Influence of DFT Functionals and Solvation Models on the Prediction of Far-Infrared Spectra of Pt-Based Anticancer Drugs: Why Do Different Complexes Require Different Levels of Theory?

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ABSTRACT: Computational modeling was applied to far-infrared (FIR) spectra of Pt-based anticancer drugs to study the hydrolysis of these important molecules. Here, we present a study that investigates the influence of different factors—basis sets on non-Pt atoms, relativistic effective core potentials (RECPs) on the Pt atom, density functional theory (DFT) functionals, and solvation models—on the prediction of FIR spectra of two Pt-based anticancer drugs, cisplatin and carboplatin. Geometry optimizations and frequency calculations were performed with a range of functionals (PBE, PBE0, M06-L, and M06-2X), Dunning’s correlation-consisted basis sets (VDZ, VTZ, aVDZ, and aVTZ), RECPs (VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp), and solvation models (IEFPCM, CPCM, and SMD). The best combination of the basis set/DFT functional/solvation model was identified for each anticancer drug by comparing with experimentally available FIR spectra. Different combinations were established for cisplatin and carboplatin, which was rationalized by means of the partial atomic charge scheme, ChelpG, that was utilized to study the charge transfer between the Pt ion and ligands in both cisplatin and carboplatin.

INTRODUCTION

Since its discovery by Rosenberg, cisplatin (Figure 1) has become one of the most commonly used anticancer drugs.1,2 The chloride ion in cisplatin helps to stabilize the drug before activation.3 After absorption via diffusion, cisplatin is activated by hydrolysis, whereby the chloride ions are replaced with water molecules (Figure 1).4 The hydrolysis occurs as the drug passes from the blood plasma to the cell cytoplasm, where the concentration of chloride decreases.5 The activated form of cisplatin interacts with the purine base on guanine of the DNA sequence to form either mono- or bifunctional adducts, mostly by binding to two neighboring guanines (G) or neighboring guanine and adenine (A).4−6 These adducts form cross-links between base pairs on the same helical chain, resulting in the localized unwinding of the helix and increasing the width of the minor groove.4,5,7 This disruption in structure thus interrupts the process of cell replication and initiates apoptotic cell death.4,7 Currently, there are uncertainties about the identity of the active form of cisplatin and in particular whether it is mono- or diaquated. Kinetic studies have indicated that the monoaquated complex is the active form; however, in vitro studies have shown that the diaquated complex should be the active form instead.8

The use of cisplatin in cancer treatments is accompanied with a number of harmful side effects, such as diminishing hearing ability, nephrotoxicity, and neurotoxicity, which results from the accumulation of the active form of the drug in the body.2,8 This has motivated the discovery of other Pt-based compounds with less side effects to act as a substitute for cisplatin, like carboplatin (Figure 2).2,4 Carboplatin has more complex functional groups based on cyclobutane, and hence, it hydrolyzes at a slower rate compared to cisplatin (at least 2 orders of magnitude slower), thus decreasing the rate of accumulation and is therefore less toxic.2 The mechanism of
carboplatin, unlike cisplatin, involves a two-step ring opening of the cyclobutanedicarboxylate group.6

Currently, there are still uncertainties with respect to the mechanism of how cisplatin and its derivatives hydrolyze prior to their binding to DNA. There is evidence that the hydrolysis of cisplatin might be a two-step process.6,10 Hambley et al. used [1H, 15N] heteronuclear single quantum coherence two-dimensional nuclear magnetic resonance spectroscopy to study the kinetics of hydrolysis of cisplatin and its binding to a 14 base pair oligonucleotide (S′-d(AATTAGTACTAATT)-3′).6 They identified that cisplatin hydrolyzed first to the monoaquated form that subsequently formed a covalent bond with the guanine base of the oligonucleotide before it hydrolyzed to the diaquated form.6

Far-infrared (FIR) spectroscopy has the potential to unravel the mechanistic detail of this process and is particularly useful for investigating low-energy metal–ligand bonds. The FIR spectrum of cisplatin and carboplatin allows us to understand the nature of the donor–acceptor bonds whose stretching and bending vibrations can only be detected between 10 and 600 cm⁻¹.11,12 In addition, the FIR region can provide an insight into changes of metal–ligand interactions and hence, their activity.4,12,13 This, in itself, has been a challenge as reliable detection of the FIR region requires a bright light source, normally absent in conventional benchtop instruments because of less sensitive detectors, such as deuterated triglycine sulfate detectors.14 Because of this limitation, the FIR region of both cisplatin and carboplatin was measured with a synchrotron source that achieves high quality of spectra as the high brightness of FIR protons provides a high signal-to-noise ratio in the FIR region.15

The characteristic FIR vibrations of cisplatin and carboplatin have been identified previously by comparing the experimental spectra to those predicted with density functional theory (DFT).14,16,17 Wood et al. assigned main experimental bands to be 155, 201, and 323 cm⁻¹ for cisplatin and 194, 348, 351, 441, 475, and 573 cm⁻¹ for carboplatin.14 The presence of the heavy Pt cation increases the difficulty of assignment of all the vibrations in the FIR region because of band splitting.14,18–20 The heavy metal ion causes factor group splitting, a phenomenon that arises from vibrational coupling interactions in molecules or crystals, affecting the Pt–N vibrations.18–21 In addition, the presence of intermolecular hydrogen bonding between the complex molecules may also contribute to splitting of the stretching Pt–Cl and Pt–N bands.11

The two Pt-based complexes—cisplatin and carboplatin—studied here possess donor–acceptor bonds between the Pt(II) ion and ligands, with Pt playing the role of an acceptor. These bonds are different from normal covalent bonds. The study by Wysokiński et al. reported results of the natural bond orbital (NBO) analysis for both cisplatin and carboplatin. It was found that the lone pair on the donor N atoms of cisplatin exhibits at least 85.3% p-type character and has occupancy of 1.719e, whereas the N atoms on carboplatin exhibit 81.5% p-type character.22 This indicates that there is a partial π-back donation to Pt orbitals, which is more apparent in carboplatin.22

Luo et al. applied LC-ωPBE, mPW1PW, and PBE0 functionals, specifically DFT, to conduct structural, IR, and molecular orbital studies of two conformations of Pt-(NH₃)₂Cl₂—cisplatin and transplatin.23 Analysis of the electrostatic potential on the two complexes revealed that cisplatin was more susceptible to nucleophilic attack compared to transplatin.23 This conclusion further supports the observation that transplatin was inactive as an anticancer drug, on top of the inability of transplatin to form bifunctional adducts with DNA.24–26 Wysokiński et al. compared the calculated spectra of carboplatin, using mPW1PW91 and MP2 methods with either LanL2DZ, D95V(d,p), and D95V++(d,p) basis sets in gas, to experimental data and identified the characteristic stretching and bending modes of carboplatin.27 It was concluded that the mPW1PW91/LanL2DZ level of theory predicted the experimental spectra to be the best out of the combinations studied.27 In addition, a study conducted by Barone et al. indicates the validity of DFT as a tool to study the Raman spectroscopy of cisplatin.28 IR spectra calculated with the B3PW91-D3 and B2PLYP-D3 functionals were compared with the experimental spectra.28 Mean absolute deviations (MADs) of 41 and 45 cm⁻¹ were reported for these functionals.28 The MAD decreased to 15 cm⁻¹ when an anharmonic force field was used. It should be pointed out that in this case, MADs were applied to the full spectrum. On closer inspection of the data, the harmonic oscillator performed equally well in the FIR region.28 Moreover, the results were computed in the gas phase, thus additionally affecting the quality of the prediction.28

Since donor–acceptor bonds are special types of covalent bonds, accurate quantum chemical methods are required to predict their properties.14,27,29–31 The Pt–N bond in cisplatin has been proven to be difficult to model in previous studies, with B3LYP resulting in a longer Pt–N bond length and thus underestimating the stretching frequency.29–31 For example, DFT functionals, such as B3LYP and B3PW91, have been shown to produce inconsistent results in determining geometries and bond dissociation energy (BDE) of the B→N dative bond.29 The study also demonstrated that MPW1K, a hybrid functional, consistently underestimated the BDE of the B→N bond by a root-mean-square deviation (rmsd) of 4.1 kcal mol⁻¹ on average, producing the best results out of the tested functionals (PBE and mPW1PW91 giving rise to RMSDs of 4.5 and 5.1 kcal mol⁻¹, respectively).29 Another study by Philips et al. indicated that it was challenging to identify a suitable DFT functional to predict IR spectra of a nitrile→BH₃ complex because of the presence of the dative bond.30

Despite these shortcomings, DFT still represents the most computationally feasible approach to studying these bonds. FIR spectroscopy represents the most definitive indirect technique in probing the mode of donor–acceptor bonding in Pt-based anticancer drugs and thus, aids in unraveling their mechanism of action in the cell. Therefore, it is important to know limitations of current DFT functionals in the prediction of FIR spectra of these drugs. To date, no systematic study has been performed on the accuracy of DFT functionals for the prediction of stretching and bending vibrations of Pt–ligand

Figure 2. Platinum-based anticancer drugs. Cisplatin (left) and carboplatin (right). Number on the complexes reflects the identity of the ligands that are given in Tables 3 and 4.
bonds. It is particularly important to establish which DFT functionals are reliable for the prediction of stretching vibrations as these are more likely to be affected by the accuracy of the selected functional as well as the inclusion of solvent effects, whereas bending vibrations might not be as sensitive. The dependency of stretching vibrations on the chosen functional was demonstrated in a study conducted by Wysokiński and Michalska, in which different DFT functionals resulted in underestimated Pt–N stretching vibrations in cisplatin. Although a number of theoretical strategies have been applied to offset systematic errors in the predicted frequencies (e.g., the application of scaling factors), different strategies might need to be applied for stretching and bending vibrations in the case of Pt–ligand native bonds. In particular, electrostatic effects of the bulk on predicted spectra were not considered in the reported studies on Pt-based anticancer drugs.

In this work, we have performed a systematic study analyzing the accuracy and reliability of a series of DFT functionals (PBE, PBE0, M06-L, and M06-2X), Dunning’s correlation consistent basis sets (VDZ, VTZ, aVDZ, and aVTZ), relativistic effective core potentials (RECPs) for Pt (VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp), and solvation models (IEFPCM, CPCM, and SMD) for the prediction of experimental FIR spectra of cisplatin and carboplatin. The M06-L functional with no contribution from exact Hartree–Fock (HF) exchange was selected as it was originally designed to study transition metal complexes, whereas PBE is traditionally used for studying metal surfaces. Instead of Grimme’s empirical dispersion correction, the use of hybrid functionals such as PBE0 and M06-2X was adopted as the inclusion of the exact HF exchange was shown to reliably treat noncovalent interactions. Although there are a number of RECPs available, RECPs developed by Peterson et al. were selected for the Pt atom because of their superior description of the valence electrons. These potentials showed excellent performance against the benchmark method, CCSD(T)/QZ for the atomic properties of 5d elements. Geometry optimizations and frequency calculations were performed on cisplatin and carboplatin, respectively, using different combinations of the DFT functionals, basis sets, and solvation models. The previously characteristic experimental peaks of both platinum complexes were used as a reference to the predicted spectra. The optimal combination of the functional, basis set, and solvation model to predict the experimental spectra was identified. In addition, the effect of each factor was also analyzed to determine the extent of its influence on the predicted spectra and stretching vibrations of Pt–ligand bonds in particular. Last, charges from electrostatic potentials grid method (ChelpG) analysis were performed on both cisplatin and carboplatin to study the electrostatic potential of the Pt metal ion and ligands and the differences between the two complex differences.

**THEORETICAL PROCEDURES**

All molecular orbital calculations were performed using the Gaussian 09 quantum chemical package. Both complexes of interest, cisplatin and carboplatin, were subjected to geometry optimization, followed by a frequency calculation. For both complexes, the Pt cation center has a square planar (C2v) symmetry. Carboplatin has a similar geometry, with the Cl–anions being replaced with the cyclobutanedicarboxylate group. Four different DFT functionals were chosen for this study: PBE, M06-L, PBE0, and M06-2X. PBE is a generalized gradient approximation (GGA) functional developed by Perdew, Burke, and Ernzerhof. PBE0, a hybrid functional developed by Adamo, builds on the PBE functional to include 25% HF exchange energy. HF exchange energy improves the accuracy of chemical property predictions, for example, atomization energies and ionization potentials, of small- to medium-sized systems, especially for noncovalent interactions and excited states. Upon the addition of the 25% HF exchange energy, PBE0 is comparable to other more heavily parameterized functionals for the prediction of structures and molecular properties, such as kinetic and thermodynamic properties. M06-L and M06-2X are Minnesota functionals, with the former being a meta-GGA functional and the latter being a hybrid meta-GGA functional. M06-L, a local density functional, takes into consideration the local spin density, the local spin gradient, as well as the spin kinetic energy density. This allows M06-L to provide higher efficiency for larger systems, specifically to study the thermodynamics of transition metal complexes. In addition, being a local density functional, M06-L has been successfully benchmarked for the MLBE21/05 database containing organometallic and inorganometallic complexes, such as CrC3H3 and Fe(CO), to reproduce the benchmark data within 5.4 kcal mol⁻¹ on average for transition metal–ligand bond energies. M06-L has also been benchmarked for intermolecular hydrogen bonds using the HB6/04 database, which contains hydrogen-bonded complexes such as dimers of ammonia and water, with M06-L predicting the smallest mean unsigned error of 0.36 kcal mol⁻¹. M06-X contains 5% of HF exchange and was formulated to meet five different criteria, including the description of noncovalent interactions, transition metal bonding, and electronic spectroscopy predictions. M06-2X has also been successfully benchmarked for the aTC13 and TME53 databases consisting of varying complexes with π–π stacking interactions and ionization potentials, producing mean unsigned errors of 1.40 and 2.54 kcal mol⁻¹, respectively.

The two complexes of interest were studied using different implicit solvation models: integral equation formalism polarizable continuum model (IEFPCM), conductor-like polarizable continuum model (CPCM), and solute model based on density (SMD), with water as the solvent. These implicit solvation models place the molecule of interest into a cavity, whose surface charge is stabilized in accordance with the dielectric constant of the selected solvent, thus simulating the effect of the solute being exposed to the solvent. Both IEFPCM and CPCM apply the dielectric permittivity, εr of the solvent as a uniform medium with the solute placed in a cavity. The difference between IEFPCM and CPCM lies in the method used to define the cavity. IEFPCM makes the use of connected spheres to model the solute, with radii of the spheres matching those of solute atoms. The uniform dielectric permittivity of the solvent acts on the wavefunction of the modeled solute. CPCM, on the other hand, makes the use of unique, small regions on these connected spheres called tesserae. These tesserae are defined by their individual position and interaction with the dielectric constant. Partial charges are then assigned to each of the tesserae based on the electrostatic potential. SMD is a model that makes use of a smooth continuous model to assign charges on the molecular surface of the solute. For SMD, the solute is polarizable by...
the charge density of the solvent and the interaction between the solute and solvent can be determined via the charge density of the former and the electric polarization field of the latter. 52 In addition, SMD has proven to be an effective solvation model for use in both charged and uncharged systems and is able to predict accurate solvation energies for various different functional groups, achieving an average of mean absolute error of 4 kcal mol$^{-1}$ for ions. 52

RECPs were employed on the Pt atom to model the inner core electrons to reduce computational costs. 46,55 Developed by Peterson et al., these RECPs were taken from multi-configuration Dirac–Hartree–Fock calculations for 5d elements that also explicitly included relativistic effects. 40 RECPs are regularly used to model heavy atoms as they aid to decrease computational costs and already take relativistic effects into consideration. 41,56 In a study conducted by Xu and Truhlar, a mean unsigned error of 1.1 kcal mol$^{-1}$ was achieved. In this study, the RECPs used for the Pt metal ion are VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp. RECPs were employed on the Pt atom to model the inner core electrons to reduce computational costs. 46,55 Developed by Peterson et al., these RECPs were taken from multi-configuration Dirac–Hartree–Fock calculations for 5d elements that also explicitly included relativistic effects. 40 RECPs are regularly used to model heavy atoms as they aid to decrease computational costs and already take relativistic effects into consideration. 41,56 In a study conducted by Xu and Truhlar, a mean unsigned error of 1.1 kcal mol$^{-1}$ was achieved. In this study, the RECPs used for the Pt metal ion are VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp. RECPs were employed on the Pt atom to model the inner core electrons to reduce computational costs. 46,55 Developed by Peterson et al., these RECPs were taken from multi-configuration Dirac–Hartree–Fock calculations for 5d elements that also explicitly included relativistic effects. 40 RECPs are regularly used to model heavy atoms as they aid to decrease computational costs and already take relativistic effects into consideration. 41,56 In a study conducted by Xu and Truhlar, a mean unsigned error of 1.1 kcal mol$^{-1}$ was achieved. In this study, the RECPs used for the Pt metal ion are VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp. RECPs were employed on the Pt atom to model the inner core electrons to reduce computational costs. 46,55 Developed by Peterson et al., these RECPs were taken from multi-configuration Dirac–Hartree–Fock calculations for 5d elements that also explicitly included relativistic effects. 40 RECPs are regularly used to model heavy atoms as they aid to decrease computational costs and already take relativistic effects into consideration. 41,56 In a study conducted by Xu and Truhlar, a mean unsigned error of 1.1 kcal mol$^{-1}$ was achieved. In this study, the RECPs used for the Pt metal ion are VDZ-pp, VTZ-pp, aVDZ-pp, and aVTZ-pp.

A series of Dunning’s basis sets—VDZ, VTZ, aVDZ, and aVTZ—were chosen for this study, enabling the systematic approximation to the complete basis set (CBS) limit. 57 Augmented basis sets, aVDZ and aVTZ, were also considered because of their superior treatment of induction interactions. 57 This study aims to identify the optimal combination of the functional, basis set for the non-Pt atoms, RECP for the Pt metal ion, and solvation model to predict the experimental FIR spectra of Pt complexes. The statistical tools used in this study are the mean deviation, denoted as mean, standard deviation (SD), and the MAD. The mean denotes how accurate the predicted spectra are to the experimental spectra. MAD is calculated with eq 1 and indicates the spread of the peaks calculated in the predicted spectra when compared to the experimental spectra. SD is calculated with eq 2.

$$\text{MAD} = \frac{\sum |v_i - \omega_i|}{n} \quad (1)$$

$$\text{SD} = \sqrt{\frac{\sum (v_i - \omega_i)^2}{n - 1}} \quad (2)$$

where $v_i$ and $\omega_i$ are experimental and calculated wavenumber values, respectively, and $n$ is the number of peaks compared.

In the following figures, the MAD is represented by the horizontal line in the box plot, as seen in Figure 3. The MAD is used to demonstrate the deviation of predicted peaks to the experimental peaks. The upper and lower quantile of the box is the SD about the MAD, and the whiskers represent the spread of twice the SD about the MAD. In this analysis, it is preferred that MAD to be as close to zero as possible and the box to be as narrow as possible.

### RESULTS AND DISCUSSION

The calculated results in this study are compared to the previously experimentally measured spectra. 14,31 Tables 1 and 2 present the characteristic peaks of both cisplatin and carboplatin, respectively. Each peak is assigned to a specific type of vibration observed in the FIR region.

#### Table 1. Comparison of Experimental and Predicted (Gas-Phase PBE/VDZ with VDZ-pp RECP on Pt) Characteristic FIR Peaks of Cisplatin

| experimental wavenumber (cm$^{-1}$) | predicted wavenumber (cm$^{-1}$) | assignment$^a$ |
|------------------------------------|----------------------------------|----------------|
| 155$^{14,31}$                      | 156                              | $\gamma$(N–Pt–N) + $\gamma$(Cl–Pt–Cl)       |
| 201$^{14,31}$                      | 223                              | $\alpha$(N–Pt–N) + $\alpha$(Cl–Pt–Cl)       |
| 323$^{14,31}$                      | 339/350                          | $\nu_{asym}$(Pt–Cl) + $\nu_{asym}$(Pt–Cl)   |

$^a$ $\gamma$—out-of-plane bending; $\alpha$—scissoring; $\nu_{sym}$—symmetric stretching; $\nu_{asym}$—asymmetric stretching.

#### Table 2. Experimental and Predicted (Gas-Phase PBE/VDZ with VDZ-pp RECP on Pt) Characteristic FIR Peaks of Carboplatin

| experimental wavenumber (cm$^{-1}$) | predicted wavenumber (cm$^{-1}$) | assignment$^a$ |
|------------------------------------|----------------------------------|----------------|
| 194$^{14,27}$                      | 192                              | $\alpha$(N–Pt–N)       |
| 348$^{14,27}$                      | 341                              | $\nu$(Pt–O)           |
| 351$^{14,27}$                      | 352                              | $\nu$(Pt–O)           |
| 441$^{14,27}$                      | 450                              | $\nu_{sym}$(Pt–N)     |
| 475$^{14,27}$                      | 465                              | $\alpha$(O–Pt–O) + $\nu_{sym}$(Pt–N)     |
| 573$^{14,27}$                      | 565                              | $\alpha$(O–Pt–O)     |

$^a$ $\alpha$—scissoring; $\nu$—stretching; $\nu_{sym}$—symmetric stretching; $\nu_{asym}$—asymmetric stretching. Differences between the calculated and experimental peaks were calculated for each combination of the DFT functional/basis set/solvent model.

In order to make an unbiased assignment of the predicted spectra to experimental bands, for each predicted peak the differences to all experimental wavenumber values were calculated. The smallest difference dictated the assignment of the predicted band to the corresponding experimental band. An independent assignment was performed this way for four varying conditions—DFT functional, basis set on non-Pt atoms, RECP basis set on Pt, and solvent model. An example of predicted and experimental band alignment is shown in Figure 4, in which the RECP basis set varied from VDZ-pp to aVTZ-pp. In order to assess the performance of each DFT functional/basis set/solvent model combination, mean and MAD values were computed. Additionally, these statistical measures were used to ensure that the correct band assignment was achieved.

In the case of cisplatin, two predicted peaks would manifest in the 335–355 cm$^{-1}$ region, with the peak with the lower wavenumber corresponding to $\nu_{asym}$(Pt–Cl) and the higher wavenumber corresponding to $\nu_{sym}$(Pt–Cl). 14,17
experimental data, only one broad peak was detected, an overlapping of both the symmetric and asymmetric Pt−Cl stretch. In this case, the closer predicted peak out of the two (symmetric and asymmetric) was taken into consideration for peak allocation. Despite being represented by one broad peak in the experimental data, the two different types of stretching—symmetric and asymmetric—manifest at slightly different wavenumber values.

The 249 cm$^{-1}$ peak that is found in the experimental spectra was initially assigned to the NH$_3$−Pt−NH$_3$ bending vibration arising from the cisplatin dimer. In this study, we focus on the vibrations that represent the Pt-based complex monomers and, therefore, this peak was not considered.

The same assignment process was performed for carboplatin, as shown in Figure 5. It was noted that there are a few weak peaks detected at 230, 248, and 320 cm$^{-1}$. Some of these peaks were originally assigned to bending/stretching vibrations of the carboxylate groups. For example, the band located at 320 cm$^{-1}$ was assigned to a rocking vibration of the cyclobutanedicarboxylate group. It was outside the scope of this study to investigate these types of vibrations, and therefore, these peaks were not considered.

Further in the text, we look at each of the four criteria for both cisplatin and carboplatin separately to identify the best combination to predict FIR spectra for each compound.

**Selection of Effective Core Potential on Pt and Basis Set on Non-Pt Atoms for Cisplatin.** The SD values calculated for the four DFT functionals in the gas phase are shown in Figure 6 by varying the basis sets applied for both Pt and non-Pt atoms. Analysis of Figure 6 reveals that apart from the PBE0 functional, the SD values fall in a narrow range of 13.5−23.0 cm$^{-1}$. PBE0 produces slightly larger errors of up to 35.0 cm$^{-1}$. On the other hand, the effect of the basis sets of both Pt and non-Pt atoms appears to be very minimal. This was studied by taking the maximum difference in both MAD and SD (labeled as ± further in the text) when different RECP and basis sets were applied. For example, the maximum difference in MAD when the VDZ basis set was applied for the non-Pt atoms is 19.0 ± 19.2 cm$^{-1}$ and the maximum difference when VDZ-pp RECP was applied for the Pt ion is 18.7 ± 20.31 cm$^{-1}$. The maximum differences of the different basis sets and RECPs were 4.0 ± 4.25 and 2.0 ± 3.6 cm$^{-1}$, respectively. The VTZ-pp RECP basis set for Pt was found to produce the smallest MAD values in the range of 15.6−21.5 cm$^{-1}$, for all functionals except PBE0, regardless of the choice of basis set on non-Pt atoms.

In order to select the best-performing basis set for non-Pt atoms, the performance of the four DFT functionals was compared while keeping the VTZ-pp RECP basis set constant for the Pt atom. The corresponding MAD and SD values are presented in a box and whisker plot in Figure 7. These box and whisker plots give an indication of the spread of the calculated peaks about the characteristic experimental peaks. Ideally, a combination of the MAD close to zero and a narrow distribution in SD indicates the best performance of the method.

Analysis of Figure 7 reveals that the increasing basis set on non-Pt atoms does not alter the performance of the DFT functionals, with triple-ζ quality basis sets giving marginally larger errors compared to double-ζ ones. Out of these, the
PBE0 functional was found to exhibit the largest MAD and SD values of 25.0 and 33.3 cm$^{-1}$, respectively. The MAD and SD values of PBE, M06-L, and M06-2X functionals are as follows: 15.0 ± 21.5, 11.0 ± 20.0, and 11.0 ± 18.4 cm$^{-1}$. Out of the four functionals, M06-L and M06-2X give the MAD values closer to zero, with the former producing slightly smaller SD values of 15.6 cm$^{-1}$ for the VDZ basis set. To this end, the VDZ basis set was established to be the optimal basis set for non-Pt atoms in the gas phase regardless of the DFT functional. Further in the text, only results calculated with the VDZ basis set on non-Pt atoms and the VTZ-pp RECP basis set on Pt are discussed for cisplatin.

The effect of solvent model is shown in a box and whisker plot in Figure 8, in which the VDZ basis set was used for non-Pt atoms and the VTZ-pp RECP basis set for Pt. Analysis of these results reveals that the choice of functionals and solvation models plays a significant role in the prediction of the characteristic FIR wavenumbers of cisplatin. Some functionals are affected more than the others. For example, the PBE0 functionals show the largest reduction in the MAD and SD values going from the gas phase to SMD. The MAD and SD values for PBE0 decreased from 24.3 ± 32.6 to 5.0 ± 9.3 cm$^{-1}$ from the gas phase to SMD. The Minnesota functionals undergo the least changes, with M06-2X giving the largest MAD errors of 19.7 and 20.7 cm$^{-1}$ in combination with the IEFPCM and CPCM models, respectively. The SMD model appears to produce the lowest MAD and SD errors for all four DFT functionals, with PBE showing the MAD value as low as 5.7 cm$^{-1}$. These results identify the importance of selecting an optimal combination of solvent model and DFT functional for studying donor–acceptor bonds in Pt-based complexes because of their polar properties, as well as the π-back donation of lone pairs on N/Cl atoms to unoccupied orbitals on Pt. It was previously hypothesized that the π-back donation could dictate the characteristic of the Pt–N bond. It has been shown previously that increasing the polarity of the solvent (from C$_6$H$_6$ to CH$_3$CN) has a stabilizing effect on the donor–acceptor bond in the previously studied compounds such as polyenes.

Out of the three FIR bands identified from the experimental spectrum of cisplatin, there is only one stretching vibration observed at 323 cm$^{-1}$. It has been previously reported that both stretching and bending vibrations are usually overestimated when calculated using HF or DFT methods in the gas phase. This was also previously observed in a cisplatin study conducted by Wang et al., where the IR spectra were calculated in the gas phase using LC-ωPBE functional, 6-311++G** basis set on the non-Pt atoms, and SDD ECP on the Pt ion in both the gas phase and SMD solvation model with water as the solvent. A calculation performed in the gas phase

**Figure 5.** Example of alignment of the five characteristic peaks of carboplatin to predicted spectra. Spectra were obtained with the PBE functional in the gas phase combined with the VDZ basis set on non-Pt atoms. RECPs on Pt are given on the left top corner of each spectrum.
predicted that the Pt–Cl bond length is shorter by 0.035 Å and the Pt–N bond length is longer by 0.076 Å compared with the experimental data.23 Both Pt–Cl and Pt–N stretching vibrations were overestimated, and a scaling factor of 0.95 was applied to the spectra.23 As the SMD solvation model was utilized in the optimization of cisplatin, it decreases the error in predicted bond lengths—Pt–N is 0.037 Å and Pt–Cl is 0.006 Å longer than the experimental data.23 The absence of the solvation field has proven to decrease the accuracy in predicting the geometry of cisplatin and, therefore, the IR spectrum.23 Stretching vibrations also appear to be more sensitive to the choice of level of theory because of their increased strength compared to that of bending ones.62 As expected, the stretching vibration is overestimated by 32 cm$^{-1}$ for the combination of PBE0 and the gas phase. This stretching vibration becomes underestimated with the inclusion of solvation models by as much as 33 cm$^{-1}$ with M06-2X and CPCM solvation model, with two exceptions (PBE0 functional with IEFPCM and SMD solvation model where the stretching vibration is overestimated by 5 and 1 cm$^{-1}$, respectively). The bending vibrations were usually overestimated, with PBE0 functional in the gas phase giving the largest SD of 33.2 cm$^{-1}$.
It was observed that γ bending vibrations were consistently overestimated when compared to the 155 cm⁻¹ experimental peak, with the largest deviation of 15 cm⁻¹ being produced with the PBE functional and the IEFPCM. α bending vibrations, an in-plane scissoring vibration that is represented by the 201 cm⁻¹ experimental peak, is considerably less consistent as compared to the prediction of γ bending, which is an out-of-plane bending vibration, with a combination of both over- and underestimation. The largest underestimation and overestimation of the α bending vibrations resulted with PBE0 in gas (32 cm⁻¹) and M06L with SMD (13 cm⁻¹), respectively. In the case of cisplatin, the absolute deviations of the only stretching vibration in cisplatin are shown in Figure 9. Upon comparison of Figures 8 and 9, the main contribution of MAD in Figure 8 is due to the MAD that arose from the stretching vibration. For example, the use of PBE0 in conjunction with the gas phase resulted in the large MAD of stretching vibration, 32.0 cm⁻¹, and a large overall MAD, of 24.3 cm⁻¹, when all three experimental peaks were compared. In other cases, with M06-2X functional and solvation models, the MAD recorded for the stretching vibration is between 30.0 and 33.0 cm⁻¹. The stretching vibration has the biggest contribution to the MAD when compared to all three experimental peaks. Overall, the PBE and PBE0 functionals reproduce the stretching vibration in cisplatin within as low as 1 cm⁻¹ when combined with the SMD solvation model. The MAD values for these functionals (see Figure 8) come entirely from overestimation of the two bending vibrations.

In the case of cisplatin, the combination of the SMD solvation model and the PBE functional appears to be the optimal combination to predict its FIR spectrum.

**Selection of Effective Core Potential on Pt and Basis Set on Non-Pt Atoms for Carboplatin.** As in the case of cisplatin, the effect of the basis set applied for non-Pt atoms was found to be minimal (see Figure 10). The PBE0 functional has been demonstrated to give rise to the larger range of SD values, a minimum of 20.0 cm⁻¹, among the four functionals. Excluding PBE0, the SD values of the other three functionals lie between a smaller range of 8.7–15.7 cm⁻¹. The maximum SD values were found to be 14.5 cm⁻¹ for the aVDZ basis set on the non-Pt atoms and 13.9 cm⁻¹ with the aVTZ-pp RECP on the Pt ion. The change in SD values across basis sets and RECPs was 0.8 and 0.4 cm⁻¹, respectively. The maximum MAD values were found to be 11.4 and 13.0 cm⁻¹ for the aVTZ basis set and aVTZ-pp RECP, respectively. The variation in MAD values across basis sets and RECPs fell in the region of 1.6 and 2.7 cm⁻¹. As for cisplatin, the effect of the RECP basis set on Pt on the carboplatin vibrations was small, with VTZ-pp showing the best trade-off between accuracy and cost as demonstrated in Figure 11 (MAD values between 5.8 and 9.8 cm⁻¹ excluding PBE0). The VDZ basis set was again sufficient for non-Pt atoms, where the VTZ-pp RECP was the best option for the Pt atom.

In the case of carboplatin, it is evident that the influence of solvation model and functional (see Figure 12) is different when compared to that of cisplatin. Out of all combinations tested, the M06-L functional together with CPCM produced the least MAD and SD values of 6.8 and 9.1 cm⁻¹, respectively. Surprisingly, the PBE0 functional in combination with the SMD model generated the largest errors, with MAD and SD being 19.0 and 30.5 cm⁻¹, respectively, which is in contrast to the trend found in cisplatin. M06-2X produced second best results, apart from the SMD model. Overall, the Minnesota functionals performed better for carboplatin than for cisplatin. This striking difference might be attributed to the differences between the description of the donor–acceptor bonds present in the two complexes: Pt–Cl bond versus the Pt–O bond. Analysis of the atomic charges fitted to reproduce the electrostatic potential using the ChelpG, it was confirmed that the Pt–Cl bond had more covalent characteristics compared to the Pt–O bond. For gas-phase optimized geometries, the predicted charges on the Cl atoms in cisplatin and O atoms in carboplatin are approximately −0.7e and −1.5e, respectively. This trend is further supported by the charges on Pt atoms, which were predicted to be 1.8e and 2.1e.
for cisplatin and carboplatin, respectively. Solvent-phase optimized geometries produced similar trends as discussed below. The partial charge on the chloride and charge on Pt < 2.0e in cisplatin clearly demonstrate a charge transfer on the Pt−Cl bond of 0.3e. In the case of carboplatin, there does not seem to be a charge transfer between the Pt and O atoms. This observation explains why M06-L performs better for carboplatin and PBE performs better for cisplatin. The outstanding performance of M06-L is expected as the functional was developed for treating transition metal complexes. As mentioned before, PBE is a GGA functional that is an improvement to the local density approximation and is able to better describe covalent bonds compared to M06-L.

In the carboplatin case, there are three pure stretching vibrations out of six (located at 348, 351, and 441 cm⁻¹) and a peak (located at 475 cm⁻¹) that has both stretching and bending contributions assigned experimentally in the FIR region. The MAD and SD values for the stretching vibrations are given in Figure 13. The stretching vibrations of carboplatin are not as consistently underestimated as compared to those cisplatin, noting that these vibrations usually manifest as a mixture of vibrations. For example, the theoretical bands at 341 and 352 cm⁻¹ assigned to the ν(Pt−O) vibration are usually

![Figure 10. Effects of RECPs on the Pt atom (y-axis) and basis sets on the non-Pt atoms (x-axis) on the MAD (horizontal line) and SD values (upper and lower quantile of box) of PBE, M06-L, PBE0, and M06-2X functionals used on gas-phase optimized geometries of carboplatin. All values given in cm⁻¹.](image1)

![Figure 11. Box and whisker plots depicting the effect of basis set (x-axis) on non-Pt atoms on the performance of DFT functionals using gas-phase optimized geometries of carboplatin and VTZ-pp RECP basis set carboplatin. All values given in cm⁻¹.](image2)

![Figure 12. Box and whisker plots depicting the effect of solvent models (x-axis) on the performance of DFT functionals of carboplatin using the VTZ-pp RECP basis set on Pt and VDZ basis set on non-Pt-atoms. All values given in cm⁻¹.](image3)
coupled with bending vibrations of the cyclobutanedicarboxylate side group. The experimental peak at 441 cm$^{-1}$ that has been assigned to a pure Pt–N symmetric vibration is usually accompanied by a Pt–O bending vibration. These mixtures of vibrations resulted in the inconsistent over- and under-estimation of the measured peaks, with the exception for the PBE0 functional that always results in an overestimation of all four characteristic peaks in the range of 85 cm$^{-1}$ with the CPCM/IEFPCM solvation model to 99 cm$^{-1}$ with the SMD solvation model. With the exception of PBE0, $\nu$(Pt–O) is more prone to be underestimated as compared to $\nu$(Pt–N). Both $\nu$(Pt–O) experimental peaks (348 and 351 cm$^{-1}$) were only overestimated with the M06-2X functional in the gas phase. $\nu$(Pt–N) experimental peaks at 441 and 475 cm$^{-1}$, on the other hand, were found to be overestimated with a few exceptions. For example, M06-L and M06-2X functionals in the gas phase underestimate the 441 cm$^{-1}$ experimental peak by 26 and 7 cm$^{-1}$, respectively. As one can see, the MAD and SD values practically reflect those in Figure 12, identifying a similar trend observed for cisplatin, with larger errors arising from stretching vibrations. The M06-L functional produces the least errors when combined with the IEFPCM and CPCM models, whereas the PBE0 functional gives the largest errors regardless of the solvent model used.

In addition, the bending vibrations of carboplatin and the experimental wavenumber of 194 and 573 cm$^{-1}$ were also studied. The peaks at 194 and 573 cm$^{-1}$ were assigned to $\alpha$(N–Pt–N) and $\alpha$(O–Pt–O), respectively. Interestingly, the O–Pt–O bending vibration at 573 cm$^{-1}$ was underestimated regardless of the functional and solvation model, with the PBE and SMD combination giving rise to the largest deviation of 31 cm$^{-1}$. The smallest deviation of 2 cm$^{-1}$ was obtained with the M06-2X functional in the gas phase. This could be due to the absence of a pure bending vibration. The presence of a more complex cyclobutanedicarboxylate group in carboplatin appears to play a role in these predictions.

Comparison of the predicted stretching vibrations of cisplatin and carboplatin, excluding the PBE0 functional that consistently produces large MAD and SD values, shows a range of MAD values from 0 cm$^{-1}$ with the PBE functional and the SMD solvation model to 33 cm$^{-1}$ with the M06-2X functional and the CPCM solvation model for cisplatin. For carboplatin, the MAD and SD (denoted as MAD ± SD) values are 7.0 ± 9.4 and 16.5 ± 21.3 cm$^{-1}$ both with PBE functional in the gas phase and SMD, respectively. These results highlight that a different scaling factor is needed not only for each DFT functional but also for their combination with a solvent model.
99 cm$^{-1}$ and 0.0865 Å, respectively. Similar to cisplatin, both Pt−O and Pt−N bond lengths are predicted to be short when calculated in the gas phase, with a range of 1.96−2.00 Å for Pt−O and 2.08−2.11 Å for Pt−N. With the inclusion of solvation models, the bond lengths increased slightly by 0.030 Å on average for Pt−O with PBE and PBE0 functionals and 0.043 Å on average with the Minnesota functionals. However, the Pt−N bond decreased by 0.026 Å with PBE and PBE0 functionals.

### Figure 15
Relationship between the Pt−O and Pt−N bond lengths and theoretical stretching vibrations in carboplatin. Vertical black lines on graphs correspond to experimental wavenumbers of stretching vibrations for the Pt−O1, Pt−O2, Pt−N1, and Pt−N2 bonds (348, 351, 441, and 475 cm$^{-1}$, respectively). Horizontal black lines show the Pt−O and Pt−N bond lengths (2.025 and 2.021 Å, respectively) taken from X-ray data. Reported Pt−N bond lengths are the average of both Pt−N bonds.

### Table 3. ChelpG Fitted Partial Atomic Charges for Cisplatin and Carboplatin

| gas/solvent model | functional  | Pt    | Cl(2) | Cl(3) | N(4) | N(7) |
|-------------------|-------------|-------|-------|-------|------|------|
| **Cisplatin**     |             |       |       |       |      |      |
| gas               | PBE         | 1.786 | −0.707| −0.707| −2.652| −2.652|
|                   | PBE0        | 1.819 | −0.707| −0.707| −2.766| −2.766|
|                   | M06-L       | 1.859 | −0.721| −0.721| −2.734| −2.734|
|                   | M06-2X      | 1.473 | −0.658| −0.658| −2.128| −2.128|
| IEPFCM            | PBE         | 1.783 | −0.700| −0.700| −2.710| −2.710|
|                   | PBE0        | 1.818 | −0.694| −0.694| −2.866| −2.866|
|                   | M06-L       | 1.771 | −0.701| −0.701| −2.675| −2.675|
|                   | M06-2X      | 1.764 | −0.694| −0.694| −2.751| −2.751|
| CPCM              | PBE         | 1.781 | −0.696| −0.696| −2.744| −2.744|
|                   | PBE0        | 1.748 | −0.685| −0.685| −2.744| −2.744|
|                   | M06-L       | 1.777 | −0.708| −0.708| −2.681| −2.681|
|                   | M06-2X      | 1.754 | −0.674| −0.702| −2.798| −2.798|
| SMD               | PBE         | 2.074 | −0.733| −0.733| −3.289| −3.289|
|                   | PBE0        | 1.86  | −0.698| −0.698| −2.96 | −2.96 |
|                   | M06-L       | 2.035 | −0.727| −0.727| −3.228| −3.228|
|                   | M06-2X      | 2.104 | −0.734| −0.734| −3.412| −3.412|
| **Carboplatin**   |             |       |       |       |      |      |
| gas               | PBE         | 2.118 | −1.479| −1.509| −2.439| −2.217|
|                   | PBE0        | 2.161 | −1.514| −1.528| −2.489| −2.339|
|                   | M06-L       | 2.063 | −1.426| −1.457| −2.412| −2.13 |
|                   | M06-2X      | 2.139 | −1.506| −1.508| −2.521| −2.236|
| IEPFCM            | PBE         | 1.987 | −1.22 | −1.282| −2.482| −2.202|
|                   | PBE0        | 1.986 | −1.212| −1.267| −2.509| −2.274|
|                   | M06-L       | 2.008 | −1.248| −1.275| −2.504| −2.178|
|                   | M06-2X      | 2.12  | −1.302| −1.362| −2.629| −2.325|
| CPCM              | PBE         | 1.987 | −1.222| −1.284| −2.479| −2.202|
|                   | PBE0        | 1.986 | −1.211| −1.267| −2.511| −2.272|
|                   | M06-L       | 2.008 | −1.247| −1.275| −2.504| −2.178|
|                   | M06-2X      | 2.048 | −1.27 | −1.332| −2.496| −2.271|
| SMD               | PBE         | 1.964 | −1.169| −1.24 | −2.509| −2.199|
|                   | PBE0        | 2.092 | −1.226| −1.299| −2.688| −2.378|
|                   | M06-L       | 2.229 | −1.247| −1.304| −2.924| −2.533|
|                   | M06-2X      | 2.033 | −1.224| −1.258| −2.594| −2.303|

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charges by analysis, combined with the HF method VDZ basis set on non-to incorrect reading of the RECPs used. Instead, the ChelpG this study because of the orbital inversion that was attributed the application of the NBO method proved to be an issue in complexes.67

Transition metals.36,40 The Minnesota functionals perform well for systems containing functionals and solvation model does not a explains molecular properties such as dipole moments.58 ChelpG, a grid-based method, utilizes points spaced by 0.3–0.8 Å, placed at the center of the atoms, to imitate the electrostatic potential surface of a molecular system.68–70 ChelpG removes any points that are located in the van der Waals radius of all atoms because of the influence of being in close proximity to the nucleus. The ionic radius selected for Pt(II) was 0.8 Å.71 The van der Waals radii used for the other atoms are the default values defined in the ChelpG scheme.69,70 Table 3 shows partial atomic charges calculated for cisplatin and carboplatin, whereas Table 4 presents the overall charges on the ligands. In cisplatin, the charges on the Cl anion were found to be significantly less negative than those of the N atom. For example, when calculated with PBE in the gas phase, the atomic charges of Cl and N were computed to be −0.707 e and −2.652 e, respectively. The overall charge of the NH3 ligand was found to be −0.202 e, indicating that the ligand is more likely to draw the electron density from the Pt center. This is in agreement with the predicted charge of 1.786 e on the Pt ion. Considering the nominal charge of +2.0 on the Pt ion, these numbers demonstrate a charge transfer of 0.293 e from the chloride anion to Pt and then a charge transfer of 0.186 e to the ammonia ligand. With a larger extent of the charge transfer between Pt and Cl, the Pt–Cl bond experiences a significant degree of ionic character.65–67

Table 4. Electrostatic Potential Obtained from ChelpG Calculations of Ligands of the Two Complexes

| gas/solvation model | functional | Cisplatin | Carboplatin |
|---------------------|------------|-----------|-------------|
|                     |            | N(4)H$_3$ | N(7)H$_3$   |
| **gas**             | PBE        | −0.186    | −0.186      |
|                     | PBE0       | −0.202    | −0.202      |
|                     | M06-L      | −0.208    | −0.208      |
|                     | M06-2X     | −0.078    | −0.078      |
| **IEFPCM**          | PBE        | −0.192    | −0.192      |
|                     | PBE0       | −0.215    | −0.215      |
|                     | M06-L      | −0.185    | −0.185      |
|                     | M06-2X     | −0.188    | −0.188      |
| **CPCM**            | PBE        | −0.195    | −0.195      |
|                     | PBE0       | −0.189    | −0.189      |
|                     | M06-L      | −0.186    | −0.186      |
|                     | M06-2X     | −0.156    | −0.156      |
| **SMD**             | PBE        | −0.304    | −0.304      |
|                     | PBE0       | −0.233    | −0.233      |
|                     | M06-L      | −0.290    | −0.290      |
|                     | M06-2X     | −0.318    | −0.318      |

Analysis of Partial Atomic Charges with ChelpG. NBO analysis, as mentioned above, is a definitive tool in providing information about the electronic charge distribution, type of bond, and charge transfer in a molecular system.65,66 However, the application of the NBO method proved to be an issue in this study because of the orbital inversion that was attributed to incorrect reading of the RECPs used. Instead, the ChelpG analysis, combined with the HF method VDZ basis set on non-Pt atoms and VTZ-pp on Pt, was used to study partial atomic charges by fitting these to reproduce the electrostatic potential of complexes.67–70 ChelpG developed by Cox and William was demonstrated the ability of atomic charge assignment to explain molecular properties such as dipole moments.58
a bigger orbital overlap than the Pt–NH$_3$ bond. This finding also indicates that the Pt–Cl bond exhibits more covalent characteristics. Table 3 also demonstrates that apart from the SMD solvation model, the charge flows away from the Pt metal ion in the range from 0.252e for the PBE0/CPCM combination to 0.181e for the PBE0/gas combination. The M06-2X functional in the gas phase as well as all DFT functionals with SMD produces slightly elevated charge-transfer values, further supporting the above established conclusion that both the DFT functional and inclusion of solvent model are important in the prediction of accurate vibrations in Pt-based complexes.

In contrast to cisplatin, the charges on the oxygen atoms in carboplatin are more negative than $-1.0e$ by at least $0.2e$ regardless of the functional/solvent model combination. In addition, the atomic charge on O is computed to be more negative when calculated in the gas phase, which is in agreement with the above results that solvation plays a role in charge transfer for carboplatin. This finding highlights that the Pt–O bond is clearly more ionic than the Pt–Cl bond, with the charge on the Pt ion being slightly higher than the nominal $+2.0$ charge. The largest difference of 0.229e was observed for M06-L with SMD, indicating the charge transfer from the Pt atom to the ligands.

In addition, by comparing the charges of ligands in carboplatin and cisplatin, the direction of charge transfer could potentially give an insight into the different rates of hydrolysis. Using the calculations conducted with PBE and gas phase as an example, a charge transfer of 0.293e from the chloride anion to Pt and then a charge transfer of 0.184e to the ammonia ligand in cisplatin. For carboplatin, charge transfer occurs from Pt to both the O atoms on the cyclobutanedicarboxylate in the amount of 0.479e, whereas the ammonia ligands experience charge transfer to a much lesser extent. This redistribution of the electron density about the ligands for carboplatin could play a pivotal role in the different rates of hydrolysis and, hence, the different levels of toxicity of the two Pt drugs.

The overall charges of NH$_3$ groups in cisplatin and carboplatin have also been analyzed. As in Table 4, the overall charges of NH$_3$ in cisplatin are found to be equivalent for all but one calculation, M06-2X and CPCSM solvation model, where one NH$_3$ is 0.066e more negative than the other NH$_3$ ligand. This gives an indication that the two NH$_3$ ligands result in the same extent of charge transfer from the Pt metal ion. This is, however, not the case for carboplatin. The overall charge of the two NH$_3$ ligands in carboplatin is significantly different, for example, $-0.06$ and $0.013$e with PBE functional and gas. This difference implies that there is an imbalance of charge transfer from the metal ion and a larger extent of orbital overlap for N(3)H$_3$ than N(5)H$_3$. Across the different combinations of functional and solvation models, the overall charge of NH$_3$ is more negative in cisplatin than that of carboplatin, indicating a stronger interaction in the Pt–NH$_3$ bond in cisplatin.

Merz–Kollman (MK) partial charge analysis was also performed to study the atomic charges of cisplatin and carboplatin. The results are presented in the Supporting Information and not discussed here as the findings further support the trends from the ChelpG analysis, whereby the Pt–O bond in carboplatin is found to exhibit a stronger ionic character compared to the Pt–Cl bond in cisplatin. MK analysis is included in the Supporting Information.

### CONCLUSIONS

This study shows that the accuracy of theoretical vibrational frequencies in the FIR region of the two Pt complexes depends on the choice of both DFT functional and solvation model. In the case of cisplatin, the combination of PBE and SMD was found to be the best for the prediction of experimentally measured characteristic bands with a MAD and SD of 5.7 ± 8.5 cm$^{-1}$, whereas the M06-L and IEFPCM or CPCM combination is the best choice for carboplatin, with a MAD and SD of 6.8 ± 9.2 and 6.8 ± 9.1 cm$^{-1}$, respectively. These findings were attributed to the differences in the covalent nature of Pt–ligand bonds present in the complex of interest.

As the Pt–Cl bond was found to exhibit more covalent characteristics than the Pt–O bond in carboplatin, it is not surprising that PBE performs better for cisplatin because it was designed to treat covalent bonds. This is indicated by a charge transfer of 0.293e from the chloride anion to Pt in cisplatin and the reduced charge on Pt below the nominal +2.0 charge. Instead, the Pt–O bonds were more ionic nature, with the Pt charge being slightly higher than the nominal +2.0 charge and a charge transfer of 0.036 and 0.013e to the cyclobutanedicarboxylate and NH$_3$ groups. Therefore, M06-L was found to perform better for carboplatin because it was designed for ionic systems. Projecting these findings to other Pt-based complexes such as oxaliplatin and nedaplatin with Pt–O bonds, the M06-L functional with SMD is recommended as the best choice.

As expected, stretching vibrations are usually overestimated when calculated in gas phase as they produce shorter Pt–ligand bonds when calculated with a solvation model. With the inclusion of the solvation model, stretching vibrations are usually found to be overestimated in cisplatin, with the exception of the PBE0 functional in combination with both IEFPCM and SMD. For carboplatin, the stretching vibrations are less accurate because of the mixing of stretching and bending vibrations. While Pt–O stretching vibrations can be found to be either under- or overestimated, Pt–N vibrations are mostly overestimated. This further affirms the conclusion that the appropriate functional–solvation model combination should be determined to study such complexes with diverse bond characteristics. In addition, the different scaling factors are required not only for pure bending and stretching vibrations but also for mixed stretching and bending vibrations.

### ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b03455.

Optimized geometries of both cisplatin and carboplatin using different combinations of functionals, basis sets, RECPs, and solvation models (ZIP)

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Notes
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ABBREVIATIONS
FIR, far-infrared; RECP, relativistic effective core potential; DFT, density functional theory; G, guanine; A, adenine; NBO, natural bond orbital method; BDE, bond dissociation energy; GGA, generalized gradient approximation; HF, Hartree–Fock; IEFFPCM, integral equation formalism polarizable continuum model; CPCPM, conductor-like polarizable continuum model; SMD, solvent model based on density; CBS, complete basis set; SD, standard deviation; MAD, mean absolute deviation; ChelpG, charges from electrostatic potential grid method

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