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Correct Modeling of Cisplatin: a Paradigmatic Case

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Abstract: *Quantum chemistry is a useful tool in modern approaches to drug and material design, but only when the adopted model reflects a correct physical picture. Paradigmatic is the case of cis-diaminodichloroplatinum(II), cis-$[Pt(NH_3)_2Cl_2]$, for which the correct simulation of the structural and vibrational properties measured experimentally still remains an open question. By using this molecule as a proof of concept, it is shown that state-of-the-art quantum chemical calculations and a simple model, capturing the basic physical flavors, a cis-$[Pt(NH_3)_2Cl_2]$ dimer, can provide the accuracy required for interpretative purposes. The present outcomes have fundamental implications for benchmark studies aiming at assessing the accuracy of a given computational protocol.*

The role played by computational chemistry as a tool for the design of pharmacological molecules, especially chemotherapeutic agents, is well recognized because of its capabilities in providing a fundamental understanding of structural and physicochemical properties, which is a mandatory starting point for the development and further improvement of new drugs.[1] Furthermore, theoretical studies can give important insight into the interaction of anticancer drugs with DNA, thus elucidating the molecular mechanisms underlying the clinical action.[2] However, the definition of efficient and reliable computational protocols aimed at modeling macrosystems of biological and pharmacological interest is still a nontrivial task, especially when metal atoms are involved. This process starts with extensive benchmarking against experimental data: in particular, structural and spectroscopic properties are well-recognized figures of merit to test computational approaches. Nevertheless, benchmarking is often carried out overlooking that models should include all key factors (e.g., environment and intermolecular interactions) tuning the experimental outcome. The lack of proper physical "flavors" may lead to inconsistent results, thus providing possibly misleading inferences and preventing the transferability of the approach to other, even similar, systems.

As a proof of concept we investigated the structural and vibrational properties of *cis*-diaminodichloroplatinum(II), *cis*-$[Pt(NH_3)_2Cl_2]$, usually referred to as cisplatin. This molecule (Figure 1a) is one of the major drugs in cancer chemotherapy,[3] successfully applied for the treatment of different cancers.[4] Unfortunately, it presents a number of dose-limiting side effects (e.g., nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression), hence some tumors develop resistance to the treatment. Despite collateral effects, cisplatin is a milestone in the treatment of neoplastic disorders and it is a prototype for the development of improved platinum compounds of general formula $[Pt(amine)_2X_2]$ showing reduced dose-limiting side effects.

The anticancer activity of cisplatin has stimulated several experimental and theoretical studies aimed at a deeper understanding of its structural and spectroscopic properties. The vibrational spectra of cisplatin have been the object of several experimental studies,[5–7] whereas its high-resolution crystal structure has been reported only some years ago.[8] Besides experimental studies, several investigations have focused on the theoretical prediction of its structure and vibrational frequencies.[6,7,9,10] These studies are often contradictory and only semi-quantitative predictions have been achieved, likely because experimental outcomes obtained using solid compounds have been simulated through calculations performed on molecules in the gas phase. Such an approach neglects intermolecular interactions, especially

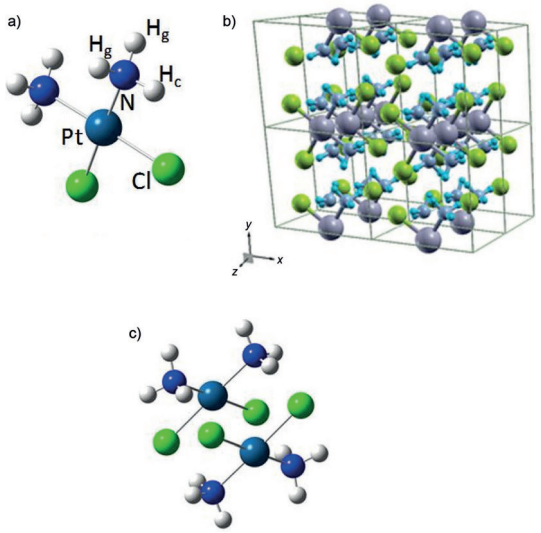

Figure 1. a) Cisplatin and atom labeling: the two H_g atoms are equivalent. b) Structure of α-cisplatin in the crystal (*x*, *y*, *z* axes coincide with the *a*, *b*, *c* crystallographic axes, respectively). c) The cisplatin dimer employed in the calculations.

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those ruling the stacking of $[Pt(NH_3)_2Cl_2]$ units in the crystal. At the same time, the prediction of vibrational frequencies has been performed at the harmonic level, with anharmonicity taken into account only by means of empirical scaling factors, in some cases determined ad hoc, thus preventing their transferability to other Pt derivatives. Furthermore, the harmonic approximation limits the analysis to fundamental transitions, although combination and overtone bands can give important contributions.

The aim of the present study is to demonstrate that an improved description of the physicochemical properties of cisplatin can be achieved by adding some physical flavors to the model. The proposed approach relies on recovering the most important intermolecular interactions occurring in the solid phase by using the *cis*-$[Pt(NH_3)_2Cl_2]$ dimer for the simulation, and on introducing a full quantum-mechanical treatment of anharmonic effects. In addition, it is shown that, when the model does not grasp the essential physical elements, improving the electronic structure treatment is useless.

In the last decade, the CCSD(T) method[11] has become the "gold standard" for the accurate prediction of structural, thermochemical, and spectroscopic properties. Even more accurate results, rivaling the most refined experimental techniques, can be obtained by employing composite schemes.[12] We now have determined the equilibrium structure and harmonic vibrational frequencies of cisplatin with a "cheap" computational protocol,[13] which is detailed in the Supporting Information (SI). As to vibrational frequencies, best-estimated harmonic values have been combined with anharmonic effects at the DFT level (B3PW91-D3[14] and B2PLYP-D3[15] functionals), thus leading to the well-documented hybrid CCSD(T)/DFT approach (see for example Ref. [16] and references therein), which is for cisplatin close to the current limit of computational feasibility.

By comparing the geometrical parameters of cisplatin computed at different levels of theory (Table S.1 of the SI), it is apparent that the free gas-phase molecule is a too crude approximation, which is not able to capture a coherent picture of the physicochemical properties issuing from experiment. The "cheap" protocol is expected to be accurate to about ± 0.002 Å and $\pm 0.2°$ for bond lengths and angles, respectively, however in the present case differences as large as 0.047 Å and 6.9° between theory and experiment are noted, which are highly suspicious at this level of theory. Furthermore, no significant improvement is observed moving from DFT to coupled-cluster-based predictions. The very same conclusion can be drawn for the vibrational properties of the gas-phase molecule. The comparison with experiment is detailed in Section S.2 of the SI; here, we only note that going beyond the harmonic approximation may have beneficial or detrimental effects depending on the normal mode considered. This aspect, somewhat overlooked in previous works on cisplatin vibrational spectra,[7,10] resulted in scaling factors larger or smaller than unit, respectively. The consequence is that the existing scaling factors are not transferable to new systems, thus impairing the predictive role of quantum chemical approaches to drug design. We recall that anharmonic fundamental frequencies computed by (double) hybrid DFT models reproduce the experimental counterparts within about 10 or 20 cm^{-1}, when the harmonic force field employed is of CCSD(T) or DFT quality, respectively.[16,17] However, for cisplatin, experimental frequencies are reproduced poorly irrespective of the level of theory adopted, with a mean absolute deviation around 40 cm^{-1}.

In conclusion, computational models based on the isolated gas-phase molecule are not able to reproduce the structural and vibrational properties of cisplatin. One of the ingredients missing in this model is the role played by intermolecular interactions in the solid compound. The crystal structure of α-cisplatin is reproduced in Figure 1b, where it can be appreciated that the most important contribution comes from intermolecular N–H···Cl hydrogen bonds responsible for the stack of square-planar molecules along the crystallographic *c* axis. To account for this interaction, we have modeled the structural and vibrational properties of cisplatin considering its dimer cut from the bulk crystal (Figure 1c). It should be stressed that our aim is not to exactly reproduce the experimental quantities, but rather to show that for interpretation purposes, the adopted models, even if simplified, should reflect the correct physicochemical picture of the system investigated.

The computed geometrical parameters and vibrational frequencies are compared with the experimental values in Table 1 and 2, respectively. To discuss structural parameters, we have considered the amino group involved in the intermolecular hydrogen bond described by the dimer (i.e. N(2)H(4)H(5)H(6) according to the notation of Ref. [8]). The structural parameters undergo relevant changes in passing from the monomer to the dimer: the Pt–N bond shortens and the Pt–Cl distance lengthens, thus moving in the direction of

Table 1: Equilibrium geometry of cisplatin and its dimer.[a]

	Dimer		Monomer			Exp.[e]
	B3PW91[b]	B2PLYP[c]	B3PW91[b]	B2PLYP[c]	BestCC[d]	
Pt–N	2.0524	2.0615	2.0713	2.0793	2.0562	2.048(3)
Pt–Cl	2.3190	2.3063	2.2921	2.2803	2.2498	2.321(8)
$N–H_c$	1.0210	1.0176	1.0267	1.0219	1.0214	0.988(17)
$N–H_g$	1.0170	1.0142	1.0173	1.0142	1.0132	0.976(17)
$N–H_g···Cl$	1.0332	1.0273	1.0173	1.0142	1.0132	1.046(15)
∡(NPtN)	94.05	94.05	98.17	97.97	97.68	90.62(12)
∡(NPtCl)	85.93	86.04	83.09	83.46	83.90	88.87(9)
∡(ClPtCl)	94.04	93.85	95.65	95.10	94.52	91.65(3)
$∡(H_cNH_g)$	107.93	108.02	108.18	108.29	108.02	109.0(10)
$∡(H_gNH_g)$	108.92	108.99	108.59	108.67	108.23	112.4(11)
$∡(H_cNPt)$	106.98	106.79	102.33	102.51	103.30	109.1(10)
$∡(H_gNPt)$	115.70	115.43	114.54	114.32	114.42	113.1(9)
$∡(H_gNPt)$[f]	109.61	109.66	114.54	114.32	114.42	112.3(8)
$δ(ClPtNH_g)$	134.2	134.6	116.8	116.9	117.2	–
$δ(ClPtNH_g)$	102.2	101.9	116.8	116.9	117.2	–

[a] Bond lengths in Å, angles in deg. [b] B3PW91-D3/SNSD for ligands / cc-pVTZ-PP for Pt. [c] B2PLYP-D3/*m*-aug-cc-pVTZ-*d*H for ligands / cc-pVTZ-PP for Pt. [d] "Cheap" composite scheme; see the SI. [e] From Ref. [8]. [f] In the dimer, the two H_g atoms are no longer equivalent.

Table 2: Assignment of vibrational bands [cm^{-1}] of cisplatin.

Exp.[a]	Monomer		Dimer	Approximate description[b]
	bestCC/B3[c]	Hyb B2/B3[d]	Hyb B2/B3[d]	
84	84	110	84	skeletal deformation
111	110	123	119	$PtCl_2$ twist
162	157	156	151	$PtCl_2$ scissor
210	235	232	199	NH_3 torsion
255	227	225	233	NPtCl wag
317	361	351	331	$PtCl_2$ asym. stretch
323	371	361	339	$PtCl_2$ sym. stretch
508	467	448	477	PtN_2 asym. stretch
524	479	459	492	PtN_2 sym. stretch
724	696	697	751	NH_3 rock
789	714	716	798	NH_3 rock
811	728	726	795	NH_3 rock
824	762	758	810	NH_3 rock
1286	1236	1216	1282	NH_3 rock, PtN_2 sym. stretch[e]
1295	1225	1214	1268	NH_3 sym. bending
1316	1384	1387	1279	NH_3 sym. bending
1537	1606	1606	1527	NH_3 asym. bending
1601	1616	1619	1583	NH_3 rock[e]
1648	1624	1627	1640	NH_3 asym. bending
3211	3155	3158	3214	NH_3 asym. bending[e]
3287	3242	3248	3296	NH_3 asym. stretch
3309	3335	3340	3298	NH_3 asym. stretch
MAD[f]	41	45	15	
max. neg.[g]	−68	−71	−26	
max. pos.[h]	83	86	37	

[a] From Ref. [7]: observed bands in Raman spectra. [b] The approximate description refers to vibrational normal modes of the cisplatin dimer. [c] Hybrid force field; see the SI. [d] Hybrid force field; see the SI. [e] Combination band. [f] Mean absolute deviation. [g] Maximum negative difference. [h] Maximum positive difference.

the experimental value, while the N−H bond involved in the intermolecular interaction lengthens from about 1.01 to 1.03 Å, thus halving the difference with respect to experiment. Also for bond angles the agreement is improved. While quantitative description can be achieved by considering a larger system, the dimer is clearly a cost-effective model for interpreting the experimental results. As a model for describing the intermolecular interactions ruling the crystal structure it is also effective in the simulation of the vibrational spectrum of the solid compound. In fact, by making use of a hybrid B2PLYP/B3PW91 anharmonic force field, the Raman spectra are now reproduced with a mean absolute deviation of 15 cm^{-1} (Table 2).

Summarizing, a model capable of quantitatively describing and interpreting the structural and vibrational properties of solid cisplatin can be obtained by adopting a dimer extracted from the crystal structure. This approach is able to capture the relevant physicochemical features, while being computationally affordable for routine applications. More generally, these results confirm that only a physically based model can provide reliable insights into the properties of molecular systems. A corollary of this statement is that: benchmarking is instrumental for the development of computational approaches, but must be carried out judiciously to avoid misleading results. In particular, properties computed for isolated molecules should be benchmarked against experimental data measured in the gas phase, which are not at all straightforwardly obtained for compounds containing heavy metals. When this is not possible (e.g. cisplatin), the performance evaluation of computational methods should be based on high-accuracy calculations (i.e., composite/hybrid schemes) instead of inappropriate experimental data. The reader is referred to the SI for the DFT functionals applied to calculate the spectroscopic properties of cisplatin.

Experimental Section

DFT computations were performed using the Gaussian suite of programs.[18] MP2 and CCSD(T) calculations were carried out with the CFOUR software.[19] All computational details are given in the SI.

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Conflict of interest

The authors declare no conflict of interest.

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