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A Very Rare Example of a Structurally Characterized 3'-GMP Metal Complex. NMR and Synthetic Assessment of Adducts Formed by Guanine Derivatives with [Pt(L^{tri})Cl]Cl Complexes with an N,N',N'' Tridentate Ligand (L^{tri}) Terminated by Imidazole Rings

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S Supporting Information

ABSTRACT: [Pt(N(R)-1,1'-Me₂dma)Cl]Cl complexes with tridentate ligands (bis(1-methyl-2-methylimidazolyl)amine, R = H; N-(methyl)bis(1-methyl-2-methylimidazolyl)amine, R = Me) were prepared in order to investigate Pt(N(R)-1,1'-Me₂dma)G adducts (G = monodentate N9-substituted guanine or hypoxanthine derivative). Solution NMR spectroscopy is the primary tool for studying metal complexes of nucleosides and nucleotides because such adducts rarely crystallize. However, [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**) was crystallized,

allowing, to our knowledge, the first crystallographic molecular structure determination for a 3'-GMP platinum complex. The structure is one of only a very few structures of a 3'-GMP complex with any metal. Complex **5** has the syn rotamer conformation, with 3'-GMP bound by N7. All Pt(N(R)-1,1'-Me₂dma)G adducts exhibit two new downfield-shifted G H8 signals, consistent with G bound to platinum by N7 and a syn/anti rotamer mixture. Anticancer-active monofunctional platinum(II) complexes have bulky carrier ligands that cause DNA adducts to be distorted. Hence, understanding carrier-ligand steric effects is key in designing new platinum drugs. Ligand bulk can be correlated with the degree of impeded rotation of the G nucleobase about the Pt–N7 bond, as assessed by the observation of rotamers. The signals of syn and anti rotamers are connected by EXSY cross-peaks in 2D ROESY spectra of Pt(N(H)-1,1'-Me₂dma)G adducts but not in spectra of Pt(N(H)dpa)G adducts (N(H)dpa = bis(2-picolyl)amine), indicating that rotamer interchange is more facile and carrier-ligand bulk is lower in Pt(N(H)-1,1'-Me₂dma)G than in Pt(N(H)dpa)G adducts. The lower steric hindrance is a direct consequence of the greater distance of the G nucleobase from the H4/4' protons in the N(R)-1,1'-Me₂dma carrier ligand in comparison to that from the H6/6' protons in the N(H)dpa carrier ligand. Although in **5** the nucleotide is 3'-GMP (not the usual 5'-GMP) and the N(H)-1,1'-Me₂dma carrier ligand is very different from those typically present in structurally characterized Pt(II) G complexes, the rocking and canting angles in **5** adhere to long-recognized trends.

INTRODUCTION

High carrier-ligand bulk leads to decreases in anticancer activity and increases in toxicity of bifunctional platinum(II) anticancer agents,^{1–5} whereas for monofunctional platinum(II) agents we believe^{6–9} that high carrier-ligand bulk correlates with increased anticancer activity.^{9–14} Bifunctional agents, such as cisplatin, form G*G* intrastrand cross-link lesions and cause large distortions in DNA structure, manifested as large changes in CD¹⁵ and NMR^{16,17} spectra. (G residues in DNA or oligomers with a Pt(II) center bound to N7 are designated as G*). In contrast, small monofunctional platinum agents, such as [Pt(dien)Cl]Cl (dien = diethylenetriamine) and [Pt(NH₃)₃Cl]Cl, cause minimal changes in the DNA CD^{14,18} and NMR^{16,17} spectra, indicating that monofunctional agents with small carrier ligands are unable to distort the DNA structure greatly upon adduct formation.⁶ Studies of oligomer duplexes having one G*G* cross-link lesion (an HMG-bound 16-mer duplex studied by X-ray methods¹⁸ and a 9-mer duplex studied by NMR methods in solution¹⁹) reveal that the DNA distortion induced by bifunctional Pt(II) agents extends over two base pair (bp) steps. The cross-link bp step (between the

5'-G*·C bp and the 3'-G*·C bp) and the adjacent bp step (between the 5'-G*·C bp and the next bp in the 5'-direction along the duplex) are both highly distorted. Both solid-state and solution structural studies have revealed that the adjacent bp step has a large shift and a large slide.^{18–20} Therefore, we considered the possibility that this highly distorted bp step could play an important role in anticancer activity.^{19,21} A distortion very similar to that found in this adjacent bp step was later observed in an X-ray structure of an oligomer adduct of a bulky monofunctional platinum anticancer agent.^{13,22} Such findings indicate that a monofunctional agent with bulky carrier ligands could manifest anticancer activity by forming DNA adducts with a highly distorted bp step similar to that found in DNA adducts formed by nonbulky bifunctional agents such as cisplatin. Understanding carrier-ligand steric effects is thus key in designing new platinum drugs. Adducts formed between the Pt agents and G ligands (G = monodentate N9-substituted guanine or hypoxanthine derivative; Figure 1) have been

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studied by NMR methods in order to assess carrier–ligand bulk.^{8,23,24}

Figure 1. (top) Numbering scheme for [Pt(N(R)-1,1'-Me₂dma)Cl]⁺ complexes containing carrier ligands based on bis(2-methylimidazolyl)amine (N(H)dma; R = H, Z = H). To our knowledge, no complexes of N(H)dma with Pt are known. (bottom) Numbering scheme for the guanine nucleobase and for 3'-GMP and 5'-GMP. Ino and 5'-IMP contain hypoxanthine, having a hydrogen instead of the amino group at position 2 of the purine ring. The atom-numbering schemes depicted here are employed in the NMR discussion.

In order to gain a fundamental understanding of the steric effects within monofunctional Pt(II) G adducts, this laboratory has used NMR techniques to assess the properties of Pt(L^{tri})G adducts (L^{tri} = N,N',N'' tridentate carrier ligand) formed by monofunctional platinum agents with L^{tri} ligands based on bis(2-picolyl)amine (N(H)dpa) or dien.^{6,7,25–27} The present study focuses on the preparation of water-soluble [Pt(II)(L^{tri})-Cl]Y complexes of tridentate imidazolyl ligands and on identifying the adducts that these complexes form in solution with various purine derivatives. We utilize both bis(1-methyl-2-methylimidazolyl)amine (N(H)-1,1'-Me₂dma, **1**) and a ligand new to the literature, N-(methyl)bis(1-methyl-2-methylimidazolyl)amine (N(Me)-1,1'-Me₂dma, **2**); we designate these ligands as N(R)-1,1'-Me₂dma (Figure 1; R = H, Me). The tridentate ligand N(H)-1,1'-Me₂dma and its derivatives (with a substituent on the central N: e.g., –CH₂CH₂OH) have been used to synthesize complexes of various metals (e.g., Re, Cu, Tc, Fe) usually intended for biomedical applications.^{28–35}

We describe the synthesis of [Pt(N(H)-1,1'-Me₂dma)Cl]Y (**3**) and [Pt(N(Me)-1,1'-Me₂dma)Cl]Y (**4**) (Y = Cl[–] (**3a** and **4a**), BF₄[–] (**3b** and **4b**)) and the structural characterization of their cations by ¹H NMR spectroscopy and single-crystal X-ray diffraction. We then use ¹H NMR spectroscopy to examine Pt(N(R)-1,1'-Me₂dma)G adducts formed from [Pt(N(R)-1,1'-Me₂dma)Cl]Cl complexes and compare the results to those of other Pt(L^{tri})G adducts. In the present study, the crystallization of one product, [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·

5H₂O (**5**), allowed characterization by single-crystal X-ray diffraction.

Structures of metal 3'-GMP complexes are particularly rare. Only two molecular structures of complexes with 3'-GMP have been described in the literature, and both are Cu(II) complexes. One, [Cu(3'-GMP)(phen)(H₂O)]₂·7H₂O,³⁶ lacks M–N7 bonding, and the other, ([Cu₃(3'-GMP)₂(3'-GMPH)₂(H₂O)₅]_n·7H₂O)_n,³⁷ is a polymeric compound exhibiting nucleotide metal coordination through both the N7 atoms and the phosphate groups. Thus, to our knowledge **5** is the first crystallographically characterized complex with any metal in which 3'-GMP is bound through only an M–N7 bond. Other relevant structures with one Pt–N7 bond do not contain a nucleotide; these are [Pt(dien)(guanosine)](ClO₄)₂,³⁸ [Pt(dien)(inosine)](NO₃)₂·H₂O,³⁹ [Pt(NH₃)₃(9-methylhypoxanthine)]Cl(NO₃)·1.5H₂O,⁴⁰ [Pt(NH₃)₃(9-ethylhypoxanthine)]Cl(NO₃)·H₂O,⁴⁰ and *cis*-[Pt(NH₃)₂(N²,N²-dimethyl-9-methylguanine)Cl]PF₆.⁴¹ In contrast, there are many reported structures of complexes with two *cis* Pt–N7 bonds to G ligands, quite often 5'-GMP.^{3,42–52}

In studies of Pt(N(H)dpa)G adducts, no quality crystals for single-crystal X-ray structures could be obtained to support the conclusions reached by using NMR methods.^{6,7,25,26} The structure of [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**) gives us deeper insights into previous findings on Pt(N(H)dpa)G adducts, in addition to confirming and supporting our previous analysis of solution results for Pt(N(H)dpa)G adducts.

EXPERIMENTAL SECTION

Starting Materials. Sodium salts of G nucleotides (5'-guanosine monophosphate (5'-GMP), 5'-guanosine diphosphate (5'-GDP), 5'-guanosine triphosphate (5'-GTP), 5'-inosine monophosphate (5'-IMP), and 3'-guanosine monophosphate (3'-GMP)), neutral purine derivatives (inosine (Ino), 1-methylguanosine (1-MeGuo), and 9-ethylguanine (9-EtG)), K₂[PtCl₄], 1-methyl-2-imidazolecarboxaldehyde, and methylamine hydrochloride (MeNH₃Cl) were used as received from Sigma-Aldrich. *cis*-Pt(DMSO)₂Cl₂,⁵³ N(H)-1,1'-Me₂dma (**1**),³¹ and 2-(chloromethyl)-1-methylimidazole hydrochloride⁵⁴ were prepared by known methods. Because the protonation state and hence the charge of the Pt(N(R)-1,1'-Me₂dma)G adducts in which G = a nucleotide are not well-defined, we omit charges for the adducts. However, charges are specified for structurally characterized isolated complexes.

NMR Measurements. NMR spectra were recorded on an Avance-III Prodigy 500 MHz Bruker spectrometer. Peak positions are relative to TMS-*d*₄ in D₂O or to the solvent residual peak with TMS as reference. A presaturation pulse to suppress the water peak was employed when necessary. All NMR data were processed with TopSpin and MestReNova 10.0.0 software. The pH values of D₂O or 65/35 D₂O/DMSO-*d*₆ solutions examined by NMR spectroscopy are stated as measured and are not corrected for D₂O. The pH (uncorrected) of all solutions, including reaction mixtures, was adjusted when necessary with DNO₃ or NaOD (0.5 M) D₂O solutions.

Mass Spectrometric Measurements. High-resolution mass spectra were recorded on an Agilent 6210 ESI TOF LCMS mass spectrometer.

X-ray Data Collection and Structure Determination. Diffraction data were collected on a Bruker Kappa Apex-II DUO CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å), equipped with an Oxford Cryosystems Cryostream. All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least squares by using SHELXL2014⁵⁵ with H atoms in idealized positions.

Table 1. Crystal Data and Structure Refinement Details for [Pt(N(H)-1,1'-Me₂dma)Cl]BF₄ (3b), [Pt(N(Me)-1,1'-Me₂dma)Cl]Cl·H₂O (4a), [Pt(N(Me)-1,1'-Me₂dma)Cl]BF₄ (4b), and [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (5)

	3b	4a	4b	5
formula	C ₁₀ H ₁₅ ClN ₅ Pt·BF ₄	C ₁₁ H ₁₇ Cl ₂ N ₅ Pt·OH ₂	C ₁₁ H ₁₇ ClN ₅ Pt·BF ₄	C ₂₀ H ₂₇ N ₁₀ O ₈ PPt·NO ₃ ·5H ₂ O
fw	522.62	503.30	536.65	913.66
cryst syst	triclinic	monoclinic	monoclinic	orthorhombic
space group	$P\bar{1}$	$P2_1/c$	$C2/c$	$P2_12_12_1$
<i>a</i> (Å)	7.4468(4)	10.7948(6)	22.684(3)	9.0409(6)
<i>b</i> (Å)	12.5154(7)	11.5052(6)	12.5272(17)	16.7570(12)
<i>c</i> (Å)	17.0151(11)	12.2870(7)	11.2101(15)	20.8873(15)
α (deg)	110.894(2)	90	90	90
β (deg)	92.093(3)	97.773(3)	95.074(6)	90
γ (deg)	97.991(3)	90	90	90
<i>V</i> (Å ³)	1460.77(15)	1537.19(15)	3173.1(7)	3164.4(4)
<i>T</i> (K)	106	90	90	90
<i>Z</i>	4	4	8	4
ρ_{calcd} (Mg/m ³)	2.376	2.175	2.247	1.918
abs coeff (mm ⁻¹)	9.83	9.48	9.06	4.58
$2\theta_{\text{max}}$ (deg)	52.8	61.0	71.8	51.4
$R(F^2 > 2\sigma(F^2))^a$	0.035	0.030	0.030	0.037
R_w^b	0.071	0.089	0.089	0.084
resid dens (e Å ⁻³)	1.46, -0.90	4.90, -2.56	2.39, -1.60	1.68, -0.94
no. of data/params	5955/430	4689/190	7527/212	5877/457

^a $R = (\sum ||F_o| - |F_c||) / \sum |F_o|$. ^b $R_w = [\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]]^{1/2}$, in which $w = 1/[\sigma^2(F_o^2) + (dP)^2 + (eP)]$ and $P = (F_o^2 + 2F_c^2)$.

N-(Methyl)bis(1-methyl-2-methylimidazolyl)amine (N(Me)-1,1'-Me₂dma, 2). A solution of 2-(chloromethyl)-1-methylimidazole hydrochloride (1.00 g, 6 mmol), K₂CO₃ (1.7 g, 12 mmol), and MeNH₂Cl (0.16 g, 2.4 mmol) in acetonitrile (100 mL) was heated at reflux under nitrogen for 18 h. After the mixture was cooled to room temperature and filtered, the solvent was removed under reduced pressure. The resulting pale yellow residue was dissolved in eluent A (acetone/5.0 M NH₄OH (80/20)) and purified by chromatography on a silica column with eluent A. The fractions collected were spotted and analyzed on TLC plates by using eluent A. The cleanest fractions, as assessed by ¹H NMR spectroscopy, were combined and taken to dryness by rotary evaporation to afford a colorless oil (0.21 g, 40% yield). ¹H NMR signals (ppm) in D₂O (pH 8.3): 7.09 (s, 2H, H5/5'), 6.96 (s, 2H, H4/4'), 3.68 (s, 4H, CH₂), 3.56 (s, 6H, CH₃), 2.25 (s, 3H, CH₃). ¹H NMR signals (ppm) in DMSO-*d*₆: 7.07 (s, 2H, H5/5'), 6.76 (s, 2H, H4/4'), 3.52 (s, 4H, CH₂), 3.48 (s, 6H, CH₃), 2.06 (s, 3H, CH₃). ESI-MS (*m/z*): [M + H]⁺ calcd for C₁₁H₁₇N₅, 220.1557; found, 220.1558.

[Pt(N(H)-1,1'-Me₂dma)Cl]Y (3a,b). A solution of N(H)-1,1'-Me₂dma (21 mg, 0.1 mmol) in methanol (1 mL) was added to a methanol solution of *cis*-Pt(DMSO)₂Cl₂ (42 mg, 0.1 mmol, in 5 mL), and the mixture was heated at 50 °C overnight. The pale yellow [Pt(N(H)-1,1'-Me₂dma)Cl]Cl (3a) solid (24 mg, 55% yield) that formed was collected by filtration, washed with cold methanol and then with ether, and air-dried. ¹H NMR signals (ppm) in D₂O (pH 4): 7.03 (d, *J* = 1.5 Hz, 2H), 6.85 (d, *J* = 1.6 Hz, 2H, H4/4'), 4.63 (d, *J* = 15.4 Hz, 2H, CH₂), 3.67 (s, 6H, CH₃); one of the methylene signals is masked by the solvent peak. ¹H NMR signals (ppm) in DMSO-*d*₆: 8.31 (bs, 1H, NH), 7.38 (s, 2H, H5/5'), 6.93 (s, 2H, H4/4'), 4.56 (d, *J* = 15.3 Hz, 2H, CH₂), 4.53 (d, *J* = 15.0 Hz, 2H, CH₂), 3.73 (s, 6H, CH₃). ESI-MS (*m/z*): [M + H]⁺ calcd for C₁₀H₁₅ClN₅Pt, 436.0737; found, 436.0639. An aqueous solution of [Pt(N(H)-1,1'-Me₂dma)Cl]Cl (3a; 80 mg, 2 mL) was treated with an excess of NaBF₄ (30 mg) to yield a yellow solid. A solution of this solid in acetone (50 mg, 2 mL) was allowed to stand at room temperature, and slow evaporation produced pale yellow, X-ray-quality crystals of [Pt(N(H)-1,1'-Me₂dma)Cl]BF₄ (3b) after 4 days. ¹H NMR signals (ppm) in DMSO-*d*₆: 8.12 (bs, 1H, NH), 7.38 (2H, H5/5'), 6.93 (2H, H4/4'), 4.55 (d, *J* = 15.3 Hz, 2H, CH₂), 4.53 (d, *J* = 15.3 Hz, 2H, CH₂), 3.73 (s, 6H, CH₃).

[Pt(N(Me)-1,1'-Me₂dma)Cl]Y (4a,b). A solution of N(Me)-1,1'-Me₂dma (22 mg, 0.1 mmol) in methanol (1 mL) was added to a methanol solution of *cis*-Pt(DMSO)₂Cl₂ (42 mg, 0.1 mmol, in 5 mL), and the mixture was heated at 50 °C overnight. The pale yellow solid (29 mg, 61% yield) that formed was collected by filtration, washed with cold methanol and then with ether, and air-dried. X-ray-quality crystals of [Pt(N(Me)-1,1'-Me₂dma)Cl]Cl (4a) were obtained by mixing equal volumes (1 mL) of acetonitrile solutions of *cis*-Pt(DMSO)₂Cl₂ (10 mg, 12.5 mM) and the ligand (5 mg, 12.5 mM) and allowing the resulting solution to stand at room temperature. Pale yellow, needlelike crystals that separated overnight were characterized by single-crystal X-ray crystallography. ¹H NMR signals (ppm) in D₂O (pH 4, uncorrected for D₂O): 7.15 (d, *J* = 1.5 Hz, 2H, H5/5'), 7.01 (d, *J* = 1.6 Hz, 2H, H4/4'), 4.97 (d, *J* = 15.4 Hz, 2H, CH₂), 4.64 (d, *J* = 15.4 Hz, 2H, CH₂), 3.73 (s, 6H, CH₃), 3.12 (s, 3H, CH₃). ¹H NMR signals (ppm) in DMSO-*d*₆: 7.43 (d, *J* = 1.6 Hz, 2H, H5/5'), 6.97 (d, *J* = 1.6 Hz, 2H, H4/4'), 4.87 (d, *J* = 15.1 Hz, 2H, CH₂), 4.72 (d, *J* = 15.4 Hz, 2H, CH₂), 3.77 (s, 6H, CH₃), 2.99 (s, 3H, CH₃). An aqueous solution of 4a (87 mg, 2 mL) was treated with an excess of NaBF₄ (30 mg) to yield a yellow solid. When a solution of this solid in acetone (50 mg, 2 mL) was allowed to stand at room temperature, slow evaporation afforded X-ray-quality, pale yellow crystals of [Pt(N(Me)-1,1'-Me₂dma)Cl]BF₄ (4b) after 2 days. ¹H NMR signals (ppm) in DMSO-*d*₆: 7.43 (d, *J* = 1.7 Hz, 2H, H5/5'), 6.96 (d, *J* = 1.7 Hz, 2H, H4/4'), 4.86 (d, *J* = 15.3 Hz, 2H, CH₂), 4.71 (d, *J* = 15.3 Hz, 2H, CH₂), 3.77 (s, 6H, CH₃), 2.99 (s, 3H, CH₃).

G Adduct Formation with [Pt(N(R)-1,1'-Me₂dma)Cl]Cl. A 10 mM solution of [Pt(N(R)-1,1'-Me₂dma)Cl]Cl (R = H, Me) in D₂O at pH 4 (uncorrected) was treated with 2.5 molar equiv of G (G = 5'-GMP, 5'-GTP, 3'-GMP, 5'-IMP, Ino for R = H, Me; G = 5'-GDP, 1-MeGuo, 9-EtG for R = H). The solution was maintained at 25 °C and at pH 4 and monitored by ¹H NMR spectroscopy until the [Pt(N(R)-1,1'-Me₂dma)Cl]Cl signals completely disappeared. The signals of the reactants are shifted by stacking interactions between free G and the [Pt(N(R)-1,1'-Me₂dma)Cl]⁺ cation. As the adduct formed (decreasing the concentrations of the reactants), the resulting decrease in the extent of stacking interactions between the reactants caused the slight shift changes. Similar results were found in studies of Pt(N(H)dpa)G adducts, and a more complete explanation can be found in the published report.⁶

Table 2. Selected Bond Distances (Å) and Angles (deg) for [Pt(N(H)-1,1'-Me₂dma)Cl]BF₄ (3b), [Pt(N(Me)-1,1'-Me₂dma)Cl]Cl·H₂O (4a), [Pt(N(Me)-1,1'-Me₂dma)Cl]BF₄ (4b), [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (5), [Pt(N(H)dpa)Cl]Cl^a and [Pt(N(Me)dpa)Cl]Cl^b

	3b	4a	4b	5	[Pt(N(H)dpa)Cl]Cl	[Pt(N(Me)dpa)Cl]Cl
Bond Distances						
Pt–N1	1.992(6)	1.992(3)	1.978(4)	2.004(8)	2.008(6)	2.006(3)
Pt–N2	2.035(13), 2.069(13)	2.042(3)	2.041(3)	2.031(9)	2.009(12)	2.017(3)
Pt–N3	1.98(2)	1.998(3)	2.002(4)	1.995(9)	2.011(5)	2.007(3)
Pt–Cl or N6	2.317(6)	2.3065(7)	2.2793(10)	2.007(8)	2.301(2)	2.3048(10)
Bond Angles						
N1–Pt–N3	164.6(2)	164.27(14)	165.32(14)	164.5(4)	166.0(2)	166.0(2)
N1–Pt–Cl or N6	97.08(18)	96.21(9)	96.85(11)	96.4(4)	97.2(2)	96.62(9)
N2–Pt–Cl or N6	167.6(6), 169.9(5)	176.63(8)	176.53(9)	178.0(6)	168.7(6)	179.52(9)
N3–Pt–Cl or N6	98.27(17)	98.63(9)	97.12(12)	98.7(4)	97.8(2)	96.82(9)
N2–Pt–N1	83.1(4), 81.5(4)	82.67(12)	83.60(15)	81.6(3)	83.3(3)	83.35(12)
N2–Pt–N3	81.8(4), 83.5(4)	82.80(11)	82.73(15)	83.3(3)	83.3(3)	83.4(2)
Pt–N3–C6 ^c	113.1(5)	111.9(2)	111.6(3)	110.6(7)	112.7(4) ^d	114.1(5) ^d
Pt–N3–C8 ^c	139.4(5)	141.0(3)	139.5(3)	140.9(8)	127.2(5) ^d	128.7(5) ^d
C6–N3–C8 ^c	107.1(6)	106.8(3)	108.8(4)	108.3(10)	120.1(6) ^d	117.0(6) ^d

^aData from ref 63. ^bData from ref 64. ^cThe angles for the other ring are similar to the values reported here. ^dFor [Pt(N(H)dpa)Cl]Cl and [Pt(N(Me)dpa)Cl]Cl the C6 and C8 numbering in the table represents the C2 and C6 atoms, respectively, in NMR discussions.

Figure 2. ORTEP plots showing the cations of [Pt(N(H)-1,1'-Me₂dma)Cl]BF₄ (3b, top left), [Pt(N(Me)-1,1'-Me₂dma)Cl]BF₄ (4b, bottom left), and [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (5, right). Thermal ellipsoids are drawn with 50% probability.

In order to compare properties for the [Pt(N(H)-1,1'-Me₂dma)-Cl]⁺ cation and Pt(N(H)-1,1'-Me₂dma)G adducts with those reported in a D₂O/DMSO-*d*₆ (65/35) solvent mixture for the [Pt(N(H)dpa)-Cl]⁺ cation and Pt(N(H)dpa)G adducts,⁶ the formation of selected Pt(N(H)-1,1'-Me₂dma)G adducts (G = 5'-GMP, 5'-GTP) from [Pt(N(H)-1,1'-Me₂dma)Cl]⁺ was studied in this solvent mixture at pH 4 (uncorrected) (Table S2 in the Supporting Information).

Crystallization of [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (5). In order to obtain X-ray-quality crystals of the Pt(N(H)-1,1'-Me₂dma)(3'-GMP) adduct, 12.2 mg of 3'-GMP (2.5 molar equiv) was added to a 20 mM solution (5.2 mg/600 μL) of [Pt(N(H)-1,1'-Me₂dma)Cl]Cl in D₂O, and the pH was adjusted to 4. The solution

was allowed to stand at room temperature. Pale yellow, needlelike crystals were collected after 2 weeks.

RESULTS AND DISCUSSION

Synthesis of N(R)-1,1'-Me₂dma and [Pt(N(R)-1,1'-Me₂dma)Cl]Y (Y = Cl, BF₄). N(H)-1,1'-Me₂dma (1) was synthesized by hydrogenation of the 1-methyl-2-imidazolecarboxaldehyde oxime as reported in the literature.³¹ Several procedures are known^{30,32,56} for coupling the appropriate amine derivative with 2 equiv of 1-methyl-2-imidazolecarboxaldehyde in the presence of sodium triacetoxyborohydride in

order to synthesize tridentate imidazolyl ligands having different substituents at the central nitrogen. However, the attempt to synthesize the $N(\text{Me})$ -1,1'- Me_2dma (**2**) ligand by this method was unsuccessful. Therefore, we employed a coupling method known to produce tridentate pyridyl derivatives, which involves coupling the appropriate amine with 2-(chloromethyl)pyridine.⁵⁷ Correspondingly, the coupling of methylamine with 2 equiv of 2-(chloromethyl)-1-methylimidazole under basic conditions produced $N(\text{Me})$ -1,1'- Me_2dma (**2**) in acceptable yield. Several platinum precursors, such as $\text{cis-Pt}(\text{DMSO})_2\text{Cl}_2$, $\text{K}_2[\text{PtCl}_4]$, and $\text{Pt}(\text{1,5-cyclooctadiene})\text{Cl}_2$, have been used in synthesizing platinum complexes of pyridyl or imidazolyl ligands.^{58–62} The procedures with the last two precursors use water as the solvent. Because our complexes are highly soluble in water, we employed $\text{cis-Pt}(\text{DMSO})_2\text{Cl}_2$ in methanol and obtained $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (**3a** and **4a**) in 55–61% yields.

Structural Results. Crystal data and details of the structural refinement for $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**3b**), $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}\cdot\text{H}_2\text{O}$ (**4a**), $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**4b**), and $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})(3'\text{-GMPH})]\text{NO}_3\cdot 5\text{H}_2\text{O}$ (**5**) are summarized in Table 1. Selected bond lengths and angles are reported in Table 2, along with data for $[\text{Pt}(\text{N}(\text{H})\text{dpa})\text{Cl}]\text{Cl}$ ⁶³ and $[\text{Pt}(\text{N}(\text{Me})\text{dpa})\text{Cl}]\text{Cl}$ ⁶⁴ for comparison. The ORTEP plots for cations of $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**3b**), $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**4b**), and $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})(3'\text{-GMPH})]\text{NO}_3\cdot 5\text{H}_2\text{O}$ (**5**) (Figure 2; the structure of **4a** is similar to that of **4b** and is not shown here) show the numbering system used to describe the solid-state data. Crystals of **3b** contain two independent complexes in the asymmetric unit, only one (A) of which is shown in Figure 2 and used in the discussion. The N2 atom of the cation $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]^+$ is disordered over two almost equivalent positions with occupancies of 0.51:0.49 (1A:2A). Compound **4b** is a nonmerohedral twin. Compound **5** was losing solvent rapidly during crystal harvesting. The resulting crystal structure has a disordered nitrate anion and water molecules. Hydrogen atoms of water molecules and the phosphate moiety were not located in the difference Fourier map. In the discussions related to the 3'-GMPH group in complex **5**, the standard numbering system for guanine derivatives (Figure 1) is employed to allow comparisons with known structures.

$[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**3b**) and $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Y}$ (**4a**, $\text{Y} = \text{Cl}$; **4b**, $\text{Y} = \text{BF}_4$). Cations of **3b** and **4a,b** have a pseudo-square-planar geometry. The four coordination sites are occupied by the N1, N2, and N3 atoms of the tridentate ligands and by a Cl atom (trans to N2). The Pt–Cl and Pt–N bond distances and N1–Pt–N3 bite angles in **3b** and **4a,b** are not significantly different from the values reported for their $[\text{Pt}(\text{N}(\text{H})\text{dpa})\text{Cl}]^+$ ⁶³ and $[\text{Pt}(\text{N}(\text{Me})\text{dpa})\text{Cl}]^+$ ⁶⁴ analogues (Table 2). In these complexes, all of the Pt–N bond distances lie within the ranges expected for Pt–N(sp²) bond distances (1.99–2.08 Å)^{26,58,65} or Pt–N(sp³) bond distances (2.01–2.12 Å).^{26,27,66,67}

For the cations in **3b** and **4a,b**, the sp³ geometry of the central N atom places the two methylene groups on the side of the coordination plane opposite to the NH or N(Me) groups (Figure 3 and Figure S1 in the Supporting Information). As a result, the plane of the imidazolyl rings (defined by the three C and two N atoms in the ring) is tilted with respect to the coordination plane (defined by Pt and the four ligating atoms N1, N3, N2, and Cl/(G)N7). The average tilt angles for rings

Figure 3. Orientation of the H4/4' protons, methylene groups, and the imidazolyl rings in the $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ cations viewed along the coordination plane: (top) **3b** ($\text{R} = \text{H}$); (middle and bottom) **4b** ($\text{R} = \text{Me}$). Also shown are designations of the *endo*-CH and the *exo*-CH protons. For clarity, the *N*-Me groups of the imidazolyl rings are hidden.

in $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**3b**), $[\text{Pt}(\text{N}(\text{H})\text{dpa})\text{Cl}]\text{Cl}$,⁶³ and $[\text{Pt}(\text{N}(\text{H})6,6'\text{-Me}_2\text{dpa})\text{Cl}]\text{Cl}$ ²⁶ structures are 7.1, 5.4, and 5.2°, respectively. Addition of a methyl group on the central nitrogen appears to force the CH₂ groups to be farther below the coordination plane (Figures S1 and S2 in the Supporting Information); consequently, the average tilt angles approximately double to 12.4, 12.9, and 12.3° in $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (**4a**), $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (**4b**), and $[\text{Pt}(\text{N}(\text{Me})\text{dpa})\text{Cl}]\text{Cl}$,⁶⁴ respectively. The tilting of all the imidazolyl rings with respect to the coordination plane results in the H4/4' protons projecting toward the same side of the coordination plane as the NH or N(Me) groups (Figure 3).

$[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})(3'\text{-GMPH})]\text{NO}_3\cdot 5\text{H}_2\text{O}$ (**5**). The Pt–N1, Pt–N2, and Pt–N3 (Table 2) bond distances of this pseudo-square-planar Pt(II) complex do not differ significantly from the values for **3b**. In addition, the N1–Pt–N3 bite angle of **5** (164.5(4)°) is comparable to the value for $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]^+$ in **3b** (164.6(2)°, Table 2). In comparison to the tilting observed for **3b** (7.1°), the imidazolyl rings in **5** have a greater degree of tilting. One of the imidazolyl rings is tilted by 19.1° and the other ring by 10.0°. The Pt–N7(G) bond of 2.007(8) Å in **5** falls within the typical Pt–N7(G) bond distance ranges reported for mono adducts^{38–41} (1.99–2.07 Å) and for bis adducts^{3,42–52} (2.02–2.08 Å). The metric parameters and conformational features of the 3'-GMPH ligand are normal and are described in the Supporting Information.

The difference, Pt–N7–C5 bond angle minus the Pt–N7–C8 bond angle, in structures of Pt(II) complexes of G (G = any derivative of guanine) is defined as the “rocking angle”.⁶⁸ The typical range of the rocking angle, identified some years ago as being about –2 to +11°,⁶⁸ indicates that the Pt–N7–C8 angle is normally smaller than the Pt–N7–C5 angle. Rocking angles in more recent structures also almost always fall in this range.^{40,42,44,45,48–50} Mono adducts tend to be at the lower end of this range. Small rocking angles usually are observed when the structure has no clear intramolecular interactions, as in $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})(3'\text{-GMPH})]^+$ (**5**), which has a positive rocking angle of 1.4°. Rare examples of highly negative values for the rocking angle occur only when the carrier ligand

Table 3. ^1H NMR Data (ppm) for the $N(\text{R})$ -1,1'-Me₂dma Carrier Ligands in $\text{Pt}(N(\text{R})$ -1,1'-Me₂dma)G and in $[\text{Pt}(N(\text{R})$ -1,1'-Me₂dma)Cl]Cl (D₂O, pH 4.0, 25 °C)

R	Cl or G	<i>t</i> (days) ^a	H4/4'		H5/5'	1/1'-Me	N-Me
			syn	anti			
H	Cl ^b			6.85	7.03	3.67	
H	5'-GMP ^c	6	6.53, 6.52	6.57, 6.55	7.07 ^d	3.75	
H	5'-GTP ^c	6	6.52, 6.51	6.56, 6.54	7.07 ^d	3.74	
H	3'-GMP ^c	10	6.56, 6.53	6.58, 6.57	7.09 ^d	3.75	
H	5'-IMP ^c	6	6.50, 6.47	6.53, 6.52	7.08 ^d	3.76	
H	5'-GDP ^c	4	6.52, 6.51	6.57, 6.55	7.07 ^d	3.74	
H	Ino ^c	10	6.51, 6.49	6.54, 6.52	7.09 ^d	3.77	
H	1-MeGuo ^c	10	6.52, 6.51	6.55	7.09 ^d	3.77	
H	9-EtG ^c	10	6.52	6.54	7.10 ^d	3.77	
Me	Cl ^e			7.01	7.15	3.73	3.12
Me	5'-GMP ^c	10	6.58, 6.57	6.65, 6.63	7.12 ^d	3.79	3.18
Me	5'-GTP ^c	10	6.58, 6.56	6.66, 6.65	7.13 ^d	3.79	3.18
Me	3'-GMP ^c	10	6.61, 6.58	6.66, 6.64	7.14 ^d	3.80	3.20
Me	5'-IMP ^c	10	6.54, 6.51	6.59, 6.58	7.12 ^d	3.79	3.20
Me	Ino ^c	10	6.55, 6.53	6.59, 6.57	7.13 ^d	3.79	3.22

^a*t* = reaction completion time. ^bThe *endo*-H6/6' signal is masked by the solvent peak and the *exo*-H6/6' signal is 4.63 ppm (15.4 Hz). ^c*exo*- and *endo*-H6/6' signals are masked by the solvent peak. ^dsyn and anti signals are overlapped. ^e*endo*- and *exo*-H6/6' signals are 4.97 and 4.64 ppm, respectively.

Table 4. Selected ^1H NMR Data (ppm) for the G Ligand in $\text{Pt}(N(\text{R})$ -1,1'-Me₂dma)G Adducts (D₂O, pH 4.0, 25 °C)

R	G	H8 free	H8 syn	H8 anti	H1' free	H1' syn	H1' anti	$\Delta\delta^a$	syn:anti
H	5'-GMP	8.10	8.69	9.00	5.91	6.05	6.10	0.31	1.07:1
H	5'-GTP	8.19	8.74	9.05	5.92	6.05	6.09	0.31	1.01:1
H	3'-GMP	8.01	8.65	8.95	5.93	6.05	6.09	0.30	1.18:1
H	5'-IMP ^b	8.44	9.08	9.40	6.12	6.28	6.31	0.32	1.05:1
H	5'-GDP	8.12	8.71	9.01	5.91	6.04	6.09	0.30	1.02:1
H	Ino ^c	8.34	9.04	9.35	6.09	6.23	6.27	0.31	1.22:1
H	1-MeGuo	7.96	8.63	8.92	5.88	6.02	6.07	0.29	1.25:1
H	9-EtG ^d	7.91	8.43	8.74				0.31	1.30:1
Me	5'-GMP	8.11	8.66	8.98	5.91	6.05	6.09	0.32	1.60:1
Me	5'-GTP	8.14	8.69	9.01	5.93	6.05	6.09	0.32	1.63:1
Me	3'-GMP	8.01	8.61	8.97	5.94	6.04	6.10	0.36	1.57:1
Me	5'-IMP ^e	8.44	9.04	9.36	6.14	6.27	6.31	0.32	1.65:1
Me	Ino ^f	8.33	8.97	9.33	6.08	6.26	6.20	0.36	1.26:1

^aShift difference between the H8 signals of the syn and anti rotamers (cf. text). ^bH2: 8.21 (free), 8.40 (syn), and 8.34 ppm (anti). ^cH2: 8.21 (free), 8.40 (syn), and 8.34 ppm (anti). ^dCH₂: 4.08 (free), 4.26 (syn), 4.21 ppm (anti). CH₃: 1.41 (free), 1.48 (syn), 1.54 ppm (anti). ^eH2: 8.21 (free), 8.40 (syn), and 8.32 ppm (anti). ^fH2: 8.21 (free), 8.40 (syn), and 8.33 ppm (anti).

has high bulk, such as for $\text{Pt}(N,N,N',N'$ -tetramethylethylenediamine)G₂ complexes, with values of -3.2° (G = 5'-GMP)⁴³ and -6.8° (G = 9-MeG).³

An analysis by Yao et al. of crystallographic data for *cis*-[PtL₂G₂] type structures available at the time demonstrated a linear correlation ($R = 0.897$) between the rocking angle and the Pt–O6 non bonded distance.⁶⁸ The linear correlation also accounts for the Pt–O6 distance in **5** (3.40 Å) and in all relevant structures published after the report by Yao et al.⁶⁸ and discussed here.^{40,42–45,48–50}

Canting is another parameter used to compare structural features of Pt(II) complexes of coordinated purines. If the dihedral angle between the plane of a base and the coordination plane is close to 90° , the base is not canted. The smaller the dihedral angle, the greater the canting. This dihedral angle in **5** is 66.5° , indicating moderate canting. As previously reported,^{52,69} 6-oxopurine Cu(II) complexes exhibit an interesting relationship between the dihedral angle and intramolecular hydrogen-bonding interactions of the 6-oxo group with protons

in *cis* carrier ligands. If the proton can project out of the coordination plane, such as a proton on a ligating sp^3 N *cis* to the purine, a hydrogen bond is then possible. When a hydrogen bond is present, the dihedral angle falls in a highly canted 40 – 60° range. In the absence of such an interaction, the angle is usually greater than 65° and is in the moderately canted range. Except for a few Pt(II) complexes exhibiting strong intramolecular base–base stacking between two adjacent *cis* purines,^{42,45,46,51} all published Pt(II) 6-oxopurine complexes also seem to follow this relationship.^{3,38–41,43,44,48–50,52} Accordingly, the small canting value exhibited by **5** (characteristic of the absence of intramolecular hydrogen-bond interactions) is consistent with the closest proton in the carrier ligand being a partially positive CH atom lying essentially in the coordination plane.

NMR Spectroscopy. ^1H NMR spectroscopy was used to characterize the $N(\text{Me})$ -1,1'-Me₂dma ligand (in D₂O and DMSO-*d*₆), the $[\text{Pt}(N(\text{R})$ -1,1'-Me₂dma)Cl]⁺ complexes (in D₂O and DMSO-*d*₆), and the $\text{Pt}(N(\text{R})$ -1,1'-Me₂dma)G

Table 5. 1D ^{13}C NMR Data (ppm) for $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (3a (R = H) and 4a (R = Me)) and for Their 5'-GMP Adducts (D_2O , pH 4.0, 25 $^\circ\text{C}$)

carbons ^a	3a	adduct		4a	adduct	
		syn	anti		syn	anti
5'-GMP C8		139.96	140.03		139.96	140.04
5'-GMP C1'		87.97			88.03	
		87.94			87.95	
C5/5'	122.32	122.48		122.36	122.78	
		122.40			122.70	
C4/4'	123.42	124.40		124.33	124.73	
		124.29			124.70	
		124.20			124.59	
					124.52	
C2/2'	153.92	153.80		152.87	152.46	
C6/6'	51.02	51.50		61.95	61.94	
		51.44			61.90	
		51.39			61.88	
C1/1'	34.58	34.62		34.72	34.74	
N(Me)				52.72	52.24	

^aFree 5'-GMP: C8, 137.48 ppm; C1', 86.85 ppm.

Figure 4. ^1H NMR spectra (25 $^\circ\text{C}$, D_2O , pH 4) of the complexes $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (3a) (top) and $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (4a) (bottom) (shifts in ppm).

adducts (in D_2O) reported here. NMR signals were assigned by analyzing their chemical shifts, splitting pattern, integration, and data from 2D NMR experiments. Selected 1D ^1H and ^{13}C NMR data and assignments in D_2O for $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$, $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$, and their G adducts are collected in Tables 3–5. The atom-numbering scheme in Figure 1 is employed in the NMR discussion. ^1H NMR results in $\text{D}_2\text{O}/\text{DMSO-}d_6$ (65/35) for $\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{G}$ adducts (G = 5'-GMP, 5'-GTP) appear in the Supporting Information.

$[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ Assignments. Complexes 3 (R = H) and 4 (R = Me) each have two downfield ^1H NMR signals (Figure 4), as expected for the H4/4' and H5/5' aromatic protons. However, the small coupling constant of ~ 1.5 Hz, combined with the effect of the nearby quadrupolar nitrogen atoms, causes the signals to appear as singlets in some spectra. In a ROESY spectrum (Supporting Information) in D_2O for $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (3a), a strong NOE cross-peak from the 1/1'-Me signal at 3.67 ppm to the most downfield signal (7.03 ppm) allows the signal to be assigned to H5/5'. The other aromatic peak (6.85 ppm) can thus be assigned to H4/4', an assignment supported by the absence of any NOE cross-peak from the H4/4' signal to any other peak except to the H5/5' signal.

The two protons in each methylene group in the $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]^+$ cations are not magnetically equivalent; these are designated as *endo*-CH and *exo*-CH (Figure 3). The

two ^1H NMR methylene signals are doublets. Analysis of NOE cross-peaks led us to assign the upfield and downfield $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ doublets to the *exo*-CH and *endo*-CH signals, respectively. A similar relationship was found for $[\text{Pt}(\text{N}(\text{H})\text{dpa})\text{Cl}]\text{Cl}$.⁶ The ^{13}C NMR shifts were determined from 1D NMR spectra (Table 5). The ^{13}C NMR signals for the C4/4', C5/5', and C1/1' carbons of $[\text{Pt}(\text{N}(\text{H})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (3a) were assigned (Table 5) with the aid of cross-peaks (in ppm) involving the H4/4' (6.85–123.4), H5/5' (7.03–122.3), and 1/1'-Me (3.67–34.6) signals, respectively, in an HSQC experiment (Supporting Information). Cross-peaks from the *endo*-CH and *exo*-CH signals assign the ^{13}C NMR signal at 51.5 ppm to C6/6'. The only signal with no HSQC cross-peak (153.92 ppm) is assigned to C2/2'. As described in the Supporting Information, this approach for assigning the signals of 3a was also used to assign the ^1H and ^{13}C NMR signals (Tables 3 and 5) for $[\text{Pt}(\text{N}(\text{Me})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ (4a).

Although the 3a and 4a structures are similar except for the different substituents on the central N atom, the methylene signals (in $\text{DMSO-}d_6$) are separated by only 0.03 ppm for 3a (an AB pattern, *endo*-CH at 4.56 and *exo*-CH at 4.53 ppm), whereas the separation between the two doublets of 4a is 0.15 ppm (in $\text{DMSO-}d_6$, *endo*-CH at 4.87 and *exo*-CH at 4.72 ppm). These separations of methylene signals in $[\text{Pt}(\text{N}(\text{R})\text{-1,1'-Me}_2\text{dma})\text{Cl}]\text{Cl}$ are significantly less than the values reported for their $[\text{Pt}(\text{N}(\text{R})\text{dpa})\text{Cl}]\text{Cl}$ analogues (in $\text{DMSO-}d_6$, 0.32⁶

and 0.64⁶⁴ ppm for R = H, Me, respectively). However, the coupling constants for all four platinum complexes are ~15 Hz regardless of the carrier ligand or the substituent at the central N.

The robustness of [Pt(N(H)-1,1'-Me₂dma)Cl]Cl (**3a**) in D₂O (pH 7), in DMSO-*d*₆, and under strongly acidic (0.2 M HCl) conditions was monitored by using ¹H NMR spectroscopy. The spectra revealed no change even 10 days after addition of HCl (Supporting Information).

Pt(N(R)-1,1'-Me₂dma)G Adducts. NMR Background for Determining Rotamer Conformation in Adducts. In simple Pt(L^{tri})G adducts, the inductive effect of the Pt(II) center causes the H8, H2 (in hypoxanthine derivatives, cf. Figure 1), and ribose H1' peaks of bound G to be shifted downfield in comparison to these signals for free G.^{70,71} Two G base orientations and hence two rotamers are possible for Pt(L^{tri})G adducts having L^{tri} ligands that are unsymmetrical with respect to the coordination plane but symmetrical about a plane perpendicular to the coordination plane (Figure 5). By

Figure 5. The two possible purine orientations for Pt(L^{tri})G adducts when the tridentate carrier ligand (L^{tri}) is unsymmetrical with respect to the coordination plane but symmetrical about a plane perpendicular to the coordination plane. Note that the nucleobase is represented by an arrow with the tip at the H8 of the purine. R can be any substituent such as H or Me.

convention,⁷⁰ the rotamer of Pt(L^{tri})G adducts having the R group and the guanine O6 on the same side of the coordination plane is named syn, and the rotamer having these groups on opposite sides of this plane is named anti (Figure 5). The syn and anti rotamers interconvert by rotation about the Pt–N7 bond.^{2,19,71–73} Furthermore, neither rotamer has a plane of symmetry in an adduct formed by G derivatives having a chiral ribose, such as 5'-GMP. Therefore, in each rotamer the corresponding protons in the halves of the carrier ligand are not magnetically equivalent. When NMR evidence is found that Pt(L^{tri})G rotamers exist, only two signals are found for each type of G proton but as many as four signals can be observed for each type of carrier-ligand proton. Such a situation, in fact, applies to the new Pt(N(R)-1,1'-Me₂dma)G adducts studied here (Figure 6).

For separate sets of NMR signals of the syn and anti rotamers to be observed, the carrier ligand must be bulky enough to slow the rotation rate of the nucleobase on the NMR time scale.^{70–78} For example, Pt(Me₃dien)G adducts (Me₃dien = N,N,N',N'',N'''-pentamethyldiethylenetriamine) exhibit two sharp H8 NMR signals, one for each rotamer, indicating that the presence of terminal dimethylamino groups provides enough bulk to hinder nucleobase rotation about the Pt–N7 bond.⁷⁰ In contrast, because of the relatively low bulk of dien,

Figure 6. Models of the two possible rotamers for Pt(L^{tri})G complexes with tridentate ligands (L^{tri}) unsymmetrical with respect to the coordination plane but symmetrical about a plane perpendicular to the coordination plane, illustrated for L^{tri} = N(H)-1,1'-Me₂dma and G = 9-EtG. Rotation of the ethyl group around the N9–CH₂ bond creates a time-averaged mirror plane, preserving the symmetry of the Pt(N(H)-1,1'-Me₂dma) moiety. However, if a chiral N-9 substituent is created by replacing one methylene proton (circled), then the halves of the Pt(N(H)-1,1'-Me₂dma) moiety become magnetically inequivalent.

the H8 proton of the Pt(dien)G adducts shows only one sharp G H8 NMR peak, indicating fast rotation of the guanine base about the Pt–N7 bond.⁶ Recently, the N(H)dpa ligand was found to possess enough bulk to impede the rotation of the guanine nucleobase in Pt(N(H)dpa)G adducts.^{6,7} Similarly, all new Pt(N(R)-1,1'-Me₂dma)G adducts examined in the present study have spectra with two sharp downfield H8 NMR signals (Figure 7 and the Supporting Information), a finding consistent with hindered rotation of the purine base.

The main factor influencing the downfield shift of ¹H NMR signals on complex formation is the Pt(II) inductive effect, and this effect is expected to fall off as the number of bonds between the proton and the Pt(II) increases. However, the inductive effect is not expected to be different for the two rotamers. Indeed, the shift difference ($\Delta\delta$) between the H8 signals of the syn and anti rotamers is only ~0.04 ppm for the Pt(Me₃dien)(5'-GMP) adduct and $\Delta\delta = 0$ for H2 in almost all closely related 5'-IMP adducts.⁷⁰ In contrast, the aromatic rings terminating both ends of the tridentate ligand lead to large $\Delta\delta$ values for H8 of ~0.36 ppm for the Pt(N(H)dpa)G adducts.⁶ The syn H8 signal is upfield from the anti H8 signal. These observations for Pt(N(H)dpa)G adducts were explained by invoking models with a relatively uncanted guanine nucleobase in both rotamers. In such a model, H8 is closer to the shielding region of tilted anisotropic pyridyl groups of the carrier ligand in the syn rotamer than in the anti rotamer, accounting for the syn rotamer having the more upfield H8 signal.⁶ As we discuss below, this explanation can be evaluated with the help of the structure of **5** because the H8 signals of Pt(N(R)-1,1'-Me₂dma)G adducts exhibit NMR features similar to those of Pt(N(H)dpa)G adducts.

Pt(N(H)-1,1'-Me₂dma)(5'-GMP) Adduct. Spectra of the reaction mixture of [Pt(N(H)-1,1'-Me₂dma)Cl]Cl (**3a**) and 2.5 molar equiv of 5'-GMP in D₂O (pH 4) showed new ¹H NMR signals clearly detectable about 1 h after mixing. The signals for **3a** disappeared in ~6 days (Figure 7), indicating that the reaction was complete. In comparison to the H8 signal for free 5'-GMP at 8.10 ppm, two sharp downfield H8 singlets characteristic of Pt(II)-bound 5'-GMP were observed. As

Figure 7. Aromatic and H1' region of the ^1H NMR spectra (25 °C, D_2O , pH 4) of $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]^+$ (10 mM, bottom) and of the reaction mixture forming $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ recorded 15 min and 14, 24, 76, and 147 h after addition of 2.5 molar equiv of 5'-GMP (shifts in ppm).

Figure 8. ^1H – ^1H ROESY spectrum of $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$, showing syn H8–anti H8 EXSY cross-peaks and H8–H4/4' and H8–H1' NOE cross-peaks (D_2O , pH 4.0, 25 °C, shifts in ppm).

discussed above, two H8 singlets (Figure 7) provide evidence for impeded rotation of the guanine nucleobase in two rotamers of the $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ adduct; for reasons given above, the H8 signals at 9.00 and 8.69 ppm are assigned to the anti and syn rotamers, respectively. Furthermore, strong EXSY cross-peaks between the syn and anti H8 signals in the ROESY spectrum of the $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ adduct (Figure 8) add further strong evidence that the two H8 signals arise from slow exchange between two rotamers. In contrast, ROESY spectra of $\text{Pt}(\text{N}(\text{H})\text{dpa})\text{G}$ adducts show no EXSY cross-peaks,⁶ indicating that the exchange between $\text{Pt}(\text{N}(\text{H})\text{dpa})\text{G}$ rotamers occurs relatively more slowly than exchange between $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{G}$ rotamers.

The two rotamers of the $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ adduct each have an H1' doublet shifted downfield similarly (~ 0.2 ppm) by metal coordination. The NOE cross-peak between the downfield anti H8 signal and the downfield H1' doublet (6.10 ppm) in the ROESY spectrum (Figure 8) assigns this H1' doublet to the anti rotamer. The NOE cross-peak from the syn H8 signal to the doublet at 6.05 ppm confirms its assignment as syn H1'. Because both the H1' and H8 protons are associated with the five-membered ring of the guanine base, the H1' and H8 signals are shielded more by the tilted imidazolyl rings in the syn rotamer than in the anti rotamer. A similar relationship was found to be caused by the tilted pyridyl rings in the $\text{Pt}(\text{N}(\text{H})\text{dpa})\text{G}$ class of adducts.⁶

The above rotamer assignments rely on shifts of the bound 5'-GMP signals as described previously.⁶ The NMR features of Pt(N(R)-1,1'-Me₂dma)G adducts and the molecular structure of **5** allow the use of NOE cross-peaks between the bound G H8 and the carrier-ligand signals to remove any doubt about previous assignments. From its characteristic shift and the integration, the singlet at 3.75 ppm is unambiguously assigned to the 1/1'-Me signal of the Pt(N(H)-1,1'-Me₂dma)(5'-GMP) adduct. The 1/1'-Me signal shows a strong cross-peak to an apparent singlet at 7.07 ppm in the ROESY spectrum (Supporting Information), allowing the assignment of the 7.07 ppm signal to H5/5'. This H5/5' singlet has a strong, broad cross-peak to four closely bunched singlets near 6.57–6.52 ppm (Figure 8). The four singlets together integrate as having the same intensity as the H5/5' singlet, and thus all can be assigned to the H4/4' protons. These signals exhibit no cross-peaks with the 1/1'-Me signal, confirming the H4/4' assignment. As mentioned above, the halves of the carrier ligand are not magnetically equivalent when the N9 substituent is chiral (Figure 6).

In the ROESY spectra of both Pt(N(H)-1,1'-Me₂dma)(5'-GMP) (Figure 8) and Pt(N(Me)-1,1'-Me₂dma)(5'-GMP) (Supporting Information), the H8–H4/4' NOE cross-peaks are stronger for the anti rotamer than for the syn rotamer. To understand this difference in NOE cross-peaks, we used the GaussView 5.0.8 software program to construct a model of the anti rotamer (Figure S3 in the Supporting Information) from the molecular structure of the syn rotamer in [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**). The 3'-GMP ligand of the syn rotamer in **5** was rotated by 180° about the Pt–N7 bond and the C8–N7–Pt angle adjusted to that of the syn rotamer (126.78°). The G H8 proton and carrier-ligand H4/4' protons are farther apart in the syn rotamer structure (~3.5 Å) than in the model of the anti rotamer (~2.8 Å). Thus, the NOE intensities confirm the rotamer assignments using the reasoning in previous work⁶ based on the effects on H8 shifts of the anisotropy of the tilted carrier-ligand aromatic rings.

The anisotropic guanine in Pt(N(Me)dpa)G,²⁵ Pt(N(H)dpa)G,⁶ and Pt(5,5'-Me₂bipy)G₂⁷⁵ (5,5'-Me₂bipy = 5,5'-dimethyl-2,2'-bipyridine) adducts caused large upfield shifts (~1.1 ppm) of the signals of the carrier-ligand protons closest (H6/6') to the coordinated G. Similarly, in the G adducts of **3a** and **4a**, the signals of the protons closest (H4/4') to the coordinated G are affected the most (upfield shifts of ~0.3–0.4 ppm in comparison to the H4/4' signal for **3a**) by adduct formation. The nonbonded distance from the chloride atom to the H4/4' protons in **3b** is ~0.4 Å longer than the corresponding distance to the H6/6' protons in [Pt(N(H)dpa)Cl]Cl.⁶³ Therefore, the coordinated guanine must be closer to the H6/6' protons in Pt(N(H)dpa)G adducts in comparison to the H4/4' protons in Pt(N(H)-1,1'-Me₂dma)G adducts (Figure 9). Hence, the guanine nucleobase will undoubtedly cause more upfield shifting of the H6/6' signals than of the H4/4' signals, as observed.

As described above, the chiral ribose in 5'-GMP makes the halves of the carrier ligand of each Pt(N(H)-1,1'-Me₂dma)(5'-GMP) rotamer inequivalent. The effect of chirality is small. Likewise, the difference in orientation of the nucleobase leads to only small differences in shifts of carrier-ligand signals. As shown in Figure 9, the distances from H4/4' to the center of the guanine rings in the syn rotamer are almost all identical with the respective distances in the anti rotamer. Thus, resolution of the four possible signals can be observed only

Figure 9. Overlap of stick drawings of [Pt(N(H)-1,1'-Me₂dma)Cl]⁺ (purple) and [Pt(N(H)dpa)Cl]⁺ (gold) cations (by superimposing the Pt, N1, N2, and N3 atoms). By using GaussView 5.0.8 software, 9-methylguanine (9-MeG) adduct models were constructed from the X-ray data by replacing the coordinated Cl atoms with a 9-MeG having a Pt–N7 distance of 2.007 Å (the distance in **5**) in the plane bisecting the halves of the cations. These halves are almost but not exactly equivalent (Table 2). For simplicity, the illustration replaces the purine with a blue arrow. The syn orientation is shown. Cones qualitatively indicate that the H4/4' and H6/6' atoms lie within the shielding region of the purine base. The thin green arrows span the distances to the center of the purine six-membered ring from the H4 and the H6 atoms in half of the carrier ligand. The averages of distances (Å) of the H4/4' and H6/6' atoms to the center of the 9-MeG rings measured using Mercury 3.7 software are as follows: for the [Pt(N(H)-1,1'-Me₂dma)(9-MeG)]²⁺ models (six-membered ring, syn 4.51 and anti 4.54; five-membered ring, syn 3.63 and anti 3.63) and for the [Pt(N(H)dpa)(9-MeG)]²⁺ models (six-membered ring, syn 4.13 and anti 4.13; five-membered ring, syn 3.14 and anti 3.14). Thus, for a given adduct and a given ring, the distances are virtually identical in both the syn and the anti 9-MeG orientations. In all cases, distances are ~0.4–0.5 Å longer for the [Pt(N(H)-1,1'-Me₂dma)(9-MeG)]²⁺ model.

for signals of nuclei close to the anisotropic nucleobase of the chiral G. The two rotamers of Pt(N(H)-1,1'-Me₂dma)(5'-GMP) exhibit four closely spaced H4/4' signals. NOE cross-peaks (Figure 8) from the anti H8 and syn H8 singlets to the two most downfield and the two most upfield H4/4' signals, respectively, assign the H4/4' signals (Table 3). The H5/5' protons in Pt(N(H)-1,1'-Me₂dma)(5'-GMP) are far from those of the coordinated 5'-GMP and exhibit an apparent singlet with a very small downfield shift change (0.04 ppm) in comparison to the H5/5' signal for **3a**.

The ¹³C NMR shifts were determined from 1D NMR spectra (Table 5). All of the carrier-ligand carbons are farther from the anisotropic nucleobase than are the H4/4' protons; thus, there are usually fewer than the four possible detectable ¹³C NMR signals arising from the two chiral rotamers of the Pt(N(H)-1,1'-Me₂dma)(5'-GMP) adduct. For example, only three peaks are assignable to C4/4' in an HSQC experiment for Pt(N(H)-1,1'-Me₂dma)(5'-GMP) (Supporting Information), in which four clustered H4/4' signals exhibit one strong cross-peak to the ¹³C NMR peaks at 124.4, 124.3, and 124.2 ppm. Similarly, the H5/5' signal has a strong cross-peak to only two closely associated peaks at 122.5 and 122.4 ppm for C5/5'. In addition, the 1/1'-Me ¹H NMR signal shows a cross-peak to the C1/1' signal at 34.6 ppm (Table 5).

The HSQC spectrum of the Pt(N(H)-1,1'-Me₂dma)(5'-GMP) adduct (Supporting Information) is in turn useful in locating the methylene *endo*-CH signals, which fall close to the HOD solvent peak and are suppressed by presaturation of the HOD signal. The two strong cross-peaks observed involve the

C6/6' signal (at 51 ppm, a characteristic shift for such methylene carbons^{6,26,31}) and the cluster of peaks at 4.60 ppm and the suppressed signals near 4.73 ppm (Supporting Information). We can confidently assign these ¹H NMR clusters respectively to the *exo*-CH and *endo*-CH protons because *endo*-CH signals are invariably downfield, as discussed above.

Other Pt(N(H)-1,1'-Me₂dma)G Adducts. With the progression of the reaction between [Pt(N(H)-1,1'-Me₂dma)-Cl]⁺ and 3'-GMP (molar ratio 1:2.5) in D₂O at pH 4, the adduct separated as pale yellow crystals. The carrier-ligand signals in the Pt(N(H)-1,1'-Me₂dma)(3'-GMP) adduct have shifts similar to those observed for the 5'-GMP, 5'-GDP, and 5'-GTP adducts (Table 3). These observations suggest that the location of the phosphate groups at the 3'- or 5'-position of the sugar groups does not appear to have a major effect on the properties of the adducts.

For the Pt(N(H)-1,1'-Me₂dma)(5'-IMP) adduct, the H8 singlets are at 9.40 (anti) and 9.08 ppm (syn), and the H2 signals are at 8.40 (syn) and 8.34 (anti) ppm (Figure 10 and

Figure 10. ¹H NMR spectra (25 °C, D₂O, pH 4) of the mixture of [Pt(N(H)-1,1'-Me₂dma)Cl]⁺ and 5'-IMP at 15 min after mixing (bottom) and of the Pt(N(H)-1,1'-Me₂dma)(5'-IMP) adduct 6 days after mixing (top) (shifts in ppm). The spectral region was selected to show the H8 and H2 signals.

Table 4). The opposite order of shifts of the H2 and H8 signals in the anti vs the syn rotamer arises because the imidazolyl anisotropy affects mainly the six-membered-ring signals in the anti rotamer and mainly the five-membered-ring signals in the syn rotamer. A similar opposite directional influence on the H2 and H8 signals by a nearby anisotropic ring was found for other 5'-IMP adducts.^{6,74} Because the rotamer abundance for the Pt(N(H)-1,1'-Me₂dma)(5'-IMP) adduct is very close to 1:1 (Figure 10), the relative intensities of the two H1' signals of the adduct were not useful for assigning the H1' signals. The Pt(N(Me)-1,1'-Me₂dma)(5'-IMP) adduct has a syn:anti intensity ratio of 1.65:1, and the relative intensities of the peaks show that the syn H1' signal is upfield and the anti H1' signal is downfield (Supporting Information); this is the expected shift relationship because H1' is on the five-membered ring. By analogy, the more upfield H1' signal for Pt(N(H)-1,1'-Me₂dma)(5'-IMP) is assigned to the syn rotamer. For these two Pt(N(R)-1,1'-Me₂dma)(5'-IMP) adducts, the order of shifts of the H2 signal in comparison to the H8 and H1' signals is opposite in the anti vs the syn rotamer. The effect of ring anisotropy is largest on H8 shifts

and smallest on H1' shifts. All of these shift relationships were found also for Pt(N(H)dpa)(5'-IMP) (in a solvent mixture),⁶ but the shift difference between rotamers for all three types of signals is greatest for Pt(N(H)dpa)(5'-IMP), consistent with our conclusion below that the anisotropy of the pyridyl ring is greater than that of the imidazolyl ring in these adducts.

[Pt(N(H)-1,1'-Me₂dma)(9-EtG)]²⁺, [Pt(N(H)-1,1'-Me₂dma)(Ino)]²⁺, and [Pt(N(H)-1,1'-Me₂dma)(1-MeGuo)]²⁺ adducts were studied to assess the influence of the phosphate group on the formation and properties of the adducts. Complete formation of Pt(N(H)-1,1'-Me₂dma)G adducts by reaction of 3a with neutral nucleobases/nucleosides required ~10 days, a longer time than for nucleotides (Table 3); the relatively shorter reaction times observed for the 3a cation with anionic nucleotides can be attributed to the electrostatic attraction between the reactants.

The ¹H NMR chemical shifts, $\Delta\delta$ values, and syn:anti ratios for these three [Pt(N(H)-1,1'-Me₂dma)G]²⁺ adducts are similar to those of the adducts with nucleotides (Tables 3 and 4 and Supporting Information), indicating that phosphate and ribose groups have at best a small influence on $\Delta\delta$ and on impeding nucleobase rotation. The absence of the chiral sugar group in the [Pt(N(H)-1,1'-Me₂dma)(9-EtG)]²⁺ adduct results in only one H4/4' signal for each rotamer, giving a total of two H4/4' signals, not four as found with adducts in which G has a ribose group. Furthermore, correlating the abundance of the two sets of CH₂ and CH₃ signals with that of the H8 signals establishes that the anti rotamer has the more downfield signals for all of the protons associated with the five-membered guanine ring (Table 4).

Comparison between Pt(N(H)dpa)G and Pt(N(H)-1,1'-Me₂dma)G Adducts. In order to compare the properties of the new adducts with those found previously for the Pt(N(H)dpa)G adducts,⁶ we conducted a few studies of Pt(N(H)-1,1'-Me₂dma)G adducts (G = 5'-GMP, 5'-GTP) in the solvent mixture (65/35 D₂O/DMSO-*d*₆ at pH 4) used previously for the Pt(N(H)dpa)G adducts.⁶ The results for both classes of adducts, such as the syn:anti ratios, are comparable (Supporting Information). Also, the $\Delta\delta$ values (in 65/35 D₂O/DMSO-*d*₆) for G = 5'-GMP, 5'-GTP are ~0.4 ppm for Pt(N(H)dpa)G adducts and are ~0.3 ppm for Pt(N(H)-1,1'-Me₂dma)G adducts. The nonbonded distances between the bound Cl and the center of the aromatic rings found in the molecular structures are shorter to the imidazolyl rings (~4.2 Å) of the [Pt(N(R)-1,1'-Me₂dma)Cl]⁺ cations than to the pyridyl rings (~4.4 Å) of the [Pt(N(R)dpa)Cl]⁺ cations.^{63,64} The difference in these distances suggests that H8 in adducts is farther from the center of the pyridyl rings than from the center of the imidazolyl rings. Together with the $\Delta\delta$ values for these adducts in the solvent mixture, the difference in these distances leaves little doubt that the anisotropy of the pyridyl ring is greater than that of the imidazolyl ring.

Upon adduct formation, the downfield shift changes of the H8 and H1' NMR signals (relative to free G) are comparatively smaller for Pt(N(H)-1,1'-Me₂dma)G than for Pt(N(H)dpa)G adducts. As an example, from data in the Supporting Information, the H8 shift changes upon adduct formation are 0.62 and 0.91 ppm for the syn and anti rotamers of Pt(N(H)-1,1'-Me₂dma)(5'-GMP), respectively, vs 0.76 and 1.12 ppm⁶ for the corresponding rotamers of Pt(N(H)dpa)(5'-GMP). Because the anisotropic effect of the pyridyl rings on H8 is greater than that of the imidazolyl rings, the conclusion is clear

that the Pt(II) center exerts a stronger electron-withdrawing effect on the nucleobase in the Pt(N(H)dpa)G than in the Pt(N(H)-1,1'-Me₂dma)G adducts. The strength of this Pt(II) inductive effect provides a rough estimate of the relative electron-donating ability of the bound aromatic rings. Thus, the imidazolyl rings have a relatively higher donating ability than the pyridyl rings, as might be expected. This difference, which undoubtedly occurs also in the chlorido complexes, may be the reason that complete formation of the Pt(N(H)dpa)(S'-GMP) adduct requires less time (~2 days) than that needed for the Pt(N(H)-1,1'-Me₂dma)(S'-GMP) adduct (≥4 days) in either D₂O (100%) or D₂O/DMSO-*d*₆ (65/35).

Pt(N(Me)-1,1'-Me₂dma)G Adducts. To examine the influence of increased bulk at the central nitrogen of the carrier ligand, we evaluated the properties of the Pt(N(Me)-1,1'-Me₂dma)G adducts (Table 4). The Pt(N(Me)-1,1'-Me₂dma)(S'-GMP) adduct showed sharp H8 singlets for the syn (upfield H8 signal at 8.66 ppm) and the anti (downfield H8 signal at 8.98 ppm) rotamers (Supporting Information and Table 4). The Δδ value for the two H8 signals (0.32 ppm) is comparable to that of Pt(N(H)-1,1'-Me₂dma)(S'-GMP) (0.31 ppm). The chemical shifts for H1' doublets of the syn and anti rotamers of the Pt(N(Me)-1,1'-Me₂dma)(S'-GMP) adduct are similar to what is observed for the Pt(N(H)-1,1'-Me₂dma)(S'-GMP) adduct (Table 4). Similarly, the Pt(N(Me)-1,1'-Me₂dma)(S'-GTP), Pt(N(Me)-1,1'-Me₂dma)(3'-GMP), Pt(N(Me)-1,1'-Me₂dma)(S'-IMP), and Pt(N(Me)-1,1'-Me₂dma)(Ino) adducts have shifts (Tables 3 and 4 and the Supporting Information) very similar to those of the corresponding Pt(N(H)-1,1'-Me₂dma)G adducts. However, the EXSY cross-peaks connecting the syn and anti H8 signals in a ROESY spectrum of the Pt(N(Me)-1,1'-Me₂dma)(S'-GMP) adduct (Supporting Information) are relatively smaller than those of the Pt(N(H)-1,1'-Me₂dma)(S'-GMP) adduct (Figure 8), suggesting that base rotation is more facile in the latter.

Another difference between the Pt(N(Me)-1,1'-Me₂dma)G adducts and the Pt(N(H)-1,1'-Me₂dma)G adducts was the relative abundance of the rotamers in D₂O when G = S'-GMP, S'-GTP, 3'-GMP, S'-IMP. The Pt(N(Me)-1,1'-Me₂dma)G adducts have a high syn:anti ratio (≥1.5:1), whereas the Pt(N(H)-1,1'-Me₂dma)G adducts have rotamers of nearly equal abundance (Table 4). Comparison of the model of the anti rotamer (Figure S3 in the Supporting Information) with the molecular structure of the syn rotamer in [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**) did not show any steric interactions that would favor either rotamer, consistent with the similar abundance of the rotamers. Finally, it is interesting to note (1) that the imidazole ring has a greater degree of tilting in **5** than in the chlorido complexes and (2) that a methyl group on the central nitrogen increases tilting. Thus, the greater abundance of the syn rotamer typically found for Pt(N(Me)-1,1'-Me₂dma)G adducts than for Pt(N(H)-1,1'-Me₂dma)G adducts may arise in part because the tilting is already greater in the starting [Pt(N(Me)-1,1'-Me₂dma)Cl]Cl complex.

Relationship of the Phosphate Group to Pt(II) and N7 in GMP Complexes. The molecular structure of [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**) allows us to compare the proximity of the phosphate group to Pt(II) and N7 to such distances in structurally characterized S'-GMP complexes, all of which are bis adducts.^{42–45,51} Nonbonded distances were obtained from crystallographically determined molecular structures by using Mercury 3.7 software. For our purposes,

we use the central P atom to gauge the distance of the phosphate group to the other atoms. The Pt to P nonbonded distance (9.7 Å) in the 3'-GMP complex (**5**) is much longer than in the S'-GMP complexes (5.0–6.2 Å). The NMR and structural data for such bis S'-GMP adducts, especially for the ΔHT conformation (head to tail orientation of the two bases and right-handed chirality), suggest that the phosphate group of S'-GMP interacts electrostatically with the Pt(II) center or the carrier ligand.^{43,44} Thus, the most abundant conformers often differ between bis adducts formed by S'-GMP and those formed by 3'-GMP.⁷⁸

The spatial position of the 3'-phosphate group in 3'-GMP bound via N7 to a metal center separates the centers of charge. This separation may explain why so few 3'-GMP complexes have been crystallized. The large number of known structures of S'-GMP complexes of many metals may indicate that charge neutralization resulting from the close proximity of the S'-phosphate group to the metal center facilitates crystallization.

Furthermore, the inability of 3'-GMP to form such electrostatic interactions explains why formation of the Pt(N(R)-1,1'-Me₂dma)(3'-GMP) adduct requires 10 days vs the 6 days or less needed to form the S'-GMP, S'-GDP, S'-GTP, and S'-IMP adducts, in which a phosphate group is closer to the Pt(II) center. The N7 to P nonbonded distance in **5** is 8.0 Å. The attraction of the negative 3'-phosphate to the positive Pt(II) center during adduct formation positions the N7 of 3'-GMP too far from Pt(II) to facilitate N7 to Pt bond formation. In contrast, the N7 to P nonbonded distances in S'-GMP adducts range from 5.1 to 6.3 Å.^{42–45,51} The attraction of the negative S'-phosphate group to the positive Pt(II) center positions the N7 of GMP closer to Pt(II) during adduct formation by S'-GMP than during adduct formation by 3'-GMP. This positioning probably accounts for the shorter times observed for reactions of S'-GMP than of 3'-GMP.

CONCLUSIONS

The presence of EXSY cross-peaks in the ROESY spectra of Pt(N(R)-1,1'-Me₂dma)(S'-GMP) adducts but not in the ROESY spectrum of the Pt(N(H)dpa)(S'-GMP) adduct⁶ revealed that rotamer interchange is more facile for Pt(N(H)-1,1'-Me₂dma)G adducts than for Pt(N(H)dpa)G adducts; we conclude that this finding establishes that the N(R)-1,1'-Me₂dma carrier-ligand steric effect is relatively lower than the N(H)dpa carrier-ligand steric effect. We believe that this lower steric effect is a consequence of the greater distance of the H4/4' protons from the G nucleobase in Pt(N(H)-1,1'-Me₂dma)G adducts in comparison to the distance of the corresponding H6/6' protons in Pt(N(H)dpa)G adducts.

The structural data for [Pt(N(H)-1,1'-Me₂dma)(3'-GMPH)]NO₃·5H₂O (**5**) confirm that the 3'-phosphate group is too far from the carrier ligand or the positive Pt(II) center to influence the properties of the complex. This finding nicely complements a study with Pt(Me₃dien)(S'/3'-GMP) adducts, which exhibited properties independent of the 3'- or S'-position of the phosphate group on the ribose.⁷⁰ The Me₃dien carrier ligand has considerable steric bulk projecting out of the coordination plane, and the S'-phosphate group cannot easily approach the positive Pt(II) center. In analogues of Pt-(Me₃dien)(S'/3'-GMP) adducts in which protons occupied the positions of some of the carrier-ligand N-Me groups,^{70,71} the rotamer distribution greatly favored the rotamer in which the S'-phosphate group could form a hydrogen bond to the carrier-ligand NH proton. The solid-state structure of **5** in the present

study thus fully supports previous less direct evidence regarding the role of the phosphate group in influencing rotamer abundance when the carrier ligand has NH groups in the cis position.

Finally, the structure of $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(3'\text{-GMPH})]\text{NO}_3\cdot 5\text{H}_2\text{O}$ (**5**) establishes the validity of features deduced from NMR results for $\text{Pt}(\text{N}(\text{H})\text{dpa})\text{G}$ adducts⁶ that have a related tridentate ligand. In particular, the structure of **5** shows that the G nucleobase has low canting and that the carrier-ligand aromatic rings in a G adduct are tilted, as found in the parent chlorido complexes. In studies of $\text{Pt}(\text{N}(\text{H})\text{dpa})\text{G}$ adducts,⁶ the tilting of the pyridyl rings served to assign signals to the syn or anti rotamer. The structure of **5** provides a basis for creating models of the syn and anti rotamers. These models indicate that the H8 to H4/4' distance is longer in the syn than in the anti rotamer. The relevant cross-peak intensity is larger for the anti than for the syn signals, a finding that provides strong support for the validity of previous rotamer assignments⁶ based on the effect of carrier-ligand anisotropic groups on H8 chemical shifts.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.7b01176.

Superimposed structures of the cations of $[\text{Pt}(\text{N}(\text{R})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{BF}_4$ (R = H, Me), models of the syn and anti rotamers based on the molecular structure of **5**, structural features of the 3'-GMPH ligand in **5**, ROESY and ^1H - ^{13}C HSQC spectra of $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{-Cl}]\text{Cl}$, carrier-ligand assignments for $[\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{Cl}$, ROESY and ^1H - ^{13}C HSQC spectra of $[\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{Cl}$, ^1H NMR stack plot of $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{Cl}$ after addition of HCl, ^1H NMR stack plots of the reaction mixtures forming the $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GTP})$, $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(3'\text{-GMP})$, $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(\text{Ino})$, $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(1\text{-MeGuo})$, $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(9\text{-EtG})]^{2+}$, $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$, $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GTP})$, $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(3'\text{-GMP})$, and $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-IMP})$ adducts, selected regions of the ROESY and the ^1H - ^{13}C HSQC spectra of $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ and the ROESY spectrum of $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$, wide scans of the 1D ^1H NMR spectra of $\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma}$, $\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma}$, $[\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{Cl}$, and $[\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})\text{Cl}]\text{Cl}$ and final traces of reaction mixtures forming $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})(3'\text{-GMP})$ and $\text{Pt}(\text{N}(\text{Me})\text{-}1,1'\text{-Me}_2\text{dma})(5'\text{-GMP})$ adducts, and ^1H NMR data for $\text{Pt}(\text{N}(\text{H})\text{-}1,1'\text{-Me}_2\text{dma})\text{G}$ adducts in $\text{D}_2\text{O}/\text{DMSO}-d_6$ (PDF)

Accession Codes

CCDC 1548844–1548847 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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