Correct Modeling of Cisplatin: a Paradigmatic Case
Nicola Tasinato, Cristina Puzzarini, and Vincenzo Barone*

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S.1 Computational Strategy

Best estimates for the equilibrium structure and harmonic force field of the gas-phase isolated cisplatin molecule (cis-diaminodichloroplatinum (II), cis-[Pt(NH$_3$)$_2$Cl$_2$]) were determined by means of the so-called “cheap” computational protocol.[1] To improve CCSD(T) [coupled-cluster singles and doubles approximation augmented by a perturbative treatment of triples] results obtained in conjunction with a triple-zeta quality basis set, this approach uses second-order Møller-Plesset theory (MP2) to recover various contributions important for high accuracy. In detail, the composite scheme employed can be summarized by the following expression:

$$X_{\text{best}} = X(\text{CCSD(T)}/cc-pCVTZ(-PP)) + \Delta_{CBS}[\text{MP2/TQ}] + \Delta_{\text{diff}}[\text{MP2/au.gTZ}]$$

where $X$ denotes a generic term, either a structural parameter or a harmonic frequency. The leading term is the CCSD(T)/cc-pCVTZ(PP) level of theory, with all electrons correlated, thus already accounting for core-valence correlation effects. The scheme then includes the correction for incorporating the extrapolation to the complete basis set (CBS) limit. This has been performed at the MP2 level employing the $n^3$ formula and basis sets of triple- and quadruple-zeta quality. A corrective term to include the effect of diffuse functions in the basis sets has also been considered. In all these calculations, the (aug)-cc-p(C)VnZ(-PP), $n$=T, Q, Dunning’s correlation consistent basis sets were used. The PP acronym above means that for platinum correlation consistent basis sets have been used together with small-core relativistic pseudopotentials, which leave 18 electrons to be handled explicitly. All these calculations were carried out by using the quantum chemical program package CFOUR.[8]

To include a quantum treatment of anharmonic effects, density functional theory (DFT) calculations were carried out for the cisplatin molecule and its dimer by using the hybrid B3PW91[7] and double-hybrid B2PLYP[9] functionals augmented for dispersion effects through the Grimme’s DFT-D3 scheme.[10] The B3PW91-D3 functional was used in conjunction with the SNSD basis set[10] for describing the ligands, while the cc-pVTZ-PP basis set supplemented by the ECP60MDF relativistic energy-consistent pseudopotential was employed for the Pt atom.[11] For B2PLYP-D3 calculations, ligands were described through the m-aug-cc-pVTZ-PPF basis set,[12] using the same effective-core pseudopotential on Pt. As usual, geometry optimizations were carried out first and then at the optimized structure, the harmonic force field was computed through analytical second-derivatives, while cubic and semidiagonal quartic force constants were evaluated by numerical differentiation. For the free molecule, anharmonic calculations were performed by using both B3PW91-D3 and B2PLYP-D3 functionals, while for the ciplatin dimer only the B3PW91-D3 functional was considered.

For the isolated cisplatin molecule, hybrid models that combine the harmonic frequencies from the “cheap” composite scheme with the anharmonic force fields computed at the B2PLYP-D3 (bestCC/B2) and B3PW91-D3 (bestCC/B3) levels were considered. For the cisplatin dimer, an hybrid force field was also obtained by correcting B2PLYP-D3 harmonic frequencies with cubic and semidiagonal quartic force constants computed with the B3PW91-D3 functional.

The vibrational spectroscopic properties were then obtained by means of vibrational second-order perturbation theory (VPT2)[13] within its generalized implementation, GVPT2,[14] applied to the semidiagonal quartic force field. DFT and GVPT2 computations were carried out using the Gaussian suite of quantum chemical programs.[15]

S.2 Results and Discussion

S.2.1 Equilibrium Geometry and Vibrational Spectrum of the Gas-phase Cisplatin Molecule

The structural parameters evaluated at different levels of theory, i.e., by means of the “cheap” computational protocol (bestCC) as well as at the CCSD(T), B2PLYP-D3 and B3PW91-D3 levels of theory, are detailed in Table S.1, where they are also compared with those determined experimentally for the solid compound. By comparing the geometrical parameters of cis-[Pt(NH$_3$)$_2$Cl$_2$] computed at different levels of theory with the experimental values, differences between experiment and theory up to 0.047 Å and 6.9° for bond lengths and angles, respectively, can be reported. Such large discrepancies are unrealistic at this level of theory (in particular for what concerns the bestCC protocol, which is usually characterized by an accuracy of about ±0.002 Å and ±0.2° for bond lengths and angles, respectively) and cannot be explained simply on the ground of the well-known shift between equilibrium and ground state geometries due to the vibrational effects. In fact, these are estimated to provide longer bond lengths by ~0.003 to 0.01 Å, and variations in bond angles within 0.3°. Furthermore, the different levels of theory show similar deviations, and no significant
improvement can be observed when moving from DFT to coupled-cluster based predictions. In passing, it should be noted that the structural parameters here obtained are in line with those reported in the most recent investigation on cisplatin. Indeed, the poor agreement with experiment deviates too much from what can be obtained nowadays by means of quantum chemical approaches, but more important, it is not able to shed lights on the atomistic properties of materials and drugs, and thus it is not able to provide reliable interpretation or predictions.

The computed harmonic and anharmonic frequencies for the 27 vibrational normal modes of the cisplatin isolated molecule, together with the available experimental data, are listed in Table S.2. Concerning the experiment, the Raman measurements by Amado et al. have been considered because they are the most recent ones and also appear to be the most complete set.

Table S1. Theoretical equilibrium geometry of PCl2(NH3)2 computed at different levels of theory and comparison to literature data[16]

|                  | Best CC [a] | CCSD(T) [b] | B3PW91-D3 [c] | B2PLYP-D3 [d] | Exp. [f] |
|------------------|------------|-------------|---------------|---------------|---------|
| Pt—N             | 2.0562     | 2.0688      | 2.0713        | 2.0793        | 2.048±3  |
| Pt—Cl            | 2.2498     | 2.2738      | 2.2921        | 2.2803        | 2.321±8  |
| N—Hc             | 1.0214     | 1.0211      | 1.0267        | 1.0219        | 0.988±17 |
| N—Hg             | 1.0132     | 1.0136      | 1.0173        | 1.0142        | 1.011±35 |
| ∆(N(PtCl))       | 83.90      | 83.29       | 83.09         | 83.46         | 88.87±9  |
| ∆(CIPtCl)        | 94.52      | 95.40       | 95.65         | 95.10         | 91.65±3  |
| ∆(HCNPt)         | 103.30     | 102.19      | 102.33        | 102.51        | 109.1±34 |
| ∆(HgNPt)         | 114.42     | 114.82      | 114.54        | 114.32        | 112.7±8  |
| ∆(OCl(NH3))      | 117.2      | 116.7       | 116.8         | -3            | -9       |

[a] Bond lengths in Å, bond angles in deg. [b] “Cheap” composite scheme: CCSD(T)(PP)+λCCSD(MP2) + Δexp(MP2). See text. [c] CCSD(T)cc-pVCTZ-(PP). [d] B3PW91-D3 in conjunction with SNSD for ligands and cc-pVTZ-PP for Pt. [e] B2PLYP-D3 in conjunction with m-aug-cc-pVTZ-df for ligands and cc-pVTZ-PP for Pt. [f] From Ref. [17]. [g] Mean value (n) Due to the large difference between the two original values, half the difference has been taken as uncertainty.

Table S2. Harmonic (ν) and anharmonic (ν′) frequencies (cm⁻¹) and anharmonic Raman activities (RA) of cis-[PCl2(NH3)2] vibrational normal modes

| Symmetry | Mode | ν [cm⁻¹] | ν [cm⁻¹] | ν′ [cm⁻¹] | ν′ [cm⁻¹] | RA [cm⁻¹] | RA [cm⁻¹] |
|----------|------|----------|----------|-----------|-----------|-----------|-----------|
| A1       | 11   | 3520     | 3525     | 3538      | 3337      | 3335      | 3335      | 1.433     | 3.309    |
| A2       | 11   | 3568     | 3576     | 3596      | 3383      | 3377      | 3391      | 3.406     | 1.27     |
| B1       | 11   | 1671     | 1675     | 1656      | 1614      | 1661      | 1681      | 1.601     | 0.109    |
| B2       | 11   | 1679     | 1682     | 1664      | 1623      | 1624      | 1625      | 1.609     | 0.093    |
| A1       | 11   | 741      | 743      | 740       | 713       | 714       | 715       | 0.111     | 0.789    |
| A2       | 11   | 167      | 169      | 163       | 164       | 164       | 163       | 0.002     | 0.002    |
| B1       | 11   | 110      | 123      | 136       | 111       | 111       | 111       | 0.027     | 0.111    |
| B2       | 11   | 3520     | 3524     | 3537      | 3338      | 3335      | 3335      | 0.353     | -        |
| A1       | 11   | 3387     | 3390     | 3393      | 3164      | 3155      | 3168      | 3.142     | 0.075    |
| A2       | 11   | 1644     | 1645     | 1652      | 1597      | 1598      | 1597      | 1.579     | 0.002    |
| B1       | 11   | 1275     | 1285     | 1251      | 1217      | 1216      | 1205      | 1.193     | 0.001    |
| B2       | 11   | 755      | 753      | 747       | 727       | 728       | 725       | 0.023     | 0.811    |
| A1       | 11   | 479      | 463      | 466       | 467       | 467       | 447       | 0.129     | 0.508    |
| A2       | 11   | 363      | 354      | 349       | 361       | 361       | 351       | 0.267     | 0.317    |
| B1       | 11   | 240      | 237      | 235       | 236       | 235       | 233       | 0.009     | 0.210    |

[a] “Cheap” composite scheme. See text. [b] B2PLYP-D3 in conjunction with m-aug-cc-pVTZ-df for ligands and cc-pVTZ-PP-ECP60MD for Pt. [c] B3PW91-D3 in conjunction with SNSD for ligands and cc-pVTZ-PP for Pt. [d] Hybrid field force obtained by using harmonic frequencies from the “cheap” composite scheme coupled to cubic- and semi-diagonal quartic-force constants computed by using the B2PLYP-D3 functional. [e] Hybrid force field obtained by using harmonic frequencies from the “cheap” composite scheme coupled to cubic- and semi-diagonal quartic-force constants computed by using the B3PW91-D3 functional. [f] From Ref. [18]. [g] Mean Absolute Deviation from experimental values. [h] Maximum negative difference from experimental values. [i] Maximum positive

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Recalling that mechanical anharmonicity usually has the effect of lowering the harmonic vibrational frequency, it is quite suspicious that the wavenumbers of different normal modes \((\nu_1, \nu_2, \nu_8, \nu_9, \nu_{11}, \nu_{12})\) are significantly underestimated already at the harmonic level. Adding the physical ingredient of anharmonicity has the disappointing effect of worsening the accord. On the other hand, a limited number of bands \((\nu_1, \nu_2, \nu_{13}, \nu_{14})\) takes benefit from the anharmonic corrections. Again, the poor agreement between theory and experiment is in contrast with what can be expected from the literature. Benchmarking studies show that anharmonic fundamental frequencies computed by means of hybrid CCSD(T)/DFT composite schemes are able to reproduce the experimental counterparts within 10 cm\(^{-1}\) even when complex resonance patterns are present. To further stress the predictive capabilities of modern quantum chemistry, it should be pointed out that DFT calculations using (double-) hybrid functionals and (at least) polarized double-\(\zeta\) basis sets show an experimental-theoretical agreement within 10-20 cm\(^{-1}\). In particular, the B3LYP functional coupled to the SNSD basis set has been shown to reach an overall mean accuracy around 15-20 cm\(^{-1}\), while the double-hybrid B2PLYP functional has been demonstrated to be able of achieving mean absolute deviations in the range 5-10 cm\(^{-1}\) for a number of molecules (see Refs. 10a and 20 and references therein). For cisplatin, on the other hand, experimental frequencies are reproduced very poorly independently on the level of theory adopted (as already noted for structural parameters) with a mean absolute deviation around 40 cm\(^{-1}\) (four times higher than expected!) and positive (negative) deviations as large as 83 (–68) cm\(^{-1}\).

**S.2.2 Benchmark of DFT functionals**

Over the years, there has been a long-standing interest in the vibrational spectra of cisplatin.\(^{[16,18,21-23]}\) This interest has been motivated in part by the clinical relevance of the molecule, but also, at a more fundamental level, by its electronic structure involving a ligand-ligand interaction through a filled \(d\)-orbital of the Pt atom.\(^{[21]}\) Various studies dealing with the vibrational properties of cisplatin have been devoted to assess the predictive skills of different levels of theory and basis set in reproducing the experimental absorptions. These include Hartee-Fock (HF), MP2, and DFT in conjunction with different all-electrons and pseudopotential basis sets. Benchmark investigations have been performed by considering the gas-phase free molecule, with fundamental transition frequencies evaluated at the harmonic level and anharmonicity taken into account through scaling factors determined ad-hoc for each normal mode, eventually grouped together according to some criteria.\(^{[16,18,23]}\) Despite the remarkable research efforts, the outcomes of these studies are often contradictory and only semi-quantitative predictions have been achieved. On one side, the controversies stem from the error compensation introduced by the use of ad hoc scaling factors, on the other, they are related to an incomplete physical picture of the model. Specifically, it is worth noticing that the approaches appeared in the literature try to simulate the experimental outcomes, which have been obtained using solid compounds, through calculations performed for the free cisplatin molecule in vacuum. This approach has only limited physical grounds; in fact, it completely neglects the intermolecular interactions, especially those ruling the stacking of the Pt(NH\(_3\))\(_2\)Cl\(_2\) units in the crystal, thus preventing the calculation of a reliable structure. A more consistent performance evaluation can be achieved by benchmarking the harmonic frequencies computed at the different levels of theory against the highly accurate values here evaluated at the “bestCC” level, as reported in Table S.3 and graphically illustrated in Figure S1. In addition to the values here obtained at the B2PLYP-D3 and B3PW91-D3 levels, those computed by Amado et al.,\(^{[18]}\) Fiuza et al.\(^{[23]}\) and Dodoff\(^{[16]}\) are also reported, thus considering the HF, DFT (B3LYP, mPW1PW, PW91) and MP2 levels.

![Figure S1](image_url)

*Figure S1*: Benchmark of harmonic vibrational frequencies computed at different levels of theory against bestCC values obtained by exploiting the “cheap” computational protocol. See Table S3.

The benchmark is restricted to the normal modes for which a confident correspondence with the assignment reported in the literature works can be found. As evident from the entries of Table S.3 and Figure S.1, benchmarking against accurate gas-phase values recovers the behavior expected for the different levels of theory. In particular, the HF theory provides the worst accord with mean
absolute deviations from reference data well above 100 cm\(^{-1}\). A sensible improvement can now be obtained by including electron-correlation either at the MP2 or DFT level. For the latter, the effects of the specific density functional as well as of the basis set employed can be appreciated: for example, it can be observed that by using ECP for both Pt and the ligands (B3LYP/ECPP1) significantly worsens the performances of the B3LYP functional. The excellent performances of B3PW91-D3 and especially the B2PLYP-D3 functional are pointed out by MADs, with respect to the reference bestCC values, of only 11 and 5 cm\(^{-1}\), respectively. These MADs are in line with the accuracy expected for these functionals when they are coupled to suitable basis sets and, in the case of cisplatin, effective core potentials.

Table S3. Benchmark of harmonic (\(\omega\)) vibrational frequencies of cis-[PtCl\(_2\)(NH\(_3\))\(_2\)] computed at different levels of theory

| Mode | bestCC \(\omega\) [\(\text{cm}^{-1}\)] | HF/ \(\text{AE4}\) | B3LYP/ \(\text{AE1}\) | mPW1PW/ \(\text{AE1}\) | MP2/ \(\text{AE1}\) | HF/ \(\text{ECP1}\) | B3LYP/ \(\text{ECP1}\) | mPW1PW/ \(\text{ECP1}\) | PW91/ \(\text{3-21G}\) | PW91/ \(\text{3-21G}\) | B2PLYP/ \(\text{AE1}\) | B3PW91/ \(\text{AE1}\) | Exp \(\omega\) [\(\text{cm}^{-1}\)] |
|------|-----------------|--------|--------|-----------------|--------|--------|--------|-----------------|--------|--------|--------|--------|--------|--------|
| cis  | 3520 | 3837 | 3568 | 3620 | 3618 | 3951 | 3596 | 3692 | 3394 | 3394 | 3525 | 3538 | 3309 |
| cis\(_2\) | 3387 | 3711 | 3388 | 3426 | 3434 | 3756 | 3389 | 3475 | 3133 | 3137 | 3390 | 3384 | 3211 |
| cis\(_3\) | 1651 | 1830 | 1673 | 1682 | \(\ldots\) | 1866 | 1798 | 1729 | 1641 | 1641 | 1652 | 1632 | 1537 |
| cis\(_4\) | 1282 | 1462 | 1303 | 1321 | 1352 | 1511 | 1340 | 1349 | 1265 | 1256 | 1272 | 1258 | 1295 |
| cis\(_5\) | 789 | 865 | 899 | 825 | 838 | 935 | 879 | 898 | 860 | 853 | 785 | 780 | 824 |
| e\(_6\) | 490 | 452 | 447 | 472 | 472 | 542 | 492 | 520 | 510 | 503 | 475 | 474 | 524 |
| e\(_7\) | 374 | 333 | 334 | 349 | 349 | 340 | 312 | 326 | 338 | 343 | 365 | 361 | 323 |
| e\(_8\) | 231 | 231 | 216 | 226 | 229 | 264 | 234 | 245 | 240 | 241 | 229 | 230 | 255 |
| e\(_9\) | 158 | 165 | 158 | 164 | 162 | 168 | 156 | 159 | 165 | 168 | 157 | 154 | 162 |
| e\(_10\) | 1671 | 1839 | 1681 | 1691 | 1710 | 1874 | 1710 | 1735 | 1649 | 1649 | 1675 | 1656 | 1601 |
| e\(_11\) | 724 | 779 | 742 | 760 | 761 | 833 | 789 | 808 | 791 | 785 | 726 | 723 | 724 |
| e\(_12\) | 1679 | 1868 | 1711 | 1721 | 1740 | 1908 | 1745 | 1770 | 1682 | 1682 | 1682 | 1664 | 1648 |
| e\(_13\) | 741 | 870 | 759 | 779 | 781 | 863 | 806 | 827 | 802 | 797 | 743 | 740 | 789 |
| e\(_14\) | 755 | 815 | 775 | 790 | 799 | 883 | 846 | 864 | 834 | 826 | 753 | 747 | 811 |
| e\(_15\) | 479 | 440 | 439 | 465 | 468 | 488 | 490 | 511 | 506 | 499 | 463 | 463 | 508 |
| e\(_16\) | 363 | 322 | 323 | 338 | 341 | 303 | 301 | 314 | 327 | 330 | 354 | 349 | 317 |
| e\(_17\) | 240 | 229 | 221 | 232 | 234 | 224 | 225 | 234 | 233 | 231 | 237 | 235 | 210 |

From a more general point of view, it should be remarked that for a reliable assessment of the performances of a given model chemistry, the physical consistency between the system object of measurements and that employed for its simulation is a fundamental requisite. Ideally, the molecular system employed in the calculations should mimic, as close as possible, the physical and chemical conditions characterizing experiments (e.g. environment, intermolecular interactions, \ldots). Furthermore, in order to retain a certain degree of transferability to different molecules, whenever possible, the degree of empiricism should be reduced, e.g. by avoiding the use of scaling factors and resorting to the use of a full treatment of anharmonicity. Finally, when little about a compound is experimentally known, the accuracy of a given model chemistry can be estimated by considering a smaller system, representative of that under investigation, and then benchmarking against accurate theoretical data (e.g. composite schemes based on the coupled cluster ansatz) whose accuracy is well established.

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Author Contributions

All authors contributed to quantum-chemical computations, data analysis, discussion and manuscript writing. All authors contributed equally.