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Exploring the Universality of Unusual Conformations of the 17-Membered Pt(d(G*pG*)) Macrochelate Ring. Dependence of Conformer Formation on a Change in Bidentate Carrier Ligand from an sp^3 to an sp^2 Nitrogen Donor

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Early studies on *cis*-PtA_2(d(G*pG*)) (A_2 = diamine or two amines, G* = N7-platinated G) and *cis*-$Pt(NH_3)_2$(d(G*pG*)) models for the key cisplatin–DNA cross-link suggested that they exist exclusively or mainly as the HH1 conformer (HH1 = head-to-head G* bases, with 1 denoting the normal direction of backbone propagation). These dynamic models are difficult to characterize. Employing carrier A_2 ligands designed to slow dynamic interchange of conformers, we found two new conformers, ΔHT (head-to-tail G* bases with a Δ chirality) and HH2 (with 2 denoting the backbone propagation direction opposite to normal). However, establishing that the non-HH1 conformations exist as an intrinsic feature of the 17-membered Pt(d(G*pG*)) ring requires exploring a range of different carrier ligands. Here we employ the planar aromatic sp^2 N-donor **5,5′-Me$_2$bipy** (5,5′-dimethyl-2,2′-bipyridine) ligand, having a shape very different from those of previously used nonplanar sp^3 N-donor bidentate carrier ligands, which often bear NH groups. The **5,5′-Me$_2$bipy** H6 and H6′ protons project toward the d(G*pG*) moiety and hinder the dynamic motion of **5,5′-Me$_2$bipy**Pt(d(G*pG*)). We again found HH1, HH2, and ΔHT conformers with typical properties, supporting the conclusions that the new ΔHT and HH2 conformers exist universally in dynamic *cis*-PtA_2(d(G*pG*)) adducts, including *cis*-$Pt(NH_3)_2$(d(G*pG*)), and that the carrier ligand typically has little influence on the overall structure of the Pt(d(G*pG*)) macrocyclic ring of a given conformer. The sizes of the G* H8 to H6/H6′ NOE cross-peaks indicate little base canting in all **5,5′-Me$_2$bipy**Pt(d(G*pG*)) conformers, suggesting that carrier-ligand NH groups favor the canting of one G* base in the HH1 and HH2 conformers of typical *cis*-PtA_2(d(G*pG*)) adducts.

Introduction

Platinum compounds are known for their anticancer activity.[1−4] The anticancer activity of cisplatin (*cis*-$Pt(NH_3)_2Cl_2$), an important example of the very heavily used *cis*-PtA_2X_2 drug type (A_2 = two amines or a diamine), is widely attributed to the formation of an adduct involving two adjacent guanines of d(GpG) sequences in DNA, cross-linked to Pt at the N7 atoms.[5−12] The extent of 1,2-G,G intrastrand cross-linking correlates well with treatment outcomes.[13] The leading experimentally supported biological hypothesis explaining the action of cisplatin as an anticancer drug involves specific recognition by proteins of distorted DNA adducts.[1,9,10,14−16] The *cis*-$Pt(NH_3)_2$(d(G*pG*)) (G* = N7-

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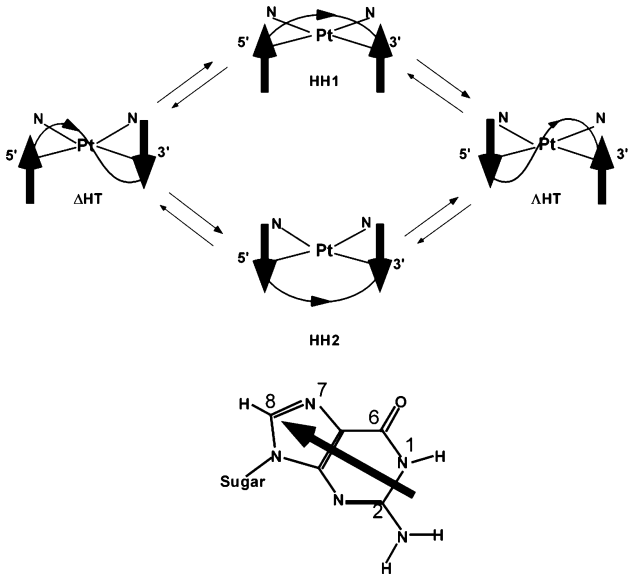

Figure 1. Four possible conformer types for *cis*-PtA_2(d(G*pG*)) adducts. An arrow represents the G base, with the arrowhead representing the G H8 (shown below the scheme). G coordination sites are forward. Carrier ligand (not shown except for N-donor atoms) is to the rear. Base rotation about the Pt−G N7 bond interconverts the HT and HH conformers.

platinated G) N7−Pt−N7 intrastrand cross-link lesion has been generally accepted to adopt primarily a head-to-head (HH) arrangement, with both G*'s maintaining the B-DNA anti conformation;[11,17−22] this HH arrangement is termed HH1 (Figure 1). In addition, we observed two new conformers, HH2 (head-to-head G* bases, and the direction of propagation of the phosphodiester backbone is opposite to that in B-DNA) and ΔHT (head-to-tail G* bases, with Δ chirality and an anti-5′-G* and a syn-3′-G*) (Figure 1).[23−26] Many of these properties were found recently in Rh(II) dimers containing a coordinated d(GpG) moiety.[27,28]

Examination of an X-ray structure of an HMG-bound 16-oligomer[10] and an X-ray/NMR-derived model of a duplex 9-oligomer,[23] both of which contain an intrastrand cisplatin lesion, suggests that hydrogen-bonding interactions involving the NH_3 ligands are weak and may not exist. If the ammonia groups are replaced by A_2 carrier ligands having sp^3 N's bearing two or more alkyl groups, modeling with the 9-mer structure suggests that clashes will occur.[23] These results on duplex models led us to hypothesize that the small size of the NH group, not its hydrogen-bonding ability, facilitates the anticancer activity of Pt compounds bearing multiple NH groups.[7] An intriguing feature of these adducts is the large 17-membered Pt(d(G*pG*)) ring. However, the effects of carrier ligand on the conformation of this large ring are not understood. Relatively few X-ray structures are available,[6,7,10] and NMR characterization is hampered, we believe, by dynamic motion in which the G* bases rotate rapidly around the Pt−N7 bonds.[25,29]

In very simple adducts lacking a sugar phosphate backbone, the bases favor an HT arrangement, whereas the evidence indicates that an HH arrangement is favored in larger adducts with a backbone. The simplest cross-link adduct, *cis*-$Pt(NH_3)_2$(d(G*pG*)), has never been characterized by X-ray crystallography, but the observation of only one set of ^{1}H NMR signals[19,20] has been taken to imply that the presence of the backbone favors the HH base arrangement over the otherwise favored HT base arrangement.[17,24] This observation of only one set of ^{1}H NMR resonances for *cis*-$Pt(NH_3)_2$(d(G*pG*)) adducts can also be attributed to dynamic interchange between multiple conformers. We call these conflicting interpretations the "dynamic motion problem."[24,29]

Retro Models. To overcome the dynamic motion problem, we used the retro-modeling approach by employing carrier ligands designed to have features that would make the spectral properties more informative, would reduce the dynamic motion by about a billion-fold compared to *cis*-Pt-$(NH_3)_2$ adducts, and would also permit the coexistence of multiple conformers.[29−33] One of our most successful carrier ligands, 2,2′-bipiperidine (**Bip**),[5,24,25,29,30,34] has two energetically favored coordinated **Bip** configurations (*S*,*R*,*R*,*S* or *R*,*S*,*S*,*R* configurations at the asymmetric N, C, C, and N chelate ring atoms) (Figure 2). Note that we distinguish bidentate carrier ligands in boldface type. For (*R*,*S*,*S*,*R*)-**Bip**Pt(d(G*pG*)), abundant HH1 and HH2 conformers of comparable stability were found;[24] these are designated as HH1 R and HH2 R to indicate that the canting is right-handed for both HH conformers (Figure 2). For (*S*,*R*,*R*,*S*)-**Bip**Pt-(d(G*pG*)), the HH1 L and ΔHT conformers were abundant (Figure 2).[23]

In subsequent studies on the **Me$_2$ppz**Pt(d(G*pG*)) adduct, we found both new conformers (HH2 and ΔHT), in addition

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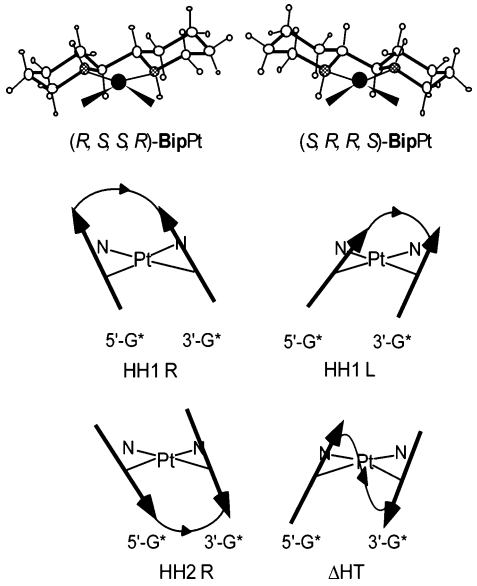
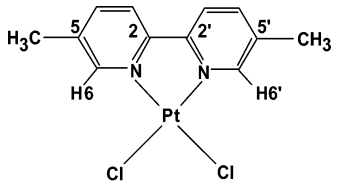


Figure 2. Top: Ball-and-stick representations of **Bip**Pt, showing the stereochemistry for the N, C, C, and N chelate ring atoms. Bottom: Depiction of right (R) and left (L) base canting for the Pt(d(G*pG*)) cross-link previously observed for the HH1, HH2, and ΔHT conformers.



5,5'-Me$_2$bipy PtCl$_2$

Figure 3. Stick representation of **5,5′-Me$_2$bipy**PtCl$_2$, showing the numbering scheme for the **5,5′-Me$_2$bipy**PtCl$_2$ ligand.

to the well-known HH1 conformer; **Me$_2$ppz** (*N*,*N*′-dimethylpiperazine) is a unique N-donor bidentate ligand having its bulk essentially in the coordination plane and having no NH groups.[26] Both **Bip** and **Me$_2$ppz** are sp^3 N donors. The adducts between d(GpG) and a platinum(II) complex bearing an unsymmetric carrier ligand having one sp^2 and one sp^3 hybridized N-donor (2-pyridylmethylamine) have been reported to have limited dynamic motion resulting from the one nearly in-plane pyridine ring.[35] We have now investigated **5,5′-Me$_2$bipy**Pt(d(G*pG*)) (Figure 3), a retro model having an sp^2 N-donor carrier ligand, 5,5′-dimethyl-2,2′-bipyridine (**5,5′-Me$_2$bipy**).

Both **Me$_2$ppz** and **5,5′-Me$_2$bipy** are achiral ligands and have no NH group. Furthermore, **5,5′-Me$_2$bipy** has protons (H6, pointing to the 5′-G* and H6′, pointing to the 3′-G*) that can be used as probes for elucidating conformer structures. Because it is planar, the **5,5′-Me$_2$bipy** ligand should not sterically limit the number of conformers for **5,5′-Me$_2$bipy**Pt(d(G*pG*)). However, the bulk of the **5,5′-Me$_2$bipy** ligand, with two in-plane pyridine rings, is expected to destabilize the transition state for rotation about both Pt-G* N7 bonds and to eliminate the dynamic motion problem. The rate of atropisomerization of the HH and HT conformers was found to be slow for the **5,5′-Me$_2$bipy**Pt**G$_2$** adducts (bold **G** = unlinked guanine derivative such as 5′-GMP) (Supporting Information). Slow atropisomerization for *cis*-PtA$_2$**G**$_2$ adducts is characteristic of retro models.[30,33,34,36−40] The **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct allows us to examine the generality of the coexistence of multiple conformers in Pt-(d(G*pG*)) adducts having the extended 17-membered macrocyclic ring.

Experimental Section

Materials. d(GpG) (Sigma) was used without further purification. **5,5′-Me$_2$bipy** was obtained from Aldrich, and *cis*-PtCl$_2$(DMSO)$_2$ was prepared by a known method.[41]

Synthesis of 5,5′-Me$_2$bipyPtCl$_2$. A solution of **5,5′-Me$_2$bipy** (0.042 g, 0.24 mmol) and *cis*-PtCl$_2$(DMSO)$_2$ (0.101 g, 0.24 mmol) in methanol (150 mL) was heated at reflux for 24 h. The yellow solid obtained after filtration was washed with ether and chloroform and dried in vacuo; yield, 0.088 g (83%). ^{1}H NMR (ppm) in DMSO-d_6: 9.27 (s, H6), 8.42 (d, H4), 8.23 (d, H3), 2.49 (s, CH$_3$). X-ray quality yellow crystals of **5,5′-Me$_2$bipy**PtCl$_2$ were obtained by mixing equimolar amounts of **5,5′-Me$_2$bipy** and *cis*-PtCl$_2$(DMSO)$_2$ in acetonitrile (5 mL). The crystals had the same unit cell parameters as the reported crystal structure.[42] Anal. Calcd for C$_{12}$H$_{12}$Cl$_2$N$_2$Pt: C, 31.98; H, 2.66; N, 6.22. Found: C, 32.08; H, 2.64; N, 6.21.

NMR Spectroscopy. NMR spectra were recorded on Bruker 500 and 400 MHz instruments. A 1−1.5 s presaturation pulse was used in ^{1}H NMR collections in order to reduce the HOD peak, and the residual HOD signal was used to reference the spectra (relative to TMS). ^{1}H-decoupled ^{31}P NMR spectra were referenced to external trimethyl phosphate. All NMR data were processed using the XWINNMR and Mestre-C softwares.

Matrixes (512 × 2048) were collected in correlation spectroscopy (COSY) and 500 ms nuclear Overhauser enhancement spectroscopy (NOESY) experiments, both conducted at 5 °C with a spectral window of ∼6000 Hz, and a presaturation pulse of ∼1 s to reduce the HOD signal. Typically, 32 scans were collected per block. An exponential apodization function with a line broadening of 0.2 Hz and a phase-shifted 90° sine bell function were used to process the NOESY t_2 and t_1 data, respectively.

Preparation of 5,5′-Me$_2$bipyPt(d(G*pG*)). A sample (2 mM) of d(GpG) prepared in D$_2$O (720 μL) was treated with 80 μL of a **5,5′-Me$_2$bipy**PtCl$_2$ solution (20 mM) in DMSO-d_6 to give a 1:1 ratio of Pt/d(GpG), and the solution (pH ≈ 4, uncorrected) was kept at room temperature. The mixed H$_2$O/DMSO-d_6 (90%:10%) solutions were used for better solubility of the **5,5′-Me$_2$bipy**PtCl$_2$ complex and also to avoid intermolecular stacking interactions. Reactions were monitored by using the G H8 NMR signals until all free d(GpG) had been consumed; when necessary, more **5,5′-Me$_2$bipy**PtCl$_2$ solution was added. After the G H8 signals indicated complete reaction, the pH was lowered to ∼1.3. The absence of

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significant chemical shift changes for the G* H8 signals confirmed Pt−G N7 binding.[23,43]

Circular Dichroism (CD) Spectroscopy. Samples in water were ∼0.03 mM in d(G*pG*). Spectra were recorded from 400 to 200 nm at a scan speed of 50 nm/min on a JASCO J-600 CD spectropolarimeter. Three scans were recorded and averaged for each sample.

Molecular Modeling. Molecular modeling and dynamics (MMD) calculations were carried out as described elsewhere.[44]

Results

Outlined here for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct are procedures for assigning signals and determining conformations on the basis of 2D NMR data. Detailed explanations appear in the Supporting Information. For each **5,5′-Me$_2$bipy**Pt(d(G*pG*)) conformer, NOESY and COSY data were used to assess structural features such as sugar puckers (S or N), G* nucleotide conformation (anti or syn), and the relative orientation of the two bases.[23,24,26,29] Intraresidue H8−H3′ NOE cross-peaks are characteristically observed for N-sugars but not for S-sugars. For all conformers of d(G*pG*) adducts, the sugar residue of the 5′-G* typically adopts an N-pucker. G* nucleotide conformations can be assessed by intraresidue H8−sugar signal NOE cross-peaks; strong H8−H2′ and H8−H2″ cross-peaks and weak (or unobservable) H8−H1′ cross-peaks are characteristic of an anti conformation, while stronger H8−H1′ NOEs compared to the H8−H2′ or H8−H2″ NOEs are typically found for syn residues. Because the G* H8 atoms are closer to each other in the HH conformers than in the HT conformers, observation of an H8−H8 cross-peak is characteristic of an HH conformer, whereas the absence of such a cross-peak is indicative of an HT conformer. The *cis*-PtA$_2$(d(G*pG*)) conformers typically give rise to characteristic NMR signal shift changes relative to the signals of free d(GpG). The ^{31}P NMR signal and one or both H8 signals are all ∼1 ppm downfield for HH conformers.[19,20,45−48] The ^{31}P NMR signal is upfield, and the H8 signals are almost unshifted for the ΔHT conformer.[23,25,26,49]

5,5′-Me$_2$bipy lacks any chirality, and therefore, NMR methods (which rely on a knowledge of carrier-ligand absolute configuration) are not useful for determining HT conformer chirality. However, in such cases, the chirality of the HT conformer can be assessed by CD spectroscopy.[26] A negative CD feature at ∼280 nm is characteristic of the ΔHT conformer of *cis*-PtA$_2$**G**$_2$ complexes,[32,33,40,50,51] and also of the **Me$_2$ppz**Pt(d(G*pG*))[26] and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts.[25] HH conformers have very weak CD signals and do not contribute significantly to CD spectra. The CD signal of **5,5′-Me$_2$bipy**Pt(d(G*pG*)) (Supporting Information) clearly shows a negative feature at ∼280 nm, indicating that this adduct has an abundant ΔHT conformer.

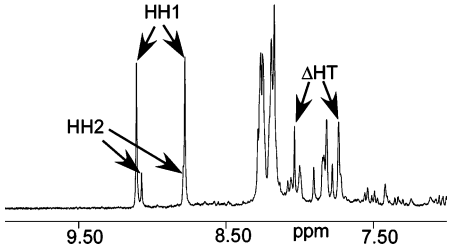

Figure 4. H8 signal region of a 1D ^{1}H NMR spectrum of **5,5′-Me$_2$bipy**Pt(d(G*pG*)).

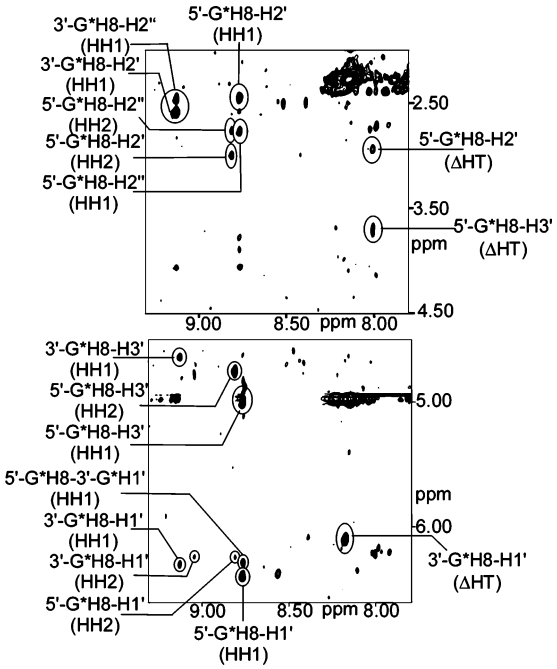

Figure 5. NOESY spectrum of **5,5′-Me$_2$bipy**Pt(d(G*pG*)) (500 ms mixing time) showing cross-peaks between the G* H8 and sugar proton signals of the HH1, HH2, and ΔHT conformers.

^{1}H NMR Spectroscopy. Equimolar amounts of **5,5′-Me$_2$bipy**PtCl$_2$ and d(GpG) were allowed to react in H$_2$O/DMSO-d_6 solution (90%:10%). Within ∼30 min, three new pairs of G* H8 signals were observed for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct. After 5 days, no free d(GpG) signals were observed, and after 15 days, the spectrum remained relatively unchanged (Figure 4).

In a NOESY spectrum, multiple G* H8 to sugar proton cross-peaks were observed for three abundant conformers (Figure 5). Although a very small fourth species (4%, G* H8 signals, ∼8.05 ppm, one G* H8 cross-peak) was not evaluated further, signals were assigned for the abundant HH1, HH2, and ΔHT conformers with a distribution of ∼52%, 10%, and 34%, respectively (Table 1).

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Table 1. ^{1}H and ^{31}P NMR Signal Assignments (ppm) for the **5,5′-Me$_2$Bipy**Pt(d(G*pG*)) Adduct at pH ≈ 4 and 5 °C

conformer	G*	H8	H1′	H2′	H2″	H3′	H4′	H6/H6′	base-sugar	^{31}P
HH1	5′	8.76	6.38	2.45	2.78	5.02	4.12	7.70	anti	−2.64
	3′	9.14	6.29	2.61	2.46	4.64	4.08	7.80	anti	
HH2	5′	8.83	6.28	3.04	2.81	4.78	4.47	7.73	anti	−2.23
	3′	9.07	6.31	2.40	2.84	4.71	4.18	7.43	anti	
ΔHT	5′	8.01	6.23	2.94	2.61	3.73	4.06	7.84	anti	−4.74
	3′	8.18	6.15	3.31	2.53	4.64	4.01	7.83	syn	

For the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH1 conformer, a 5′-G* H8 to 3′-G* H8 cross-peak, a characteristic feature of HH conformers,[23,24] was observed (not shown). The G* H8−H2′ and G* H8−H2″ cross-peaks were stronger than the G* H8−H1′ cross-peaks (Figure 5), indicating a predominantly anti conformation for both 5′-G* and 3′-G* nucleotides. As with the HH1 conformers of other Pt(d(G*pG*)) adducts,[25,26] a strong H8−H3′ cross-peak indicates that the 5′-G* sugar has an N-pucker (Figure 5). The N-pucker for the 5′-G* is universal in such cross-links.[7,23,24,26,47,48] A 3′-G* H8−H3′ cross-peak was observed, but its weakness suggested a mainly S-character for the 3′-G* sugar (Figure 5). NOE cross-peaks to the G* H8 signals allowed us to assign the signals of the **5,5′-Me$_2$bipy** H6 (closer to the 5′-G*) and H6′ (closer to the 3′-G*) protons (Table 1).

For the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH2 conformer, the observation of an H8−H8 cross-peak (not shown) and H8-to-sugar peaks is consistent with the usual HH2 anti,anti conformation. A 5′-G* H8−H3′ cross-peak was observed, indicating an N-pucker for the 5′-G* sugar. No 3′-G* H8−H3′ cross-peak was observed, indicating an S-pucker for the 3′-G* sugar. A weak **5,5′-Me$_2$bipy** H6′−3′-G* H8 cross-peak was observed, but no H6−5′-G* H8 cross-peak was detected.

The third pair of G* H8 signals (8.01, 8.18 ppm) appears upfield to the G* H8 signals of the HH1 and HH2 conformers. This pair showed no H8−H8 NOE cross-peak. These features indicate that the bases of this conformer adopt the HT arrangement.[23−25] The CD signal of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct has a negative feature at ∼280 nm (Supporting Information); therefore, the HT conformer has Δ chirality. For 5′-G*, the H8−H2′ and H8−H2″cross-peaks were stronger than the H8−H1′ cross-peak, indicating an anti 5′-G* conformation, and the H8−H3′ cross-peak (Figure 5) indicates a 5′-G* N-sugar pucker. For 3′-G*, a strong H8−H1′ cross-peak and the absence of H8−H2′/H2″cross-peaks indicate a syn 3′-G* conformation, and the absence of an H8−H3′ cross-peak indicates a 3′-G* S-sugar pucker. These 5′- and 3′-G* nucleotide and sugar conformations are consistent with the findings for the ΔHT conformer of other adducts.[25,26] The energy-minimized model of the ΔHT conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct reveals a 5′-G* anti and 3′-G* syn conformation and 5′-G* N and 3′-G* S sugar puckers (Supporting Information). These results agree with the experimental results and also with previously reported MMD computations.[23,25] Both the 5′-G* H8−H6 and the 3′-G* H8−H6′ cross-peaks were observed (Supporting Information), consistent with the similar 5′-G* H8−H6 and the 3′-G* H8−H6′ distances, 3.65 and 3.72 Å, respectively, of the ΔHT MMD model.

^{31}P NMR Spectroscopy. Compared to the free d(GpG) signal (∼−4.0 ppm), the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ^{31}P NMR signals are downfield for the HH1 and HH2 conformers and upfield for the ΔHT conformer (Table 1). These ^{31}P NMR shift relationships are similar to those observed for other Pt(d(G*pG*)) adducts.[24−26]

Discussion

The **5,5′-Me$_2$bipy** carrier ligand is unique for a Pt(d(G*pG*)) adduct because it is a planar, aromatic sp^2 N donor, in which the significant bulk of the ligand is located essentially in the coordination plane. To understand the effects of this ligand, we compare the properties of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct with the results reported for other adducts. In this section, the conformers of the **Me$_2$ppz**Pt(d(G*pG*)), **Bip**Pt(d(G*pG*)), and **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adducts are compared on the basis of the following points: (i) conformer distribution, (ii) conformational features of the sugar phosphodiester backbone, and (iii) base canting of the conformers.

Distribution of Conformers. For **Me$_2$ppz**Pt(d(G*pG*)),[26] (*R,S,S,R*)-**Bip**Pt(d(G*pG*)),[24] and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts,[23] the HH1 conformer is always more favored than the HH2 or the ΔHT conformer.[23−26,49] The distribution of conformers for **5,5′-Me$_2$bipy**Pt(d(G*pG*)) (52% HH1, 10% HH2, and 34% ΔHT) is similar to that observed for **Me$_2$ppz**Pt(d(G*pG*)) (50% HH1, 20% HH2, and 30% ΔHT). We believe that the similarity in the amounts of the ΔHT conformer observed for these adducts provides evidence for only minimal contact of the (d(G*pG*)) moiety with the **5,5′-Me$_2$bipy** and **Me$_2$ppz** carrier ligands. Because the ammonia protons of *cis*-Pt(NH$_3$)$_2$(d(G*pG*)) are farther from the d(G*pG*) moiety than are the **Me$_2$bipy** H6/6′ protons of **5,5′-Me$_2$bipy**Pt(d(G*pG*)), it is likely that a similar ΔHT conformer exists as part of a dynamic mixture of *cis*-Pt(NH$_3$)$_2$(d(G*pG*)) conformers.

In contrast to our conclusions for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) and **Me$_2$ppz**Pt(d(G*pG*)) adducts, the conformer distributions for the **Bip**Pt(d(G*pG*)) adducts indicate that a nonplanar chiral carrier ligand can indeed influence distribution. No evidence for an HH2 conformer was observed for the (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adduct (65% HH1, 35% ΔHT). For the (*R,S,S,R*)-**Bip**Pt(d(G*pG*)) adduct, in which the ΔHT conformer was at best a very minor form, the abundances of the HH1 and HH2 conformers (∼65% HH1, ∼35% HH2) were high. We attribute these findings to unfavorable interactions with the piperidine rings of the (*S,R,R,S*)-**Bip** ligand in the HH2 conformer and the (*R,S,S,R*)-**Bip** ligand in the ΔHT conformer. In the absence of carrier-ligand effects, the distribution of conformers in

the Pt(d(G*pG*)) moiety is ~50% HH1, ~35% ΔHT, and ~15% HH2. In other words, the long-known HH1 conformer accounts for about only half of the population of d(G*pG*) adducts.

Comparison of the Sugar Phosphodiester Backbone of 5,5′-Me$_2$bipyPt(d(G*pG*)) and *cis*-PtA$_2$(d(G*pG*)) Conformers. The 5′-G* residue of all the conformers of **5,5′-Me$_2$bipy**Pt(d(G*pG*)) was found to adopt the N-sugar pucker universally found for the 5′-G* sugar in *cis*-PtA$_2$(d(G*pG*))-type cross-links.[18,24,26,47,48] Thus, the favored N-pucker observed for the 5′-G* sugar appears to be independent of the carrier ligand. For the three abundant **5,5′-Me$_2$bipy**Pt(d(G*pG*)) conformers, the absence or weakness of the 3′-G* H8−H3′ cross-peak indicates that the 3′-G* sugar has the S-pucker favored by the 3′-G* in free d(GpG) and also in the abundant conformers of **Me$_2$ppz**Pt(d(G*pG*))- and **Bip**Pt(d(G*pG*))-containing adducts.[23−26] Moreover, the sugar proton signals of the three conformers of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) and **Me$_2$ppz**Pt(d(G*pG*)) adducts had similar chemical shifts. Such similar chemical shifts indicate that the sugar phosphodiester backbone structures of the adducts are similar.

Although the **Bip** carrier ligand can influence base canting (see below), the structure-sensitive ^{31}P NMR chemical shifts observed for the three more-abundant conformers of **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct (Table 1) agree with those of the corresponding conformers found for the (*S*,*R*,*R*,*S*)-**Bip**Pt(d(G*pG*)),[23] (*R*,*S*,*S*,*R*)-**Bip**Pt(d(G*pG*)),[24] and **Me$_2$ppz**Pt(d(G*pG*)) adducts.[26] The similarity observed for the ^{31}P NMR data, combined with the NOESY data on sugar pucker, leaves little doubt that the carrier ligand has minimal influence on the sugar phosphodiester backbone structure for any given conformer.

H8 Shifts and Base Canting. In addition to the HH or HT base orientation, another significant parameter that involves the G* bases is base canting. The G* bases are not oriented exactly perpendicularly to the coordination plane, and the degree and direction (left- or right-handed, Figure 2) of canting differ depending on the carrier ligand, the presence or absence of a linkage between the bases, and also the single-stranded or duplex character of the DNA. The chemical shifts of the G* H8 signals can be used efficiently to assess the degree and direction of canting.[23] In general, the G* base cants so that the six-membered ring of the purine points away from the *cis*-G*. For such a "6-out" canted G* base, the H8 is close to the *cis*-G*, and this H8 signal is shifted upfield by the anisotropic effect of the *cis*-G* base.[22] In an uncanted base, the H8 atom is positioned away from the *cis*-G* base and farther out of the coordination plane containing the heavy platinum atom. As a result, the shift of the H8 signal is downfield because there is less shielding (or even deshielding) by the *cis*-G* and possibly deshielding by the anisotropic Pt atom.[40,52−54]

According to the H8 shift method for assessing canting of the HH1 conformers in d(G*pG*) adducts in which the carrier-ligand donors are two sp^3 N's, the H8 signal of an uncanted G* base was proposed to have a shift of ~9.0 (3′-G*) and ~8.7 (5′-G*) ppm.[23] Because of the inductive effect of the Pt(II), these shifts are relatively downfield from those of free d(GpG). The G* H8 shifts of the HH1 conformer of the **Me$_2$ppz**Pt(d(G*pG*)) adduct, 8.93 (3′-G*) and 8.51 (5′-G*) ppm, indicate that both bases have low canting with a slight 6-out canting of the 5′-G* (left-handed).[26] Before applying this shift method, we wished to allow for any difference in the inductive effect between a Pt(II) with an sp^3 N-donor carrier ligand and one with an sp^2 N-donor carrier ligand. We compared guanosine (Guo) complexes to avoid complications arising from the presence of phosphate groups. The H8 shifts of the ΛHT, ΔHT, and HH conformers of **5,5′-Me$_2$bipy**Pt(Guo)$_2$ were ~0.3 ppm more downfield than those of the corresponding **Me$_2$ppz**Pt(Guo)$_2$ conformers (Supporting Information).[40] Thus, Pt(II) in the **5,5′-Me$_2$bipy** complexes has the greater inductive effect, which we attribute to the poorer electron-donating ability of the aromatic **5,5′-Me$_2$bipy** carrier ligand compared to that of **Me$_2$ppz**.

Canting in the HH1 Conformer. For the HH1 conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct, the H8 shifts (9.14 ppm for the 3′-G* H8 and 8.76 ppm for the 5′-G* H8) indicate two essentially uncanted bases. However, these G* H8 shifts are ~0.2 ppm more downfield than the corresponding shifts of the HH1 conformer of **Me$_2$ppz**Pt(d(G*pG*)).[26] The H8 shifts adjusted for inductive effects are ~8.5 (5′-G*) and ~9.0 ppm (3′-G*), suggesting slight L canting (5′-G* base 6-out, 3′-G* base uncanted) in the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH1 conformer. It was concluded previously that the **Me$_2$ppz**Pt(d(G*pG*)) HH1 conformer showed slight L canting. Consistent with this analysis, the difference between the H8 signals (0.38 ppm) for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH1 conformer is very similar to this difference (0.42 ppm) for the **Me$_2$ppz**Pt(d(G*pG*)) HH1 conformer; such a result is expected when the canting is similar, as we conclude here. For a canted HH1 conformer, the distance between the H8 proton of the more-canted 6-out G* base and the H6/H6′ proton of **5,5′-Me$_2$bipy** will be greater than that between the H8 proton of the other G* (less canted) base and the H6′/H6 proton, resulting in unequal volumes for the 5′-G* H8−H6 and 3′-G* H8−H6′ cross-peaks. For the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH1 conformer, the volume of the 3′-G* H8−H6′ cross-peak was only 20% greater than that of the 5′-G* H8−H6 cross-peak (Supporting Information). This slight difference in volume supports the shift analysis that there is some slight L canting. L canting is typically favored in single-strand adducts.[29]

After accounting for the G* H8 shift differences due to the carrier ligand, the canting is similar for the HH1 conformers of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) and **Me$_2$ppz**Pt(d(G*pG*))[26] adducts. However, the G* H8 signals of the canted base in the HH1 conformer of these two d(G*pG*) adducts are downfield from those of the canted base in the HH1 conformer of **Bip**Pt(d(G*pG*)) adducts. The relatively

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upfield shifts (7.9 to 8.2 ppm) for the G* H8 signal of the canted base of the HH1 conformer of the **Bip**Pt(d(G*pG*)) adducts[23,24] demonstrate that this base is more canted compared to the 3′ G* base of the HH1 conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) and the **Me$_2$ppz**Pt(d(G*pG*)) adducts.

Base Canting of the ΔHT Conformer. The G* H8 signals of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ΔHT conformer are significantly more upfield than those of the HH1 and HH2 conformers (Table 1). If one applies the H8 shift method used above for assessing canting of the G* bases for the HH1 conformer, the H8 shifts of ∼7.8 ppm reported for the ΔHT conformer of the **Me$_2$ppz**Pt(d(G*pG*))[26] and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts[25] would be indicative of a highly canted G* base.[23] However, for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ΔHT conformer, G* base canting can be assessed by using the G* H8−H6/6′ cross-peak volumes. For this conformer, the 3′-G* H8−H6′ and the 5′-G* H8−H6 cross-peak volumes were very similar. After accounting for the difference in abundance of the conformers, these volumes were about the same size as the relatively uncanted 5′-G* base in the HH1 conformer (Supporting Information). By this criterion, both the 3′-G* and the 5′-G* bases of the ΔHT conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct are only slightly canted.

The G* H8 shifts of the ΔHT conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct (Table 1) were more downfield (∼0.3 ppm) than the nearly identically shifted 5′- and 3′-G* H8 signals (∼7.78 and ∼7.90 ppm, respectively) of the ΔHT conformer of the **Me$_2$ppz**Pt(d(G*pG*))[26] and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts.[23] However, allowing for the poorer electron-donating effect of **5,5′-Me$_2$bipy** (described above), this comparison of the G* H8 shifts indicates that the G* bases in the ΔHT conformer of these three adducts undoubtedly cant in an almost identical manner.[23,25,26] Our finding that the NOE data indicate little canting in the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ΔHT conformer suggests that the G* bases are not canted in the ΔHT conformer of the **Me$_2$ppz**Pt(d(G*pG*)) and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts. Furthermore, in recent studies of adducts with bulky ligands appearing to allow no possibility for a high degree of G* base canting, the ΔHT conformer nevertheless forms and has upfield G* H8 signals at ∼8 ppm.[55] It thus appears that the H8 shift method, which appears to be so useful for the HH conformers, fails for the ΔHT conformer. One possible way to explain the relatively upfield G* H8 signals without invoking high G* base canting is to hypothesize that the ΔHT conformer has a highly compressed distorted form with unusual anisotropic effects from the Pt atom or the *cis*-G* base. Further work is needed to determine the details of the structure and the reasons for the unusual shifts of the ΔHT conformer.

Base Canting of the HH2 Conformer. NOESY data for the HH2 conformer of **5,5′-Me$_2$bipy**Pt(d(G*pG*)) show an H6′−3′-G* H8 cross-peak, but no H6−5′-G* H8 cross-peak, consistent with R-canting for the HH2 conformer. In the R-canted HH2 conformer, the H6′−3′-G* H8 distance is smaller (larger NOE) than the H6−5′-G* H8 distance. Past studies have suggested a preference for R-canting in the HH2 conformer.[24−26] The difference in shift (0.24 ppm) between the G* H8 signals of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH2 conformer is larger than this difference (0.06 ppm) for the **Me$_2$ppz**Pt(d(G*pG*)) HH2 conformer, suggesting slightly greater R-canting in the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH2 conformer. Compared to the (*R,S,S,R*)-**Bip**Pt(d(G*pG*)) adduct, which has significant base canting in the HH2 conformer, the canting is relatively low for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) HH2 conformer.

Conclusions. Our data show that the same abundant HH1, HH2, and ΔHT conformers as found in Pt(d(G*pG*)) adducts having sp^3 N-donor ligands can also form in a *cis*-PtA$_2$(d(G*pG*)) adduct having a planar, aromatic sp^2 N-donor carrier ligand (**5,5′-Me$_2$bipy)**. From the distribution of conformers of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)), **Bip**Pt(d(G*pG*)), and **Me$_2$ppz**Pt(d(G*pG*)) adducts, we conclude that the HH1 conformer is dominant regardless of carrier ligand. NMR results in this study also show that the structure of the sugar phosphate backbone differs for the three abundant conformers, but for a given conformer, the backbone structure does not depend on the carrier ligand. This conclusion is in agreement with observations made earlier.[26]

In previous studies, the G* H8 shift was the only simple gauge for base canting. In adducts with the **5,5′-Me$_2$bipy** ligand, the 5′-G* H8−H6 and 3′-G* H8−H6′ cross-peaks are useful as probes for determining G* base canting. From assessments of both these cross-peaks and the G* H8 shifts, the results for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct are quite consistent with the few reported previous studies and indicate that HH1 and HH2 conformers prefer left- and right-handed canting, respectively. The new results provide clear support for previous conclusions with the **Bip**Pt(d(G*pG*)) adducts, confirming that the chiral **Bip** carrier ligands, which have secondary amine donors and a less symmetrical distribution of bulk, influence both G* base canting and the relative stability of conformers.[23,24]

The main consequence of the presence of the aromatic sp^2 N-donor ligand in the new **5,5′-Me$_2$bipy**Pt(d(G*pG*)) complex is a slight downfield shift of the G* H8 signals, attributed to inductive effects of Pt(II) increased by a lower electron-donating ability of the aromatic **5,5′-Me$_2$bipy** ligand compared to carrier ligands in previously studied adducts. After accounting for the effect of the less-electron-donating **5,5′-Me$_2$bipy** carrier ligand, the G* H8 shifts of the ΔHT conformer of the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct are similar to those of the ΔHT conformer of the **Me$_2$ppz**Pt(d(G*pG*)) and (*S,R,R,S*)-**Bip**Pt(d(G*pG*)) adducts. Such comparable chemical shifts of the G* H8 signals suggest that the structural features of the ΔHT conformer are not affected by the carrier ligand and that even the **Bip** carrier ligand has no influence on base canting in this conformer. The 5′-G* H8−H6 and 3′-G* H8−H6′ cross-peak volumes

(55) Saad, J. S.; Benedetti, M.; Natile, G.; Marzilli, L. G. Manuscript in preparation.

for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ΔHT conformer provide the first direct experimental evidence indicating that the base canting is low. Our new results suggest that the Pt(d(G*pG*)) 17-membered macrocyclic chelate ring moiety of the ΔHT conformer has an unusually distorted compressed structure, that this distorted 17-membered d(G*pG*) chelate ring is intrinsic to all adducts with a ΔHT base arrangement, and that the G* bases in this ring make minimal contacts with the carrier ligand, including the **5,5′-Me$_2$bipy** carrier ligand studied here.

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Supporting Information Available: Descriptions of ^{1}H NMR signal assignments of the conformers for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) adduct; CD spectra of **5,5′-Me$_2$bipy**Pt(d(G*pG*)); molecular modeling of the ΔHT and HH1 conformers, showing G* nucleotide orientations similar to those indicated by the ^{1}H NMR data for **5,5′-Me$_2$bipy**Pt(d(G*pG*)); comparison of the G* H8 shifts of the **Me$_2$ppz**Pt**G**$_2$ and **5,5′-Me$_2$bipy**Pt**G**$_2$ adducts (**G** = 5′-GMP, 3′-GMP, and Guo); G* H8−H6/H6′ cross-peak volumes of the three **5,5′-Me$_2$bipy**Pt(d(G*pG*)) conformers; and G* H8−H6/H6′ distances for the **5,5′-Me$_2$bipy**Pt(d(G*pG*)) ΔHT conformer for varying C5−N7−Pt−*cis* amine N dihedral angles (deg) in an MMD model. This material is available free of charge via the Internet at http://pubs.acs.org.

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