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Synthesis and Characterization of Pt(II) Complexes with Pyridyl Ligands: Elongated Octahedral Ion Pairs and Other Factors Influencing $^1$H NMR Spectra

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Supporting Information

ABSTRACT: Our goal is to develop convenient methods for obtaining trans-$\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ complexes applicable to 4-substituted pyridines (4-Xpy) with limited volatility and water solubility, properties typical of 4-Xpy, with X being a moiety targeting drug delivery. Treatment of cis-$\left[\text{Pt}^{II}(\text{DMSO})_2\text{Cl}_2\right]$ (DMSO = dimethyl sulfoxide) with 4-Xpy in acetonitrile allowed isolation of a new series of simple trans-$\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ complexes. A side product with very downfield H2/6 signals led to our synthesis of a series of new $\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ salts. For both series in CDCl$_3$, the size of the H2/6 $\Delta$ [coordinated minus “free” 4-Xpy H2/6 shift] decreased as 4-Xpy donor ability increased from 4-CNpy to 4-Me$_2$Npy. This finding can be attributed to the greater synergistic reduction in the inductive effect of the Pt(II) center with increased 4-Xpy donor ability. The high solubility of $\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ salts in CDCl$_3$ (a solvent with low polarity) and the very downfield shift of the $\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ H2/6 signals for the solutions provide evidence for the presence of strong $\left\{\left[\text{Pt}^{II}(4-X\text{py})_4\right]^2-,2\text{Cl}^-\right\}$ ion pairs that are stabilized by multiple CH···Cl contacts. This conclusion gains considerable support from $\left[\text{Pt}^{II}(4-X\text{py})_4\right]\text{Cl}_2$ crystal structures revealing that a chloride anion occupies a pseudoaxial position with nonbonding (py)C–H···Cl contacts (2.4–3.0 Å). Evidence for (py)C–H···Y contacts was obtained in NMR studies of $\left[\text{Pt}^{II}(4-X\text{py})_4\right]Y_2$ salts with Y counterions less capable of forming H-bonds than chloride ion. Our synthetic approaches and spectroscopic analyses are clearly applicable to other nonvolatile ligands.

INTRODUCTION

We have been exploring the metal-binding chemistry of strongly coordinating pyridyl ligands as one means of bioconjugation of targeting biological groups to create complexes with potential therapeutic or diagnostic utility.1 One highly useful synthon for our purposes is the symmetrical amine, 1-(4-pyridyl)piperazine (pyppzH, Figure 1). The piperazine N attached to the pyridyl ring increases the donor ability of the pyridyl ring N, whereas the remote piperazine NH group can be used for linking chemistry. In this work we pursue fundamental Pt(II) chemistry relevant to the eventual use of such bioconjugated pyridyl ligands to prepare complexes having anticancer activity.

Cisplatin, cis-$\left[\text{Pt}(\text{NH}_3)_2\text{Cl}_2\right]$, is one of the most effective chemotherapeutic agents being used in clinical therapy.2,3 Many closely related cis bifunctional analogues of cisplatin also show good anticancer activity.4–6 In contrast, the inactivity of the trans-$\left[\text{Pt}(\text{NH}_3)_2\text{Cl}_2\right]$ isomer has led to a presumption that trans compounds are inactive.7–10 Historically, trans-$\left[\text{PtL}_2\text{Cl}_2\right]$ complexes have been neglected. In recent years, however, several types of platinum compounds with trans geometry have shown promising in vitro activity against several cancer cell lines, including some that are resistant to cisplatin.7–9,11–17 Among the recently studied trans platinum complexes, the iminoether complex trans-$\left[\text{Pt(E-HN=CH-CH}_3\text{)}_2\text{Cl}_2\right]$ has been studied most intensively and has demonstrated significant activity against several cisplatin-resistant tumor cell lines.8,11,12,18 We propose that, whereas bulky ligands have been reported to decrease activity of cis bifunctional Pt(II) agents, bulky ligands are needed to allow trans bifunctional as well as monofunctional Pt(II) agents to form DNA adducts in which the DNA structure is distorted in such a way as to lead to cancer cell cytotoxicity.19–22

Because evidence exists that trans-$\left[\text{PtL}_2\text{Cl}_2\right]$ complexes with L = 4-substituted pyridyl ligands (4-Xpy) exhibit cancer cell cytotoxicity,16,17 we believe that 4-Xpy ligands have sufficient bulk to cause DNA distortions necessary for anticancer activity. Thus, we initiated an investigation of the preparation of trans-$\left[\text{Pt}^{II}(4-X\text{py})_2\text{Cl}_2\right]$ complexes containing strongly coordinating pyridyl ligands such as 4-piperidynopyridine (4-(CH$_2$)$_5$Npy, Figure 1). Syntheses reported for related complexes often yield the cis isomer, require harsh conditions (such as 100–150 °C or the use of concentrated HCl), or depend on using aqueous conditions or volatile ligands.23–27 Such restrictions are not amenable to pyridine ligands containing sensitive linking groups, such as the sulfonamide group that we employ for bioconjugation.28

Received: May 19, 2017
Published: August 3, 2017
In the present study, we identify versatile approaches for preparing new trans-[Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]Cl\textsubscript{2} complexes. Our syntheses do not require high temperatures or rely on using volatile or water-soluble 4-Xpy. Because the binding of purine heterocycles to Pt(II) causes ~1 ppm downfield shift changes, we expected that large downfield 1H NMR shift changes of the pyridyl H\textsubscript{2}/6 signals would guide us in our synthetic work.\textsuperscript{19,22,25,29,30} However, in our initial studies we were surprised to find only a ~0.1 ppm downfield shift change of the pyridyl H\textsubscript{2}/6 signal and even an upfield shift change of the H3/5 signal (~0.1 ppm) for ligands such as 4-(CH\textsubscript{2})\textsubscript{5}Npy. As an aim in improving methods for the synthesis and characterization of trans-[Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]Cl\textsubscript{2} complexes, we explored fundamental features of the NMR spectra of these complexes. The relatively few known cis-trans-[Pt(py)\textsubscript{2}]Cl\textsubscript{2} and [Pt(Xpy or X2py)\textsubscript{4}]Y\textsubscript{2} complexes (mostly with Y = halide or heterocycles) contain ligands such as py, picolines (Me\textsubscript{2}py), and lutidines (Me\textsubscript{2}py) of similar donor ability as 4-Xpy ligands with substituents at ring position 4. Our use of 4-Xpy ligands with substituents at ring position 4 varied widely in donor ability (e.g., 4-CNpy and 4-MeOpy, 4-Mepy, 4-MeOpy, 4-(CH\textsubscript{2})\textsubscript{5}Npy, and even an upfield shift change of the pyridyl 1H NMR signal). This choice allowed us to assess the through-space and trans-influence of the chloride counterions to the Pt(II) center is usually a few tenths of an angstrom longer than the Pt···Cl contact distance of ~3.5 Å.\textsuperscript{36,37} Such NMR studies often were reported with the unusual NMR features of [Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]Cl\textsubscript{2} complexes, and also the resulting low charge of the [{Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]\textsuperscript{2+},2Cl\textsuperscript{−}] ion pairs is consistent with the high solubility in CDCl\textsubscript{3} of these salts containing [Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]\textsuperscript{2+} cations; such salts are otherwise expected to be poorly soluble.

### EXPERIMENTAL SECTION

#### Starting Materials.
Pyridine (py), 4-cyanopyridine (4-CNpy), 4-trifluoromethylpyridine (4-CF\textsubscript{3}py), 4-acetylpyridine (4-Mepy), 4-methylpyridine (4-Mepy), 4-methoxy pyridine (4-MeOpy), 3,4-dimethylaminopyridine (4-Me\textsubscript{2}Npy), 4-piperidinopyridine (4-(CH\textsubscript{2})\textsubscript{5}Npy), NaPF\textsubscript{6}, NaBF\textsubscript{4}, Na\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}SO\textsubscript{4}, Na\textsubscript{2}CO\textsubscript{3}, and NaCl were obtained from Sigma-Aldrich. cis-[Pt(DMSO)\textsubscript{2}]Cl\textsubscript{2} was prepared by a known method.\textsuperscript{26}

#### NMR Measurements.
\textsuperscript{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer or on an Advance-III Prodigy 500 MHz Bruker spectrometer. Peak positions are relative to 3-(trimethylsilyl)-propionic-2,2,3,3-d4 acid in D\textsubscript{2}O, or solvent residual peak (DMSO-d\textsubscript{6}, CHD\textsubscript{2}CN, or CHCl\textsubscript{3}) with internal tetramethylsilane (TMS) as a reference. All NMR data were processed with TopSpin and MestReNova software. For specific assignments of signals, please see Tables 1-3 and Supporting Information.

#### Mass Spectrometric Measurements.
High-resolution mass spectra recorded on an Agilent 6120 ESI TOF LCMS mass spectrometer are reported in Supporting Information.

#### X-ray Data Collection and Structure Determination.
Intensity data were collected at low temperature on a Bruker Kappa Apex-II diffractometer. Supporting Information (Figure S2).

### Table 1. H\textsubscript{2}/6 Chemical Shifts (ppm) and Shift Differences (\(\Delta\delta\), ppm) in CDCl\textsubscript{3} at 25 °C for 4-Xpy Ligands (5 mM) Both Free and in trans-[Pt(4-Xpy)\textsubscript{2}]Cl\textsubscript{2} Complexes

<table>
<thead>
<tr>
<th>X</th>
<th>pK\textsubscript{a}</th>
<th>4-Xpy</th>
<th>trans-[Pt(4-Xpy)\textsubscript{2}]Cl\textsubscript{2}</th>
<th>H\textsubscript{2}/6 (\Delta\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>2.10\textsuperscript{a}</td>
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<td>8.83</td>
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<td>9.13</td>
<td>0.24</td>
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<tr>
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<td>8.71</td>
<td>0.24</td>
</tr>
<tr>
<td>Me\textsubscript{O}</td>
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<td>8.45</td>
<td>8.69</td>
<td>0.24</td>
</tr>
<tr>
<td>Me\textsubscript{N}</td>
<td>9.61\textsuperscript{b}</td>
<td>8.22</td>
<td>8.35</td>
<td>0.13</td>
</tr>
<tr>
<td>(CH\textsubscript{2})\textsubscript{5}N</td>
<td>9.60\textsuperscript{b}</td>
<td>8.23</td>
<td>8.34</td>
<td>0.11</td>
</tr>
</tbody>
</table>

\textsuperscript{a} cis-[Pt(py)\textsubscript{2}]Cl\textsubscript{2}, this study, 8.92 ppm; reported, 8.91 ppm.\textsuperscript{23}
\textsuperscript{b} cis-[Pt(py)\textsubscript{2}]Cl\textsubscript{2}, 8.74 ppm.\textsuperscript{24}
\textsuperscript{c} cis-[Pt(py)\textsubscript{2}]Cl\textsubscript{2}, 8.69 ppm.\textsuperscript{27}
\textsuperscript{d} Estimated from the equation of the line: y = −0.0884x + 9.472 (see Supporting Information, Figure S2).

Figure 1. Pyridyl ligands (+Xpy) used to synthesize complexes studied in the current work organized by donor ability to metals centers with the weakest donors in upper left and strongest donors in lower right. Also shown is the pyramid synthet in used in our bioconjugation approach. Bold numbers below the ligands are used to designate complexes prepared with the ligand having that number. trans-[Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]Cl\textsubscript{2} complexes are designated with these bold numbers alone, and [Pt\textsuperscript{II}(4-Xpy)\textsubscript{4}]Y\textsubscript{2} complexes are designated with these bold numbers plus a letter that identifies the counterion Y\textsuperscript{−} as follows: Y\textsuperscript{−} = Cl\textsuperscript{−} (a), PF\textsubscript{6}\textsuperscript{−} (b), BF\textsubscript{4}\textsuperscript{−} (c), BPh\textsubscript{4}\textsuperscript{−} (d), and NO\textsubscript{3}\textsuperscript{−} (e). For example, [Pt\textsuperscript{II}(4-CNpy)\textsubscript{4}]Cl\textsubscript{2} is numbered 1a.
DUO CCD diffractometer fitted with an Oxford Cryostream cooler and graphite-monochromated Mo Kα (λ = 0.710 73 Å) radiation from an InS microfocus source with multilayer optics. Data reduction included absorption corrections by the multi-scan method, with SADABS.  All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least-squares methods by using SHELLXL2014  with H atoms in idealized positions.

**General Syntheses of trans-[Pt(4-Xpy)2Cl2] and [Pt(4-Xpy)4]Y2 Complexes.** The general synthetic method is illustrated in Scheme 1, and the numbering key for compounds in this study appears in Figure 1. Specific details on quantities used, yields, MS data, etc. can be found in Supporting Information.

![Scheme 1. Synthesis of trans-[Pt(4-Xpy)2Cl2] and [Pt(4-Xpy)4]Y2 Complexes, showing Numbers for Product Complexes and the Numbering System for the 4-Xpy Ligands](image)

Complexes that have numbers only are trans-[Pt(4-Xpy)2Cl2] complexes. Numbers correlate with ligands [X = CN (1); CF₃ (2); MeO (3); Me₂N (4); (CH₂)₅N (5); MeCO (6); and Me (7)].

4-Xpy was added to an acetonitrile or methanol solution of cis-[Pt(DMSO)₂Cl₂] (42 mg, 0.1 mmol, in 5 mL) in a 2:1 or 10:1 (4-Xpy/Pt) molar ratio, and the reaction mixture was heated at reflux for 4 h. The mixture was left undisturbed (∼20 min) and a filter, washed and dried in air. For all of these products, ¹H NMR spectra (in CDCl₃ at 25 °C) were obtained by mixing equal volumes (1 mL) of 4-Xpy and cis-[Pt(DMSO)₂Cl₂] (5.3 mg, 12.5 mM) in 2:1 or 10:1 (4-Xpy/Pt) molar ratios in acetonitrile and allowing the mixture to stand at room temperature for 4–24 d. When this room-temperature procedure was followed with 4-Mepy, 4-MeOpy, 4-MeNpy, and 4-MeCOpy, 4-Xpy was collected on a filter, washed with diethyl ether, and dried in air.

X-ray quality crystals of trans-[Pt(4-Xpy)₂Cl₂] (X = CF₃ (2), MeO (3), and (CH₂)₅N (5)) and [Pt(4-Xpy)₂Cl₂] (X = MeO (3a), Me₂N (4a), (CH₂)₅N (5a), and Me (7a)) were obtained by mixing equal volumes (1 mL) of 4-Xpy and cis-[Pt(DMSO)₂Cl₂] (5.3 mg, 12.5 mM) in 2:1 or 10:1 (4-Xpy/Pt) molar ratios in acetonitrile and allowing the mixture to stand at room temperature for 4–24 d. When this room-temperature procedure was followed with 4-Mepy, 4-MeOpy, 4-MeNpy, and 4-MeCOpy, 4-Xpy was collected on a filter, washed with diethyl ether, and dried in air.

**Table 2. H₂/₆ Chemical Shifts (ppm) and Shift Differences (Δδ, ppm) in CDCl₃ at 25 °C for 4-Xpy Ligands (5 mM) Both Free and in [Pt(4-Xpy)₄]Y₂ Complexes (5 mM)**

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<tr>
<th>X/Y</th>
<th>H₂/₆ δ</th>
<th>pKᵣ</th>
<th>Cl⁻</th>
<th>NO₃⁻</th>
<th>BF₄⁻</th>
<th>PF₆⁻</th>
<th>H₂/₆ Δδ</th>
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</thead>
<tbody>
<tr>
<td>CN</td>
<td></td>
<td>2.10₉</td>
<td>8.82</td>
<td>10.66₉</td>
<td>ins</td>
<td>ins</td>
<td>ins</td>
</tr>
<tr>
<td>CF₃</td>
<td></td>
<td>2.46₉</td>
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<tr>
<td>(CH₂)₅N</td>
<td></td>
<td>9.60₁</td>
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<td>9.00₁</td>
<td>8.44</td>
<td>8.22</td>
<td>8.22</td>
</tr>
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</table>

**pKᵣ value from ref 52.** Contains 50 mM [Et₄N][Cl]. [Pt(4-CF₃py)₄](BF₄)₂ is insoluble in CDCl₃ at 25 °C. **Estimated from the equation of the line: y = -0.0884x + 9.0472 (see Supporting Information, Figure S2).** pKᵣ value from ref 53. **pKᵣ value from ref 54.** Contains 40 mM [Et₄N][Cl]. **pKᵣ value from ref 55.** [Pt(4-MeNpy)₄](BF₄)₂ | 7.28 ppm. **pKᵣ value from ref 56.** **pKᵣ value from ref 1.**

DOI: 10.1021/acs.inorgchem.7b01294
Table 3. H2/6 Chemical Shifts (ppm) and Shift Differences (Δδ, ppm) in CD3CN at 25 °C for 4-Xpy Ligands (5 mM) Both Free and in [Pt(4-Xpy)4]Y2 Complexes (5 mM)

<table>
<thead>
<tr>
<th>X/Y</th>
<th>H2/6</th>
<th>H2/6 Δδ</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>MeNf</td>
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</tr>
<tr>
<td>(CH2)5N</td>
<td>9.60e</td>
<td>8.13</td>
</tr>
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</table>

a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z

pKw value from ref 52. aContains 50 mM [Et4N]Cl. b[Pt(4-CF3py)4]Cl2 9.01 ppm. cEstimated from the equation of the line: y = −0.0884x + 9.0472 (see Supporting Information, Figure S2). dContains 40 mM [Et4N]Cl. eContains 40 mM [Et4N]Cl. fContains 50 mM [Et4N]Cl.
g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z

DMSO-d6, D2O, and CD3CN at 25 °C appear in Tables 2 and 3 and in Supporting Information. [Et4N]Cl Addition to [Pt(4-Mepy)4][NO3]2 in CD3CN or DMSO-d6. The effect of [Et4N]Cl on a 5 mM solution of the desired [Pt(4-Xpy)4]Y2 complex in CD3CN (except for [Pt(4-MeNpy)4][PF6]2, which was poorly soluble) or DMSO-d6 was studied by a 600 mM stock solution of [Et4N]Cl prepared from a 5 mM solution of the complex to keep the complex concentration constant throughout the experiment. 1H NMR spectra were recorded for each solution (1−125 mM in [Et4N]Cl) after the addition of each [Et4N]Cl aliquot. As the [Et4N]Cl concentration was increased from 0−125 mM, a downfield shift (0.05 ppm) was observed for the residual CHCl3 signal (from 7.2629 to 7.3080 ppm) relative to TMS as reference. To account for this shift change, shifts of all peaks were adjusted accordingly.

[Et4N]Cl Addition to [Pt(4-Xpy)4][NO3]2 in CD3CN or DMSO-d6. Solutions (5 mM) of selected [Pt(4-Xpy)4]Y2 complexes in CD3CN or DMSO-d6 (600 μL) at 25 °C were treated with 10 molar equiv of [Et4N]Cl (5 mg) for [Pt(4-Xpy)4][NO3]2 salts or with 8 molar equiv of [Et4N]Cl (4 mg) for [Pt(4-Xpy)4][PF6]2 salts; each solution was examined by 1H NMR spectroscopy.

### RESULTS AND DISCUSSION

**Synthesis.** As illustrated in Scheme 1, the treatment of cis-[Pt4(DMSO)4]Cl2 in acetonitrile with 2 equiv of 4-Xpy afforded 26−51% yields of solids containing pure trans-[Pt4(4-Xpy)4]Cl2 complexes (X = CN, CF3, MeCO, Me, MeO, and (CH2)5N). However, when methanol was used as the solvent, mixtures of cis and trans isomers of [Pt4(4-Xpy)4]Cl2 were obtained, as could be deduced from reported NMR data25,24,27 on a few [Pt4(4-Xpy)4]Cl2 complexes; in addition, spectra showed small signals with very downfield shifts that did not correspond to those in any literature reports.

When a methanol solution of cis-[Pt4(DMSO)4]Cl2 was treated instead with 10 equiv of relatively good 4-Xpy donor ligands (X = Me, MeO, Me2N, and (CH2)5N), [Pt4(4-Xpy)4]Cl2 complexes were formed in 49−84% yields. These dicationic complexes were very soluble in CDCl3 and exhibited the unusual, very downfield minor H2/6 NMR signals observed in reactions with only 2 equiv of 4-Xpy. Factors leading to the high solubility and very downfield shifts are discussed below.

To expand the range of 4-Xpy basicity and donor ability in the [Pt4(4-Xpy)4]Y2 series, a modified synthetic approach was employed. When 4-CNpy, 4-CF3py, or MeCO was added to a methanol solution of cis-[Pt4(DMSO)4]Cl2 in a 40:1 (4-Xpy/ Pt) molar ratio and the solution heated to reflux in the presence of AgNO3, the respective [Pt4(4-Xpy)4](NO3)2 complexes were obtained in 68%, 78%, or 76% yields. Aqueous solutions of [Pt4(4-Xpy)4](NO3)2 (X = CN (3a), MeCO (3a), Me2N (3a), and (CH2)5N (7a)) were then treated with solid NaPF6 to produce the respective [Pt4(4-Xpy)4][PF6]2 (1b−7b) or [Pt4(4-Xpy)4](BF4)2 (1c−7c) complexes.

**Structural Results. Overall Aspects.** Crystal data and details of the structural refinement for complexes 2, 3, 4, 5, 3a−5a, and 7a are summarized in Supporting Information; ORTEP plots for these compounds are shown in Figures 2−4, along with the atom-numbering schemes used to describe the solid-state data. Selected bond lengths and bond angles are presented in Tables 4−6. In the trans-[Pt4(4-Xpy)4]Cl2 complexes (2, 3, and 5), the Pt4 metal center has two trans chloro ligands and two N-bonded pyridyl ligands (Figure 2). [Pt4(4-Xpy)4]Cl2 Structures. Even though the 4-Xpy ligands differ considerably in donor potential, the values of the Pt−N, Pt−Cl, C1−N1, and C5−N1 bond distances and the Pt−N−C and C−N−C bond angles for trans-[Pt4(4-Xpy)4]Cl2 were treated with 10 molar equiv of [Et4N]Cl (5 mg) for [Pt(4-Xpy)4][NO3]2 salts or with 8 molar equiv of [Et4N]Cl (4 mg) for [Pt(4-Xpy)4][PF6]2 salts; each solution was examined by 1H NMR spectroscopy.

**Supporting Information.** ORTEP plots for the cations [Pt(4-MeNpy)4]Cl2 (3a), [Pt(4-MeNpy)4]Cl2 (4a), [Pt4(4-(CH2)5Npy)4]Cl2 (5a), and [Pt4(4-Mepy)4]Cl2 (7a)
Inorganic Chemistry

1. Article

**Inorganic Chemistry**

2. Article

3. Article

4. Article

5. Article

**Figure 2.** ORTEP plots of trans-[Pt(4-CF$_3$py)$_2$Cl$_2$] (2), trans-[Pt(4-MeOpy)$_2$Cl$_2$] (3), and trans-[Pt(4-(CH$_2$)$_5$Npy)$_2$Cl$_2$] (5). Thermal ellipsoids are drawn with 50% probability. The asymmetric unit has only half of each molecule. For the figure, the other half of each structure was generated by using the inversion center. The trifluoromethyl group in 2 is disordered over three positions; only one position is shown for clarity.

**Figure 3.** ORTEP plot of cis-[Pt(4-Me$_2$Npy)$_2$Cl$_2$] (4'). Thermal ellipsoids are drawn with 50% probability. The asymmetric unit has only half of a molecule. For the figure, the other half of the structure was generated by a twofold rotational axis.

are shown in Figure 4. The asymmetric unit of 4a has two independent molecules (A and B), one of which lies on an inversion center. Two independent molecules are also found in the asymmetric unit of 5a, both of them lying on an inversion center. The molecular structure of 7a has a twofold axis through the central Pt atom.

The Pt–N and C–N bond distances and the C–N–C, C–N–Pt, and N–Pt–N bond angles (Table 6) all suggest very similar binding of the 4-Xpy ligands in the [Pt(4-Xpy)$_4$]$^{2+}$ cation of 3a, 4a, 5a, and 7a, with N–Pt–N bond angles close to 180°. In general, the Pt–N bond distances for [Pt(4-Xpy)$_4$]$^{2+}$ (X = MeO (3a), Me$_2$N (4a), (CH$_2$)$_5$N (5a), and Me (7a)) (Table 6) compare well with other Pt–N(sp$^2$) bond distances ranging from 1.99 to 2.08 Å. The canting angle for [Pt(4-Xpy)$_4$]$^{2+}$ cations varies from ~89.2° in 4a to ~76.4° in 5a, indicating less canting than in trans-[Pt(4-Xpy)$_4$]Cl$_2$ compounds. The large differences in the canting angles indicate that there is a very low barrier preventing changes in the dihedral angle.

The Pt–Cl and CH···Cl Nonbonded Distances in [Pt(4-Xpy)$_4$]Cl$_2$ (X = MeO (3a), Me$_2$N (4a), (CH$_2$)$_5$N (5a), or Me (7a)) Crystals. In almost all cases, the chloride counterions of the new crystals lie along pseudoaxial sites of the Pt(II) center but usually at distances that are a few tenths of an angstrom longer than the Pt···Cl contact distance of ~3.5 Å.

Including the two counterions and the cation, we can describe the configuration as resembling an axially elongated octahedron for both independent molecules in [Pt(4-(CH$_2$)$_5$Npy)$_4$]Cl$_2$, 4H$_2$O (5a) (in which Pt atoms occupy inversion centers with Pt···Cl distances of 3.885 and 3.912 Å for the A and B molecules, respectively; see Supporting Information, Table S3) and Molecule B of [Pt(4-Me$_2$Npy)$_4$]Cl$_2$ (4a) (with the Pt atom at an inversion center and the Pt···Cl distance = 3.793 Å). Molecule A of 4a, the Pt atom has an elongated pseudo square pyramidal arrangement (Pt···Cl distance = 3.675 Å), a structure serving as a model for [[Pt(4-Xpy)$_4$]Cl$_2$, 4H$_2$O (bearing the least basic 4-Xpy ligand in the structures obtained here) have an average = 3.631 Å. The Pt···Cl distance of 4a, 5a-4H$_2$O, and 7a-4H$_2$O, the distance between many of the pyridyl H$_2$/6 protons and the Cl anions, precluding detailed geometric comparison of the arrangement of the Cl anions relative to the cation; however, the elongated pseudo-octahedral arrangement appears to be present in this case also. Finally, although this topic was neither noted nor discussed in the report of the structure of [Pt(4-me$_3$py)$_4$]Cl$_2$ (8a), the structure does have axially located chlorides (Pt···Cl distance 3.631 Å).

In the structures of 4a, 5a-4H$_2$O, and 7a-4H$_2$O, the distance between many of the pyridyl H$_2$/6 protons and the Cl anions are short enough to be considered as a CH···Cl intermolecular contact. The contacts for 4a are shown in Figure 5. Although invariably weak, such contacts are known to occur widely in crystals and possibly to extend beyond the 3.0 Å van der Waals separation. The CH···Cl intermolecular contacts can be described as short (<2.6 Å, d $\ll$ $\sum_{vdw}$), medium (2.6–3.0 Å, d $\leq$ $\sum_{vdw}$), or long (>3.0 Å, d $>$ $\sum_{vdw}$).

The four nonbonding (py)C–H···Cl distances found in each structure range from 2.711 to 2.884 Å and from 2.802 to 2.980 Å for molecules A and B, respectively, of 4a, from 2.718 to 3.171 Å and from 2.807 to 3.111 Å for molecules A and B, respectively, of 5a-4H$_2$O, and from 2.702 to 2.814 Å for 7a-4H$_2$O (see Supporting Information, Table S3). In [Pt(4-Me$_2$Npy)$_4$]Cl$_2$ (3a), there are disordered Cl anions, precluding detailed geometric comparison of the arrangement of the Cl anions relative to the cation; however, the elongated pseudo-octahedral arrangement appears to be present in this case. In the structures of 4a and 5a-4H$_2$O, the distance between many of the pyridyl H$_2$/6 protons and the Cl anions are short enough to be considered as CH···Cl intermolecular contacts. The contacts for 4a are shown in Figure 5. Although invariably weak, such contacts are known to occur widely in crystals and possibly to extend beyond the 3.0 Å van der Waals separation. The CH···Cl intermolecular contacts can be described as short (<2.6 Å, d $\ll$ $\sum_{vdw}$), medium (2.6–3.0 Å, d $\leq$ $\sum_{vdw}$), or long (>3.0 Å, d $>$ $\sum_{vdw}$). The four nonbonding (py)C–H···Cl distances found in each structure range from 2.711 to 2.884 Å and from 2.802 to 2.980 Å for molecules A and B, respectively, of 4a, from 2.718 to 3.171 Å and from 2.807 to 3.111 Å for molecules A and B, respectively, of 5a-4H$_2$O, and from 2.702 to 2.814 Å for 7a-4H$_2$O (see Supporting Information, Table S3). Most of these contacts are in the medium range. The nonbonding (py)C–H···Cl distances observed for 7a-4H$_2$O (bearing the least basic 4-Mepy ligand in the structures obtained here) have an average = 2.761 Å, a value which is slightly shorter than the averages for...
and for 5a·4H₂O (2.954 Å), the complexes with the highly basic 4-Me₂Npy and 4-(CH₂)₅Npy ligands, respectively. This trend is expected and can be attributed to the higher δ⁺ charge on the (py)C−H protons of 4-Mepy (7a·H₂O), which leads to stronger CH···Cl intermolecular interactions and thus shorter (py)C−H···Cl contacts. All of the [PtX₆(4-Xpy)₄]Cl₂ crystals obtained in this study have relatively good 4-Xpy donors. For the analogues with weaker

<table>
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<tr>
<th>Bond Distances (Å) and Angles (deg) for trans-[Pt(4-Xpy)₂Cl₂] [X = CF₃ (2), MeO (3), (CH₂)₅N (5), H, and Me] Complexes</th>
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<tr>
<td><strong>bond distances</strong></td>
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<td><strong>Note:</strong> Pt atom occupies an inversion center (half of the molecule is generated by an inversion center). Data for X = H (refs 24 and 41) and Me (ref 24) are obtained from the literature, and no standard deviation was obtained from the database.</td>
</tr>
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</table>
donor 4-Xpy ligands (X = CN, CF₃, and MeCO), the chloride displaces the 4-Xpy ligand, as discussed below, precluding the isolation of crystals. However, we expect that the (py)C···Cl contacts for complexes possessing less basic 4-Xpy donors would be shorter than those observed here for 4a, 5a·4H₂O, and 7a·H₂O.

**NMR Spectroscopy.** Selected ¹H NMR spectroscopic data for 4-Xpy ligands and complexes, including the H₂/6 (more downfield) and H₃/5 aromatic ¹H NMR signals assigned in accordance with the widely observed pattern,¹⁴,¹⁵ are collected in Tables 1–3 and in the Supporting Information. The atom-...
numbering system used in this NMR discussion is shown in Scheme 1.

Previous limited NMR studies on cis/trans-[PtII(py)2Cl2] and cis/trans-[PtIV(4-Xpy)2Cl2] complexes employed pyridine-type ligands having properties in a narrow range.25-27 In CDCl3, the H2/6 signal of py in trans-[PtIV(py)2Cl2] was shifted downfield by ∼0.3 ppm as compared to free ligand24 (see footnotes in Table 1 and Supporting Information, Table S5); this characteristic downfield chemical shift change giving a positive value for the parameter δH2/6 (δH2/6 = δcomplex − δligand) is approximately the expected value24 and is usually interpreted as resulting from the decrease in the electron density of the ligand upon coordination.17,24,27

In the present study, we first examined relatively basic ligands that can be used in our bioconjugation approach and found that the trans-[PtIV(4-Xpy)2Cl2] products had rather small H2/6 Δδ values in CDCl3 (∼0.1 ppm). This H2/6 Δδ value is comparable to that reported for the [PtIV(py)2Cl2] cis isomer (∼0.1 ppm) as compared to the trans isomer (∼0.3 ppm).23,24 The smaller H2/6 Δδ value for cis-[PtIV(py)2Cl2] versus trans-[PtIV(py)2Cl2] was attributed to the mutual anisotropic shielding effect exerted by adjacent cis anisotropic py ligands.25,27 Thus, the NMR data do not provide a very useful guide in synthetic studies of trans-[PtIV(4-Xpy)2Cl2] complexes. In addition, we also observed side products having very downfield H2/6 signals. Thus, to understand the factors that influence H2/6 Δδ values, we prepared and examined complexes of 4-Xpy ligands having a wide range of donor ability.

trans-[PtIV(4-Xpy)2Cl2] Complexes. As expected, coordination of 4-Xpy to form trans-[PtIV(4-Xpy)2Cl2] complexes led to positive Δδ values for the H2/6 signal (Table 1). For both the free 4-Xpy ligands and the trans-[PtIV(4-Xpy)2Cl2] complexes, the H2/6 and H3/5 signals in CDCl3 appeared farther upfield with increasing basicity of the 4-Xpy ligand (Table 1). This trend can be attributed to the greater electron richness of the more basic 4-Xpy ligands. Plots of the chemical shift of the H2/6 signals of 4-Xpy and of trans-[PtIV(4-Xpy)2Cl2] complexes versus the pKa of 4-Xpy are linear and have a negative slope (Figure 6). For plots of both series of complexes in Figure 6, the order is as follows: 4-CNpy (1) > 4-CFpy (2) > 4-MeCOpy (6) > 4-Mepy (7) > 4-MeOpy (3) > 4-MeNpy (4) ≈ 4-(CH2)2Npy (5). The slightly steeper negative slope for the complexes than for the free ligand (Figure 6) can be attributed to the size of the synergistic decrease of the inductive effect of the Pt(II) metal center caused by the two mutually trans pyridyl rings. This decrease of the Pt(II) inductive effect is much smaller when the 4-Xpy ligand is a poor donor. Thus, H2/6 Δδ values decrease linearly with increasing pKa of 4-Xpy from 0.35 to 0.11 ppm (Table 1 and Figure 7) in the same order as the plots in Figure 6.

Dependence of NMR Spectra (in CDCl3) of [PtIV(4-Xpy)4]Cl2 Complexes on the Nature of X. As mentioned, side products having very downfield H2/6 signals found in early phases of this study were later identified as the [PtIV(4-Xpy)4]Cl2 salts. To obtain related products ([PtIV(4-Xpy)4]Y2) with poor donor 4-Xpy ligands, we used other poorly coordinating or non-coordinating counterions. Within any series of [PtIV(4-Xpy)4]Y2 complexes regardless of the identity of the Y counterion, the H2/6 and H3/5 signals appeared farther upfield with increasing basicity of the 4-Xpy ligands, as we found for the trans-[PtIV(4-Xpy)2Cl2] complexes.

We begin the discussion with the [PtIV(4-Xpy)4]Cl2 complexes in CDCl3 (Table 2), because we have the most extensive solution and structural data for the Y = Cl complexes and because Δδ is greater by ∼1 ppm when Y = Cl than when Y = other counterions; we conclude with a discussion of other solvents and [PtIV(4-Xpy)4]Y2 complexes with other Y counterions. In plots of the H2/6 shifts of [PtIV(4-Xpy)4]Cl2 and trans-[PtIV(4-Xpy)2Cl2] in CDCl3 versus the pKa of 4-Xpy (Figure 6), the negative slope for the [PtIV(4-Xpy)4]Cl2 series is much steeper than for the trans-[PtIV(4-Xpy)2Cl2] series. This observation can be interpreted as discussed above by noting that now there are four 4-Xpy ligands synergistically influencing the inductive effect of the Pt(II) metal center and that the H2/6 shift is sensitive to this inductive effect. As a further illustration of the synergism, the Δδ values in CDCl3 for [PtIV(4-Xpy)4]Cl2 (1.91−0.77 ppm, Table 2) decrease linearly with increasing pKa of 4-Xpy (Figure 7) to a much greater extent than the trans-[PtIV(4-Xpy)2Cl2] series.
The \[^1H\] NMR shift data, especially for H2/6 at 8.84 ppm, reported by Pazderska et al.\textsuperscript{23} \([Pt(4-py)]Cl_2\) in CDCl\(_3\) do not agree at all with the H2/6 shifts (\(\sim 10\) ppm) observed here for the \([Pt(4-Xpy)]Cl_2\) complexes with moderate donor 4-Xpy ligands (Table 2 and Supporting Information, Table S5). To independently verify the reported preparation\textsuperscript{23} and characterization\textsuperscript{8a} of \([Pt(4-py)]Cl_2\) (8a), we prepared \([Pt(4-py)]Cl_2\) by our method and obtained colorless crystals with unit-cell parameters identical to those reported for \([Pt(py)]Cl_2\);\textsuperscript{42} The H2/6 shift (10.36 ppm) in CDCl\(_3\) at 25 °C for our \([Pt(py)]Cl_2\) crystals (see Supporting Information, Table S5) is entirely consistent with the shift value expected from our data. Concluding that some error was made in the previous work,\textsuperscript{23} we turned our attention to elucidating the factors contributing to the very downfield position of these H2/6 signals.

**Cause of the Unusually Large Downfield H2/6 Signals of \([Pt(4-Xpy)]Cl_2\) Complexes.** Understanding the specific factors causing the larger Δ\(\delta\) H2/6 values for \([Pt(4-Xpy)]Cl_2\) salts than for salts with other counterions (Table 2) is an important goal of our study. Another interesting feature observed for the \([Pt(4-Xpy)]Cl_2\) salts is their high solubility in CDCl\(_3\), a solvent of low polarity. We believe that the \([Pt(4-Xpy)]Cl_2\) solubility in CDCl\(_3\) provides clear evidence that the H2/6 shifts are consistent with the presence of CH···Cl hydrogen bonds similar to those found in the solid state (Figure 5 and Supporting Information, Table S3).

We believe that there can be no doubt that ion pairs between \([Pt(4-Xpy)]_2^+,2Cl^-\) dication and the various Y anions do exist in the low-dielectric solvent CDCl\(_3\). We hypothesize that in CDCl\(_3\) solutions of \([Pt(4-Xpy)]Cl_2\) complexes the close proximity of the Cl\(^-\) counterion to the H2/6 protons of the coordinated 4-Xpy pyridyl ring within such ion pairs results in the formation of multiple CH···Cl contacts between H2/6 and Cl\(^-\) and in dynamic ion pairs similar to the elongated pseudooctahedrons found in the solid (Figure 5). The formation of hydrogen bonds is known to lead to downfield shift changes in the \(^1H\) NMR signals.\textsuperscript{50,51} Thus, the very downfield H2/6 signals for \([Pt(4-Xpy)]Cl_2\) complexes in CDCl\(_3\) are consistent with the presence of CH···Cl hydrogen bonds, proving beyond any doubt that specific cation–anion contacts exist within such dynamic ion pairs in solution is probably not possible, but we believe that the results of several solution studies to be described next lead to a very compelling case for the existence of fully formed \([Pt(4-Xpy)]_2^+,2Cl^-\) ion pairs containing multiple CH···Cl interactions in CDCl\(_3\).

To assess our hypothesis, we first examined the effect of [Et\(_4\)N]Cl addition on the H2/6 signals of \([Pt(4-Xpy)]Cl_2\) in CDCl\(_3\) for X = MeO (3a), Me\(_2\)N (4a), (CH\(_2\))\(_2\)N (5a), and Me (7a). If the \([Pt(4-Xpy)]_2^+,2Cl^-\) ions were not fully formed, the H2/6 signal would shift downfield because the added chloride would drive the equilibrium toward the formation of more \([Pt(4-Xpy)]_2^+,2Cl^-\) ions. Downfield shifts are also expected if the ion pairs have only one chloride ion, \([Pt(4-Xpy)]_2^+,Cl^-\). As the Cl\(^-\) concentration was increased, the H2/6 signals shifted slightly *upfield* by \(< 0.02\) ppm for 3a and 7a, by 0.17 ppm for 4a, and by 0.18 ppm for 5a as up to 25 mM [Et\(_4\)N]Cl was added (see Supporting Information, Figure S5). The absence of downfield shifts supports the proposal that \([Pt(4-Xpy)]_2^+,2Cl^-\) ion pairs are already fully formed in the absence of added chloride salt. The minor upfield shifting is most consistent with salt effects.

A similar [Et\(_4\)N]Cl salt effect study could not be conducted for \([Pt(4-Xpy)]Cl_2\) with the very weak donor 4-Xpy ligands (X = CN, CF\(_3\), and MeCO) because the chloride salts could not be isolated. However, solutions containing \([Pt(4-Xpy)]_2^+,2Cl^-\) ion pairs in CDCl\(_3\) at 25 °C could be generated easily by adding [Et\(_4\)N]Cl to suspensions of \([Pt(4-Xpy)]_2^+,2Cl^-\) salts, which are insoluble or poorly soluble in CDCl\(_3\) shift data from NMR spectra recorded within \(\sim 5\) to 30 min after addition of [Et\(_4\)N]Cl can be found in Table 2 and Figures 6 and 7. The Δ\(\delta\) values found for \([Pt(4-Xpy)]_2^+,2Cl^-\) ion pairs (Table 2) are \(\sim 1.8\) to 1.9 ppm when 4-Xpy is one of these poor ligands, as compared to Δ\(\delta\) \(\approx 1.5\) ppm for a medium donor ligand (e.g., X = Me) and Δ\(\delta\) < 0.9 ppm for the stronger donor ligand (X = 4-Me\(_2\)N). These Δ\(\delta\) values are fully consistent with a decrease in the partial positive charge \(\delta\) of the H2/6 protons with increasing 4-Xpy pyridyl ring electron richness. A decrease in Δ\(\delta\) of the H2/6 protons in turn diminishes the strength of the specific H2/6 H-bonding interactions with the chloride ion within the ion pair.

As an aside, as expected, NMR scans of these suspensions gave no or very weak signals (cf. Figure 8 for X = CN (1e)).

However, relatively soon after addition of [Et\(_4\)N]Cl to \([Pt(4-Xpy)]_2^+,2Cl^-\) (1e), 5 mM with [Et\(_4\)N]Cl (125 mM). Signals for the trans-[Pt(4-CNpy)Cl\(_2\)] complex are labeled *trans*. Procedures for obtaining spectra starting from such nitrate salts are explained in the text.

**Effect of [Et\(_4\)N]Cl on the H2/6 Signals of \([Pt(4-Xpy)]PF_6\) and of \([Pt(4-Mepy)]PF_6\) Complexes in CDCl\(_3\).** In our studies of 5 mM solutions of \([Pt(4-Xpy)]PF_6\) and \([Pt(4-Mepy)]PF_6\) complexes in various solvents, we ranked the ability of the Y anions both to form ion pairs and to form hydrogen bonds as follows: Cl\(^-\) > NO\(_3^-\) > Br\(^-\) > Cl\(^-\) > Br\(^-\) > PF\(_6^-\). We begin by describing results leading to this order with our assessment of the effects of addition of [Et\(_4\)N]Cl to CDCl\(_3\) solutions of \([Pt(4-Xpy)]_2^+,2Cl^-\) (X = MeO (3b), (CH\(_2\))\(_2\)N (5b), and Me (7b)) complexes. Such an addition was expected to convert a \([Pt(4-Xpy)]_2^+,2Cl^-\) ion pair to a \([Pt(4-Xpy)]_2^+,2PF_6^-\) ion pair. The change of
the counterion in the ion pair caused downfield shift changes of the H2/6 signals in CDCl3 (Figure 9 and Supporting Information, Figure S7).

The curves showing the dependence of the downfield shift changes of H2/6 signals for 7b and 5b on adding [Et4N]Cl have the smooth shape most often found in our studies (Figure 9 and Supporting Information, Figure S7). For 5b (bearing the highly basic 4-(CH2)5Npy ligand), the [Et4N]Cl concentration (Figure 9 and Supporting Information, Figure S7) required to reach a plateau (∼20 mM) was higher than that for 7b (∼12 mM), as expected, because 4-(CH2)5Npy in 5b is much more electron-rich than is 4-Mepy in 7b. Thus, the δ+ charge on the H2/6 protons is relatively smaller, and the CH···Cl interactions within the ion pair are weaker for 4-(CH2)5Npy in 5b than those for 4-Mepy in 7b; a higher [Cl−] is therefore required by 5b than by 7b to fully form [[Pt5(4-Mepy)4][Cl−]+,PF6]− ion pairs. The H2/6 signals for 7b and 5b initially at 8.86 and 8.22 ppm shifted downfield to 10.04 ppm at ∼12 mM [Cl−] and 9.02 ppm at ∼20 mM [Cl−], respectively (Figure 9 and Supporting Information, Figure S7). The shift change observed for 7b (∼1.2 ppm) was much larger than for [[Pt5(4-(CH2)5Npy)4][PF6]2 (5b) (∼0.8 ppm). The smaller H2/6 shift change observed for 5b, bearing the highly basic 4-(CH2)5Npy ligand, can be attributed to the electron richness of the pyridyl ring, which in turn lowers the partial positive charge of the H2/6 protons and diminishes the hydrogen-bonding ability of these hydrogens. The results for solutions are consistent with the solid-state data; the average nonbonding (py)C···H···Cl distances observed for [[Pt5(4-(CH2)5Npy)4][Cl−]+ (5a) are slightly longer than those observed for [Pt5(4-Mepy)4][Cl−]2 (7a) (Supporting Information). These comparative results for 7b and 5b are readily rationalized only if specific contacts occur between the Cl− anion and the H2/6 protons in the ion pairs.

The curve of the shift changes observed for the H2/6 signal of [[Pt5(4-Mepy)4][PF6]2 (3b) has a different shape than those found for 5b and 7b. This different shape was found in a few cases (Figure 9 and Supporting Information). Both 3b and 7b have moderately basic 4-Xpy ligands, and the starting and ending H2/6 shifts are very similar. Likewise, the H2/6 shift change upon addition of the first aliquot of ∼5 mM Cl− (∼1 equiv of Cl−) is similar for 3b and 7b. However, as more Cl− was added, the chemical shift of the H2/6 signal of 3b plateaued and then increased again, and finally plateaued at a shift similar to that of 7b. Such a finding cannot be easily explained if there are no specific contacts in the ion pair. However, if the first equivalent of added Cl− altered the canting angles within the [[Pt5(4-Mepy)4][PF6]2,Cl−]− ion pair, a higher amount of Cl− would then be needed for a second Cl− to fully displace the remaining PF6− from this ion pair to form the [[Pt5(4-Mepy)4][PF6]2,2Cl−]− ion pair.

To assess the effect of counterions other than PF6− on Cl− ion-pairing interactions with [[Pt5(4-Mepy)4][PF6]2,Et4N]+, [Et4N]Cl addition experiments using [[Pt5(4-Mepy)4][BF4]2 (7c) and [[Pt5(4-Mepy)4][NO3]2 (7e) were conducted (Figure 10 and Supporting Information, Figure S9). As the [Et4N]Cl concentration was increased from 0−125 mM, the H2/6 signals for 7c and 7e shifted downfield from 9.11 and 9.39 ppm to 10.02 and 10.00 ppm, respectively. The shift change of the H2/6 signal (∼1.2 ppm) observed for [[Pt5(4-Mepy)4][PF6]2 (7b) was more than that observed for 7c (∼0.9 ppm) and 7e (∼0.6 ppm, in CDCl3 at 25 °C). The concentration of [Et4N] Cl required to reach a plateau was much lower (∼13 mM) for 7b (with the PF6− anion) than for 7c (∼25 mM) or 7e (∼50 mM) (with the BF4− or NO3− counterions, respectively). Of greater interest, the curve for 7c rose sharply to an ∼1:1 ratio of Cl−, and then rose more gradually. This curve indicates that very likely a mixed [[Pt5(4-Mepy)4][Cl−]+,BF4−]− ion pair forms readily with one Cl− and one BF4−, as proposed above for the [[Pt5(4-Mepy)4][Cl−]+,PF6−]− ion pair. Perhaps the H-bonding interactions within the [[Pt5(4-Mepy)4][Cl−]+,BF4−]− ion pair causes changes in the canting of the bound 4-Mepy ligands. The solid-state structural data show that large changes in canting are feasible. Such a change in canting could favor H-
bonding by the tetrahedral BF₄⁻ remaining in the mixed ion pair. The BF₄⁻ could then be more difficult to substitute from the mixed ion pair than the octahedral PF₆⁻ in the [{PtIII(4-Xpy)}₄Cl₂]⁺{Cl⁻,PF₆⁻} ion pair. In any case, the shape of the curve is further evidence that there are specific contacts within these ion pairs. The interaction of the Y anions with the H2/6 protons in [{PtIII(4-Xpy)}₄]⁺{Cl²⁻,Y²⁻} ion pairs thus decreases in the order: Cl⁻ > NO₃⁻ > BF₄⁻ ≈ PF₆⁻.

Shift of the H2/6 Signals of [{PtIII(4-Xpy)}₄(NO₃)₂]⁺ and Other [{PtIII(4-Xpy)}₄]⁺ Complexes in CD₃CN. When the counterion is not chloride, [{PtIII(4-Xpy)}₄]⁺Y₂ salts are often not soluble in CDCl₃ (cf. Table 2). We decided to conduct broader studies in the more polar solvents in the hope that we could obtain data relevant to ion pairing on more [{PtIII(4-Xpy)}₄]⁺Y₂ compounds in a given solvent. Because D₂O and DMSO-d₆ are too polar to allow extensive ion pairing (Supporting Information), we chose to explore CD₃CN. All [{PtIII(4-Xpy)}₄]⁺Y₂ complexes prepared in this study were soluble at 5 mM concentration in CD₃CN. This solvent could thus allow NMR spectra to be recorded at 25 °C but was not so polar as to preclude formation of ion pairs (Tables 3 and S8). Furthermore, addition of [Et₄N]Cl to the chloride salt, [{PtIII(4-Me₂Npy)}₄]⁺Cl₂ (4a), in CD₃CN caused a downfield shift of 0.33 ppm of the H2/6 signal (Table 3). This finding indicates that the ion pair is not fully formed in CD₃CN. In contrast, [Et₂N]Cl addition to 4a and other chloride salts in CDCl₃ led to upfield H2/6 shifts (Figure S5), indicating that the ion pair was fully formed in the less polar CDCl₃ solvent.

3H NMR spectra of [{PtIII(4-Xpy)}₄(NO₃)₂]⁺ CD₃CN solutions were recorded ∼5 min after addition of sufficient [Et₂N]Cl to make the solutions 50.0 mM in [Et₂N]Cl. For all five complexes studied, downfield H2/6 shift changes were observed as expected (Table 3, Figure 11, and Supporting Information). Figure 11. Stacked plot of the aromatic region of 3H NMR spectra (in CD₃CN, 25 °C) for the treatment of [{PtIII(4-CNpy)}₄(NO₃)₂](1e, 5 mM) with [Et₂N]Cl (50 mM). Signals for trans-[PtIII(4-CNpy)]Cl₂ are labeled trans.

The dependence of the chemical shifts of 4-Xpy H2/6 3H NMR signals of many new complexes in two series, namely, trans-[PtIII(4-Xpy)]Cl₂ and [PtIII(4-Xpy)]Y₂, were investigated by employing 4-Xpy with very diverse donor abilities. For both series in CDCl₃, downfield shift changes (Δδ) were observed for the H2/6 signals upon coordination of 4-Xpy to form the respective trans-[PtIII(4-Xpy)]Cl₂ or [PtIII(4-Xpy)]Cl₂ complexes. The size of H2/6 Δδ decreased linearly with increasing 4-Xpy donor ability. The decrease in Δδ was greater for the [{PtIII(4-Xpy)}₄]Cl₂ series than for the trans-[PtIII(4-Xpy)]Cl₂ series. We conclude that this finding can be attributed to the synergistic reduction in the inductive effect of the Pt(II) center by the other three 4-Xpy donor ligands in the [{PtIII(4-Xpy)}₄]Cl₂ series as compared to only one other 4-Xpy donor ligand in the trans-[PtIII(4-Xpy)]Cl₂ series.

Systems of [{PtIII(Xpy)}₄]Cl₂ salts in CDCl₃ have very downfield 4-Xpy H2/6 3H NMR signals and exhibit much larger H2/6 Δδ values than those of the corresponding [{PtIII(4-Xpy)}₄]Cl₂ (Y = PF₆, BF₄, and NO₃) salts. We conclude that strong ion pairing between Cl⁻ and [{PtIII(4-Xpy)}₄]⁺ is facilitated by multiple H2/6⋅Cl⁻ H-bonding contacts, explaining the large downfield shifts. Also, strong ion pairing explains the high solubility of the [{PtIII(4-Xpy)}₄]Cl₂ salts that contain a [{PtIII(4-Xpy)}₂]⁺ dication. Other [{PtIII(4-Xpy)}₄]⁺Y₂ salts were often much less soluble or even insoluble. Crystal structures revealed that the chloride counterions occupy axial positions with nonbonding (py)C−H···Cl distances well within the range of a typical CH···Cl H-bonding contact (2.4−3.0 Å). Thus, the crystallographic data confirm our conclusion that the relatively larger H2/6 Δδ values (in CDCl₃ at 25 °C) observed for [{PtIII(4-Xpy)}₄]Cl₂ arise from ion pairing, which in turn is stabilized by multiple (py)C−H···Cl contacts.

Several 3H NMR studies in various solvents allowed us to correlate the dependence of the relative stability of the ion pairs of [{PtIII(4-Xpy)}₄]Y₂ based on their H-bonding ability as follows: Cl⁻ > NO₃⁻ > BF₄⁻ > PF₆⁻. The poor solubility of some [{PtIII(4-Xpy)}₂]⁺Y₂ (Y = PF₆, BF₄, and NO₃) complexes as compared to the [{PtIII(4-Xpy)}₂]⁺Cl₂ analogues is probably a result of the weaker ion pairing.

Because our procedures for synthesizing model trans-[PtIII(4-Xpy)]Cl₂ and [{PtIII(4-Xpy)}₂]⁺Cl₂ complexes do not rely on high temperatures, water solubility, or Xpy volatility, the methods are clearly applicable to other nonvolatile monodentate ligands, such as those bearing biological targeting groups. The NMR spectroscopic trends we have elucidated can serve as a guide for the synthesis of these and similar complexes.
during the synthesis and characterization of such Pt(II) complexes.

■ ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.7b01294.

Details of the syntheses and characterization of all complexes prepared in this study; descriptions and figures of the effect of [Et₂N]Cl addition on ¹H NMR signals of [Pt(4-Xpy)₂]Y₂ in various solvents; descriptions and figures of replacement of weak 4-Xpy ligands by chloride upon [Et₂N]Cl addition to [Pt(4-Xpy)₂]-(NO₃)₂ suspensions or solutions; tables of crystallographic data for complexes 2, 3, 4, 5, 6, 7a, and 7a in CIF format; tables of selected nonbonding Pt···Cl and (py)C–H···Cl distances and dihedral angles; tables of ¹H NMR data in CDCl₃, CD₂CN, DMSO-d₆, and D₂O for free 4-Xpy and for [Pt(4-Xpy)]Y₂ complexes both with and without added [Et₂N]Cl, figure showing the orientation of the pyridyl rings relative to the coordination plane in cis-[Pt(4-Me₂Npy)₂Cl₂]; plots of ¹H NMR data in CDCl₃ (PDF) for complexes prepared in this study; descriptions and graphic data for complexes and for −[Pt(4-Xpy)₂Cl₂] (including X = H) in CDCl₃.

Accession Codes

CCDC 1551057−1551064 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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The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Upgrade of the diffractometer was made possible through Grant No. LEQSF(2011-12)-ENH-TR-01, administered by the Louisiana Board of Regents.

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