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NMR and X-ray Structural Characterization of a Cisplatin Analogue Able To Slow Down the Pt−N7 Rotation of a Coordinated Guanine Base by a Billion-Fold Times: 2,2′-Bipiperidine(dimethylmalonato)platinum(II) Complex

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The synthesis and the NMR and X-ray structural characterization of a cisplatin analogue designed to reduce the Pt−N7 rotation of a coordinated guanine base by a billion times are reported. The [Pt(dmm){(±)-bip}] (dmm = dimethylmalonato; bip = 2,2′-bipiperidine) complex crystallizes in the *C*2/*m* space group, which contemplates a mirror plane bisecting the bip and dmm ligands. Because the bip moiety (*R*,*R* or *S*,*S* configuration at the 2,2′-carbon atoms) does not have planes of symmetry, the requirements of the crystal symmetry are satisfied by a statistical disorder made of bip molecules of *R*,*R* or *S*,*S* configurations alternating at the same crystallographic site. Such an unexpected arrangement has been permitted by a "quasi planarity" of the bip ligand [maximum deviation from the mean plane through the C and N atoms of 0.2927(9) Å], which allows bip molecules of different chiralities to fit in the same space. The bip array of heavy atoms is overlaid, from both sides, by a layer of "quasi axial" (C)H and (N)H atoms (six per side). Those on one side are hydrogen-bonded to the dmm oxygen atoms of another complex molecule joined in a pair. The distance between the average platinum coordination planes is as short as 3.498(1) Å, comparable to those found in crystals of the [$PtCl_2$(bipy)] complex (bipy = 2,2′-bipyridine) and of graphite, in which, however, all atoms of each unit are rigorously coplanar and there are no out-of-plane hydrogen atoms. The NMR data show a net chemical shift separation between geminal methylene protons, with the "quasi axial" protons being always at higher field with respect to the "quasi equatorial" ones. This is in accordance with a rigid bip ligand frame and the inability of the bip methylene protons adjacent to the coordinated nitrogen to rotate away from a *cis*-G base (*G* = guanine) during G rotation around the Pt−N7 bond.

Introduction

Cisplatin mainly targets DNA by binding to N7 of adjacent purines[1–6] of the same strand[7–10] or of opposite strands. The intrastrand adducts are thought to be the lesions that are responsible for cell death, but the mechanism is not entirely understood.

In solution, *cis*-$\mathbf{A}_2$Pt$\mathbf{G}_2$ complexes ($\mathbf{A}_2$ = two amines or a diamine and $\mathbf{G}_2$ = two detached or tethered guanine bases)

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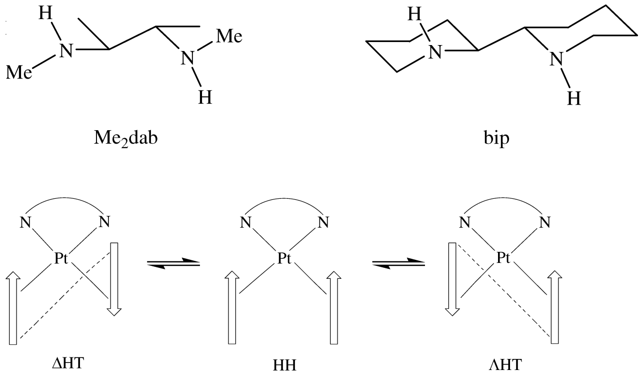
Chart 1. Schematic Drawing of Me$_2$dab and bip Ligands and Possible Conformers (Head-to-Head, HH, and Head-to-Tail, HT) of Complexes with Two *cis*-Guanine Ligands (Arrows with the Tip Representing H8)



usually exhibit unrestricted rotation about the Pt−N7 bond.[11–14] This results in great complexity in the investigation of dynamic nucleos(t)ide complexes. The structure in the solid state may be very different from that in solution because of crystal-packing interactions. In solution, because of fast interconversion between possible conformers, only one set of signals, the average of those of individual conformers, is observed.

The "dynamic motion problem" led us to construct analogues of cisplatin with bulky ligands designed to reduce the dynamic motion by destabilizing the transition state for Pt−N7 rotation. An important feature of the design was to minimize steric effects in the ground-state equilibrium species to allow conformers likely to be present in dynamic *cis*-$\mathbf{A}_2\mathrm{Pt}\mathbf{G}_2$ adducts to exist in the new adducts also. By reduction of the rotation rates by a billion-fold, these ligands enabled us to understand the adducts of the highly fluxional cisplatin drug with DNA constituents.[15]

N,*N*′-Dimethyl-2,3-diaminobutane (Me$_2$dab) was the first carrier ligand used in such a detailed NMR retro model study (Chart 1).[16–18] The 2,2′-bipiperidine ligand (bip) is analogous to Me$_2$dab but is much more sterically hindered. This rigidity has two components: first, the chelate ring is part of a three-ring system; second, the CH groups projecting toward the G coordination sites are unable to rotate away from the G bases during G base rotation around the Pt−N7 bond. The bip ligand was able to decrease the dynamic motion roughly a billion times with respect to $(NH_3)_2$ and ca. 100 times with respect to Me$_2$dab in *cis*-$\mathbf{A}_2\mathrm{Pt}\mathbf{G}_2$ complexes.[19–24] The use of Me$_2$dab and bip ligands allowed the simultaneous observation by ^{1}H NMR spectroscopy of all possible conformers (two HT and one HH conformers; Chart 1) that can be formed in *cis*-$\mathbf{A}_2\mathrm{Pt}\mathbf{G}_2$ complexes with a C_2-symmetrical carrier ligand.

Notwithstanding the big contribution that these ligands have given to the understanding of the structure and dynamics of platinum adducts with nucleobases in nucleotides and DNA, up to now no X-ray structure supporting the in-plane bulk of these ligands and the near absence of out-of-plane steric effects that could influence the ground-state equilibrium composition of different conformers present in dynamic *cis*-$\mathbf{A}_2\mathrm{Pt}\mathbf{G}_2$ adducts has been reported. Finally, we have succeeded in crystallizing the dimethylmalonato (dmm) derivative of bip-Pt, whose X-ray analysis has shown, beyond any doubt, a bip ligand squeezed into the platinum coordination plane. The details of the synthesis and of the enantiomeric resolution of the ligand and the NMR characterization of the complex are also described for the first time. Although the crystal was affected by disorder with two enantiomeric bip ligands alternating at the same site, the selection of good-quality crystals and adequate instrumentation, together with a careful choice of data collection conditions, has allowed us to reach remarkably low standard deviations on atomic positions and thermal parameters.

Experimental Section

Apparatuses. NMR spectra were run on Bruker Instruments Avance DPX 300 and Avance II 600 MHz. Standard Bruker automation programs were used for 2D NMR experiments. ^{1}H NMR chemical shifts were referenced to tetramethylsilane (TMS) by using the residual protic peak of the solvent as the internal reference (7.24 ppm for chloroform-d_1 and 4.76 ppm for HOD peak). ^{13}C NMR chemical shifts were referenced to TMS. IR spectra were obtained with a Perkin-Elmer Spectrum One IR spectrophotometer using KBr as a solid support for pellets. Elemental analyses were performed with a Carlo Erba elemental analyzer model 1106 instrument. High-performance liquid chromatography (HPLC) analysis was performed with a Waters system equipped with a U6-K universal injector, a model 626 solvent delivery system, UV/vis detector models 481 and 486, and a millennium 2010 workstation. Operating conditions were as follows: column (*R*,*R*)-dach-DNB (250 × 4 mm i.d.), column temperature 20 °C, mobile phase *n*-hexane/isopropyl alcohol (99:1, v/v), flow rate 1 mL/min. X-ray diffraction experiments were performed at 120 ± 2 K using a Nonius Kappa CCD area detector situated at the window of a rotating anode (EPSRC, National Crystallographic Service, School of Chemistry, University of Southampton, Southampton, U.K.), equipped with a low-temper-

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ature device Oxford Instruments cryo-stream.[25] Data were collected to a maximum 2θ value of 54° and processed through *SAINT-2*[26] and *XPREP*[27] software packages, whereas absorption corrections were performed using *SADABS*.[28]

Starting Materials. Commercial reagent-grade chemicals were used as received. 2,2′-Bipyridine (bipy) was purchased from Aldrich, and $[PtCl_2(DMSO)_2]$ (DMSO = dimethyl sulfoxide) was prepared according to a reported procedure.[29]

Preparation of (±)-2,2′-Bipiperidine (bip). bipy was reduced to bip by the method of Krumholz (metallic sodium in absolute ethanol) and then recovered by fractionated distillation under reduced pressure (0.05 mmHg, 60 °C).[30]

The separation of the racemic form from the meso form was accomplished by taking advantage of the different solubilities of the corresponding trifluoroacetyl derivatives in ethanol. Briefly, a solution of bip (28 g, 0.16 mol) in diethyl ether (0.5 L) cooled to 0 °C was treated with trifluoroacetic anhydride (70 g, 0.33 mol). The mixture was then brought to 25 °C and left under stirring for 24 h. The solution was evaporated to dryness, and the crude trifluoroacetyl derivatives of bip were recovered as a solid residue (45 g). Calcd for $C_{14}H_{18}F_6N_2O_2$ (M_w, 360.30): C, 46.67; H, 5.04; N, 7.78. Found: C, 47.00; H, 5.06; N, 7.73.

The solid residue was extracted with 95% ethanol (30 mL). The meso isomer, which is about 10 times less soluble than the (±)-racemic form in this solvent, remains as a solid residue and can be further purified by crystallization from hot ethanol, affording white needle-shaped crystals (20 g). Found: C, 46.15; H, 5.03; N, 7.65. ^1H NMR ($CDCl_3$, ppm): 5.10 (2H), 3.85 (2H), 3.15 (2H), 2.00−1.30 (12 H). HPLC: one peak on dach-DNB, eluent *n*-hexane/isopropyl alcohol (99:1, v/v).

The ethanolic extract containing the racemic form was concentrated to a small volume and kept at 4 °C. This allows precipitation of a solid fraction containing residual meso impurities. The solution was then filtered, and the (±)-racemic form was recovered by evaporation of the solvent under reduced pressure (15 g). Found: C, 46.60; H, 4.96; N, 7.50. ^1H NMR ($CDCl_3$, ppm): 5.15 (2H), 3.70 (2H), 3.50 (2H), 1.90−1.30 (12 H). HPLC: two peaks having the same area on dach-DNB, eluent *n*-hexane/isopropyl alcohol (99:1, v/v).

The conversion of the trifluoroacetylated forms into the corresponding dihydrochlorides was performed by dissolving the trifluoroacetyl derivatives (10 g) in a mixture (1:1, v/v; 0.3 L) of concentrated hydrochloric acid and methanol and warming to reflux for about 3 days. The formed dihydrochloride salts were recovered by filtration of the solution (yield 80%). Calcd for $C_{10}H_{22}N_2Cl_2$ (M_w, 241.20): C, 49.80; H, 9.19; N, 11.61. Found (meso form): C, 49.81; H, 9.16; N, 11.31. ^1H NMR (D_2O, ppm): 3.5−2.80 (6H), 2.12−1.36 (12H). Found (racemic form): C, 49.63; H, 9.47; N, 11.59. ^1H NMR (D_2O, ppm): 3.50−2.90 (6H), 2.00−1.40 (12H).

Separation of the Enantiomers of (±)-2,2′-Bipiperidine. The resolution of (±)-bip into the two enantiomers (+)-2,2′-bipiperidine [(*S*,*S*)-bip] and (−)-2,2′-bipiperidine [(*R*,*R*)-bip] was accomplished by using, as resolving agents, the ammonium salts of either D (1*R*) or L (1*S*) 3-bromo-1,7-dimethyl-2-oxobicyclo[2.2.1]heptane-8-sulfonate (D- or L-3-bromocamphor-8-sulfonate) and following the procedure already reported for the isolation of (−)-bip.[31] Briefly, free (±)-bip and $Na_3[Co(NO_2)_6]$ were allowed to react in water at 60 °C and then to cool at 5 °C to afford a precipitate composed of a 1:1 mixture of *trans*-$[Co(NO_2)_2\{(+)\text{-bip}\}_2](NO_2)$ and *trans*-$[Co(NO_2)_2\{(-)\text{-bip}\}_2](NO_2)$. The precipitate was dissolved in water at 60 °C and treated with ammonium D-3-bromocamphor-8-sulfonate, (NH_4)(D-Y), at a 1:1 ratio. By slow cooling of the solution down to 0 °C, yellow needlelike crystals of *trans*-$[Co(NO_2)_2\{(-)\text{-bip}\}_2]$(D-Y) separated out. The precipitate was crystallized a few more times under similar conditions and finally passed through a column of Amberlite anion-exchange resin (NO_2^- form) to remove the resolving agent (D-Y) and get back the nitrito salt that was isolated from the eluted water solution by evaporation of the solvent under reduced pressure. The diamine was recovered from the Co^{III} complex by reduction with hydrazine hydrochloride (0.1 g) of *trans*-$[Co(NO_2)_2\{(-)\text{-bip}\}_2](NO_2)$ (1.2 g) dissolved in water (10 mL), layered under *n*-hexane (200 mL), and treated with a large excess of KOH pellets (10 g). After refluxing of the mixture for 2 h and cooling back to room temperature, the organic phase was separated, treated with gaseous HCl, and taken to dryness by evaporation of the solvent under reduced pressure, affording a white solid of (−)-2,2′-bipiperidine dihydrochloride (0.5 g). Found: C, 49.59; H, 9.45; N, 11.72. ^1H NMR (D_2O, ppm): 3.50−2.90 (6H), 2.00−1.40 (12H).

An analogous procedure was used to separate the (+)-bip enantiomer. In this case, the resolving agent was the ammonium salt of L-3-bromocamphor-8-sulfonate, (NH_4)(L-Y). Found: C, 49.69; H, 9.26; N, 11.51. ^1H NMR (D_2O, ppm): 3.50−2.90 (6H), 2.00−1.40 (12H). The enantiomeric purity (ca. 98%) was checked on an (*R*,*R*)-dach-DNB chiral colum after derivatization of the diamine with trifluoroacetic anhydride.

Preparation of $[PtCl_2\{(\pm)\text{-bip}\}]$ and $[Pt(NO_3)_2\{(\pm)\text{-bip}\}]$. The $[PtCl_2\{(\pm)\text{-bip}\}]$ complex was prepared by the reaction of *cis*-$[PtCl_2(DMSO)_2]$ with racemic (±)-bip. In a typical experiment, a suspension of *cis*-$[PtCl_2(DMSO)_2]$ (0.42 g, 1 mmol) in methanol (90 mL) was treated with a solution containing a stoichiometric amount of bip (1 mmol) in the same solvent (10 mL). After stirring for a few hours, the initial suspension transformed into a colorless solution, from which a yellow solid started to precipitate. After standing overnight, the solution was filtered and the collected yellow precipitate washed with water and dried in vacuo (yield 80%). The compound proved to be pure $[PtCl_2\{(\pm)\text{-bip}\}]$. Anal. Calcd for $C_{10}H_{20}Cl_2N_2Pt$ (M_w, 434.26): C, 27.66; H, 4.64; N, 6.45. Found: C, 28.10; H, 4.74; N, 6.32.

The nitrato compound was obtained by the reaction of the chlorido compound with $AgNO_3$. In a typical experiment, $[PtCl_2\{(\pm)\text{-bip}\}]$ (1 mmol) was suspended in acetone (150 mL) and treated with a stoichiometric amount of $AgNO_3$ (2 mmol dissolved in 5 mL of water). After stirring for 6 h at room temperature in the dark, the solution was filtered through Celite and evaporated to dryness. The white solid residue proved to be the nitrato compound. Anal. Calcd for $C_{10}H_{20}N_4O_6Pt$ (M_w, 487.37): C, 24.64; H, 4.14; N, 11.50. Found: C, 25.11; H, 4.30; N, 11.72.

Preparation of $[Pt(dmm)\{(\pm)\text{-bip}\}]$. A solution of $[Pt(NO_3)_2\{(\pm)\text{-bip}\}]$ (0.157 g, 0.322 mmol) in water (10 mL) was treated with $K_2[(CH_3)_2C(COO)_2]$ (0.100 g, 0.48 mmol) and then heated to 50 °C for 0.5 h. The clear solution was left at 4 °C for several days, while crystals of the title compound separated from the solution. These were collected on a sintered glass filter and dried (yield 40%). Calcd for $C_{15}H_{26}N_2O_4Pt\cdot H_2O$ (M_w, 511.47): C, 35.22; H, 5.52; N, 5.48. Found: C, 35.57; H, 5.64; N, 5.49.

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Table 1. Selected Crystallographic Data for [Pt(dmm){(±)-bip}]·4H_2O

parameter	value
empirical formula	$C_{15}H_{34}N_2O_8Pt$
fw	565.52
temperature (K)	120(2)
wavelength (Å)	0.710 73
cryst syst	monoclinic
space group	*C*2/*m*
unit cell dimensions	
a (Å)	13.078(3)
b (Å)	15.063(3)
c (Å)	10.485(2)
β (deg)	106.90(3)
volume (Å^3)	1976.3(7)
Z	4
D_{calcd} (Mg/m^3)	1.901
abs coeff (mm^{-1})	7.130
F(000)	1120
cryst size (mm^3)	0.2 × 0.2 × 0.1
reflns collected	8916
indep reflns	2350 [*R*(int) = 0.0227]
refinement method	full-matrix least squares on F^2
data/restraints/param	2350/2/218
GOF on F^2	0.759
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0168, wR2 = 0.0418
R indices (all data)	R1 = 0.0176, wR2 = 0.0424

^{1}H NMR [H_2O/D_2O (9:1 v/v), ppm]: 5.72 (2H, *H*N), 3.09 (2H, $H_{6\mathrm{eq}}$), 2.64 (2H, $H_{6\mathrm{ax}}$), 2.29 (2H, H_2), 1.76 (2H, $H_{4\mathrm{eq}}$), 1.70 (6H, C*H*$_3$), 1.67 (2H, $H_{3\mathrm{eq}}$). 1.52 (2H, $H_{5\mathrm{eq}}$), 1.45 (2H, $H_{5\mathrm{ax}}$), 1.41 (2H, $H_{4\mathrm{ax}}$), 1.17 (2H, $H_{3\mathrm{ax}}$). ^{13}C [H_2O/D_2O (9:1, v/v), ppm]: 69.89 (C_2), 50.97 (C_6), 25.60 (C_3), 25.10 (CH_3), 24.46 (C_5), 22.54 (C_4).

X-ray Diffraction. A data set for crystals of [Pt(dmm)(bip)] was initially collected at room temperature with a Siemens P4 machine working under *XSCANS* software. The symmetry of the crystal was consistent with that of the monoclinic system, and the lattice type was C. No specific systematic absences consistent with other lattice types were detected.

The analysis of statistics on intensities was in agreement with an acentric space group; therefore, the structure solution and refinement was performed in the space group *C*2. The best refinement for all of the atoms of the complex molecule and for the oxygen atoms of the four water molecules gave R1 = 0.0547. At least four atoms (two oxygen and two nitrogen atoms from the complex molecule) had nonpositive-definite anisotropic *U* values, and some bond distances and angles were unrealistic [e.g., Pt−N(bip) 1.335 Å, Pt−O(dmm) 1.508 Å, and N−C(bip) 1.780 Å; C−N−C(bip) 85.0°]. Because the statistics on intensities are significant only if all atoms have comparable size (in other words, crystals containing platinum and carbon, hydrogen, nitrogen, and oxygen atoms may fail to respect the statistics on intensities), it was decided to solve and refine the structure in the centric space group *C*2/*m*. However, because the bip molecule (*R*,*R* or *S*,*S* configuration at the C2 carbon atoms) cannot have such a mirror plane, the requirements of the crystal symmetry could only be satisfied by a statistical disorder where ligand molecules with *R*,*R* and *S*,*S* configurations alternate at the same crystallographic site. The refinement converged to R1 = 0.0428, and no atom had nonpositive-definite anisotropic *U* values; moreover, all bond distances and angles and estimated standard deviations were reasonable.

At this stage of the study, a new data collection was performed at low temperature (120 K) using a more powerful machine (see the Apparatuses section) and a well-formed colorless crystal of dimensions 0.20 × 0.20 × 0.10 mm (Table 1). Full details are given only for this latter data collection and processing. The structure was solved and refined in the *C*2/*m* space group via *SHELX-97*[27] by using direct methods, followed by a series of difference Fourier syntheses and least-squares cycles.

The disorder of the bip ligand was solved without restraints on the geometrical parameters. For each set of bip nitrogen and carbon atoms was assigned a statistical occupancy factor (sof) of 0.5. The difference Fourier map, computed after all the atoms were located, showed a significant elongation of the thermal ellipsoids for the platinum-bound oxygen atoms of the dmm ligand, in a direction essentially perpendicular to the coordination plane. The *SHELX-97* package suggested splitting of the oxygen donor atoms into two positions. This was done by imposing sof = 0.5 to each position. All of the thermal parameters for bip atoms from the two sets as well as those for the atoms from dmm converged to reasonable values; thus, the assignment of sof = 0.5 was considered correct. There are two water molecules per asymmetric unit (four water molecules per molecule of the complex). The thermal parameters for the oxygen atom of the water molecule that donates a hydrogen bond to a carboxylato group are normal, whereas those relevant to the water molecule that accepts a hydrogen bond from the bip moiety are much larger. This is in agreement with some disorder in the latter water molecule, which reflects the disorder of the bip ligand to which the water molecule is hydrogen-bonded. Because the *SHELX-97* package does not suggest any splitting for this oxygen atom, the final model contemplates only one position with sof = 1. All of the hydrogen atoms from bip were located through the HFIX and AFIX options of *SHELX-97* and restrained to ride on the atoms to which they are bound. Their thermal parameters were refined isotropically, and the values were 1.2 times those of the nitrogen or carbon atoms to which they are bonded. The hydrogen atoms from dmm and from the water molecules were located through the difference Fourier maps and their positions refined freely; their thermal parameters were refined freely and treated as isotropic. Furthermore, Fourier calculations at this stage showed that O2W is surrounded by two more peaks that are reasonably attributable to two further hydrogen atoms. The presence of these additional peaks suggests that the water molecule is disordered in such a way as to present at least two different orientations, while the oxygen atom is almost in the same location (this is in agreement with the relatively high values for the thermal parameters for O2W). Owing to the difficulty in refining hydrogen atoms with sof < 1, it was decided to include just two hydrogen atoms (those that fit the requirements for N−H···O2W and C−H···O2W hydrogen bonds) in the subsequent cycles of the refinement. However, it has to be noted that the short O2W···O2W_4 contact [2.794(10) Å] agrees with the presence of a water−water hydrogen bond. All of the non-hydrogen atoms were refined anisotropically. All of the attempts aimed at solving and refining the structure in other crystal systems and space groups failed. The conventional R1 and wR2 agreement factors converged down to 0.0168 and 0.0424, respectively. All computations relevant to the X-ray analyses were performed via the *WinGX* software package,[32] implemented on Pentium machines operating under the Windows-XP system.

Results and Discussion

Although the Pt-bip complexes have been extensively used to investigate adducts with nucleotides and DNA, the full

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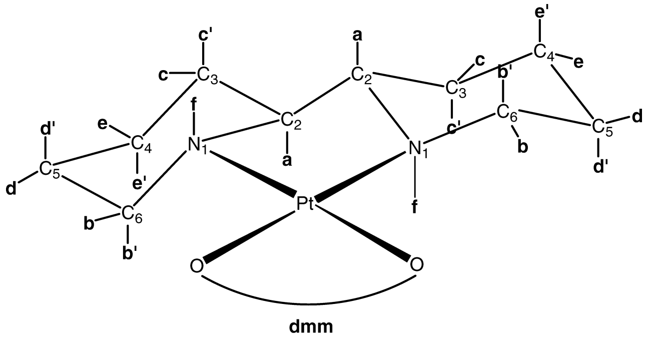
(32) (a) Farrugia, L. J. *WinGX an Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-Ray Diffraction Data*, version 1.64.05; University of Glasgow: Glasgow, U.K., 1999−2003. (b) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

Chart 2. Schematic Representation of [Pt(dmm){(±)-bip}][a]



[a] The carbon and nitrogen atoms are numbered according to IUPAC rules. Close to each hydrogen atom is the letter marking the corresponding cross peak in the $^1H-^{13}C$ HETCOR NMR spectrum. The numbering of the hydrogen atoms (not shown in the scheme) is the same as that of the carbon atoms to which they are attached and are distinguished as "quasi equatorial" (eq) and "quasi axial" (ax). For instance, b corresponds to H_{6eq}. dmm stands for dimethylmalonate.

details of their synthesis and their structural characterization by NMR and X-ray crystallography have never been reported. The synthesis of the bip ligand by reduction of bipy[30] and the separation of (*R*,*R*)-bip by complexation to Co^{III} and fractional crystallization of *trans*-$[Co(NO_2)_2\{(R,R)\text{-bip}\}_2](1R\text{-3-bromocamphor-8-sulfonate})$[31] have already been reported. Our innovations with respect to the reported procedures were (i) the trifluoroacetyl derivatization of bip to accomplish the separation of the *meso*-bip from racemic (±)-bip by fractional crystallization from ethanol, (ii) the use of 1*S*-3-bromocamphor-8-sulfonate for the fractional crystallization of *trans*-$[Co(NO_2)_2\{(S,S)\text{-bip}\}_2](1S\text{-3-bromocamphor-8-sulfonate})$ never isolated before, and (iii) the use of hydrazine as a reducing agent for Co^{III}. The purity of the enantiomers was checked by HPLC using a (*R*,*R*)-dach-DMB column and was found to be very high (about 98%).

The synthesis of the complexes was accomplished by the reaction of the bip ligand with *cis*-$[PtCl_2(DMSO)_2]$ in methanol. The initially formed colorless [PtCl(DMSO)(bip)]Cl complex, upon standing in solution, transforms into $[PtCl_2(bip)]$, which precipitates from solution as a yellow crystalline solid. The dmm derivative used for the NMR and X-ray structural characterization was obtained from the chloro species, which was first converted to the nitrato species by reaction with $Ag(NO_3)$ in acetone/water (150:5, v/v) and then to the dmm species by reaction with $K_2(dmm)$ in water.

NMR Characterization of [Pt(dmm)(bip)]. The full assignment of ^1H and ^{13}C NMR signals for the [Pt(dmm){(±)-bip}] complex has been accomplished by using 1D and 2D NMR methods. The presence of a 2-fold axis of symmetry makes the halves of the molecule magnetically equivalent; therefore, 5 carbon and 10 hydrogen signals are expected for bip (Chart 2).

The cross peaks in the $^1H-^{13}C$ HETCOR NMR spectrum (Figure 1) were labeled with letters from a−e, starting from those having less shielded ^{13}C NMR signals. When for a given value of the ^{13}C NMR chemical shift there were two cross peaks differing for the ^1H NMR chemical shift, the two peaks were labeled with the same letter but a prime was added to the letter labeling the more shielded ^1H NMR signal [therefore, the same letter identifies the carbon and the attached hydrogen atom(s)].

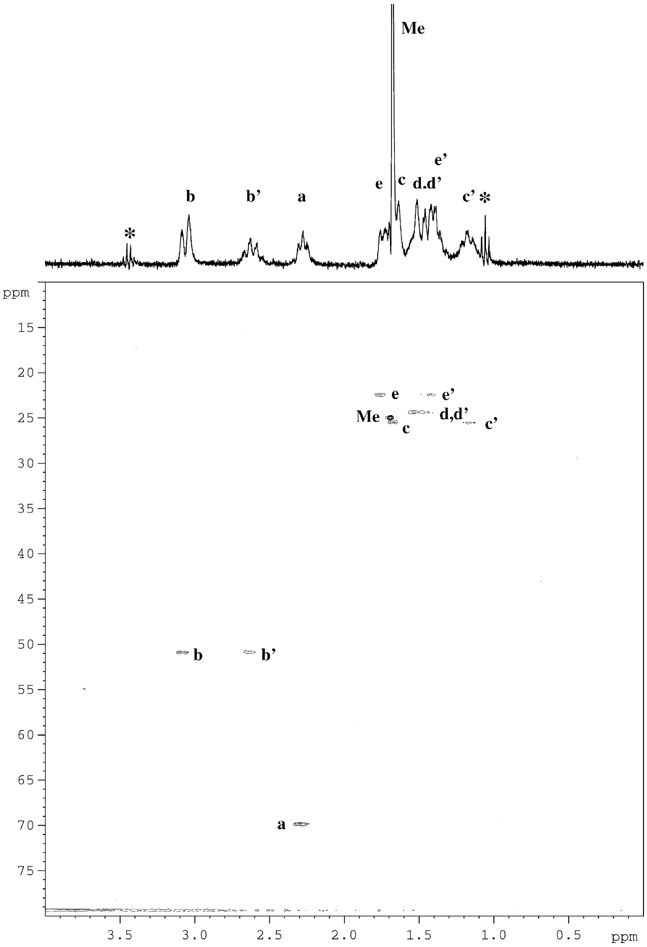


Figure 1. 2D $^1H-^{13}C$ HETCOR NMR spectrum of [Pt(dmm){(±)-bip}] in H_2O/D_2O (9:1) using solvent suppression. The cross peaks are labeled by conventional letters starting from the less shielded ^{13}C NMR signals. Where for a given value of the ^{13}C NMR chemical shift there are two cross peaks differing for the ^1H NMR chemical shift, the two cross peaks are labeled with the same letter but a prime is added to the letter labeling the more shielded signal. Asterisks mark impurities.

The signals in the $^1H-^{13}C$ HETCOR NMR spectrum fall in three different regions. The carbon signal at lowest field (69.89 ppm, a) is coupled with only one proton; therefore, it can be assigned directly to the tertiary carbon atom (C_2 according to IUPAC numbering; Chart 2). The small shielding of this carbon is in accordance with it being adjacent to an electron-attracting nitrogen atom. The second less-shielded carbon falls at 50.79 ppm and is coupled to two protons; therefore, it can be identified with the methylene group directly bonded to the nitrogen atom (C_6 in Chart 2). Finally, the remaining carbon signals falling in the range 25.0−20.0 ppm must belong to methylene groups that are not contiguous to nitrogen atoms (C_3, C_4, and C_5 in Chart 2). In the same region also fall the methyl groups of dmm.

The chemical shifts of carbons C_3, C_4, and C_5 and of individual methylene protons were assigned with the help of the 2D NOESY NMR spectrum shown in Figure 2.

The 1D ^1H NMR spectrum (top of Figure 2) shows, in addition to the (C)H signals (for which we have kept the

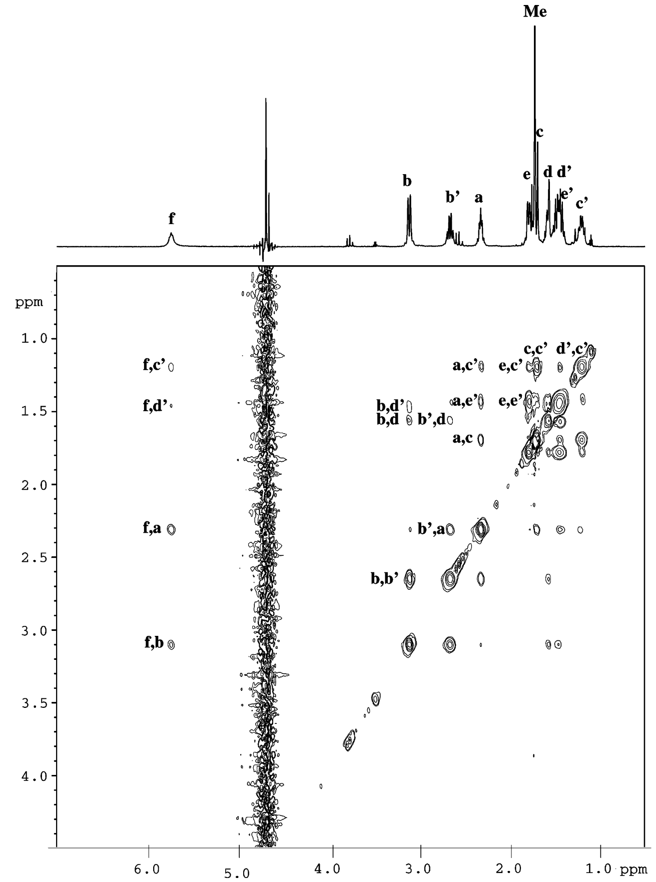


Figure 2. 2D NOESY NMR spectrum of [Pt(dmm){(±)-bip}] in H_2O/D_2O (9:1) using solvent suppression. The cross peaks are labeled by conventional letters as in Figure 1.

same labeling as that in Figure 1), also a signal (f) at 5.7 ppm belonging to the aminic proton (H_{1ax} with reference to Chart 2). Proton f has NOE cross peaks with b (a proton bound to the C_6 carbon) but not with b′. From inspection of Chart 2, we can see how only H_{6eq} comes close to N_1H (H_{1ax}); therefore, we can assign proton b to H_{6eq} and, consequently, b′ to H_{6ax}. Proton b (H_{6eq}) has intense cross peaks with protons d and d′, while proton b′ (H_{6ax}) has a cross peak only with d; therefore, we can assign d to H_{5eq} and d′ to H_{5ax}. It remains to assign the groups of protons c and c′ and e and e′. Proton f (H_{1ax}) has a cross peak with proton c′ but not with c. This assigns c′ to H_{3ax} and c to H_{3eq}. Finally, proton a (H_{2ax}) has an intense cross peak with e′ but not with e; this assigns e′ to H_{4ax} and e to H_{4eq}. All other cross peaks observed in the NOESY NMR spectrum are in agreement with the given assignment.

The assignment of the proton signals also fixes the assignment of the carbon resonances; therefore, c−e carbon resonances ($^1H-^{13}C$ HETCOR NMR spectrum) belong to C_3, C_5, and C_4 carbons, respectively.

X-ray Structure. The asymmetric unit comprises only half of a molecule of the complex. This result was rather unexpected because, starting with racemic bip, we expected to find in the crystal enantiomeric molecules containing (*R*,*R*)- and (*S*,*S*)-bip, respectively. However, the X-ray investigation has shown that, instead of having separate molecules with enantiomeric bip ligands, there is only one molecule with a disordered ligand [either (*R*,*R*)- or (*S*,*S*)-bip].

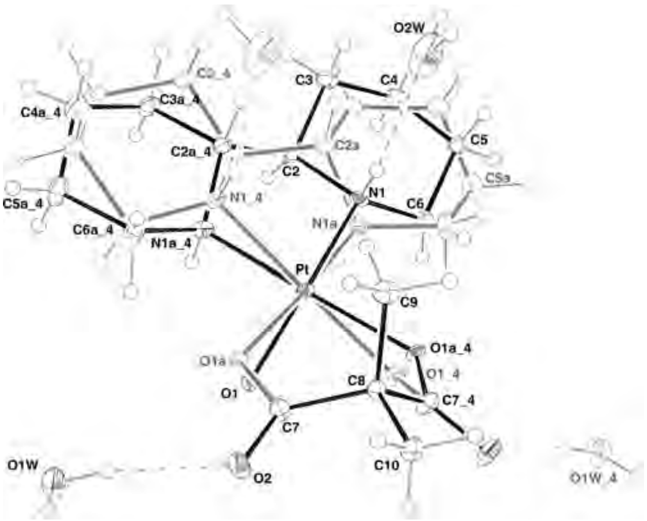


Figure 3. ORTEP representation of the molecular structure for [Pt(dmm){(±)-bip}]·$4H_2O$. The second set of coordinates for bip and dmm oxygen donor atoms is labeled with a. The symbol extension _4 means that the symmetry operation *x*, −*y*, *z* is applied to the coordinates from the asymmetric unit set. Significant hydrogen bonds that involve water molecules are represented by dashed lines. Ellipsoids enclose 30% probability.

The complex molecule and the four water molecules of crystallization are represented in Figure 3; selected bond lengths and angles are reported in Table 2.

dmm Ligand. In the asymmetric unit comprising half of a complex molecule, the C8 atom bridging the two carboxylic groups of dmm and the carbon atoms of the two methyl groups lie on a crystallographic mirror plane comprising also the platinum atom. They have regular bond distances and angles [average 1.533(3) Å and 108.8(3)°, respectively] and regular thermal parameters. Their hydrogen atoms were located by the difference Fourier map and refined freely without any restraint for the positions and thermal parameters [final C−H bond distances in the range 0.94(4)−0.98(3) Å and H−C−X bond angles in the range 105(2)−119(2)°].

Also the platinum atom and the dmm carboxylic group had regular thermal parameters with the exception of only the platinum-bonded oxygen, which had an anomalously elongated thermal ellipsoid, the elongation being essentially perpendicular to the coordination plane. The *SHELXL-97* software package suggested two possible positions for this oxygen, with occupancy factors (sof) of 0.5. Upon refinement of the model with O1 and O1a in the two positions suggested by the package, a nice convergence was reached. The anisotropic treatment for O1 and O1a produced reasonable thermal ellipsoids. The carboxylic group is essentially planar [maximum deviations 0.0700(10) and 0.0625(10) Å for C7 in *R*,*R* and *S*,*S* isomers, respectively]. The C−O bond distance involving the platinum-coordinated oxygen is 1.308(8) Å, whereas that involving the noncoordinated oxygen is 1.229(3) Å. This is in agreement with corresponding values for monodentate carboxylato ligands.[33]

It appears clear from this analysis that the platinum and dmm ligand atoms (with the exception of only the two

Table 2. Selected Bond Distances (Å) and Angles (deg) for [Pt(dmm){(±)-bip}]·$4H_2O$[a]

Pt1−N1	2.053(6)	N1−C2	1.508(9)	O1−Pt1−O1a#4	87.8(2)
Pt1−N1a#4	1.983(6)	C2−C3	1.515(9)	O1−Pt1−N1a#4	95.8(3)
Pt1−O1	2.001(8)	C3−C4	1.523(9)	N1a#4−Pt1−N1	84.0(2)
Pt1−O1a#4	2.053(7)	C4−C5	1.501(10)	O1a#4−Pt1−N1	92.5(3)
O1−C7	1.307(8)	C5−C6	1.525(9)	Pt1−N1−C2	107.4(4)
O1a#4−C7#4	1.308(7)	C6−N1	1.470(9)	Pt1−N1a#4−C2a#4	110.7(4)
C7−C8	1.537(3)	N1a#4−C2a#4	1.486(9)	C2−N1−C6	111.6(5)
C7−O2	1.229(3)	C2a#4−C3a#4	1.515(9)	C2a#4−N1a#4−C6a#4	111.5(5)
C8−C9	1.542(5)	C3a#4−C4a#4	1.519(10)	O1−C7−O2	120.5(4)
C8−C10	1.517(5)	C4a#4−C5a#4	1.500(11)	O1−C7−C8	118.1(4)
C2−C2a#4	1.519(10)	C5a#4−C6a#4	1.502(9)	C7−C8−C9	110.1(2)
		C6a#4−N1a#4	1.472(9)	C7−C8−C10	110.3(2)

[a] The symmetry transformation (#4) used to generate equivalent atoms is *x*, −*y*, *z*.

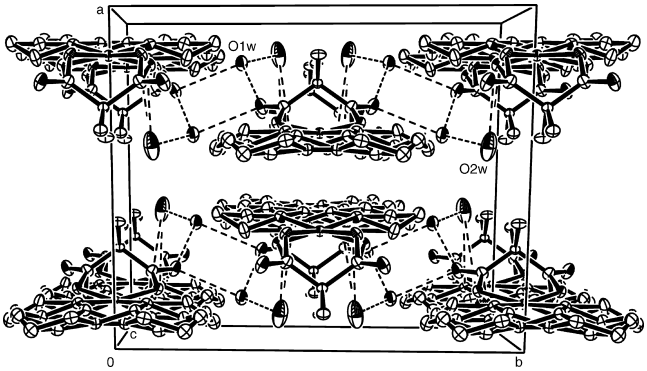


Figure 4. View of the packing along the *c* cell edge for [Pt(dmm){(±)-bip}]·$4H_2O$.

platinum-bonded oxygen atoms) are not affected by disorder, so that a large part of the electron density of the asymmetric unit for this space group fits well the real molecule.

bip Ligand. The crystallographic mirror plane passing through Pt, C8, C9, and C10 does not fit the structure with a single configuration for the chelating bip molecule. The bip ligand can have either a *R*,*R* or *S*,*S* configuration at the asymmetric carbon atoms, and none of them admits a plane of symmetry. However, if this portion of the complex molecule is disordered and bip ligands of *R*,*R* and *S*,*S* configurations alternate at the Pt(dmm) coordination sites with equal sof (0.5), the average situation could mimic the crystallographic symmetry plane required by the *C*2/*m* space group. Therefore, the structure was solved assuming a statistical disorder for the bip ligand with a sof of 0.5 for the *R*,*R* and *S*,*S* enantiomers.

For both bip configurations, bond distances and angles have regular values, with C−N distances (1.470−1.508 Å) slightly shorter than C−C distances (1.500−1.525 Å).

Coordination Sphere. The coordination arrangement around platinum is square-planar with bond angles of 83.9(2)° (N−Pt−N), 87.8(2)° (O−Pt−O), and 95.8(3)° and 92.6(3)° (N−Pt−O), totaling 360.1°, so that the metal center is sitting on the least-squares plane defined by the four donors [deviation of platinum, 0.0119(8) Å].

The two Pt−O bond distances are 2.001(8) and 2.053(8) Å, whereas the two Pt−N bond lengths are 1.980(6) and 2.053(6) Å, respectively. It has to be noted that the differences in the bond distances and angles can be rationalized by taking into account the structural disorder and the different hydrogen-bonding patterns of the cocrystallized water molecules.

Crystal Packing. A view of the crystal packing along the *c* cell edge is shown in Figure 4. It can be seen how the complex molecules are assembled in layers extending in the *b*/*c* directions. The interactions between complex molecules of the same layer are mediated by water molecules of crystallization, while the interactions between layers are provided by direct hydrogen bonds involving complex molecules of different layers and will be described in the following section. There are two water molecules, O1W and O2W, per asymmetric unit (four water molecules per molecule of complex). The oxygen atom O1W is hydrogen-bonded to the dmm O2 atom of the same asymmetric unit [*x*, *y*, *z*, O···O 2.817(10) Å and O−H···O 166.2(1)°] and to the dmm O2 and the water of an adjacent unit [1.5 − *x*, 0.5 − *y*, 1 − *z*, O···O 2.890(10) Å and O−H···O 170(1)°; 1.5 − *x*, 0.5 + *y*, 2 − *z* O···O 2.826(10) Å and O−H···O 174(1)°]. O2W is hydrogen-bonded to the bip N1 or C2a atom [*x*, *y*, *z* N···O 3.330(10) Å, N−H···O 162(1)° or *x*, −*y*, *z* C···O 3.359(10) Å and C−H···O 145(1)°] and to the water O2W [*x*, −*y*, *z* O···O 2.794(10) Å]. It has already been noted that a certain degree of disorder (or a high thermal motion) for the O2W water molecule was deduced from the shape and size of the relevant ellipsoid. This is the consequence of the water molecule having to fit different positions in order to optimize hydrogen bonds with either the N−H or C−H of the proximal bip ligand.

Association of Molecules in Pairs. It has already been anticipated that the interactions between layers of complex molecules extending in the *b*/*c* directions are provided by hydrogen bonds between complex molecules of adjacent layers; these involve bip (N)H and (C)H atoms of one complex molecule and dmm oxygen atoms of the twin molecule. As a consequence, the complex molecules result associated in pairs (Figure 5). Within a pair, the distance between average planes through twin molecules is 3.498(1) Å. As a matter of comparison, the distance between bipy planes in stacking [$PtCl_2$(bipy)] complexes is 3.402 and 3.321 Å at 294 and 20 K, respectively,[34] and 3.40 Å in graphite.

However, it should be noted that while in the latter two cases all atoms of each molecule (the [$PtCl_2$(bipy)] molecule

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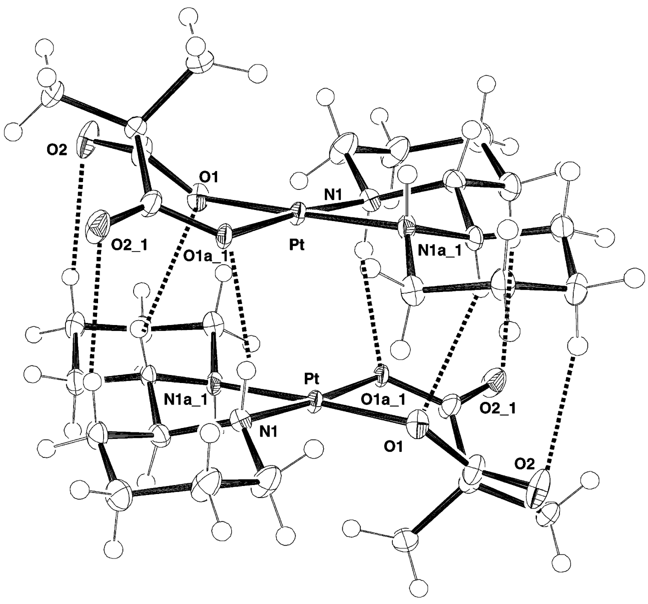

Figure 5. Hydrogen bonds in a pair of [Pt(dmm){(±)-bip}] molecules.

or the sheet of carbon atoms in graphite) lie exactly in a plane, this is not the case for the bip complex, where the frame of heavy atoms is not rigorously planar and, furthermore, it is coated by a sheet of "quasi axial" (C)H and (N)H atoms that are displaced by ca. 0.95 Å from the average plane through the C and N atoms. Nevertheless, the distance between the coordination planes of twin molecules is as short as 3.498(1) Å. We believe that in the present case the intermediate sheet of "quasi axial" (N)H and (C)H atoms, far from creating steric impediment, promotes the closer approach of the planes of the two complex molecules by forming a network of hydrogen bonds (eight) involving bip N−H (one) and C−H (three) protons of one molecule and dmm oxygen atoms (four) of the twin molecule.

As expected, the strongest hydrogen bond involves the aminic proton (N1···O1 2.57 Å, N−H···O 163.3°); however, those also involving methylene protons are rather strong (C2···O1 2.50 Å, C2−H···O 135.4°; C3···O2 2.93 Å, C3−H···O2 168.8°; C4···O2 2.99 Å, C4−H···O2 161.9°). Thus, the X-ray structure has shown that in the bip ligand all heavy atoms are squeezed in a plane (maximum deviation from the average plane through the C and N atoms of 0.2927(9) Å for N1 in *R*,*R* and N1_4 in *S*,*S* isomers) and are overlaid by sheets of "quasi axial" (N)H and (C)H atoms (six hydrogen atoms per side). As a consequence, the steric bulk and the hydrogen-bonding properties of the bip ligand become "quasi independent" from its configuration (*R*,*R* or *S*,*S*), so explaining why bip ligands of opposite configurations can occupy the same crystallographic sites.

Conclusions

As pointed out in the Introduction, a major aim of this investigation was a structural characterization of the bip carrier ligand, which could account for the billion times decrease in the dynamic motion of G's in **bip**Pt**G**$_2$ relative to *cis*-$(NH_3)_2$Pt**G**$_2$ adducts.

The synthesis of the ligand and the separation of the meso form from the racemic form were rather straightforward and were accomplished by using standard procedures. However, we introduced some significant innovations such as (i) the trifluoroacetyl derivatization of bip to accomplish the separation of the *meso*-bip from racemic (±)-bip by fractional crystallization from ethanol, (ii) the use of 1*S*-3-bromocamphor-8-sulfonate for the fractional crystallization of *trans*-$[Co(NO_2)_2\{(S,S)\text{-bip}\}_2]$(1*S*-3-bromocamphor-8-sulfonate), which leads to the isolation of the pure (*S*,*S*)-bip enantiomer for the first time, and (iii) the use of hydrazine as a reducing agent for Co^{III}.

Also the ^1H and ^{13}C NMR characterization of the [Pt(dmm)(bip)] complex was rather straightforward. The rigidity of the bip ligand allowed observation of very nice well-defined NOESY cross peaks and therefrom assignment of individual ^1H and ^{13}C NMR resonances. It is to be noted that for geminal methylene protons the one with "quasi axial" character was always more shielded than that with "quasi equatorial" character. The difference was greatest for the methylenes directly attached to the chelate ring, C_3H_2 (0.50 ppm) and C_6H_2 (0.45 ppm). The large chemical shift difference between H_{ax} and H_{eq} emphasizes, once more, the great rigidity of the bip framework, which is entangled in a three-ring system, and the inability of H_{6eq} to rotate away from a *cis*-G base during G rotation around the Pt−N7 bond in **bip**Pt**G**$_2$ adducts. This explains the billion times decrease in dynamic motion of bip relative to $(NH_3)_2$ derivatives.

The X-ray structure has revealed an unexpected coplanarity of the carbon and nitrogen atoms of the bip framework with deviations from the mean plane through these atoms, ≤0.2927(10) Å. Also "quasi equatorial" methylene protons lie in the same plane. Our major objective, in designing this ligand, was to create the greatest in-plane steric hindrance, so as to reduce the dynamic motion by destabilizing the transition state for Pt−N7 rotation, accompanied by the smallest out-of-plane steric effect, so as to allow conformers likely to be present in dynamic *cis*-**A**$_2$Pt**G**$_2$ adducts to be present in the new adducts also. Both requisites appear to be fulfilled by the bip ligand, whose remarkable planarity allows different enantiomers to fit the same crystallographic site.

It is interesting to note that the "quasi axial" (C)H and (N)H atoms, six hydrogen atoms on each side of the frame of heavy carbon and nitrogen atoms, are "positively charged" (particularly NH and C_2H) and therefore ideally suited to form hydrogen bonds with cocrystallized water molecules or with the dmm oxygen atoms of a twin complex molecule. The surprising result is that pairs of complex molecules come close together with a distance between average coordination planes as small as 3.498(1) Å, comparable to that observed in the $[PtCl_2(bipy)]$ complex and in graphite in which, however, all atoms of each subunit were perfectly coplanar. Finally, the dmm carbon atoms rising out of the coordination plane are accommodated in the inner part of the layer of complex molecules glued by water molecules of crystallization and extending in the *b*/*c* directions, so that each layer can now exhibit very smooth external surfaces and can be packed very closely [3.498(1) Å distance] along the *a* direction. We are currently exploiting how the choice of anionic ligands with different steric requirements (e.g., oxalate instead of dmm) can affect crystal packing and solid-state properties.

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Supporting Information Available: X-ray crystallographic data in CIF format. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (deposition numbers, CCDC 685927) or via the Internet at http://pubs.acs.org.

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