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Computational study of the anticancer drug cisplatin

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Systems containing platinum are more challenging for reliable computations, since Pt has 78 electrons and requires relativistic treatment. However, to reduce computational demands, most previous workers used effective core potentials. In this investigation, we perform numerous computations on the cisplatin molecule with *ab initio* methods and density functional theory, some of which involve all electron and zero-order relativistic approximation. Tentative conclusions on the reliability of various methods are drawn from comparison of our results with previous calculations and available experimental data. Vibrational and electronic spectra are calculated and compared with previous studies and available experimental data.

Key words: cisplatin, structure, ionizations, excitations, electron spectra, density functional theory (DFT), relativistic *ab initio* methods.

Introduction

For decades, not only has cisplatin been recognized as a powerful anticancer agent for chemotherapy, but it has also stimulated the growth of bioinorganic chemistry. Not surprisingly, hundreds of publications, including several books,¹⁻⁵ have reported studies on cisplatin and many more papers continue to appear in the literature. Because of the continuing importance of cisplatin in chemotherapy, more knowledge about cisplatin is expected to lead to better understanding of the action of cisplatin. Moreover, reliable values for the physical properties of cisplatin may be useful to workers interested in drug design and in quantitative structure-activity relationship.

Although cisplatin is a relatively small molecule, it remains a challenge to theoretical studies because of the presence of platinum with 78 electrons. Consequently, theoretical methods in studying Pt containing molecules are not as well established as those for organic and other small molecules. Almost all previous workers used effective core potentials (ECPs)⁶ to reduce the size of basis sets. Of various ECPs the most popular choice appears to be **LanL2DZ**,⁷⁻⁹ with or without additional polarization d-type function on chlorine. However, approximations that seem to perform well may not be as reliable for Pt containing systems. For example, density functional theory (DFT) studies using the exchange-correlation energy (E_{xc}) known as mPW1PW^{10,11} was preferred^{12,13} for the geometry optimization and prediction of the vibrational spectrum of cisplatin. E_{xc} = mPW1PW was considered “clearly superior”¹² to other choices of E_{xc} . It should be emphasized that mPW1PW is a rather old method and may not fair as well in comparison with other methods made possible by the recent advances in computer hardware and software. As shown below, mPW1PW is far from being the best choice. More recently, Gao et al¹⁴ concluded that the local spin density approximation (LSDA) was “clearly superior” to the other density functionals. In view of the large advances made by both computers and quantum chemistry programs, we decide to test DFT and *ab initio* methods to increase our experience in theoretical study of Pt containing molecules, by calculations including involve all electrons using scalar as well as spinorbit zero-order relativistic approximation (ZORA). Tentative

conclusions about the reliability of various methods will be drawn from comparison of our results with previous computations and with available experimental data.

Throughout this paper, we use the Pople shorthand notation of method1/basis1//method2/basis2 to denote that method 1 with basis set 1 is used to compute the property of interest at the geometry optimized by method 2 with basis set 2. When method2/basis2 is the same as method1/basis1, the geometry specification is sometimes omitted.

Methodology

In this study, we use two programs: Gaussian09¹⁵ and ADF2013.¹⁶ Within the Gaussian09 package,¹⁵ the ECP known as LanL2DZ is available. Following previous workers,¹⁷⁻²⁰ we add the following Gaussian-type polarization functions: $p(\alpha = 1.0)$ to the basis set of H,^{17,18} $d(\alpha = 0.8)$ to N,^{18,19} and $d(\alpha = 0.75)$ to Cl.²⁰ Although the choice of these exponents is somewhat arbitrary, we do not expect large differences with other reasonable choices. The expanded basis set will be called **LanL2DZP** below. On the other hand, the ADF Program¹⁶ allows us to treat relativistic effects with ZORA. The ZORA basis set of Slater-type orbitals of TZP quality is more flexible than even the polarized triple-zeta sets of Gaussians such as 6-311G** because the latter contains triple-zeta valence with single-zeta core basis, whereas TZP set in ADF contains triple-zeta valence and double-zeta core basis. The TZ2P basis set available in the ADF package is even more flexible than TZP, but its use requires more computer time.

For the structure of drugs in aqueous solutions, the solvent is modeled as a dielectric continuum. For the Gaussian09 program,¹⁵ we use the Polarizable Continuum Model (**PCM**) by including

SCRF=(Solvent=Water)

in the input. For ADF2013 program,¹⁶ we use the Conductor-like Screening Model by adding the following three input lines

Solvation

SOLV Name=Water

End

For the dipole moments and static polarizabilities, we prefer the exchange-correlation potential V_{xc} known as statistical averaging of orbital potentials (**SAOP**),²¹⁻²³ in the belief that use of V_{xc} = SAOP will lead to better description of the electron density. For vertical ionization energies (VIEs) of valence electrons, the method we developed in 2009,²⁴ abbreviated as Δ PBE0(SAOP), is used. It means the energy difference between parent and cation calculated with the parameter-free exchange-correlation functional E_{xc} known as parameter-free Perdew-Burke-Ernzerhof functional (**PBE0**)^{25,26} for the electron density computed with V_{xc} = SAOP.²¹⁻²³ For core-electron binding energies (**CEBEs**) of C to F, we recommend the method developed in 1999,²⁷⁻²⁹ namely Δ PW86-PW91+C_{rel}, which stands for the energy difference between parent and core-hole cation calculated with the exchange-functional PW86³⁰ and the correlation functional PW91.³¹ A small relativistic correction C_{rel}, derived empirically in 1995,³² is added. These methods have been tested on many organic molecules (see our recent paper³³ and references therein). Similarly, the CEBEs of 2p for Si to Ar can be estimated by the procedure proposed in 2006.³⁴ The method may be described as scalar-ZORA Δ OPTX-LYP + C_{rel}.

Although the performance of various density functionals used within time-dependent DFT has been compared in several investigations (see Ref. 35 and references therein), those studies are all for gas-phase molecules. The study of UV absorption of organic drugs in aqueous solution is more difficult. Cossi and Barone³⁶ pointed out the important consideration of time scale: during electronic excitation, relaxation of solvent electrons is fast but geometric relaxation is much slower. In their

procedure of nonequilibrium solvation therefore, the static dielectric constant was used in the PCM for the structure and ground state electron density, but the optical dielectric constant was used for the TD-DFT step. Although the results for the first strong absorptions of diazabenzenes in a few solvents using the density functional known as PBE0 were already quite good,³⁶ Cossi and Barone concluded that the best results for diazabenzenes in aqueous solution were obtained with the cluster model of the solutes with two water molecules. Jacquemin et al³⁷ followed the lead and applied the nonequilibrium procedure to study the visible absorption spectra of organic dyes in several nonaqueous solvents. These workers concluded that the density functionals PBE0 and CAM-B3LYP outperform the other functionals tested. Sanna et al³⁸ studied the UV absorption spectra of anticancer camptothecin family drugs in aqueous solution with the popular B3LYP functional and concluded that the second strong absorption was not produced unless water molecules were included in the solute-water clusters. In this work, however, we stay with the polarizable continuum model (without any explicit inclusion of water molecules in the solute clusters) and follow Cossi and Barone³⁶ in the use of nonequilibrium solvation. Because a maximum absorption of UV/visible light by molecules in liquid solutions may correspond to several calculated excited states, we have to convolute computed excitation energies with their oscillator strengths to synthesize a simulated spectrum. To perform the convolution, we model each excitation with a Gaussian line-shape and estimate the full width at half maximum (FWHM) necessary to produce a reasonably looking spectrum. For example, the absorptions of fluorouracil(aq) and tirapazamine(aq) can be simulated by a choice of FWHM = 34 nm for UV absorptions and 73 nm for the visible region.³⁹ The choice of FWHM needs to change when we study other molecules in water or in other solvents. This approximation for the effect of solvation is fairly crude for aqueous solutions, in which hydrogen bonds between solutes and solvent are undoubtedly present. To include the effects of hydrogen bonds would require inclusion of discrete water molecules with procedures such as the ONIOM method,¹⁵ which is beyond the scope of the present study. In spite of such limitations, we venture ahead and try to determine the best exchange-correlation functionals (or potentials) to use in time-dependent DFT calculations. Since the available experimental absorption maxima of cisplatin(aq) lie between 200 nm and 420 nm, we try our TDDFT calculations with the lowest 70 excited states. Some calculations on 60 and 85 excited states are also tested. Our target is to perform all-electron spinorbit ZORA calculations with the basis set TZP.

Ideally, for every physical property, one would like to use the best procedure CCSD with large basis sets such as aug-cc-pV5Z. However, practical limitations of computer speed, and perhaps memory capacity as well, force us to use the best combination of method/basis available. The properties requiring most demanding computations are vibrational spectra and UV/visible absorption spectra. Consequently, smaller basis sets are usually used.

Results and Discussion

Structure and vibrations

As mentioned above, almost all previous calculations used effective core potentials to approximate the core electrons of Pt. Most of the previous theoretical studies on cisplatin focused on its molecular structure. Moreover, the calculated results on a single molecule were compared with the experimental structure of *solid* cisplatin.^{40,41} Therefore, the conclusion drawn from such comparisons may not be based on concrete grounds.

Let us first consider ECP computations on a single cisplatin molecule using ECP = LanL2DZP. The high-level *ab initio* “gold standard” procedure, accepted by most scientists, is called CCSD(T), which is coupled cluster singles and doubles (CCSD)⁴² with perturbative triples corrections. However, because the Gaussian program does not have gradients for the CCSD(T) procedure, geometry

optimization would take months, if not years, of computer time. In the present work, therefore, we regard the theoretical level of CCSD as most reliable, and use it as standard to compare the bond lengths and bond angles from other methods in **Table 1**. The numerical values in Table 1 have been given more significant figures than justified; and thus the last figure in each value could very well be incorrect. All bond lengths and bond angles in Table 1 are shown in units of Angstroms and degrees, respectively. It can be seen that neither mPW1PW nor LSDA is superior to other methods with or without added polarization functions. A general trend we observe in using ECP for cisplatin is that the angle $\angle \text{ClPtCl}$ is smaller than $\angle \text{NPtN}$.

Next, we study the effect of including all electrons using scalar ZORA with TZ2P basis set of Slater-type orbitals. The results are summarized in **Table 2**. The inclusion of all electrons, with the use of ZORA, (a) reverses the general trend regarding the two angles mentioned above, (b) increases the angle $\angle \text{ClPtN}$ considerably making better agreement with experiment, and (c) decrease the PtCl bond length further. Based on the results shown in Table 1, we believe that the best geometry is the all-electron calculation using the B1LYP density functional with scalar ZORA. Another trend we noticed but did not display in Table 1 is that the addition of polarization functions in LanL2DZP shortens the PtCl bond length predicted by LanL2DZ basis, but has only a small effect on the PtN bond length.

Finally, we compare our best geometry from the B1LYP energy functional using ZORA/TZ2P with previous calculations and experimental results in **Table 3**. Various functionals have been used by previous workers and only the popular choices of mPW1PW and B3LYP are selected to be displayed in Table 3. Except for our results labelled ZORA-B1LYP/TZ2P, the calculated bond angles tend to overestimate $\angle \text{ClPtCl}$ and $\angle \text{NPtN}$, thereby to underestimate $\angle \text{ClPtN}$. We regard the geometry optimized by ZORA-B1LYP with TZ2P basis set to be most reliable. At this geometry, the dipole moment is 10.61 debyes; and results for the static polarizability are $\alpha_{\text{ave}} = 86.97$ au and $\Delta\alpha = 48.24$ au.

Before we started on vibrational spectra of molecules, we expected that the best procedure for equilibrium geometry would also lead to best results for vibrational frequencies. In **Tables 4 and 5**, we display some of our computational results with the experimental and calculated results of previous workers.^{8,10,22,26-28} There is always an ambiguity in the symmetry labelling for any molecule with C_{2v} symmetry. The labels B_1 and B_2 are sometimes interchanged. For our choice, the vibrational modes are labelled $9A_1 + 5A_2 + 5B_1 + 8B_2$. We do not follow the other workers^{8,10,22,23} to use scale factors to correlate the calculated results to the observed ones. We note that the predicted vibrations have been calculated on a single molecule, whereas the experimental measurements were performed on the single crystal. Moreover, we compute harmonic frequencies and not the vibrational fundamentals. It is therefore not possible to give a quantitative assessment of the performance of various procedures. Nevertheless, from the pattern of the vibrational spectra and possible trends, especially with so many previous studies, we can draw the following qualitative conclusions from Tables 4 and 5: (a) The NH_3 moieties are far apart in cisplatin and the symmetric and antisymmetric combinations of NH_3 vibrationals occur in pairs of similar frequencies: A_2 with B_1 , and B_2 with A_1 . (b) Surprisingly, the ZORA-B1LYP method does not appear to provide the best vibrational spectrum, contrary to our expectation. (c) The method of ECP-mPW1PW, favoured by earlier workers, gave quite reasonable account of the vibrational spectrum, even though the optimized geometry predicted by ECP-mPW1PW is far from being the best choice as shown in Table 1. (d) A few of the previous assignments appear to be incorrect, while most of the others are confirmed. (e) In spite of the qualitative nature of the computed intensities, they are very helpful in the assignment. (f) Having the complete spectra including some unobserved modes is also helpful.

Electron spectra

Experimental ESCA ionization energies of cisplatin vapour were reported as early as 1979.⁵³ As far as theoretical studies were concerned, the early methods used $\text{SCF} = \text{X}\alpha$,⁵³ relativistic extended Huckel,⁵⁴ and Dirac scattered wave.⁵⁵ In this work, we used both Hartree-Fock (HF) and outer-valence

Green's function (OVGF) methods with ECP and LanL2DZP basis set, as well as DFT methods meta-Koopmans' theorem (**mKT**)⁵⁶ and Δ PBE0(SAOP)²⁴ including all electrons and scalar ZORA. For the simple mKT method,⁵⁵ we approximate vertical ionization energies with the negative of the orbital energies from a DFT calculation using the model potential called SAOP; and for the better method,²⁴ Δ PBE0(SAOP) means the difference between the energies of the cation and the neutral parent calculated with the parameter-free Perdew-Burke-Ernzerhof functional (PBE0) for the electron density computed with the SAOP potential. In **Table 6**, we compare our results with previous calculations and experiment. Because the calculations are for a single cisplatin molecule, whereas the experiment was made on the solid, the former is always higher. The difference between the ionization energies for gas-phase and solid-state molecules can be attributed to three factors: (a) intermolecular interaction in solids, such as hydrogen bonds, (b) the difference between the Fermi and vacuum levels, and (c) other dielectric effects. The difference is sometimes given the symbol WD. When the factor (a) is small, WD is dominated by the work function W of the solid. Zuloaga and Arratia-Perez⁵⁵ used the value of 2.07 eV, and we use an empirical value of 5.16 eV. It can be seen from the comparison in Table 6 that the performance of our Δ PBE0(SAOP) procedure is not as good as for gas-phase molecules. In spite of those effects, we wish to encourage experimental scientists to measure the valence ionizations of solid cisplatin with modern techniques, especially to see whether or not there is an ionization corresponding to the missing entry in Table 6.

In general, it is difficult to calculate reliable core-electron binding energies (CEBEs). In the past, we developed DFT methods for the CEBEs of C to F²⁷⁻²⁹ and 2p CEBEs for Si to Ar.³⁴ So far, no one seems to have as reliable methods for the other core electrons in cisplatin. In this work, therefore, we only compare the calculated value of 204.60 eV for CEBEs of Cl 2p in cisplatin(g) with experiment and present the predicted value of 407.26 eV for the CEBE of N 1s in cisplatin(g). In their 1979 paper, Barber et al.⁵³ reported 189.4 and 199.8 eV for the CEBE of Cl 2p in solid cisplatin. Since we know that the average splitting between 2p_{1/2} and 2p_{3/2} in gas phase molecules is about 1.63 eV,³⁴ the two values observed by Barber et al could not be for Cl 2p_{1/2} and Cl 2p_{3/2}. We believe that the 199.8 eV value is the average <2p> for solid cisplatin and, with a shift of 5.2 eV estimated from Table 6, the approximate <2p> would be 205.0 eV for a single cisplatin molecule. More recently, Xiao et al.⁵⁷ reported the values of 199.6 and 201.1 eV for the CEBE of Cl 2p of solid cisplatin. Since their splitting of 1.5 eV is close to the average splitting of 1.63 eV,⁵⁵ we believe that their two values are for Cl 2p_{3/2} and Cl 2p_{1/2} in cisplatin solid. Their average <2p> is then 200.1 eV for solid cisplatin. Xiao et al.⁵⁷ reported a work function of 4.38 eV, so that the value for a single cisplatin molecule would be 204.5 eV, not far from 205.0 eV estimated from the earlier experiment of Barber et al.,⁵¹ and is surprising close to the value of 204.60 eV calculated in this work.

Finally, the absorption of UV/visible light requires much study (lasting about a year). Fortunately, we have the pioneering work of Wang and Ziegler⁵⁸ on the electronic spectra of [PtX₄]²⁻ for X = Cl, Br, and CN, based on two-component relativistic TDDFT. We decided to use the absorption spectrum of [PtCl₄]²⁻(aq) to guide us about which exchange-correlation functionals would perform better than others for cisplatin. Our study on [PtCl₄]²⁻ is summarized in **Appendix A**. We confirm the finding of Wang and Ziegler⁵⁸ that application of scalar ZORA is not good enough for the excitation spectrum of [PtCl₄]²⁻(aq) and that we need to use spinorbit ZORA instead. In addition, we find that many E_{xc} can provide quite reasonable absorption spectra. In the study of cisplatin, we first examine the observed spectra of aqueous solution reported by previous workers and try to obtain the best estimates of the experimental absorption maxima. The results are shown in **Table 7**. Note that the best estimates of the **observed** absorption maxima are not precise and have an uncertainty around 1 to 2 nm. Then, we perform all-electron TDDFT calculations with various exchange-correlation functionals/potentials on cisplatin using spinorbit ZORA. The performance of over 20 exchange-correlation functionals is summarized in **Table 8**. There are many sources of error in the deviations: (a) Because the best estimates of **experimental** absorption maxima are approximate, as mentioned

above, the deviations in Table 8 are also approximate. (b) For each exchange-correlation functional/potential, there are errors in the **calculated** absorption maxima themselves since they are dependent on the calculated f -values and on the choice of FWHM as well as the number of excited considered in the TDDFT procedure. (c) Since Gaussian line shape has been used in the convolution in the generated spectra, the calculated absorption maxima include inherent convolution errors. (d) The implementation of TDDFT in most quantum chemical programs involves approximations. (e) The effect of solvent is approximated by polarizable continuum. In any event, we conclude that, of the few exchange- correlation functionals/potentials (O3LYP, B3LYP*, SAOP, M06-L, and TPSSH), capable of providing reasonable approximations of the UV/visible spectra fluorouracil(aq) and tirapazamine(aq),³⁸ only the model exchange-correlation potential SAOP can perform well for cisplatin(aq) in spite of the many approximations mentioned above. Finally, the stimulated UV absorption spectrum of cisplatin(aq) based on TDDFT calculations using the model exchange-correlation potential SAOP with spinorbit ZORA is shown in **Fig. 1**.

Conclusions

Just as what was said about our recent study on three small anticancer drug molecules (fluorouracil, hydroxyurea, and tirapazamine), the physical properties of cisplatin reported in this work cannot predict the biological effects, beneficial or harmful; nor can they predict what modifications would be needed to have similar or better therapeutic value. However, our results may help drug designers looking for possible anticancer drugs of similar structure. In this work, we conclude that the most reliable geometry of cisplatin is provided by the exchange-correlation functional B1LYP used in an all electron scalar ZORA calculation. The infrared spectrum of cisplatin computed in the present study compares well with previous investigation and with available experiments. Ionization energies for valence and some core electrons are calculated with established methods, whereas we gain some experience in predicting UV absorption spectrum in aqueous solution, namely, the model exchange-correlation potential SAOP seems to perform quite well even under many approximations.

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Table 1. Comparison of the geometry of cisplatin computed by various methods using LanL2DZP except the column labelled DZ. Bond lengths and bond angles are given in Angstroms and degrees, respectively. Entries are shown with more figures than warranted and the last figure in each entry are therefore uncertain.

	Pt-Cl	Pt-N	MAD ^a	DZ ^b	ClPtCl	ClPtN	NPtN	MAD ^a	DZ ^b
CCSD	2.35391	2.11645	(0.0000)	(0.0000)	95.852	83.278	97.592	(0.000)	(0.00)
B1LYP	2.35589	2.11558	0.0014	0.0161	95.842	82.773	98.613	0.51	1.08
mPW1LYP	2.35454	2.11344	0.0018	0.0177	95.845	82.741	98.673	0.54	1.12
B3LYP	2.35555	2.11327	0.0024	0.0172	95.843	82.657	98.844	0.63	1.21
X3LYP	2.35336	2.11057	0.0032	0.0194	95.849	82.658	98.835	0.62	1.20
PKZB	2.34880	2.11295	0.0043	0.0204	94.857	83.404	98.335	0.62	0.99
M062X	2.34606	2.11556	0.0044	0.0222	95.804	82.997	98.203	0.31	1.00
MP3	2.34924	2.11217	0.0045	0.0081	96.023	83.204	97.569	0.09	0.13
B971	2.35143	2.10720	0.0059	0.0224	95.666	82.771	98.792	0.63	1.05
M06L	2.35245	2.12681	0.0059	0.0106	96.130	82.250	99.371	1.03	1.74
OLYP	2.34970	2.10753	0.0066	0.0214	95.399	82.981	98.639	0.60	1.03
M06	2.34342	2.11963	0.0068	0.0225	96.130	82.250	99.371	1.03	1.09
B98	2.35093	2.10491	0.0073	0.0236	95.604	82.836	98.725	0.61	0.96
BP86	2.35308	2.10226	0.0075	0.0226	95.979	82.063	99.894	1.21	1.81
TPSS	2.35093	2.10389	0.0078	0.0231	95.777	82.248	99.729	1.08	1.63
mPWPW	2.35129	2.10168	0.0087	0.0238	95.823	82.101	99.796	1.14	1.67
HCTH	2.34566	2.10728	0.0087	0.0226	95.506	82.969	98.555	0.54	1.08
BPBE	2.35044	2.10114	0.0094	0.0242	95.755	82.284	99.676	1.06	1.61
PBEPBE	2.34853	2.09813	0.0118	0.0264	95.859	82.153	99.835	1.13	1.74
HF	2.36536	2.12902	0.0120	0.0069	96.338	84.038	95.587	1.08	0.95
PW91	2.34822	2.09777	0.0122	0.0271	95.842	82.139	99.881	1.15	1.74
G96PW	2.34718	2.09629	0.0134	0.0280	95.684	82.342	99.631	1.05	1.53
G96LYP	2.37262	2.12475	0.0135	0.0124	96.113	82.149	99.590	1.13	1.77
O3LYP	2.34198	2.10080	0.0138	0.0291	95.360	83.117	98.407	0.49	0.85
BHandHLYP	2.34086	2.10080	0.0143	0.0316	95.818	83.199	97.783	0.10	0.56
TPSSh	2.34297	2.09780	0.0148	0.0309	95.654	82.516	99.316	0.89	1.30
VSXC	2.35753	2.14331	0.0152	0.0042	94.861	82.478	100.184	1.46	1.80
MP2	2.33905	2.09797	0.0167	0.0129	95.644	83.100	98.155	0.32	0.22
TPSSLYP	2.37490	2.13006	0.0173	0.0093	96.242	82.015	99.728	1.26	1.87
tHCTH	2.33953	2.09596	0.0174	0.0322	95.545	82.649	99.158	0.83	1.27
mPWLYP	2.37596	2.12997	0.0178	0.0117	96.170	82.068	99.694	1.21	1.85
CAM-B3LYP	2.33871	2.09590	0.0179	0.0348	95.766	82.855	98.524	0.48	0.97
B972	2.33540	2.09650	0.0192	0.0352	95.398	83.056	98.489	0.52	0.83
B3PW91	2.33781	2.09274	0.0199	0.0359	95.544	82.776	98.903	0.71	1.02
B3PW	2.33774	2.09268	0.0200	0.0358	95.542	82.780	98.899	0.71	1.04
BLYP	2.37787	2.13270	0.0201	0.0115	96.148	82.104	99.644	1.17	1.85
mPW3PBE	2.33503	2.08870	0.0233	0.0392	95.523	82.754	98.970	0.74	1.05
PBEhLYP	2.38085	2.13624	0.0234	0.0111	96.421	81.827	99.925	1.45	2.12
B1B95	2.33160	2.09010	0.0243	0.0416	95.479	82.771	98.980	0.76	1.09
B3P86	2.33320	2.08665	0.0253	0.0409	95.661	82.633	99.074	0.77	1.14
mPW1PW	2.33251	2.08687	0.0255	0.0415	95.514	82.857	98.771	0.65	0.92

mPW1PW91	2.33251	2.08687	0.0255	0.0416	95.514	82.857	98.771	0.65	0.92
mPW1PBE	2.33025	2.08452	0.0278	0.0438	95.433	82.888	98.792	0.67	0.94
PBE1PBE	2.33053	2.08398	0.0279	0.0439	95.552	82.801	98.846	0.68	0.97
M06HF	2.33361	2.06313	0.0368	0.0525	95.293	83.716	97.276	0.44	0.20
XAlpha	2.32597	2.05533	0.0445	0.0585	96.192	81.633	100.542	1.65	2.06
BHandH	2.30775	2.05277	0.0549	0.0709	95.737	82.798	98.668	0.52	0.88
LSDA	2.31410	2.04581	0.0552	0.0689	96.240	81.496	100.769	0.71	2.16
HFB	2.48540	2.18710	0.0763	0.0588	96.879	81.842	99.437	0.71	1.37

^a Mean absolute deviation. See text for exponents of polarization functions.

^b Mean absolute deviation using LanL2DZ.

Table 2. Effect of including polarization functions and of using scalar ZORA^a on the calculated bond lengths and bond angles of cisplatin.

Method	Pt-Cl	Pt-N	ClPtCl	ClPtN	NPtN
CCSD/LanL2DZ	2.4191	2.1357	96.27	83.20	97.33
CCSD/ LanL2DZP	2.3539	2.1165	95.85	83.28	97.59
B1LYP/ LanL2DZ	2.4102	2.1123	96.72	82.12	99.03
B1LYP/ LanL2DZP	2.3559	2.1156	95.84	82.77	98.61
B1LYP/ZORA/TP2Z	2.3113	2.1093	95.76	86.59	91.07
B3LYP/ LanL2DZ	2.4103	2.1102	96.69	81.99	99.32
B3LYP/ LanL2DZP	2.3556	2.1133	95.84	82.66	98.84
B3LYP/ZORA/TP2Z	2.3103	2.1073	95.79	86.47	91.26
X3LYP/ LanL2DZ	2.4081	2.1079	96.72	82.00	99.27
X3LYP/ LanL2DZP	2.3534	2.1106	95.85	82.66	98.84
X3LYP/ZORA/TP2Z	2.3081	2.1045	95.81	86.47	91.25
M06-2X/ LanL2DZ	2.4025	2.1078	96.90	82.20	98.71
M06-2X/ LanL2DZP	2.3461	2.1156	95.80	83.00	98.20
M06-2X/ZORA/TP2Z	2.2904	2.1096	94.87	87.04	91.04
M06-L/ LanL2DZ	2.4141	2.1194	97.21	81.46	99.86
M06-L/ LanL2DZP	2.3525	2.1268	96.13	82.25	99.37
M06-L/ZORA/TP2Z	2.2958	2.1117	96.08	85.89	92.15
OLYP/ LanL2DZ	2.4091	2.1029	96.31	82.17	99.36
OLYP/ LanL2DZP	2.3497	2.1075	95.40	82.98	98.64
OLYP/ZORA/TP2Z	2.2900	2.0953	95.42	86.63	91.31
BP86/ LanL2DZ	2.4094	2.1001	96.79	81.39	100.42
BP86/ LanL2DZP	2.3531	2.1023	95.98	82.06	99.89
BP86/ZORA/TP2Z	2.2964	2.0943	95.62	85.92	92.54
TPSS/ LanL2DZ	2.4068	2.1018	96.65	81.57	100.21
TPSS/ LanL2DZP	2.3509	2.1039	95.78	82.25	99.73
TPSS/ZORA/TP2Z	2.2941	2.0958	95.73	85.84	92.59
Neutron diffraction ^b	2.320	2.050	91.9	88.8	90.6

^a Zero-order relativistic approximation..

^b Ref. [40].

Table 3. Comparison of optimized geometry of cisplatin obtained in this work with previous calculations and **experiment**.

Year	Authors	Ref.	Method	Pt-Cl	Pt-N	ClPtCl	ClPtN	NPtN
1966	Milburn & Truter	40	X-ray	2.33(1)	2.01(4)	91.9(3)	90(1)	87(1.5)
1995	Carloni et al	43	BP86	2.31 ₅	2.06 ₅	95.5	83	98
1999	Pavankumar et al	44	ECP-MP4	2.320	2.105	94.0	85.0	96.0
2001	Zhang et al	45	ECP-mPW1PW	2.386	2.086	96.2	82.3	99.2
			ECP-B3LYP	2.411	2.111	96.7	82.0	99.3
			ECP-B1LYP	2.411	2.113	96.7	82.2	99.0
2001	Wysokinski & Michalska	12	ECP-mPW1PW/DZ	2.386	2.085	96.3	82.3	99.2
			ECP-B3LYP/DZ	2.411	2.110	96.8	82.0	99.2
			ECP-mPW1PW/DZP	2.320	2.086	95.5	83.0	98.6
2007	Amado et al	46	ECP-mPW1PW	2.285	2.069	95.5	83.0	98.6
			ECP-B3LYP	2.312	2.095	95.5	83.0	98.4
2008	Fiuza et al	47	ECP-mPW1PW	2.318	2.080	94.7	83.9	97.6
			ECP-B3LYP	2.343	2.106	95.0	83.6	97.8
2010	Berredo and Jorge	48	AE-scalar relativistic-mPW1PW/DZP	2.240	1.975	97.9	83.2	95.8
2010	Ting et al	41	Neutron diffraction & X-ray	2.321 α 2.319 β	2.048 α 2.052 β	91.7 α 92.0 β	88.9 α 88.7 β	90.6 α 90.6 β
2011	Gao et al	14	ECP-mPW1PW/DZ	2.383	2.090	96.3	81.5	100.7
			ECP-LSDA/DZ	2.364	2.053	96.7	80.4	102.6
2012	Dodoff	49	ECP-PW91	2.323	2.094	96.1	82.1	99.8
2016	Chong	This work	ECP-mPW1PW/DZ	2.386	2.086	96.3	82.3	99.2
			ECP-mPW1PW/DZP	2.333	2.087	95.5	82.9	98.8
			ECP-B3LYP/DZ	2.410	2.110	96.7	82.0	99.3
			ECP-B3LYP/DZP	2.356	2.113	95.8	82.7	98.8
			ZORA-B1LYP/TZ2P	2.311	2.109	95.8	86.6	91.1

Table 4. Comparison of earlier studies of the vibrations of cisplatin: wavenumbers in cm⁻¹ (with IR intensies in km/mole in parentheses), and [Raman (R) intensities in .A⁴/amu. in aquare brackets]

	1956	1965	1986	1999	2001				2007			
	Barrow et al ⁵⁰	Nakamoto et al ⁵¹	Roe et al ⁵²	Pavankumar et al ⁴⁴	Wysokinski & Michalska ¹²				Amado et al ⁴⁶			
	Obs IR	Obs IR	Obs IR	MP4	Obs IR	Obs R	mPW ^a	mainly	Obs R	mPW ^a	mainly	
Q1												Q1
Q2												Q2
Q3												Q3
Q4												Q4
Q5									162	164		Q5
Q6		222							210	213	δ(Cl-Pt-N)	Q6
Q7		256		214 (22)	253 s	253 s	230 (27) [3] A ₁	β(N-Pt-N)	255	251	δ(N-Pt-N)	Q7
Q8		317		353 (35)	318 vs		335 (26) [6] B ₂	v _a (Pt-Cl)	317	321	v _a (Pt-Cl)	Q8
Q9	322	324	323	362 (29)	326 sh	322vs	349 (24) [7] A ₁	v _s (Pt-Cl)	323	332	v _s (Pt-Cl)	Q9
Q10		508	510	450 (8)	510w	506 s	467 (8) [5] B ₂	v _a (Pt-N)	508	516	v _a (Pt-N)	Q10
Q11		517		457 (3)	517 sh	522 vs	457 (3) [10] A ₁	v _s (Pt-N)	524	524	v _s (Pt-N)	Q11
Q12									724	760	ρ'(NH ₃)	Q12
Q13	796	795							789	779	ρ(NH ₃)	Q13
Q14									811	790	ρ'(NH ₃)	Q14
Q15	826		805	812 (84)	795s	809w	782 (87) [6] A ₁	ρ _t (NH ₃)	824	825	ρ(NH ₃)	Q15
Q16	1299	1301	1300	1374 (153)	1298vs	1294w	1239 (195) [2] B ₂	δ _s (NH ₃)	1295	1255	δ' _s (NH ₃)	Q16
Q17	1309	1316	1315	1383 (98)	1312vs	1314w	1246 (119) [3] A ₁	δ _s (NH ₃)	1316	1263	δ _s (NH ₃)	Q17
Q18	1546	1544	1530	1709 (39)					1537	1598	δ _a (NH ₃)	Q18
Q19									1601	1606	δ' _s (NH ₃)	Q19
Q20		1625	1610			1625w	1616 (0) [10] A ₂	δ _d (NH ₃)	1628	1628	δ' _a (NH ₃)	Q20
Q21	1626			1743 (52)	1626m		1624 (50) [0] B ₁	δ _d (NH ₃)	1648	1635	δ _a (NH ₃)	Q21
Q22												Q22
Q23		3232	3200		3203s	3210s	3230 (58) [182] A ₁	v(NH ₃)	3211	3152	v _s (NH ₃)	Q23
Q24	3290		3280	3486 (16)					3287	3280	v _a (NH ₃)	Q24
Q25		3297		3592 (50)	3285vs	3306m	3372 (88) [107] A ₁	v(NH ₃)	3309	3330	v _a (NH ₃)	Q25
Q26												Q26
Q27												Q27

^a mPW = mPW1PW; scaled.

Table 5. Recent results on the vibrations of cisplatin: wavenumbers in cm^{-1} (with IR intensities in km/mole in parentheses), and [Raman (R) intensities in A^4/amu in aquare brackets].

	2008	2011		2012	2015					
	Fiuza et al ⁴⁷	Gao et al ¹⁴		Dodoff ⁴⁹	Present work					
	mPW ^a	mPW ^a	Mainly	PW91	CCSD	mPW1PW	Z-mPW1PW ^b	B1LYP	Z-B1LYP ^b	
Q1					A ₂ 96 (0)	110 (0)	119 (0)	108 (0)	115 (0) [0]	Q1
Q2					B ₁ 102 (0)	134 (0.1)	145 (0.1)	132 (0.1)	159 (11) [0]	Q2
Q3				122 A ₂	A ₂ 125 (0)	142 (0)	145 (0)	138 (0)	428 (0) [0.3]	Q3
Q4				144 A ₁	A ₁ 146 (0)	146 (0)	153 (0)	143 (0.1)	15 (0.1) [0.7]	Q4
Q5	161			165 B ₁	B ₁ 154 (14)	159 (16)	163 (12)	154 (15)	426 (0.1) [0.4]	Q5
Q6	213			240 B ₂	B ₂ 221 (0.3)	231 (0.2)	234 (0.4)	221 (0.1)	277 (0) [0]	Q6
Q7	247	214 (27) A ₁	β(N-Pt-N)	233 A ₁	A ₁ 221 (25)	229 (27)	230 (29)	218 (25)	263 (27) [3]	Q7
Q8	317	337 (25) B ₂	ν _a (Pt-Cl)	327 B ₂	B ₂ 335 (29)	335 (27)	348 (31)	323 (27)	385 (28) [5]	Q8
Q9	329	343 (20) A ₁	ν _s (Pt-Cl)	338 A ₁	A ₁ 345 (25)	346 (25)	358 (26)	334 (25)	397 (25) [4]	Q9
Q10	516	487 (4) B ₂	ν _a (Pt-N)	506 B ₂	B ₂ 432 (13)	463 (10)	457 (6)	436 (11)	529 (6) [4]	Q10
Q11	525	488 (14) A ₁	ν _s (Pt-N)	510 A ₁	A ₁ 436 (3)	470 (1)	469 (0.3)	443 (2)	538 (0) [12]	Q11
Q12	776			791 A ₂	A ₂ 708 (0)	740 (0)	711 (0)	726 (0)	821 (0) [0]	Q12
Q13	794			802 B ₁	B ₁ 730 (19)	760 (19)	730 (10)	746 (20)	836 (7) [0.8]	Q13
Q14	829			834 B ₂	B ₂ 760 (2)	760 (19)	739 (0)	769 (2)	876 (1) [0]	Q14
Q15	862	804 (31) A ₁	ρ _r (NH ₃)	860 A ₁	A ₁ 796 (78)	814 (83)	772 (75)	802 (78)	907 (85) [9]	Q15
Q16	1305	1249 (278) B ₂	δ _s (NH ₃)	1265 B ₂	B ₂ 1318 (190)	1274 (198)	1246 (152)	1271 (191)	1303 (156) [2]	Q16
Q17	1309	1261 (137) A ₁	δ _s (NH ₃)	1266 A ₁	A ₁ 1327 (110)	1281 (112)	1254 (106)	1277 (107)	1308 (13) [10]	Q17
Q18	1573			1641 B ₂	B ₂ 1674 (37)	1640 (39)	1638 (25)	1644 (38)	1650 (22) [0.1]	Q18
Q19	1579	1621 (60) A ₁	δ _d (NH ₃)	1649 A ₁	A ₁ 1680 (20)	1647 (0)	1645 (14)	1651 (21)	1655 (9) [21]	Q19
Q20	1604			1676 A ₂	A ₂ 1705 (0)	1673 (0)	1667 (0)	1677 (0)	1681 (0) [7]	Q20
Q21	1611			1682 B ₁	B ₁ 1712 (49)	1680 (51)	1675 (33)	1683 (50)	1688 (27) [0.7]	Q21
Q22		3284 (18) B ₂	ν(NH ₃)	3133 B ₂	B ₂ 3493 (30)	3431 (24)	3394 (16)	3419 (26)	3099 (12) [27]	Q22
Q23	3162			3133 A ₁	A ₁ 3494 (14)	3432 (63)	3394 (93)	3419 (48)	3100 (199) [216]	Q23
Q24	3320			3327 B ₂	B ₂ 3620 (10)	3588 (3)	3554 (2)	3558 (4)	3368 (1) [93]	Q24
Q25	3360		ν(NH ₃)	3327 A ₁	A ₁ 3620 (83)	3589 (93)	3556 (70)	3559 (87)	3370 (36) [292]	Q25
Q26				3393 A ₂	A ₂ 3660 (0)	3650 (0)	3613 (0)	3612 (0)	3433 (0) [41]	Q26
Q27		3415 (127) B ₁		3394 B ₁	B ₁ 3660 (65)	3650 (85)	3615 (75)	3613 (74)	3435 (63) [128]	Q27

^a Scaled.

^b Z-mPW1PW = ZORA-mPW1PW, Z-B1LYP = ZORA-B1LYP.

^c Raman intensities from Becke88-Perdew86.

Table 6. Comparison of valence ionization energies (in eV) of cisplatin.

1979		1980	1986	Present work 2016							1979	Ave - Obs	
Barber et al ⁵³		Carsey & Boudreaux ⁵⁴	Zuloaga & Arratia-Perez ⁵⁴			LanL2DZP		Scalar ZORA/TZ2P			Barber et al ⁵³		
X α		REH ^a	DSW ^b			HF	OVGF	SAOP	Δ PBE0(SAOP)	−5.16	Ave	Obs	
TS ^c model	Mainly		− ϵ_k − 2.07	MO				mKT ^d					
11.62	Cl 3p	8.79	3.92	7a ₂	π	9.84	8.78	9.33	8.41	3.25	3.70	4.2	−0.50
12.93	Cl 3p	10.16	4.39	12b ₂	σ	10.27	9.37	9.55	8.66	3.50			
11.66	Cl 3p	11.02	4.45	28a ₁	σ	10.21	9.16	9.60	8.72	3.56			
12.77	Cl 3p	12.78		27a ₁	σ	10.78	9.51	9.88	9.14	3.98			
11.69	Cl 3p			19b ₁	π	10.21	9.14	10.07	9.36	4.2			
16.94	Pt d _{yz}		5.50	11b ₂	σ	11.85	11.12	11.28	10.36	5.20	5.63	6.0	−0.37
16.95	Pt d _{xz}			6a ₂	π	12.91	9.31	11.34	10.43	5.27			
13.46	NH ₃ 3a ₁ + Cl 3p			26a1	σ	11.95	10.84	11.61	10.82	5.66			
14.09	Cl 3p			18b ₁	π	12.75	10.91	11.89	11.12	5.96			
16.68	Pt d _{xy}			25a ₁	σ	13.78	11.70	11.93	11.21	6.05			
18.56	NH ₃ 3a ₁			17b ₁	π	20.06	18.75	14.77	14.29	9.13	9.27	8.7	+0.57
18.18	Pt d _{zz} + NH ₃ 3a ₁			24a ₁	σ	16.94	15.32	14.95	14.56	9.40			
18.85	NH ₃ 1e+			16b ₁	π			17.34	17.39	12.23	12.44	Missing ^e	
19.00	NH ₃ 1e-		8.84	5a ₂	π	19.95	18.64	17.56	17.61	12.45			
19.42	NH ₃ 1e-			23a ₁	σ	20.18	18.67	17.63	17.68	12.52			
19.24	NH ₃ 1e+			10b ₂	σ	16.22	14.96	17.64	17.70	12.54			
24.41	Cl 3s			15b ₁	π			22.50	23.04	17.88	17.97	17.1	+0.87
24.51	Cl 3s		17.50	22a ₁	σ			22.67	23.22	18.06			
27.56	NH ₃ 2a ₁		17.96	14b ₁	π			27.57	28.55	23.39	23.44	24.0	−0.56
27.70	NH ₃ 2a ₁			21a ₁	σ			27.66	28.64	23.48			

^a Relativistic extended Huckel.

^b Dirac scattered wave.

^c Transition state.

^d meta-Koopmans’s theorem: VIP_k = −ε_k(SAOP).

^e Waiting for new measurement.

Table 7. Absorption maxima (in nm) in UV/visible spectra of cisplatin.

		State						
1958	Chatt et al ⁵⁹	aq	417 w	366 m	302 s			
1981	Patterson et al ⁶⁰	in frozen DMF aq		370 w	308 m	282 m	220 s 220	202 s 202
1985	Riley & Sternson ⁶¹	0.1 N HCl		362 w	301 m			203 s
1994	Macka et al ⁶²	aq		~370	302	~280		
2008	Fumarel et al ⁶³	aq			310 w			207 s
2011	Ramos et al ⁶⁴	aq			305 m		220 s	
	Best estimates	aq	417 w	366 w	305 m	282 m	220 s	204 s

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Table 8. Comparison of $\lambda_{\max}$ values (in nm) calculated by TDDFT using 27 exchange correlation functionals/potentials.

		FWHM ^a					MAD ^b	MAD ^c	MAD ^d
Obs ^e			204 s	220 s	282 m	305 m	(0)	A2	A
SAOP	model	8	210	234	284	318	9	26	8
RPBE	GGA	9	205	230	277	330	10	—	20.5
TPSS	metaGGA	8	204	249	268	315	13	17	12.5
BLYP	GGA	8	211	236	282	334	13	—	22.5
TPSSH	metaHybrid	4	198	233	249	309	14	—	9
M06	metaHybrid	6	203	220	229	303	14	—	13.5
SSB-D	GGA	7	210	226	265	275	15	—	17
PBE	GGA	8	212	226	262	279	15	—	21
O3LYP	Hybrid	6	206	240	264	331	16.5	46	6.5
KT2	GGA	8	208	259	282	328	16.5	—	17
B3LYP	Hybrid	4	197	236	243	320	17	35	11
BP86	GGA	6	213	251	282	333	17	—	20.5
OPBE0	GGA	6	211	252	278	331	17	30	18
B1PW91	Hybrid	6	203	214	231	316	17	32	16
M06-L	metaHybrid	3	199	224	244	281	18	—	9
OPBE	GGA	6	212	257	280	332	18.5	33	16
B1LYP	Hybrid	3	207	230	233	318	19	35	14
mPW1PW	GGA	8	212	259	279	332	19	34	16
B3LYP*	Hybrid	6	199	243	251	323	19	35	7
X3LYP	Hybrid	3	208	235	239	320	19	35	12
KT1	GGA	10	208	266	278	326	19	—	19
revPBE	GGA	10	207	266	279	331	19.5	—	20
PBE0	GGA	9	211	262	279	332	20	33	15
PW91	GGA	10	209	269	282	333	20.5	—	21.5
VWN	LDA	8	210	258	287	339	21	—	24
LB94	Model	4	214	233	242	334	23	—	24
mPBE	GGA	9	227	263	279	331	24	—	21

^a Full width at half maximum (in nm) of Gaussian shape used in convolution.

^b Mean absolute deviation for the four absorption maxima

^c Mean absolute deviation from Table A2 for PtCl_4^{2-} .

^d Mean absolute deviation from Table A in Ref. [39] for calculated $\lambda_{\max}$ of UV/visible absorption of fluorouracil(aq) and tirapazamine(aq).

^e See Table 7.

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Caption of Figure 1

Stimulated UV absorption spectrum of cisplatin(aq) based on TDDFT calculations using model exchange-correlation potential $V_{xc} = \text{SAOP}$ with spinorbit zero-order relativistic approximation

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Fig. 1. Stimulated UV absorption spectrum of cisplatin(aq) based on TDDFT calculations using model exchange-correlation potential $V_{xc} = \text{SAOP}$ with spinorbit zero-order relativistic approximation.

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