The prediction of Raman spectra of platinum(II) anticancer drugs by density functional theory

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Abstract

We present the method of theoretical calculations of the Raman intensities and the simulated Raman spectra of platinum(II) complexes. Theoretical Raman spectra of the anticancer agents: cisplatin (1), carboplatin (2), cis-\([\text{Pt(ornotato)}(\text{NH}_3)_2]\) (3), cis-\([\text{PtCl}_2(\text{NH}_3)(2\text{-picoline})]\), ZD0473 (4), and the two transient species of 4 (the hydrolysis products) were calculated by density functional mPW1PW method with several basis sets. For comparison, the experimental Raman spectra of compounds 1–3 were measured. The clear-cut assignment of the Pt–ligand vibrations in the Raman spectra of the investigated compounds has been made on the basis of the calculated potential energy distribution.

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1. Introduction

In the past decade, one of the most successful applications of quantum chemistry has been the accurate prediction of the infrared spectra of fairly large molecules. Ab initio calculations have aided the interpretation of vibrational spectra, and many incomplete or incorrect assignments have been revised and improved. In our earlier studies we have shown that density functional theory (DFT), particularly the B3LYP functional, very well reproduces vibrational frequencies and infrared intensities of the aromatic molecules, whereas both ab initio Hartree–Fock and second-order Möller–Plesset (MP2) methods fail in predicting the frequencies of the so-called troublesome modes [1,2]. Several research groups [3,4] evaluated density functional theory as a tool for predicting infrared absorption intensities of the series of transition-metal carbonyls. Recently [5], we have studied the performance of different density functional methods and basis sets in the calculation of molecular structures and the infrared spectra of two platinum(II) anticancer drugs: cisplatin and carboplatin. We have demonstrated that the modified Perdew–Wang density functional model (mPW1PW) introduced by Adamo and Barone [6,7] is clearly superior to other density functional methods (including B3LYP) in a simultaneous prediction of both molecular geometries and vibrational frequencies of platinum(II) complexes. The mPW1PW functional has been especially tuned on van der Waals interactions [6], but it also yields very good results for platinum–ligand covalent or coordination bonds [5].

In continued search of new platinum-based drugs of the improved anticancer activity, thousands of platinum(II) complexes have been prepared and tested against various types of tumors [8,9]. Theoretical predictions of molecular structures and vibrational spectra using quantum chemistry methods can greatly facilitate the design of a new compound. In the case of platinum(II) complexes the Raman spectra are of special interest, because some of the platinum–ligand vibrations (e.g., Pt–NH\textsubscript{3} stretching vibrations) give rise to very weak bands in infrared, whereas they are strong...
in the Raman spectra [10]. Moreover, the hydrolytic reactions of platinum(II) drugs can be studied in aqueous solution using Raman spectroscopy. Water is a weak Raman scatterer, while infrared spectroscopy suffers from the strong absorption of water. Thus, the clear-cut assignment of the Raman bands corresponding to Pt–L vibrations (where L is the leaving group in hydrolytic cleavage) becomes extremely important.

Four platinum(II) complexes have been considered in this work. Cisplatin, cis-diaminedichloroplatinum(II), cis-[PtCl2(NH3)2] (1) is the parent of the platinum complexes applied in cancer chemotherapy [11]. The second-generation drug, carboplatin, [cis-diamine(1,1-cyclobutanedicarboxylato)platinum(II)] (2), is less nephrotoxic than cisplatin and has received a worldwide approval in clinical use [12]. Recently, orotate ligand has attracted growing attention in medicine due to its proposed biological carrier function for metal ions [13]. The platinum–orotate complex, cis-diamineorotatoplatinum(II) (3) has been investigated on account of its potential antitumor activity [14]. The fourth studied complex is very promising new anticancer agent, cis-[PtCl2(NH3)(2-picoline)] (4), known as ZD0473 (formerly called AMD473 or JM473) which is now undergoing worldwide phase II and III clinical trials [15]. It has been shown that this drug possesses remarkable activity against Pt-resistant cells, is less toxic than cisplatin, and it can be administrated orally. It is interesting that the DNA-binding properties of ZD0473 differ from those of cisplatin [15]. Sadler and coworkers [16] determined the hydrolysis rates for each chloride ligand and the X-ray crystal structure of (4). The Raman spectra of the complexes (3) and (4) have not been reported, as yet.

The first purpose of this work is the investigation of the performance of the mPW1PW functional and different basis sets in predicting the Raman spectra of platinum(II) complexes. The theoretical studies of the Raman spectra have been performed for the above four complexes and for two transient species, the products of hydrolysis of 4. For comparison, the experimental solid-state Raman spectra of 1–3 compounds were measured. The platinum–ligand stretching vibrations have been assigned on the basis of the calculated potential energy distribution (PED).

The second purpose is an attempt to clarify some confusion in literature regarding the calculations of Raman spectra using the output from the Gaussian program [17]. It should be emphasized that Gaussian set of programs does not calculate the Raman spectra (as stated in the manual [18]), although it computes directly the infrared intensities and infrared spectra. Several authors (see, for example [19–22]) simulated incorrect ‘Raman spectra’ using the computed Raman scattering activity coefficients and compared them directly with the experimental Raman spectra. Thus, they totally neglected the dependence of Raman intensities on the other factors (the frequency of excitation laser line and the frequencies of vibrational modes). A brief description of the theoretical method for calculating Raman spectra is presented in Section 2.

2. Theoretical method

The calculation of Raman intensities is based on Placzek’s polarizability theory [23]. It should be noted that the theoretical values are obtained within the double harmonic approximation, i.e., the force constants are assumed to be harmonic, and only the linear terms are retained in the series expansion of the polarizability tensor components with respect to a normal mode.

The non-resonant Raman intensity associated with the vibrational normal mode \(Q_i\) is defined by the following two quantities:

The scattering activity coefficient \(S_i\)

\[
S_i = g_i \left[ 45 (\gamma_i')^2 + 7 (\gamma_i'')^2 \right] \left( \text{A}^4 / \text{amu} \right),
\]

and the depolarization ratio \(\rho_i\)

\[
\rho_i = \frac{3 (\gamma_i'')^2}{45 (\gamma_i')^2 + 4 (\gamma_i'')^2}
\]

where \(g_i\) is the degeneracy of the normal mode; \(\gamma_i'\) and \(\gamma_i''\) are, respectively, the derivatives of the trace and of the anisotropy of the polarizability tensor

\[
(\gamma_i')^2 = \frac{1}{9} \sum_u \left( \frac{\partial \alpha_{uu}}{\partial Q_i} \right)^2, \quad u = x, y, z,
\]

\[
(\gamma_i'')^2 = \frac{1}{2} \sum_{uu} \left[ 3 \left( \frac{\partial \alpha_{uu}}{\partial Q_i} \right)^2 - \left( \frac{\partial \alpha_{uu}}{\partial Q_i} \frac{\partial \alpha_{uu}}{\partial Q_i} \right) \right].
\]

The expressions for \(S_i\) and \(\rho_i\) correspond to plane-polarized incident light and observations made in the direction perpendicular to the electric field and to its propagation direction [23].

The absolute differential Raman scattering cross-section (in \(\text{m}^2/\text{sr}\)) corresponds to the measured absolute Raman intensity, and is given by [23,24]

\[
\frac{\partial \sigma_i}{\partial \Omega} = \frac{(2\pi)^4}{45} (v_0 - v_i)^4 \frac{h}{8\pi^2 c v_i B_i} S_i,
\]

where \(B_i\) is a temperature factor which accounts for the intensity contribution of excited vibrational states, and is represented by the Boltzmann distribution

\[
B_i = 1 - \exp \left( - \frac{h v_i c}{k T} \right)
\]

In Eqs. (5) and (6) \(h, k, c, \) and \(T\) are Planck and Boltzmann constants, speed of light and temperature in Kelvin,
respectively; $v_0$ is the frequency of the laser excitation line ($v_0 = 1/\lambda_0$, where $\lambda_0$ is the laser wavelength); $v_i$ is the frequency of normal mode. The scattering cross-section is represented by $\sigma$, while $\Omega$ represents the solid angle of light collection. It should be noted that some authors missed the term $1/v_i$ in the expression for differential Raman scattering cross-section (Eq. (13) in [25] and Eq. (1) in [26]).

The theoretical Raman intensity ($I^R$), which simulates the measured Raman spectrum can be calculated according to the formula

$$I^R_i = C(v_0 - v_i)^4 \cdot v_i^{-1} \cdot B_j^{-1} \cdot S_i,$$

where $S_i$ is the Raman scattering activity of the normal mode $Q_i$ calculated by ab initio or DFT methods [17], $C$ is a constant (in our calculations $C$ is equal $10^{-12}$) and $I^R_i$ is given in arbitrary units. In this work, we have assumed the excitation frequency, $v_0 = 9398.5$ cm$^{-1}$, which corresponds to the wavelength of 1064 nm of a Nd:YAG laser. Initially, we have included the $B_j$ factor (Eq. (6)) for $T = 300$ K. However, this seriously overestimates the Raman intensities of fundamentals observed in the solid state, in the range of frequencies below 200 cm$^{-1}$. It seems that the contribution to non-resonance Raman scattering from the excited vibrational states, in the solid platinum complexes at room temperature, is negligible. Thus, the presented theoretical Raman intensities have been computed assuming $B_j$ equal 1. The theoretical Raman spectra have been calculated by the own program [27]. The simulated spectra were plotted using a Lorentzian band shape with a half-width at half-height (HWHH) of 3 cm$^{-1}$.

The optimized structures, vibrational frequencies and Raman scattering activities of Pt(II) complexes were calculated by the mPW1PW protocol [6,7], which is the Becke-style one-parameter functional coupled with the modified Perdew–Wang exchange and correlation functionals. To account for the relativistic effects in Pt, we have used the effective core potential (ECP) of Hay and Wadt [28] and the concomitant basis set (LanL2DZ). Calculations were performed using different basis sets for the ligand atoms: D95V(d,p) and D95V++(d,p) which are the Dunning/Huzinaga valence double zeta basis sets augmented by polarization and diffuse functions [29], and Pople’s group basis sets, 6-311G(d,p) and 6-311++G(d,p) [30]. To provide the unequivocal assignment of the calculated Raman spectra, the potential energy distributions (PEDs) have been calculated according to the procedure described earlier [31].

3. Experimental

The FT-Raman spectra of 1–3 complexes were obtained on Nicolet 2000 spectrometer. The samples were studied in the solid state, placed in quartz capillary tubes. The NIR excitation was provided by a Nd:YAG laser operating at 1064 nm. A power of 100 mW was used and the spectra were recorded at 4 cm$^{-1}$ resolution.

![Fig. 1. The calculated molecular structures of cisplatin (1), carboplatin (2), cis-[Pt(orotato)(NH$_3$)$_2$] (3) and cis-[PtCl$_2$(NH$_3$)(2-picoline)] (4).](image-url)
4. Results and discussion

Fig. 1 shows the calculated molecular structures of the investigated platinum(II) complexes. In Fig. 2 we compare the experimental Raman spectrum of carboplatin (2) and the theoretical Raman spectra calculated by the density functional mPW1PW method with different basis sets for the ligand atoms. It is worth mentioning that the theoretical results refer to the isolated molecule in the gas phase at 0 K, whereas comparison is made with the Raman spectrum of the solid molecule. Unfortunately, no gas-phase or low-temperature matrix isolation Raman spectra of the investigated platinum complexes, are available. Nevertheless, the simulated Raman spectra closely resemble the observed solid-state spectrum of carboplatin. Some of the differences in the calculated versus experimental frequencies or intensities may result from hydrogen bonding in the solid, and also from anharmonicity of vibrations (this effect refers, in particular, to the NH\textsubscript{3} group vibrations) [5]. As expected, the calculated frequencies of all the C–H and N–H stretching vibrations are overestimated, in harmonic approximation, regardless of the basis set used. In our earlier papers [1,2,31], we scaled the theoretical frequencies to obtain better agreement with experiment. However, in this study we have left all the calculated frequencies unscaled, to facilitate pure comparison of the results obtained with different basis sets. As seen in Fig. 2, the choice of the basis sets has very little effect on the calculated Raman spectrum of carboplatin.

For cisplatin (1) the experimental and theoretical Raman spectra in the region between 100 and 550 cm\textsuperscript{-1} are shown in an expanded view in Fig. 3. It should be noted that the experimental Raman intensities are almost reproduced by the mPW1PW method. The two bands observed at 522 cm\textsuperscript{-1} (very strong) and 506 cm\textsuperscript{-1} (weak) arise from the symmetric and antisymmetric υ(Pt–N) stretching vibrations, respectively. The corresponding theoretical υ(Pt–N) frequencies obtained with the LanL2DZ basis set show quite good agreement with

![Fig. 2. Comparison of the experimental and theoretical Raman spectra of carboplatin (2) calculated by the mPW1PW functional with different basis sets for the ligand atoms. The theoretical frequencies are unscaled (the excitation wavelength is 1064 nm).](image)

![Fig. 3. Comparison of the experimental and theoretical Raman spectra of cisplatin (1), in the range of frequencies 100–550 cm\textsuperscript{-1}. Calculations performed by the mPW1PW functional combined with different basis sets for the ligand atoms and LanL2DZ for platinum. The theoretical frequencies are unscaled (the excitation wavelength is 1064 nm).](image)
experiment (although the splitting between the two bands is somewhat underestimated), whereas the v(Pt–N) frequencies calculated with other basis sets are all underestimated by about 40–50 cm$^{-1}$. The v(Pt–Cl) stretching vibrations observed as an asymmetric broad-band at 322 cm$^{-1}$ are well reproduced by calculations with all basis sets employed. Very good agreement between the experimental and theoretical Raman spectra of cisplatin allows for the unequivocal assignment of all the observed bands. From the calculated potential energy distribution (PED), it is evident that the band at 253 cm$^{-1}$, previously assigned to the symmetric Pt–Cl stretching vibration (!) [10] must be undoubtedly assigned to the N–Pt–N bending vibration.

In Fig. 4 are displayed the Raman spectra of cis-[Pt(orotato)(NH$_3$)$_2$]$_3$ (3) in the region of 100–650 cm$^{-1}$. The corresponding fundamentals in the experimental and theoretical spectra have been numbered to facilitate comparison (the detailed assignment of the spectrum of (3), based on the calculated PED, will be published elsewhere). The theoretical spectrum obtained with the mPW1PW/LanL2DZ method reproduces fairly well the experimental Raman spectrum. The use of the extended D95V++(d,p) basis set for all ligand atoms leads to an underestimation of the frequencies of the normal modes Q17 and Q18, which involve the Pt–NH$_3$ stretching vibrations, v(Pt–N$_a$). Some differences between the theoretical and experimental spectra are observed in the range below 280 cm$^{-1}$. There are two possible reasons for these discrepancies. First, solid-state effects (crystal field splitting, intermolecular hydrogen bonding) may cause a broadening of some bands and a shift of their position. Second, the sensitivity of the Raman spectrometer (instrumental response curve) is relatively flat for the Raman bands between 3400 and 200 cm$^{-1}$, with a dramatic decrease in the range of frequencies below 150 cm$^{-1}$ and above 3400 cm$^{-1}$ [32]. Thus, the reliable measurements of Raman scattering intensities could be made only within the region of the flat detector response curve.

In Fig. 5, we show the Raman spectra predicted for the new anticancer drug, 4A, and for two products of its hydrolysis: [PtCl(H$_2$O)(NH$_3$)(2-picoline)]$^+$, 4B, in which one Cl$^-$ trans to 2-picoline is substituted by water molecule; and cis-[Pt(H$_2$O)$_2$(NH$_3$)(2-picoline)]$^{2+}$, 4C. Sadler and coworkers [16] reported that the hydrolysis of the Cl$^-$ trans to 2-picoline is faster than the Cl$^-$ cis to 2-picoline. This is in agreement with our recent theoretical study on 4, which revealed that the Pt–Cl bond trans to 2-picoline is weaker than the other one [33]. Thus, the transient species, B and C, should be observed in the Raman spectrum of 4 during the stepwise hydrolysis. As follows from Fig. 5, in the case of B, the new band corresponding to Pt–OH$_2$ stretching vibration arises at about 430 cm$^{-1}$. In the spectrum of C, all the bands due to the Pt–Cl stretching vibrations disappear,

![Fig. 4. Comparison of the experimental and theoretical Raman spectra of cis-[Pt(orotato)(NH$_3$)$_2$]$_3$ (3). The excitation wavelength is 1064 nm. Abbreviations: $\delta_r$, uracilate ring def.; $\delta_c$, deformation of coordination ring; other as in the table.](image)

![Fig. 5. The predicted Raman spectra for cis-[PtCl$_3$(NH$_3$)$_2$(2-picoline)] (A), [PtCl(H$_2$O)(NH$_3$)$_2$(2-picoline)]$^+$ (B), and cis-[Pt(H$_2$O)$_2$(NH$_3$)$_2$(2-picoline)]$^{2+}$ (C). The excitation wavelength is 1064 nm. The dotted lines connect the corresponding vibrations observed in A, B and C. Abbreviations: $\rho$H$_2$O, water deformation; other as in the table.](image)
while the two new bands at about 420 and 440 cm\(^{-1}\), appear upon substitution of chloride ions by water molecules. It is interesting to note that the Pt–NH\(_3\) stretching frequency increases, to 544 cm\(^{-1}\), in the hydrolyzed complex \(4\). This theoretical result is supported by the experimental Raman spectroscopic studies on binding of cisplatin to DNA, in aqueous solution [34]. The authors reported that two (Pt–NH\(_3\)) vibrations in cisplatin were shifted to higher frequencies, 532 and 550 cm\(^{-1}\), in the Raman spectrum.

The observed and calculated frequencies of platinum–ligand vibrations in the investigated compounds are gathered in Table 1. The vibrational assignments shown in this table can be helpful in further studies of the interaction between platinum(II)-based drugs and DNA, using Raman spectroscopic methods.

### 5. Conclusion

The most important findings of this work are the following:

1. It is remarkable that the density functional mPW1PW protocol combined with the LanL2DZ basis set yields the theoretical Raman spectra of platinum(II) complexes in very good overall agreement with the experimental Raman spectra of the complexes in the solid state. The use of more extended basis set does not introduce significant improvements in the calculated Raman spectra, particularly in the frequency range below 600 cm\(^{-1}\), where the platinum–ligand vibrations occur.

2. The unequivocal assignment of the platinum–ligand stretching vibrations has been made in the experimental Raman spectra of the anticancer agents 1–3, and in the theoretical Raman spectra predicted for the new anticancer drug \(4\) (ZD0473) and for its two hydrolysis products. As follows from calculations performed for the diaqua derivative of \(4\), all the bands due to the Pt–Cl stretching vibrations (at about 340 cm\(^{-1}\)) disappear, while the two new bands, at about 420 and 440 cm\(^{-1}\), should appear in the spectrum, upon substitution of chloride ions by water molecules. Moreover, the Pt–NH\(_3\) stretching band should be observed at about 540 cm\(^{-1}\), in the diaqua derivative of ZD0473.

3. The presented calculations can greatly facilitate studies of the Raman spectra of new Pt-based drugs and the transient species, which are formed during the stepwise hydrolysis of these drugs, in aqueous solutions.

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### References