λ. The shoulder at 270 nm had nearly disappeared by pH 9.8.

The CD signal of ((*R,R,R,R*)-Me_2DAP)Pt(3′-GMP)$_2$ was also Λ at pH 3.5 with a broad peak centered at 280 nm. Since 3′-GMP complexes with nonstereocontrolling ligands are Δ, this result indicates that the Me_2DAP ligand controls the atropisomer distribution at pH 3.5. As the pH was raised to 6.8, the peak shifted to 295 nm and sharpened; also, the CD signal inverted to Δ. The preference of ((*R,R,R,R*)-Me_2DAP)Pt(3′-GMP)$_2$ for the ΔHT atropisomer at pH 7 is possibly due to internucleotide phosphate−N1H hydrogen bonding. When the pH was raised to 9.9, the signal reverted to Λ, although at this pH the peaks were shifted slightly relative to those at pH 3.5 (Supporting Information).

The [((*R,R,R,R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ complex had a Λ CD signal at pH 3.5 (Figure 7). The preference for Λ, even when no phosphate group is present, indicates that amine−phosphate and phosphate−N1H hydrogen bonding are not the exclusive factors that determine the atropisomer distribution. As the pH was raised to 10, the spectrum showed a dramatic decrease in intensity in the peak at 290 nm, along with a large increase in intensity in the peak at 225 nm. These changes could be due to amine−O6 hydrogen bonding at high pH, as the O6 will become a better hydrogen bond acceptor upon N1H deprotonation.

***S,R,R,R* Complexes.** The [((*S,R,R,R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ complex had a Λ CD signal at pH 5.8 with a broad positive feature from 270 to 290 nm (Supporting Information). This positive feature sharpened and the negative feature at 250 nm disappeared when the pH was raised to 9.2. Thus, these changes may be the result of amine−O6 hydrogen bonding.

Molecular Mechanics Calculations. *S,R,S,R* Complexes. MMD calculations on [((*S,R,S,R*)-Me_2DAP)Pt(9-EtG)$_2$]$^{2+}$ indicated that the chair conformations of the Me_2DAP ligand were the most energetically favorable structures (Table 1). The δ-chair conformation was more stable by ∼0.5 and ∼3 kcal/mol than the λ-chair and either skew conformation, respectively, when the 9-EtGs are in the HT orientations. The NMR results on ((*S,R,S,R*)-Me_2DAP)Pt(5′-GMP)$_2$ suggested that fluxional skew or fluxional chair conformations of Me_2DAP are favored in solution. The NMR results obtained for $PtCl_2$((*S,R,S,R*)-Me_2DAP) suggested that fluxional skew conformations are favored.[19] Regardless of the Me_2DAP conformation, the HT atropisomers were calculated to be ∼0.5 kcal/mol more stable than either HH atropisomer.

Table 1. Calculated Low-Energy Conformations of $[(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ Complexes

confign	rotamer	conformn	energy (kcal/mol)
S,R,S,R	HT[a]	δ-chair	−1.44
	HT[a]	λ-chair	−0.99
	HH #1[b]	skew[c]	−1.04
	HH #2[b]	λ-chair	−0.12
R,R,S,S	HT[a]	λ-chair	−4.99
	HH #1[b]	λ-chair	−4.44
	HH #2[b]	λ-chair	−3.11
R,R,S,R	Δ	λ-chair	−3.80
	Λ	λ-chair	−3.72
	HH #1[b]	λ-chair	−2.91
	HH #2[b]	λ-chair	−2.13
S,R,R,R	Δ	δ-chair	−3.72
	Λ	δ-chair	−3.91
	HH #1[b]	δ-chair	−3.34
	HH #2[b]	δ-chair	−1.94
R,R,R,R	Δ	λ-skew	−3.59
	Δ	δ-/λ-chair	−3.06
	Λ	λ-skew	−3.97
	Λ	δ-/λ-chair	−3.65
	HH	λ-skew	−3.76
	HH	δ-/λ-chair	−2.44
S,R,R,S	Δ	δ-/λ-chair	−2.65
	Λ	δ-/λ-chair	−2.64
	HH	δ-/λ-chair	−1.86

[a] ΔHT and ΛHT are enantiomeric in these complexes and hence give identical energies. [b] In the case in which two HH atropisomers exist, HH #1 is used to designate the one that has the H8 atoms on the same side of the coordination plane as the *N*-Me groups of Me_2DAP. The exception is for *R,R,S,R*/*S,R,S,S*, in which HH #1 designates the HH with the H8 atoms on the same side of the coordination plane as the *C*-Me groups of Me_2DAP. [c] This is a skew conformation that did not have the Pt coplanar with the three ring carbons and therefore is not designated δ or λ.

The calculated energy barrier for rotation of the 9-EtG around the Pt−N7 bond was found to be affected by the conformation of the Me_2DAP ligand. When the Me_2DAP ring is in the λ-chair conformation with the *N*-methyl groups equatorial, there is a minimum rotation barrier of 21.9 kcal/mol between the ΔHT and the HH #1 rotamer, where HH #1 designates the head-to-head rotamer with the H8 atoms on the same side of the Pt coordination plane as the *N*-Me groups (Figure 2). The barrier for rotation from ΔHT to HH #2 was 24.2 kcal/mol. In contrast, these barriers dropped to 12.8 and 12.5 kcal/mol, respectively, when the Me_2DAP ring was in the δ-chair conformation with the *N*-methyl groups in the axial positions. The energy barrier for interconversion of the two chair conformations was computed to be 10.3 kcal/mol.

The rotation barrier for $[cis\text{-}Pt(NH_3)_2(9\text{-}EtG)_2]^{2+}$ conformers, which are in fast rotation on the NMR time scale, has previously been calculated to be ~10 kcal/mol.[22] C_2-symmetrical complexes of $[(Me_2DAB)Pt(9\text{-}EtG)_2]^{2+}$, which are in slow rotation on the NMR time scale, were experimentally determined to have minimum rotation barriers of 15.7 and 20.4 kcal/mol for minor HT to HH and major HT to HH, respectively.[25] Our calculations, which place the rotation barrier of $[((S,R,S,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ with an axial *N*-methyl group between that of $[cis\text{-}Pt(NH_3)_2(9\text{-}EtG)_2]^{2+}$ and $[(Me_2DAB)Pt(9\text{-}EtG)_2]^{2+}$, agree with our experimental observation of fast rotation.

***R,R,R,R* Complexes.** $PtCl_2((R,R,R,R)\text{-}Me_2DAP)$ was found by NMR spectroscopy and MMD calculations to favor the λ-skew conformation, which has axial *N*-methyl groups and equatorial *C*-methyl groups.[19] Calculations on $[((R,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes suggested that the three primary conformations are the two equivalent chair conformations and the λ-skew conformation. The λ-skew conformation was calculated to be 0.3−1.3 kcal/mol more stable than the chair conformations, depending on the 9-EtG orientations. However, these calculations do not take into account the ~0.4 kcal/mol of favorable entropic contribution due to the degeneracy of the chair conformations. Therefore, the λ-skew and chair conformations would be expected to have similar populations on the basis of the calculations, while the δ-skew conformation is ~7.5 kcal/mol higher in energy.

The energy barriers for the exchanges between chair conformations or between the λ-skew conformation and a chair conformation, both calculated to be 11.0 kcal/mol, suggest that the conformations should exchange rapidly at room temperature and therefore maintain a time-averaged C_2 symmetry. For the chair conformations, the barrier for rotation from the ΛHT to the HH conformation is 22.1 kcal/mol when the cis *N*-methyl group is in the equatorial position and 12.9 kcal/mol when the cis *N*-methyl group is in the axial position; similarly, the barrier for rotation from the ΔHT to the HH conformation is 21.7 kcal/mol when the cis *N*-methyl group is in the equatorial position and 12.2 kcal/mol when the cis *N*-methyl group is in the axial position. For the λ-skew conformation, the rotation barriers are 12.6 and 13.6 kcal/mol for ΛHT to HH and ΔHT to HH, respectively.

The ΛHT atropisomer was calculated to be more stable than ΔHT for $[((R,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ regardless of whether the Me_2DAP ligand was in the λ-skew or chair conformations, in agreement with our experimental CD results. In the λ-skew conformation, the ΛHT atropisomer was calculated to have two amine−O6 hydrogen bonds, whereas no amine−O6 hydrogen bonds were observed when the Me_2DAP ligand was in a chair conformation (Figure 8). In the ΔHT rotamer, the $O6-C^{1,5}$ nonbonded distance was 3.36 Å in the chair conformations and 3.81 Å in the λ-skew conformation, suggesting that nonbonding interactions could be raising the energy of this rotamer. The HH atropisomer, which had one amine−O6 hydrogen bond when the Me_2DAP ligand was in the λ-skew conformation, was calculated to have an energy between the two HT atropisomers. In contrast to the preference of $[((R,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ for ΛHT, $[((R,S,S,R)\text{-}Me_2DAB)Pt(9\text{-}EtG)_2]^{2+}$ was experimentally determined to favor the ΔHT atropisomer.[17]

***S,R,R,R* Complexes.** The $[((S,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complex was calculated to favor the δ-chair conformation for all atropisomers, consistent with the NMR results. The δ-chair conformation was found previously to be favored for $PtCl_2((S,R,R,R)\text{-}Me_2DAP)$ as well.[19] The ΛHT rotamer was calculated to be more stable than the ΔHT rotamer, in accordance with the CD results. The calculations suggested that possible sources of the higher energy of the ΔHT rotamer were nonbonded interactions involving the G O6. The closest nonbonded distance was 3.58 Å for $O6-C^1$, while a second close distance was $O6-C(N^5)$ (3.86 Å).

Calculation of Relative Stabilities. The minimum-energy conformations were determined for all possible $[((R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ and $[((R,S)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ species (Table 1). The calculated energies of the $[((R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ species showed good correlation with the experimentally determined ratio when the entropic factors (e.g., the degeneracy of the *S,R,R,R* configuration) are considered (Supporting Information). The ratios were calculated to be 9:8:1 for *R,R,R,R*:*S,R,R,R*:*S,R,R,S*, whereas experimentally the ratios were determined to be 2:4:1. The difference between the

(25) Natile, G.; Williams, K. M.; Marzilli, L. G. Unpublished results, 1998.

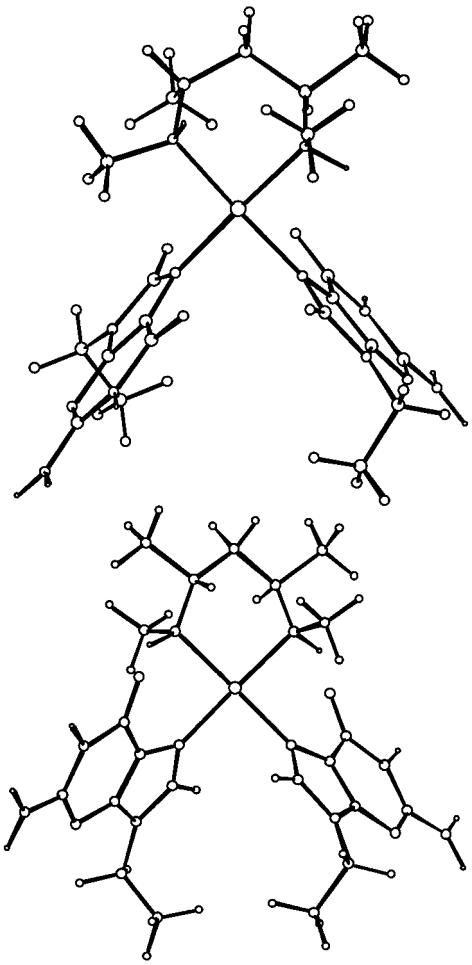

Figure 8. MMD calculated stuctures of the ΛHT atropisomer of $[((R,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes with the chair (top) and λ-skew (bottom) Me_2DAP conformations.

theoretical and calculated ratios corresponds to an error of <1 kcal/mol for each configuration. The $[((R,S)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ species had calculated ratios of 245:57:1 for *R,R,S,S*:*S,R,S,S*/*R,R,S,R*:*S,R,S,R*, whereas the experimentally determined ratios were 1.5:2.4:1. Thus, the calculations seem to be most reliable in identifying unstable forms. It must be realized that the solvent was not part of the calculations.

Discussion

In two previous reports, 1D and 2D NMR spectroscopy revealed that $(Me_2DAB)Pt(G)_2$ complexes[9,10] exhibit rotation around the Pt−N7 bond that is slow on the NMR time scale. For 5′-GMP complexes, in which the five-membered chelate Me_2DAB ligand has C_2-symmetrical configurations, *R,S,S,R* and *S,R,R,S*, the Me_2DAB stereochemistry dictated which HT rotamer was favored.[9] The NMR results in the present study demonstrate that $(Me_2DAP)Pt(G)_2$ complexes have rapid rotation around the Pt−N7 bond on the NMR time scale, regardless of the configuration of the coordinated Me_2DAP ligand. The MMD calculations suggest that the additional flexibility of the six-membered ring results in low-energy structures with axial *N*-methyl groups. The calculations also suggest that rapid rotation about the Pt−N7 bond is possible when the *N*-methyl groups occupy the axial positions.

Two previous studies have been performed on $Pt(A)_2(G)_2$ systems in which A_2 is a bidentate amine that forms a six-membered chelate ring and contains *N*-Me groups.[13,14] The 1D NMR spectrum of unresolved $(Me_2tn)Pt(G)_2$, where Me_2tn is *N,N′*-dimethyl-1,3-propanediamine, showed two unequal sets of resonances.[13] It was suggested that the G bases were in fast rotation and that the *N*-methyl groups were able to adopt an axial position. However, no conformational analysis of the Me_2-tn ligand was included. It was further concluded that the Me_2tn ligand was able to isomerize at pH 5−6 and that the meso:racemic ratio was influenced by the presence of the G bases. The Me_2DAP ligand, which differs from Me_2tn only in the presence of two *C*-methyl groups, showed no evidence of isomerization at pH 6 and only slow isomerization at pH 10 on coordination to platinum. In a more recent study with unsymmetrical bidentate amine ligands, fast rotation about the Pt−N7 bond was found for $(Metn)Pt(5'\text{-}GMP)_2$ and $(Ettn)Pt(5'\text{-}GMP)_2$, where Metn is *N*-methyl-1,3-propanediamine and Ettn is *N*-ethyl-1,3-propanediamine.[14] It was again suggested that the *N*-Me or *N*-Et group could occupy an axial position and thus provide a low-energy path to rotation. Overall, these results are consistent with the observations of fast rotation in our Me_2-DAP systems.

For $(Me_4tn)Pt(G)_2$, where Me_4tn is *N,N,N′,N′*-tetramethyl-1,3-propanediamine, slow rotation around the Pt−N7 bond was observed.[13] Regardless of the six-membered-ring configuration, two of the four *N*-Me groups are in the equatorial positions and can interfere with rotation of the G bases.[13] The observation of slow rotation in the $(Me_4tn)PtG_2$ system is consistent with our calculations showing that equatorial *N*-Me groups result in a high barrier for rotation around the Pt−N7 bond.

Because $(Me_2DAP)Pt(G)_2$ complexes are in fast rotation on the NMR time scale at room temperature, NMR spectroscopy cannot be used to determine the favored atropisomer. Also, the broadening of the Me_2DAP signals that is caused by rotation of the guanine bases complicates a conformational analysis of the Me_2DAP ligand, such as the analysis performed for $PtCl_2(Me_2DAP)$ compounds.[19] To obtain information about the $(Me_2DAP)Pt(G)_2$ compounds, we employed a combination of CD and NMR spectroscopy along with the MMD calculations.

For $[((S,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes, the MMD calculations suggest that the δ-chair conformation is favored in solution. This conformation minimizes interligand interactions between the *N*-methyl groups and the guanine bases and allows rapid rotation around the Pt−N7 bond. The δ-chair conformation was also favored for $PtCl_2((S,R,R,R)\text{-}Me_2DAP)$.[19]

For $((S,R,S,R)\text{-}Me_2DAP)Pt(G)_2$ complexes, the MMD results suggest that the δ-chair conformation is slightly favored over the λ-chair conformation. The NMR results on $((S,R,S,R)\text{-}Me_2$-$DAP)Pt(5'\text{-}GMP)_2$ suggest that δ-chair cannot be the exclusive conformation in solution; however, fluxional chair conformations are possible. Thus, the *N*-methyl groups will spend approximately equal time in the axial and equatorial positions. Rotation around the Pt−N7 bond is expected to be much faster when the cis *N*-methyl group of the Me_2DAP ligand is axial rather than equatorial.

For the $((R,R,R,R)\text{-}Me_2DAP)Pt(G)_2$ compounds, the λ-skew and the chair conformations are calculated to have similar energies. In contrast, the δ-skew conformation is much higher in energy. Therefore, fluxional chair conformations with a contribution from the λ-skew conformation appear to be most appropriate in accounting for the NMR results. For $PtCl_2((R,R,R,R)\text{-}Me_2DAP)$, the λ-skew conformation, which minimized both interligand and intraligand interactions, was found to be the favored conformation.[19] Because the guanine bases are primarily oriented perpendicular to the Pt coordination plane, the calculations suggest that the interligand strain caused

by an equatorial *N*-Me group is less severe in the ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt$(G)_2$ complexes than in the dichloro complex.

For the ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt$(G)_2$ and the $[((S,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes, we found that the Me_2DAP ligand could dictate which rotamer is favored, at least at pH 3. Interestingly, the ΛHT rotamer, which has the amine hydrogen and the O6 of the cis G on the same side of the coordination plane for the ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt$(G)_2$ complexes, was favored in contrast to the typical case. This difference might be due to amine−O6 hydrogen bonding in ((*R*,*R*,*R*,*R*)-Me_2DAP)-Pt$(G)_2$ complexes; these hydrogen bonds were observed in calculated $[((R,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ structures with the Me_2DAP ligand in the λ-skew conformation. However, this type of hydrogen bonding does not explain the preference for ΛHT that was also observed in the $[((S,R,R,R)\text{-}Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes. An alternative explanation suggested by the calculations is that nonbonded interactions between the O6 and an axial cis *C*-Me group would raise the energy of the ΔHT rotamer in these systems and thereby lead to a favored ΛHT rotamer.

Previously reported decreases in pK_a of the phosphate group of purine 5′-nucleotides upon coordination to platinum[26−28] have typically been attributed to hydrogen bonding between the phosphate group and an amine hydrogen, although the potential electrostatic effect of the positively charged platinum has also been noted.[29] However, our studies on the (*S*,*R*,*S*,*R*)-Me_2DAP complexes showed that the phosphate groups had the same pK_a despite the fact that the cis amine hydrogens were of opposite chirality. Furthermore, the pK_a values of the 3′-GMP complexes were lowered more than those of the 5′-GMP complexes, suggesting that amine−phosphate group hydrogen bonding has no significant effect on the pK_a in our systems.

In our report on $PtCl_2(Me_2DAP)$ complexes, we were unable to rank the stability of the different diastereomers because the experimental isomer distribution was under kinetic control.[19] In this study, we were able to equilibrate the isomer distribution by raising the pH to allow base-catalyzed isomerization at the nitrogen centers. Interestingly, for $[(Me_2DAP)Pt(9\text{-}EtG)_2]$ complexes with all of the possible configurations of the Me_2DAP ligand, fast rotation around the Pt−N7 bond was found by NMR methods. Because of the isomer equilibration, we were able to compare the relative experimental stabilities with the calculated stabilities. For the ((*R*,*R*)-Me_2DAP)Pt$(9\text{-}EtG)_2$ systems we found good agreement between experimental and calculated stabilities. For the ((*R*,*S*)-Me_2DAP)Pt$(9\text{-}EtG)_2$ systems we found that the *S*,*R*,*S*,*R* complex was more stable than had been calculated. The primary contribution to the higher energy was the strain of the $C^{1,5}-C^{2,4}-C^3$ angles, suggesting that this force constant might need to be reduced. It should be noted that the calculations were performed on complexes with N1H protonated, whereas the experimental isomerization occurred with N1H deprotonated. We have not yet developed a force field for deprotonated G's, since this is not the physiological state and there are no relevant X-ray structures.

In summary, we found that the $(Me_2DAP)Pt(G)_2$ systems give results consistent with previous reports on Pt complexes of amines with six-membered chelate rings. However, the results differ significantly from the $(Me_2DAB)Pt(G)_2$ systems studied previously.[9,10] The more flexible six-membered chelate ring in the Me_2DAP systems results in low-energy conformations with axial *N*-methyl groups; these conformations allow rapid rotation around the Pt−N7 bonds. Furthermore, steric interactions with axial *C*-methyl groups were found to be important in determining the favored HT rotamer in ((*S*,*R*,*R*,*R*)-Me_2DAP)- and ((*R*,*R*,*R*,*R*)-Me_2DAP)Pt$(G)_2$ complexes.

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Supporting Information Available: Full table of calculated energies of $[(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes, tables of NMR chemical shifts, population distributions for low-energy structures of $[(Me_2DAP)Pt(9\text{-}EtG)_2]^{2+}$ complexes, and wavelengths and intensities for CD spectra of $(Me_2DAP)Pt(G)_2$ complexes, and a figure showing H8 and Me_2DAP regions of the ^{1}H NMR spectrum of ((*R*,*R*,*R*,*R*)-Me_2DAP)-Pt(5′-GMP)$_2$ at −20 °C in 2:1 D_2O:CD_3OD (8 pages). Ordering information is given on any current masthead page.

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