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Hydration of platinum(II) complexes: a molecular mechanics study using atom-based force-field parameters

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Abstract. This work is related to the interaction of water with two platinum(II) complexes, $[Pt(NH_3)_4]^{2+}$ (denoted 1) and *trans*-$[Pt(OH)_2(NH_3)_2]$ (denoted 2). We have considered two approaches of a water molecule to complexes 1 and 2 along the *z*-axis normal to the platinum(II) coordination plane: approach I, with the water oxygen oriented towards Pt, and approach II, with one water hydrogen directed towards Pt. Calculations have been performed within a molecular mechanics method based upon the interaction potentials proposed earlier by Claverie et al. and subsequently adjusted to results obtained with symmetry – adapted perturbational theory as well as with supermolecule (up to second-order Møller–Plesset, MP2) methods. We discuss some possible simplifications of the potentials mentioned. The results relative to the hydration of Pt complexes 1 and 2 following approach I or II are discussed and compared to recent (MP2) ab initio energy–distance curves that we have recently determined. The MP2 calculations have shown that besides exchange–repulsion contributions, which are very similar in all hydrated complexes, approach I is mainly governed by electrostatics, whereas for approach II both electrostatic and dispersion contributions are important.

Key words: Platinum complexes – Molecular mechanics – Ab initio second-order Møller–Plesset

1 Introduction

The scope of our activity during the last decade has consisted in improving the molecular mechanics method proposed earlier by Claverie [1] and later revised by adjustment of symmetry-adapted perturbation theory (SAPT) calculations [2, 3]. Tests on several hydrogen-bonded and van der Waals systems against ab initio results obtained within the SAPT framework [4–8] and with supermolecule (up to second-order Møller–Plesset, MP2) calculations [9, 10] have shown good agreement between empirical and ab initio energy curves. More recently we have been interested in platinum(II) complexes which represent a topic of current interest, since Cisplatin, *cis*-diamminedichloroplatinum(II), is one of today's prominent antitumor drugs [11]. The finding that DNA is the crucial biological target of the platinum(II) drugs has prompted a number of structural studies [12]. Modelling of platinum–DNA adducts has been hampered by the lack of reliable force-field parameters [13–15]. Because of the size of systems to be treated in this case, it appeared interesting to derive a simplified version of the interaction potential proposed by Claverie et al. As a benchmark, we have studied the interaction between a water molecule and either of two platinum(II) complexes, $[Pt(NH_3)_4]^{2+}$ (denoted 1) and $[Pt(OH)_2(NH_3)_2]$ (denoted 2). This study has been prompted by recent (MP2) ab initio results [16] concerning the hydration of complexes 1 and 2 following two approaches of a water molecule. The major interest in these calculations resides in the determination of the main factors governing the interaction energy.

In this article we present results obtained within the methodology developed by Claverie et al. (summarized in Sect. 2.1), in which some simplifications were introduced, as described in Sect. 2.2. After a brief account of the computational details (Sect. 2.3), we discuss our results in Sect. 3 and correlate them with those from the ab initio calculations.

2 Method

2.1 Intermolecular interaction potential

Our molecular mechanics approach resides in the simple assumption that the interaction energy between two subsystems A and B may be decomposed into

1. A non-additive mutual induction energy (E_I) involving the induction of molecule A by the electric field of B and vice versa.
2. A sum (E_{ij}) of pair energies arising from pairs of atoms *i* and *j* respectively, belonging to A and B.

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$$E_{\text{int}} = E_{\text{I}} + \sum_{i=1}^{N_{\text{A}}} \sum_{j=1}^{N_{\text{B}}} E_{ij} \ , \tag{1}$$

where N_{A} and N_{B} are the number of atoms of molecules A and B, respectively.

The calculation of the induction energy involves calculation (by the classical formulae of electrostatics) of the total field created by molecule B on atoms i of molecule A and evaluation of the atomic polarisability obtained by sharing bond polarisabilities taken from Le Fèvre [17] between atoms forming the bond; the partitioning device is described in Refs. [1, 18, 19].

The total pair contribution, E_{ij}, between atoms i and j is given by

$$E_{ij} = E_{\text{el}}(ij) + E_{\text{p}}(ij) + E_{\text{rep}}(ij) + E_{\text{disp}}(ij) + E_{\text{disp-ex}}(ij) \ . \tag{2}$$

In the methodology proposed by Claverie et al., the different terms contributing to E_{ij} are represented by simple analytical functions (exponential or R^{-n} functions) depending on atomic distances, R_{ij}, between atoms i and j. Two sets of parameters are used:

1. Universal parameters denoted C_X and α_X, which characterize the nature of the interaction X (exchange–repulsion, dispersion, etc.) and are independent of atomic properties. They have been determined previously by adjusting the different contributions of interaction energy of simple dimers or rare-gas clusters on SAPT ab initio results [8].
2. Specific atomic parameters reflecting atomic quantities denoted C_{ij} and α_{ij}.

Here, we give a brief description of all formulae established by Claverie et al., all details being given in Ref. [1].

E_{el} is the long-range multicentre multipolar classical electrostatic contribution and E_{p} is the (short-range) penetration contribution, which is calculated as follows:

$$E_{\text{p}}(ij) = -C_{\text{p}} C_{ij} R_{ij}^{-1} \exp(-\alpha_{\text{p}} \alpha_{ij} R_{ij}) \ . \tag{3}$$

It has to be noted that the sum $E_{\text{el}} + E_{\text{p}}$ represents the Coulomb energy calculated within the Morokuma decomposition [20] of the Hartree–Fock (HF) energy (for more details see Ref. [1] and references therein).

E_{rep} is the exchange–repulsion energy:

$$E_{\text{rep}}(ij) = C_{\text{rep}} C_{ij} \exp(-\alpha_{\text{rep}} \alpha_{ij} R_{ij}) \ . \tag{4}$$

The atomic parameters C_{ij} appearing in Eqs. (3) and (4) are calculated from

$$C_{ij} = k_i k_j \left(\frac{1 - q_i^{\text{pop}}}{N_{\text{val}}^i} \right) \left(\frac{1 - q_j^{\text{pop}}}{N_{\text{val}}^j} \right) \ , \tag{5}$$

with q_i^{pop} and q_j^{pop} being the Mulliken populations of atoms i and j and N_{val}^i and N_{val}^j corresponding to the respective numbers of valence electrons. The ratio $q_i^{\text{pop}}/N_{\text{val}}^i$ accounts for the effect of the atomic electron population on both the exchange–repulsion and the penetration contributions [1].

The parameters k_i and k_j have been determined so as to reproduce the energy minima for a number of small systems of interacting molecules [18, 19].

The atomic parameters α_{ij} are calculated from

$$\alpha_{ij} = (2R_{\text{w}i} 2R_{\text{w}j})^{-1/2} \ , \tag{6}$$

with $R_{\text{w}i}$ and $R_{\text{w}j}$ being the van der Waals radii of atoms i and j.

$E_{\text{disp}}(ij)$ is the dispersion energy calculated beyond the R^{-6} term as

$$E_{\text{disp}}^{(2)}(ij) = -\sum_{m=6,8,10} C_{\text{disp}}^m C_{ij}^m R_{ij}^{-m} \ . \tag{7}$$

The atomic parameters C_{ij}^m are calculated as

$$C_{ij}^m = k_i k_j (2R_{\text{w}i} 2R_{\text{w}j})^{m/2} \ . \tag{8}$$

$E_{\text{disp-ex}}(ij)$ is the second-order exchange counterpart of the dispersion contribution:

$$E_{\text{disp-ex}}(ij) = C_{\text{disp-ex}} C_{ij} \exp(-\alpha_{\text{disp-ex}} \alpha_{ij} R_{ij}) \ , \tag{9}$$

with C_{ij} and α_{ij}, respectively, as in Eqs. (5) and (6).

The basic idea underlying this empirical potential is to use as much as possible atomic parameters reflecting specific physical properties. The principal adjustment to an ab initio energy–distance curve consists in treating the parameters C_{rep} and C_{disp}^m as functions of the interatomic distance. The variation of C_{rep} with R_{ij} accounts for the charge-transfer contribution, while the variation of C_{disp}^m reflects the fact that as R_{ij} approaches zero, the dispersion contribution does not tend to infinity (as any function R^{-m}) but converges towards a constant value. All these theoretical considerations go beyond the scope of this work and may be found in Refs. [1, 18, 19].

2.2 *Simplifications of the interaction potential*

Our main objective in this work was to develop an interaction potential reproducing at best the MP2 intermolecular energy curves which could be used in molecular mechanics packages. Thus, we simplified the interaction potential of Claverie et al. [1, 4–8] in the following way:

1. The induction contribution has been neglected. This appears justified, since according to our preliminary calculations, it contributes, at the energy minimum, less than 5% of the total intermolecular interaction energy.
2. The multicentre (atoms plus middle of bond) multipolar (up to quadrupoles) expansion typically used in the electrostatic calculations has been replaced by atomic monopoles.
3. The Dispersion (Eq. 7) has been calculated using only the R_{ij}^{-6} component. The coefficients C_{disp}^6 have been optimized so as to reproduce the interaction energies for rare-gas dimers and hydrogen-bonded dimers of small molecules.

We have considered the C_{rep} and C_{disp}^6 parameters as constants. All our universal and specific parameters are listed in Table 1.

2.3 *Computational details*

In the same way as in Ref. [16], we have considered two approaches of a water molecule towards the platinum(II) complexes 1 and 2. In

Table 1. Universal parameters C_X and α_X (X = p, disp, disp–ex, rep) and atomic parameters k_i and $R_{\text{w}i}$ for atoms i used in the Dinter potential. Merz–Kollman charges: $H_1(N)$ in plane (cf. Fig. 1); $H_2(N)$ out of plane (cf. Fig. 1)

Universal parameters

C_{rep}	C_{p}	C_{disp}^6	$C_{\text{disp-ex}}$	α_{rep}	α_{p}	$\alpha_{\text{disp-ex}}$
10^5	5700	0.19	471.25	12.35	13.10	9.35

Atomic parameters

i	Pt	N	O	H
k_i	1.60	1.18	1.36	1.00
$R_{\text{w}i}$	2.20	1.60	1.50	1.20

Merz–Kollman charges

	Pt	N	$H_1(N)$ $H_2(N)$	O	H(O)
1	0.552	−0.985	0.443		
			0.452		
2	0.382	−1.075	0.497		
			0.424	−0.854	0.392
H_2O				−0.722	0.361

the two cases, the water molecule moves along the z-axis normal to the platinum(II) coordination plane. In approach I (Fig. 1a), the water oxygen is oriented towards Pt, leading to two hydrated complexes denoted I/1 and I/2, indicating the involment of complex 1 or complex 2. In approach II (Fig. 1b) one water hydrogen is directed towards Pt, leading to the hydrated complexes II/1 and II/2. Calculations of the interaction energy, E_{int}, (and its components) were performed for several distances ($R_{\mathrm{Pt-O}}$) between Pt and the water oxygen using the program Dinter [21], in which we introduced the simplifications described in Sect. 2.2.

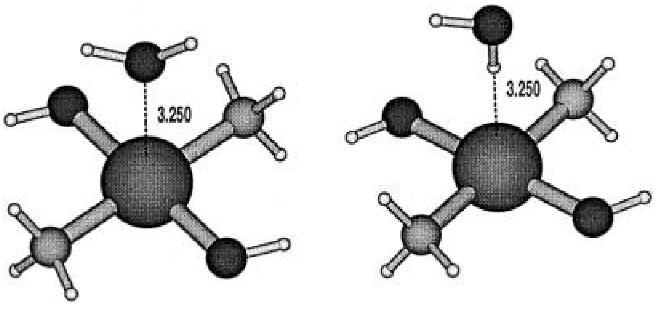

Fig. 1a, b. Two approaches between Pt(II) and H_2O examplified for complex 2 **a** Approach I, **b** approach II

In, our calculations we used

1. The geometries of water and Pt complexes 1 and 2 recently optimized [16] at the MP2 level using the program Gaussian94 [22], with the Dolg–Pélissier pseudopotential/pseudoorbital basis set for Pt [23] and the 6-311++G(2p,2d) all-electrons basis set for N, O and H atoms. The intrinsic geometries of 1, 2 and water remain unchanged in the different hydrated complexes since it has been shown that at the MP2 level the relaxation of systems 1, 2 and H_2O in complexes I and II is negligible.

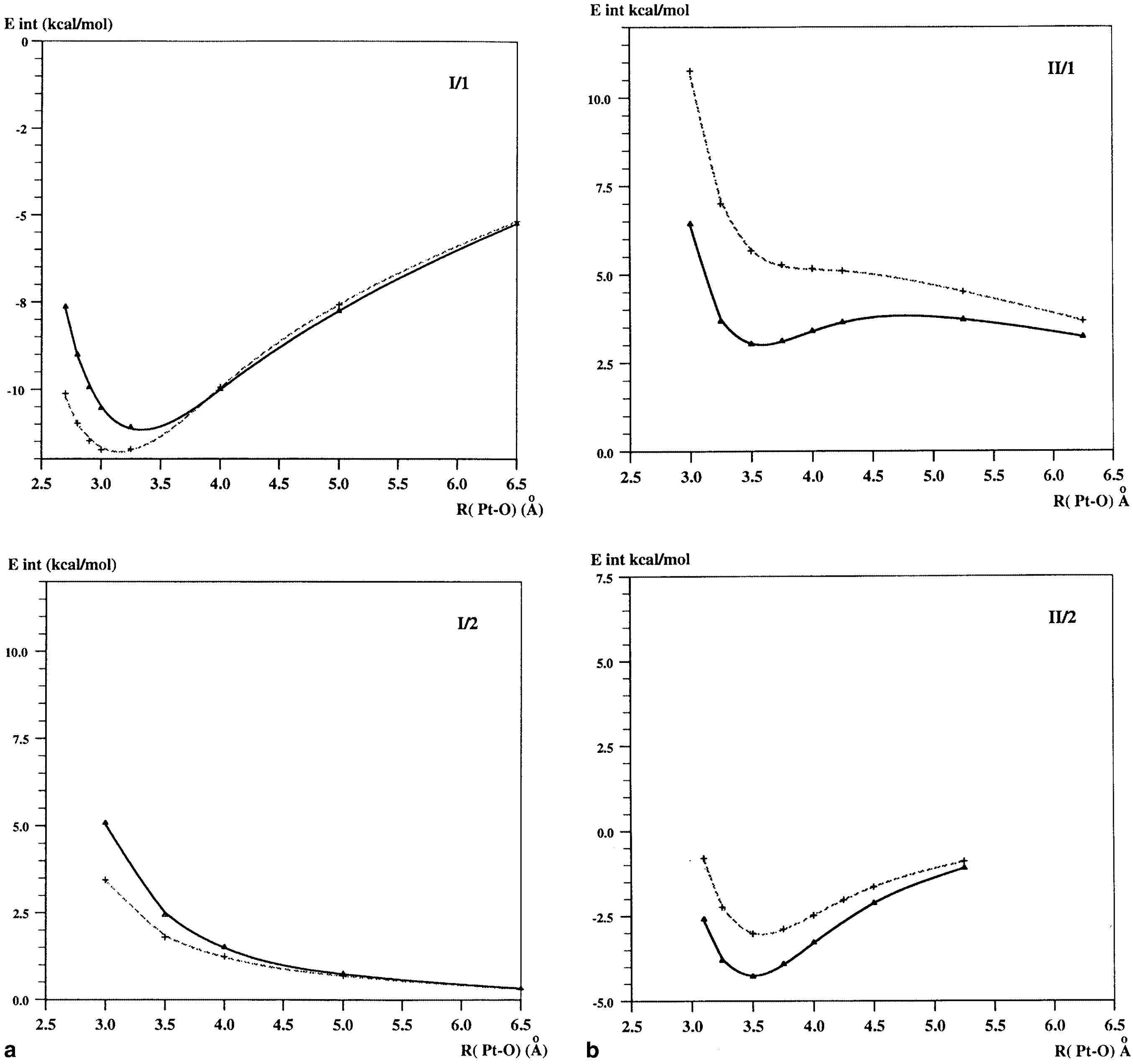

Fig. 2a, b. Interaction of water with Pt(II) complexes. E_{int}(Dinter) (×); E_{int}(MP2) (△)

2. The atomic charges of each isolated subsystem determined from fits to the MP2 electrostatic potential following the Merz–Kollman [24] routine implemented in Gaussian94. These charges are listed in Table 1.

3 Results and discussion

We first present for each of the four hydrated complexes the E_{int} profiles as a function of $R_{\text{Pt-O}}$ calculated within the Dinter framework and at the MP2 level (Fig. 2).

The results obtained with the two methods indicate that

1. The complexes I/2 and II/1 are unstable, with E_{int} being positive at any distance $R_{\text{Pt-O}}$.
2. The interactions I/1 and II/2 lead to stable states with the minimum interaction energies (E_{min}) at the corresponding distances (R_{min}) given in Table 2. The different contributions to the intermolecular energy at the minimum distance of the two stable complexes are given in Table 3.

An analysis of the different contributions to E_{int} calculated within the Dinter framework has shown that interaction I/1, where the negatively polarized water oxygen is oriented towards the positively charged platinum(II) complex, is obviously governed by an electrostatic contribution, whereas for II/2 the dispersion component dominates since the negative electrostatic component is counterbalanced by the positive repulsion one. The interaction II/2 resembles a hydrogen bond with the Pt atom acting as a proton acceptor. That a d^8 metal ion can indeed act as a hydrogen-bond acceptor has been demonstrated previously [25–27], but in all instances the platinum(II) complex was negatively charged and the interaction was thought to be mainly of electrostatic origin. Our calculations indicate that even neutral platinum(II) complexes may be hydrogen-bonded, thanks to the strong dispersion component of the interaction energy.

Figure 2 and Table 2 show that whereas the agreement between E_{int}(Dinter) and E_{int}(MP2) is very good for approach I, the E_{int}(MP2) curves are significantly lower for approach II over the whole range of $R_{\text{Pt-O}}$. In order to identify the origin of this different behaviour, we compared for the complexes I/1 and II/2 the following components:

Table 2. Characteristics of the stable complexes I/1 and II/2. R_{min} is the distance $R_{\text{Pt-O}}$ at the energy minimum E_{min}

	I/1		II/2	
	Dinter	MP2	Dinter	MP2
R_{min} (Å)	3.12	3.25	3.50	3.50
E_{min} (kcal/mol)	−11.8	−11.1	−3.0	−4.3

Table 3. Intermolecular energies and their components for the complexes I/1 and II/2 at the MP2 energy minima

	$R_{\text{Pt-O}}$	E_{el}	E_{rep}	E_{disp}	$E_{\text{disp-ex}}$	E	E_{tot}
I/1	3.25	−10.82	1.04	−2.00	0.16	−0.09	−11.8
II/2	3.5	−2.10	2.47	−3.15	0.28	−0.52	−3.0

1. The sum $E^{(1)} = E_{\text{el}} + E_{\text{p}} + E_{\text{rep}}$ (calculated within the Dinter framework) with the ab-initio E_{int} (HF) energy. Following Morokuma [20 and references therein], E_{int}(HF) corresponds to $E^{(1)} + E_{\text{ind}}$; since there are indications that E_{ind} is relatively insignificant in the systems investigated here (Sect. 2.2), $E^{(1)}$ should roughly reproduce the E_{int}(HF) curves.
2. The sum $E_{\text{dispT}} = E_{\text{disp}} + E_{\text{disp-ex}}$ (determined with the Dinter program) with the ab initio estimate of the correlation energy $E_{\text{corr}} = E_{\text{int}}(\text{MP2}) - E_{\text{int}}(\text{HF})$.

Figure 3 shows that

1. In interaction I/1, the apparent agreement between the E_{int}(Dinter) and E_{int}(MP2) curves results from a

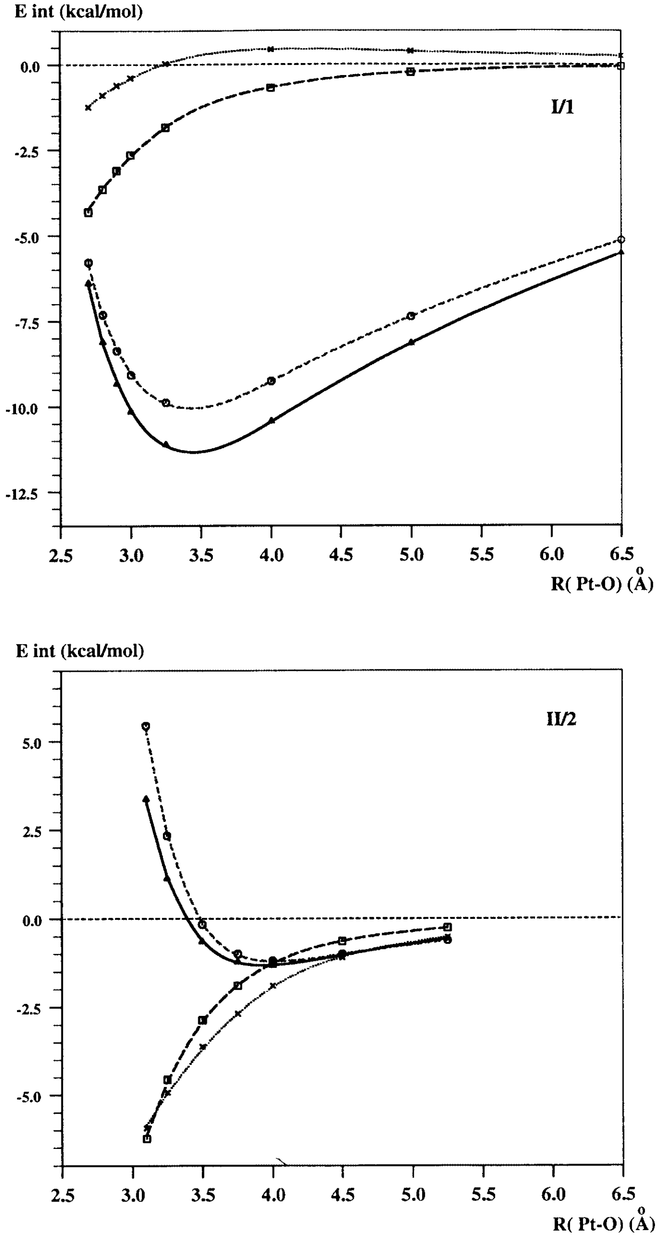

Fig. 3. Interaction of water with Pt(II) complexes. Evolution of the different contributions to E_{int}(Dinter) and E_{int}(MP2) as a function of $R_{\text{Pt-O}}$. E_{dispT} (□); E_{corr} (×); $E^{(1)}$ (○); $E_{(\text{HF})}$ (△)

compensation of small discrepancies between $E^{(1)}$ versus $E_{\mathrm{int}}(\mathrm{HF})$ (slight underestimation of $E^{(1)}$) and E_{dispT} versus E_{corr} (slight overestimation of E_{dispT}).

2. In interaction II/2, both $E^{(1)}$ and E_{dispT} are slightly underestimated with respect to their ab initio counterparts.

Finally, Fig. 3 indicates that the comparison of E_{dispT} with E_{corr} is not completely straightforward. In fact, it has been shown [28 and references therein] that the MP2 correction to the HF energy includes besides the dispersion contribution and its exchange counterpart, intramolecular correlation effects (positive) and ionic contributions (negative) which are very important in the hydrogen-bonded water dimer [29]. There is apparently a very subtle balance, depending on the specific nature of the interaction (ionic or hydrogen bond), between the positive and negative terms constituting E_{corr}.

4 Conclusion

The results presented here are very encouraging since they demonstrate a fairly good performance of our simplified potential derived from the methodology of Claverie et al. The empirical energy curves reproduce correctly the behaviour of the $E_{\mathrm{int}}(\mathrm{MP2})$ curves for all four approaches studied here, which encompass both classical ligation (approach I) and hydrogen bonding (approach II) and involve a charged (1) as well as an uncharged (2) platinum complex, and also show quite satisfactory quantitative agreement. It would be interesting to go beyond the present simplifications of the interaction potential and to replace, for instance, some of the exponential functions with R^{-n} terms. The purpose of such modifications is to render our potential compatible with current molecular mechanics packages. In addition, we shall try to obtain a deeper insight into the nature of the correlation effects, which obviously significantly contribute to the O—H...Pt(II) hydrogen-bond-like interaction (II) using the local MP2 partitioning scheme, for instance.

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