A solid-state $^{17}$O NMR study of platinum-carboxylate complexes: carboplatin and oxaliplatin

Xianqi Kong, Victor Terskikh, Abouzar Toubaei, and Gang Wu

Abstract: We report synthesis and solid-state NMR characterization of two $^{17}$O-labeled platinum anticancer drugs: cis-diammine(1,1-cyclobutane-$^{17}$O$_4$)dicarboxylato(platinum(II) [carboplatin] and ([$^{17}$O$_4$]oxalato)(IR,2R)(−)-1,2-cyclohexanediamine)platinum(II) [oxaliplatin]. Both $^{17}$O chemical shift (CS) and quadrupolar coupling (QC) tensors were measured for the carboxylate groups in these two compounds. With the aid of plane wave DFT computations, the $^{17}$O CS and QC tensor orientations were determined in the molecular frame of reference. Significant changes in the $^{17}$O CS and QC tensors were observed for the carboxylate oxygen atom upon its coordination to Pt(II). In particular, the $^{17}$O isotropic chemical shifts for the oxygen atoms directly bonded to Pt(II) are found to be smaller (more shielded) by 200 ppm than those for the non-Pt-coordinated oxygen atoms within the same carboxylate group. Examination of the $^{17}$O CS tensor components reveals that such a large $^{17}$O coordination shift is primarily due to the shielding increase along the direction that is within the O=C–O–Pt plane and perpendicular to the O–Pt bond. This result is interpreted as due to the donation from the oxygen nonbonding electron lone pair to the Pt(II) empty $d_z^2$ orbital, which results in large energy gaps between $d$ Pt–O and unoccupied molecular orbitals, thus reducing the paramagnetic shielding contribution along the direction perpendicular to the O–Pt bond. We found that the $^{17}$O QC tensor of the carboxylate oxygen is also sensitive to Pt(II) coordination, and that $^{17}$O CS and QC tensors provide complementary information about the O–Pt bonding.

Key words: solid-state NMR, oxygen-17, tensor, anticancer drug, platinum-carboxylate complex.
In the present work, we use solid-state $^{17}$O NMR to study two platinum anticancer drugs: carboxplatin and oxaliplatin (Scheme 1). Although several thousand platinum-based anticancer drug molecules have been developed in research laboratories over the past 30 years, only about two dozen have ever gone into clinical trials. Carboxplatin and oxaliplatin are the only two Pt compounds that have gained international marketing approval. Both carboxplatin and oxaliplatin show significantly less toxicity than cisplatin, the first commercial platinum-based drug. While both solution and solid-state NMR techniques utilizing $^1$H, $^{13}$C, $^{15}$N, $^{195}$Pt, and $^{31}$Cl as nuclear probes have been extensively employed to study Pt anticancer drugs, $^{17}$O NMR has not yet been explored in the studies of this class of drug molecules.

In carboxplatin and oxaliplatin, the mode of bonding between the carboxylate group and the Pt(II) metal center can be described as being monodentate, $\text{O=C-O-Pt(II)}$, where the 4 atoms are essentially in the same plane. While there have been a number of experimental solid-state $^{17}$O NMR and computational studies on the $^{17}$O QC and CS tensors in carboxylic acids and their salts, the primary goals of the present study are (i) to experimentally determine the $^{17}$O CS and QC tensors in these important Pt(II) anticancer drugs and (ii) to examine the effect of bonding to a transition metal on these $^{17}$O NMR tensors. In carboxplatin and oxaliplatin, since the mode of bonding is $\text{O=C-O-Pt(II)}$, the non-Pt-coordinated oxygen atom can serve as an internal reference, making it easier to examine the effect of metal bonding on $^{17}$O NMR tensors. Another reason for us to choose these two platinum anticancer drugs is that their crystal structures have been reported.[25,27] The known crystal structures would allow us to perform plane wave DFT calculations of the $^{17}$O NMR tensors in these compounds. These calculations have been proven to produce reliable tensor orientations in the molecular frame of reference and thus can aid the interpretation of the experimental data.

**Experimental section**

**Synthesis of $^{17}$O-labeled Pt(II) complexes**

Preparations of $[^{17}$O]carboxplatin and $[^{17}$O]oxaliplatin were carried out by following literature procedures[38,39] with necessary modifications for $^{17}$O isotopic incorporation. Schematic diagrams illustrating the employed synthetic strategies are given in the Supplementary data, and the synthetic details are described below.

**Dipotassium 1,1-cyclobutane-$[^{17}$O$_4$]-dicarboxylate**

1,1-Cyclobutanedicarboxylic acid (300 mg) was dissolved in 40% $^{17}$O-enriched water (310 μL, purchased from CortecNet) and heated at 80 °C for 22 h. After cooling to room temperature (RT), the solution was neutralized by addition of a solution of KOH (233 mg) in EtOH (8 mL). After the mixture was left in a refrigerator for 20 min, the white solid was collected by filtration, washed with EtOH (3 × 3 mL), and then dried under vacuum. A total of 366 mg of the title compound was obtained.

Dipotassium 1,1-cyclobutane-$[^{17}$O$_4$]-dicarboxylate

![Scheme 1. Molecular structures of carboxplatin and oxaliplatin.](image)

$[^{17}$O$_2$]Carboxplatin

cis-Diaminodihiodoplatinum(II) (567 mg, 1.17 mmol) and AgNO$_3$ (400 mg, 2.34 mmol) were added to H$_2$O (30 mL), and the solution was stirred in an oil bath at 45–50 °C (under darkness) for 3 h. After cooling to RT, the insoluble material was removed by filtration through a pad of Celite. The filter pad was washed with H$_2$O (5 mL). The filtrate and washing were combined in a flask containing diptosodium 1,1-cyclobutane-$[^{17}$O$_4$]-dicarboxylate (244 mg, 1.10 mmol), forming a clear solution. The mixture was concentrated to dryness on a rotary evaporator at 55 °C. The residual material was treated in H$_2$O (5 mL) followed by addition of 2 drops of 30% ammonium hydroxide solution. The mixture was heated briefly to dissolve most of the solid and filtered (a small amount of yellowish insoluble material was thus removed), and the filtrate was concentrated to dryness. The residual material was treated with H$_2$O (1 mL), heated briefly, then cooled to 4 °C. The solid material was collected, washed with cold H$_2$O (2 × 0.5 mL) and ethanol (0.5 mL), and dried under vacuum. The title compound was obtained as a white, free-flow crystalline solid (220 mg, yield 54%). $^1$H NMR (500 MHz, D$_2$O): δ 1.80 ppm (qt, 2H, $J = 7.75$ Hz), 2.78 ppm (t, 4H, $J = 7.75$ Hz), $^{17}$O NMR (67.7 MHz, D$_2$O): δ 126.8 ppm (br, 20), 310.0 ppm (br, 20). The $^{17}$O NMR spectrum is shown in the Supplementary data.

$[^{17}$O$_2$]Oxaliplatin

Dichloro[R,R-cyclohexane-1,2-diamine]platinum(II) (540 mg, 1.42 mmol) and AgNO$_3$ (460 mg, 2.70 mmol) were added to 30 mL of H$_2$O. In the dark, the mixture was stirred in an oil bath at 90 °C for 5 min, and then cooled for over 1 h to RT. The mixture was stirred at RT overnight. Insoluble material was removed by filtration through a pad of Celite, and then the pad was washed with H$_2$O (5 mL). The filtrate was collected in a 100 mL flask, to which dipotassium 1,1-cyclobutane-$[^{17}$O$_4$]-dicarboxylate (220 mg, 1.32 mmol) was added. The mixture was concentrated to dryness on a rotary evaporator at 35–40 °C. The residual material was treated with H$_2$O (5 mL). The solid material was collected by filtration and washed with cold H$_2$O (4 × 3 mL, and 2 × 4 mL). After drying the solid under vacuum, the title compound was obtained as a white powder (285 mg, yield 54%). $^1$H NMR (600 MHz, D$_2$O): δ 5.101 (m, 2H), 1.15 (m, 2H), 1.42 (m, 2H), 1.90 (m, 2H), 2.20 (m, 2H). $^{17}$O NMR (81.0 MHz, D$_2$O): δ 134.7 (br, 20), 306.9 (br, 20). The $^{17}$O NMR spectrum is shown in the Supplementary data.

**Solid-state $^{17}$O NMR**

Solid-state $^{17}$O NMR experiments were performed on Bruker Avance-600 (14.1 T) and Bruker Avance-II 900 (21.1 T) NMR spectrometers. A Hahn-echo sequence was used for both static and magic-angle spinning (MAS) experiments to eliminate the acoustic ringing from the probe. Effective 90° pulses of 1.7 and 1.0 μs were used for the $^{17}$O central transition (CT) experiments at 14.1 and 21.1 T, respectively. The $^{17}$O MAS NMR spectra at 14.1 T were obtained using a 4 mm Bruker MAS probe at a spinning frequency of 14.5 kHz. The $^{17}$O MAS NMR spectra at 21.1 T were obtained with a 1.3 mm Bruker MAS probe at a sample spinning frequency of 50.0 kHz. Static experiments at 14.1 T were performed with the 4 mm MAS probe, and powder samples were packed in 4 mm rotors. At 21.1 T, a homebuilt 5 mm H/X
Fig. 1. (Colour online) Experimental (blue trace) and simulated (red trace) $^{17}$O MAS NMR spectra of (a) $[^{17}$O]$^4$carboplatin and (b) $[^{17}$O]$^4$oxaliplatin at two magnetic fields. The simulated spectra for individual sites are shown in green and purple. The sample spinning frequencies were 14.5 and 50.0 kHz for experiments at 14.1 and 21.1 T, respectively. For each compound, the same $^{17}$O NMR parameters as summarized in Table 1 were used to simulate the spectra recorded at two magnetic fields. Note that the spinning sidebands are clearly visible in the simulated spectra at 14.1 T. Other data acquisition parameters are given in the text.

![Fig. 1](image)

Table 1. Experimental and computed $^{17}$O CS* and QC* NMR tensor parameters for carboplatin and oxaliplatin.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$ (ppm)</th>
<th>$\delta_{iso}$ (ppm)</th>
<th>$\delta_{11}$ (ppm)</th>
<th>$\delta_{22}$ (ppm)</th>
<th>$\delta_{33}$ (ppm)</th>
<th>$C_Q$ (MHz)</th>
<th>$\eta_Q$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CeO1</td>
<td>Exptl. 310.0</td>
<td>326(1)</td>
<td>522(5)</td>
<td>422(5)</td>
<td>34(5)</td>
<td>8.15(2)</td>
<td>0.15(5)</td>
</tr>
<tr>
<td></td>
<td>CASTEP 327</td>
<td>523</td>
<td>433</td>
<td>25</td>
<td>8.145</td>
<td>0.318</td>
<td></td>
</tr>
<tr>
<td>CeO2–Pt</td>
<td>Exptl. 126.8</td>
<td>134(1)</td>
<td>369(5)</td>
<td>99(5)</td>
<td>−66(5)</td>
<td>−6.50(2)</td>
<td>0.33(5)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CeO1</td>
<td>Exptl. 306.9</td>
<td>327(1)</td>
<td>503(5)</td>
<td>425(5)</td>
<td>41(5)</td>
<td>8.20(2)</td>
<td>≤0.05</td>
</tr>
<tr>
<td></td>
<td>CASTEP 336</td>
<td>508</td>
<td>450</td>
<td>48</td>
<td>8.383</td>
<td>0.147</td>
<td></td>
</tr>
<tr>
<td>CeO2</td>
<td>Exptl. 306.9</td>
<td>320(1)</td>
<td></td>
<td>—</td>
<td>—</td>
<td>8.10(2)</td>
<td>0.00(5)</td>
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<tr>
<td></td>
<td>CASTEP 328</td>
<td>495</td>
<td>436</td>
<td>51</td>
<td>8.231</td>
<td>0.189</td>
<td></td>
</tr>
<tr>
<td>CeO3–Pt</td>
<td>Exptl. 134.7</td>
<td>138(1)</td>
<td>411(5)</td>
<td>64(5)</td>
<td>−67(5)</td>
<td>−5.90(2)</td>
<td>0.40(5)</td>
</tr>
<tr>
<td></td>
<td>CASTEP 145</td>
<td>457</td>
<td>140</td>
<td>−26</td>
<td>−6.150</td>
<td>0.296</td>
<td></td>
</tr>
<tr>
<td>CeO4–Pt</td>
<td>Exptl. 134.7</td>
<td>135(1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−5.90(2)</td>
<td>0.30(5)</td>
</tr>
<tr>
<td></td>
<td>CASTEP 184</td>
<td>449</td>
<td>127</td>
<td>−24</td>
<td>−6.131</td>
<td>0.372</td>
<td></td>
</tr>
</tbody>
</table>

Note: The estimated errors for experimental data are shown in parentheses.

*Computed chemical shifts ($\delta$) were obtained from computed shielding values ($\sigma$) by using $\delta = \sigma_{ref} - \sigma$, where $\sigma_{ref}$ was chosen to be 290.0 ppm so that the trend line relating the computed and experimental chemical shift data passes the origin.

*The sign of $C_Q$ was assumed to be the same as the computed one.

*For both compounds, the experimental Euler angles that define the relative orientation between the $^{17}$O QC and CS tensors are: CeO, $\alpha = 0$, $\beta = 90 \pm 5$, $\gamma = 60 \pm 10$°; CeO–Pt, $\alpha = 0$, $\beta = 90 \pm 5$, $\gamma = 40 \pm 10$°.

*Measured in D$_2$O at 298 K.

*Averaged values between O1 and O2.

*Averaged values between O3 and O4.

solenoid probe was used for static experiments, and solid samples were packed into a 5 mm Teflon tube to reduce the background signal. High-power CW $^1$H decoupling (70 kHz) was applied in all static experiments. For carboplatin at 21.1 T, the recycle delay was 20 s, and a total of 512 transients were accumulated for both static and MAS spectra. For oxaliplatin at 21.1 T, the recycle delay was 60 s for both static and MAS spectra. A total of 896 transients and 1500 transients were accumulated in the static and MAS experiments, respectively. For carboplatin at 14.1 T, the recycle delay was 5 s for collecting both static (8348 transients) and MAS
First, one obtains good-quality $^{17}$O NMR spectra under the MAS condition, and spectral simulations were performed with DMfit.\textsuperscript{40} Computational details Plane wave pseudopotential DFT calculations of the NMR shielding and electric field gradient parameters were performed using the Cambridge Serial Total Energy Package (CASTEP) software and Materials Studio 4.4 program (Accelrys)\textsuperscript{41,42} on a HP xw4400 workstation with a single Intel Dual-Core 2.67 GHz processor and 8 GB DDR RAM. The Perdew, Burke, and Ernzerhof (PBE) functionals were used in all calculations in the generalized gradient approximation (GGA) for the exchange correlation energy.\textsuperscript{43,44} On-the-fly pseudopotentials were used as supplied with NMR CASTEP with a plane wave basis set cut-off energy of 550 eV, and the Monkhorst-Pack $k$-space grid sizes of $2 	imes 2 	imes 2$ (2 $k$-points used) and $2 	imes 3 	imes 3$ (9 $k$-points used) for carboplatin and oxaliplatin, respectively. The reported crystal structures of carboplatin\textsuperscript{36} and oxaliplatin\textsuperscript{57} were used as starting structures, and then geometry optimization was performed using the BFGS method\textsuperscript{45} without the cell optimization. The following convergence tolerance parameters were used in the geometry optimization process: total energy $5 	imes 10^{-5}$ eV/atom, maximum displacement 0.005 Å, maximum force 0.1 eV/Å, and maximum stress 0.2 GPa. Nuclear magnetic shielding calculations were also performed with the Amsterdam Density Functional (ADF, version 2012)\textsuperscript{46} software package. Vosko-Wilk–Nusair (VWN) exchange-correlation functional\textsuperscript{47} was used for the local density approximation (LDA), and the PBE exchange-correlation functionals\textsuperscript{43,44} was applied for the generalized gradient approximation (GGA). Standard Slater-type orbital (STO) basis sets with triple-zeta quality plus polarization functions (TZ2P) were used for all the atoms. The spin orbital relativistic effect was incorporated via the zero-order regular approximation (ZORA).\textsuperscript{48–51} The ADF calculations were carried out on Sun SPARC Enterprise M9000 servers at the High Performance Computing Virtual Laboratory (HPCVL) of Queen’s University. Each of the servers consists of 64 quad-core 2.52 GHz Sparc64 VII processors with 8 GB of RAM per core (2 TB of total memory).

Results and discussion

Experimental determination of $^{17}$O NMR tensors

The general solid-state NMR approach for the experimental characterization of $^{17}$O CS and QC tensors consists of two steps. First, one obtains good-quality $^{17}$O NMR spectra under the MAS condition, from which the values of $\delta_{\alpha\beta\gamma}$, $\eta_{Q}$, and $\eta_{\alpha}$ can be obtained for each oxygen site. Second, one records $^{17}$O static NMR spectra preferably at multiple magnetic fields. An analysis of the static spectra would allow determination of the $^{17}$O CS tensor components ($\delta_{\alpha\beta\gamma}$) and their relative orientations with respect to the QC tensor. A detailed theoretical background can be found in the literature.\textsuperscript{52,53} Figure 1 shows the $^{17}$O MAS spectra obtained for $[^{17}$O$_4]$carboplatin and $[^{17}$O$_4]$oxaliplatin at two magnetic fields. In each MAS spectrum, two groups of signals were observed, corresponding to the two types of oxygen atoms (directly Pt-bonded and non-Pt-coordinated) in carboplatin and oxaliplatin. At 14.1 T, since the sample spinning frequency was only 14.5 kHz, weak spinning sidebands are visible for each central band from the simulated spectra. As these weak spinning sidebands happen to overlap with the central bands, they somewhat obscure the fine spectral features. At 21.1 T, in contrast, the sample spinning frequency was 50 kHz, and the MAS spectra, now free of spinning sidebands, exhibit very high spectral resolutions. It is interesting to note that while two oxygen sites are observed for carboplatin, a total of 4 oxygen sites (2 pairs) are detected for oxaliplatin. The crystal structure of carboplatin\textsuperscript{36} indicates the presence of a mirror plane that contains the Pt(II) center and the average cyclobutane ring bisecting the molecule. As a result, the two carboxylate groups in carboplatin are symmetry related. In comparison, the crystal structure of oxaliplatin\textsuperscript{57} suggests that all 4 oxygen atoms of the oxalate group are crystallographically distinct. Therefore, the solid-state $^{17}$O NMR observations shown in Fig. 1 are in agreement with the crystal structures of these compounds. As also seen from Fig. 1, experimental MAS spectra recorded at two magnetic fields for the same compound are matched very well by the simulated ones using the same set of NMR parameters. The experimental values of $\delta_{\alpha\beta\gamma}$, $\eta_{Q}$, and $\eta_{\alpha}$ are summarized in Table 1. In general, carboplatin and oxaliplatin exhibit similar $^{17}$O NMR parameters. The most interesting finding is that the $^{17}$O chemical shifts for the oxygen atoms directly bonded to Pt(II) and the non-Pt-coordinated oxygen atoms differ by 200 ppm (vide infra); also see the solution $^{17}$O spectra of these compounds in the Supplementary data. The directly Pt-bonded oxygens exhibit smaller $C_Q$ values (ca. $|C_Q| \approx$ 6 MHz) than do the non-coordinated oxygens ($|C_Q| \approx$ 8 MHz), in agreement with previous observations on the effect from metal-ligand interactions.\textsuperscript{54} It is important to note that the sign of $C_Q$ cannot be readily determined simply from MAS and static spectra.

Figure 2 shows the $^{17}$O static NMR spectra of carboplatin and oxaliplatin recorded at 21.1 T. Similarly, the static spectra were...
also obtained at 14.1 T (shown in the Supplementary data). Because of the low resolution in the static spectra, it was not possible to treat all 4 crystallographically distinct oxygen sites in oxaliplatin individually. Thus we assumed only 2 CS tensors (O1/O2 and O3/O4) in the spectral simulation. As seen from Fig. 2, the general agreement between experimental and simulated static spectra is satisfactory. Again, all experimental 17O CS tensor components for carboplatin and oxaliplatin are listed in Table 1.

Plane wave DFT calculations and the tensor orientations

As the crystal structures for carboplatin and oxaliplatin are known, we performed plane wave DFT calculations using the CASTEP program. This approach will produce results that can be directly compared with solid-state NMR data without any assumption on the size of the molecular cluster. The CASTEP results for 17O NMR tensors are summarized in Table 1. In general, the computational results are in good agreement with the experimental data. A correlation plot (slope = 0.964; $R^2 = 0.988$) between experimental and computed 17O CS tensor components is given in the Supplementary data. We should point out that the agreement between calculated and experimental results is clearly better for the non-Pt-coordinated oxygen atoms than for the directly Pt-coordinated ones, which is likely due to the neglect of relativistic effects in the CASTEP calculations. The computations also reveal a sign change in $C_Q$ between the 2 types of oxygen atoms. For the non-Pt-coordinated oxygen atom, $C_Q$ is positive, and it becomes negative for the directly Pt-bonded oxygen (vide infra).

Another benefit of the CASTEP calculations is that the 17O CS and QC tensor orientations can be unambiguously determined in the molecular frame of reference. As we have shown previously, the absolute orientations of the 17O NMR tensors in the molecular frame of reference can be reliably predicted by modern quantum chemical calculations. The CASTEP results for the tensor orientations in carboplatin and oxaliplatin are depicted in Fig. 3.

For the non-Pt-coordinated oxygen atom, $\chi_{xx}$ and $\chi_{yy}$ both lie in the O=C–O plane, being perpendicular to and along the C=O bond, respectively. This makes $\chi_{yy}$ perpendicular to the O=C–O plane. This 17O QC tensor orientation is typical of a carbonyl functional group. The 17O QC tensor orientation is quite different for the chelating oxygen, for which the $\chi_{zz}$ component is in plane but essentially along the C–O bond. The 17O CS tensors are also quite different for the two types of oxygen atoms. For the directly Pt-bonded oxygen atom, $\delta_{11}$ of the 17O CS tensor is oriented along the...
components between the non-Pt-coordinated and directly Pt-bonded oxygen atoms in Carboplatin.

For the non-Pt-coordinated oxygen atoms, the net change in the chemical shift is 8.15 MHz from −6.50 MHz. This change is associated with the largest effect, as the apparent sign change from +5.65 MHz to −6.50 MHz is due to the larger change in the <i>O</i> coordination bond.

It is especially worth noting that the 17O NMR tensor orientations found in carboplatin and oxaliplatin are very similar to those in the α-oxalic acid dihydrate determined from a single-crystal 17O NMR study (see Fig. 3). This similarity suggests that the O-Pt coordination bond in O=C–O–Pt resembles the O–H covalent bond in O=C–H (vide infra).

It is also worth commenting on the sign change in C, noted earlier. Since the definition of C is associated with the largest QC component (in its absolute value), the apparent sign change from −6.50 MHz for the non-Pt-coordinated oxygen to +5.65 MHz for the directly Pt-bonded oxygen does not mean that the net change in C is 8.15 MHz. Rather, one must examine the individual 17O QC tensor components using the respective C–O bond as the frame of reference. As seen from Fig. 3, the changes in the 3 directions with respect to the C–O bond are: along the C–O bond, −6.50 MHz; perpendicular to the C–O bond but in the O–C–O plane, −3.46 MHz; and perpendicular to the C–O plane, +5.65 MHz. Thus, the largest change is 5.65 MHz, occurring in the direction perpendicular to the O–C–O plane.

A survey of 17O coordination shifts from carboxylate-metal interactions

As mentioned in the previous section, the most interesting result in this study is the 200 ppm difference in δ<sub>17O</sub> between the directly Pt-bonded and non-Pt-coordinated oxygen atoms. To put this in perspective, we surveyed the solid-state 17O NMR data in the literature for metal-carboxylate interactions. To make direct comparison of NMR data from different compounds meaningful, we focused only on those carboxylates that exhibit the monodenate mode of binding to the metal ion, i.e., O=C–O–M<sup>n+</sup> to O=C–O–H. In this case, the corresponding 17O chemical shift difference is typically −150 ppm. In this context, the observed 17O coordination shift of −200 ppm in carboplatin and oxaliplatin is quite remarkable and deserves further investigation as presented in the next section.

Table 2. ADF analysis of the diamagnetic (a) and paramagnetic (b) contributions to the total 17O magnetic shielding in two Pt-carboxylate complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Pt-bound oxygen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-coordinated oxygen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pt-bound oxygen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-coordinated oxygen&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>394</td>
<td>400</td>
<td>395</td>
<td>402</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>394</td>
<td>400</td>
<td>395</td>
<td>402</td>
</tr>
</tbody>
</table>

<sup>a</sup>Averaged over the two related oxygen atoms within the same molecule.

The origin of 17O coordination shifts

To better understand the very large 17O coordination shifts, we decided to carefully examine the 17O NMR tensors. To aid discussion, we label the tensor components according to their directions with respect to the carboxylate plane. As shown in Fig. 5, the in-plane tensor components parallel and perpendicular to the C–O bond are denoted as || and ⊥, respectively, while the tensor component perpendicular to the C–O–Pt plane is denoted as π.

Figure 5 illustrates the changes in tensor components between the two types of oxygen atoms. This analysis immediately reveals that while all three components of the 17O QC tensors change considerably upon Pt coordination, the change in the || component of the 17O CS tensor is significantly larger than those in the other two components. Furthermore, because of the large change...
in the \( \parallel \) component, the orientations of the \( \delta_{11} \) and \( \delta_{22} \) components in the molecular frame of reference appear switched between the directly bonded and non-Pt-coordinated oxygen atoms. As a result, a “cross-over” effect is seen in Fig. 5. A similar “\( \delta_{11} \rightarrow \delta_{22} \) cross-over” effect was previously reported for the phenolic oxygen atom of tyrosine between the protonated and deprotonated states.64

To further identify the origin of the observed \(^{17}\text{O}\) coordination shift in terms of specific molecular orbitals (MOs), we performed a detailed magnetic shielding analysis using the ADF program.46 According to the Ramsey formalism of nuclear magnetic shielding, the total magnetic shielding at a nucleus can be divided into diamagnetic and paramagnetic contributions:

\[
\sigma_{\text{total}} = \sigma_{\text{d}} + \sigma_{\text{p}}
\]

In general, the diamagnetic shielding term is dominated by core electrons and consequently exhibits essentially no orientation dependence. In contrast, the paramagnetic shielding contribution is responsible for the anisotropic nature of the magnetic shielding tensor. In the formulation implemented in the ADF software package, \( \sigma_{\text{p}} \) is further partitioned into three different parts:\(^{46}\)

\[
\sigma_{\text{p}} = \sigma_{\text{p}(\text{gauge})} + \sigma_{\text{p}(\text{occ-occ})} + \sigma_{\text{p}(\text{occ-vir})}
\]

where \( \sigma_{\text{p}(\text{gauge})} \), \( \sigma_{\text{p}(\text{occ-occ})} \), and \( \sigma_{\text{p}(\text{occ-vir})} \) denote the paramagnetic shielding contributions from the gauge, magnetic coupling among occupied MOs, and magnetic coupling between occupied and virtual MOs, respectively. Table 2 lists a summary of individual shielding contributions in oxaliplatin and carboplatin. It is quite clear that \( \sigma_{\text{p}} \) is indeed responsible for the observed coordination shift in Pt-carboxylate complexes. Furthermore, \( \sigma_{\text{p}(\text{occ-vir})} \) makes the largest contribution to \( \sigma_{\text{p}} \). So what kind of occupied and unoccupied MOs can be magnetically coupled to induce a large paramagnetic shielding effect when the magnetic field is along the C-O bond (that is, the \( \parallel \) direction)? It is also well-known from Ramsey’s theory\(^{66}\) that the paramagnetic shielding contribution from magnetic coupling of a pair of occupied and virtual MOs is inversely proportional to the energy gap between them, provided that the two MOs satisfy the symmetry requirement.\(^{66}\)

Previous \(^{17}\text{O}\) NMR studies of C–O and N–O compounds have shown\(^{56,57,64,67}\) that the high-lying nonbonding orbitals (electron lone pairs) on the oxygen atom often make the largest paramagnetic shielding contribution. Use oxaliplatin as an example. As seen in Fig. 6, MO#92 and #93 (HOMO) are largely localized on the non-Pt-coordinated oxygen atoms, each having a similar shape as a pure 2p atomic orbital perpendicular to the C–O bond. The ADF analysis showed that the magnetic coupling between these two MOs and all virtual MOs contributes −204 and −48 ppm of paramagnetic shielding for the non-Pt-coordinated and directly Pt-bonded oxygen atoms, respectively (see Table 2). We also found that the magnetic coupling between MO#84 and #85 and all virtual MOs makes comparable paramagnetic shielding contributions on both types of oxygen atoms. Among the virtual MOs, the most important ones are of the \( \pi^* \) type such as MO#97 and #114, which can be magnetically coupled with MO#84, #85, #92, and #93 when the magnetic field lies along the \( \parallel \) direction, as also shown in Fig. 6. So the above discussion has shown quite clearly that the large \(^{17}\text{O}\) coordination shift observed in the Pt-carboxylate complexes is due to the significantly reduced paramagnetic shielding contribution on the directly Pt-bonded oxygen atom when the magnetic field is along the \( \parallel \) direction, which couples MO#92 and #93 with all virtual MOs with the right symmetry.

Conclusions

We have synthesized two \(^{17}\text{O}\)-labeled platinum-carboxylate complexes (carboplatin and oxaliplatin) that are well-known antican-
cur drugs and carried out solid-state $^{17}$O NMR experiments to determine the complete $^{17}$O CS and QC tensors in these compounds. We found that the $^{17}$O CS and QC tensors for the 2 oxygen atoms within the same carboxylate group are very different, reflecting the monodentate mode of binding between the carboxylate group and Pt(II), i.e., $\equiv$O–O–Pt. The observed large coordination shifts in these Pt-carboxylate complexes is a good example to illustrate that $^{17}$O CS and QC tensors often provide complementary information about the chemical bonding. It is certainly an advantage of solid-state $^{17}$O NMR spectroscopy that these tensor properties can be measured simultaneously. The experimental solid-state $^{17}$O NMR results were very well reproduced by plane wave DFT calculations. The demonstrated sensitivity of $^{17}$O NMR tensors toward metal-ligand interactions makes $^{17}$O NMR a useful tool for studying other metallo-drugs. It may also be possible to use solid-state $^{17}$O NMR to probe polymorphism of drug compounds.

Supporting information

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References

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