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## Monoligand Zn(II) Complexes: Ab Initio Benchmark Calculations and Comparison with Density Functional Theory Methodologies

Víctor M. Rayón,<sup>\*,†</sup> Haydee Valdés,<sup>‡</sup> Natalia Díaz,<sup>§</sup> and Dimas Suárez<sup>\*,§</sup>

*Departamento de Química Física y Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47005 Valladolid, Spain, Center for Biomolecules and Complex Molecular Systems, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 16610 Prague 6, Czech Republic, and Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, 33007 Oviedo, Spain*

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**Abstract:** A systematic theoretical study on several models of Zn(II) complexes has been carried out employing both ab initio correlated wave function and density functional methods. The performance of five different functionals namely PW91, PBE, B3LYP, MPWLYP1M, and TPSS in the prediction of metal–ligand bond distances, binding energies, and proton affinities has been assessed comparing the results to those obtained with the MP2 and CCSD(T) wave function methodologies. Several basis sets ranging from double- $\zeta$  up to quintuple- $\zeta$  quality have been used, including the recently developed all-electron correlation consistent basis sets for zinc. It is shown that all the tested functionals overestimate both the metal–ligand bond distances and the binding energies, being that the B3LYP and TPSS functionals are the ones that perform the best. An analysis of the metal–ligand interaction energy shows that induction and charge-transfer effects play a prominent role in the bonding of these systems, even for those complexes with the less polarizable ligands. This finding highlights the importance of a correct description of the polarization of the monomers' charge densities by any theoretical method which aims to be applied to the study of Zn(II) complexes.

### Introduction

Zinc, following iron, is the second-most abundant transition metal in biology and plays a prominent role in many structural and reactive biochemical processes.<sup>1</sup> It is present in more than 120 enzymes involved in the metabolism of nucleic acids, proteins, and carbohydrates. A combination of different factors, flexible coordination geometry, lack of redox activity, intermediate polarizability, and borderline hard–soft character, makes divalent zinc, Zn(II), capable of

satisfactorily coordinating with the broad spectrum of “hard” and “soft” ligands present in metalloenzymes. Thus, an accurate and well-balanced theoretical description of the ligand binding ability and hydration of Zn(II) ions is required in order to increase our understanding of zinc enzymology using the tools of computational quantum chemistry.

In principle, ab initio quantum mechanical (QM) methodologies provide the most accurate results, specially if coupled-cluster (CC) methods<sup>2</sup> are combined with correlation-consistent basis sets, which allow the systematic extension of one-particle basis set calculations of molecular properties toward the complete basis set (CBS) limit.<sup>3,4</sup> Until recently, accurate ab initio calculations with correlation consistent basis sets were feasible only for main group elements. Fortunately, a similar strategy is now possible for

\* Corresponding author fax: 34-983-423013; e-mail: vmrr@qf.uva.es (V.M.); fax: 34-985-103125; e-mail: dimas@uniovi.es (D.S.).

<sup>†</sup> Universidad de Valladolid.

<sup>‡</sup> Academy of Sciences of the Czech Republic.

<sup>§</sup> Universidad de Oviedo.

systems containing first-row transition metals thanks to Peterson and co-workers,<sup>5</sup> who developed a family of nonrelativistic and relativistic correlation basis sets for Sc–Zn that are expected to facilitate accurate and reliable calculations for metal complexes. However, the large computational cost of the highly correlated QM methods determines that their applicability is limited to small systems. This is not the case, however, of the density functional theory (DFT),<sup>6</sup> which offers quite accurate results for about the price of a Hartree–Fock (HF) calculation. For this reason, DFT has become the most popular correlated methodology for the study of biomolecules including zinc-enzymes.<sup>7,8</sup> Additionally, the development of linear scaling techniques<sup>9–11</sup> and tight-binding models<sup>12,13</sup> have pushed further the applicability of DFT. Since the design of the most commonly used density functionals is ultimately based on parametrization procedures, the question of the applicability of a given functional outside the scope for which it was developed is always a matter of concern. This is particularly true when dealing with systems containing transition metal atoms because most functionals have not been parametrized to fit data for inorganic or organometallic molecules.<sup>14</sup>

Several computational studies on zinc-containing biomolecules have been published<sup>15–18</sup> in which the application of DFT or semiempirical methodologies was assessed by performing ab initio calculations on small zinc complexes. In general the model systems considered in these studies were limited to what was required for the particular problem being analyzed as in a recent comparative study of semiempirical, ab initio, and DFT methods in Zn-biomimetic complexes,<sup>19</sup> which is focused on models of histidine side chains. In addition, most of the previous ab initio calculations were carried out using the HF and the second-order Møller-Plesset (MP2) methods with medium-sized basis sets. Nevertheless, either DFT or MP2 methods have been employed to provide reference data in order to derive optimum parameters for Zn(II) ions within the context of approximate methodologies like the semiempirical PM3 method,<sup>20</sup> the approximate tight binding DFT method,<sup>21</sup> and the molecular mechanics “Sum of Interactions Between Fragments Ab initio Computed” (SIBFA) method.<sup>22–24</sup>

The first goal of this study is to provide reliable high-level benchmark ab initio results for a set of 1:1 complexes in order to improve the energetic, structural, and electronic description of the ligand binding ability of Zn(II), which we think is a convenient first step for the assessment of DFT or parametrized methods. Thus, a set of 18 complexes modeling the typical Zn(II)-ligand interactions existing in living systems was characterized by means of high level ab initio calculations. The following ligands were chosen: water, formaldehyde, methanol, acetic acid, formamide, ammonia, methanimine, methylamine, 1H-imidazole, hydrogen sulfide, methanethiol, benzene, hydroxide, methanolate, acetate, imidazolate, hydrosulfide, and methanethiolate. Taking into account the prevalence of Zn(II) ions in biomolecular systems and the efficacy with which DFT methods can be applied to large systems, we also carried out a systematic analysis of the performance of DFT on Zn(II)-ligand interactions by comparing the results obtained from several density func-

tionals with those provided by the correlated wave function methods. A third goal of this study is the analysis of the nature of the metal–ligand bond in the Zn(II) complexes by means of an energy decomposition method. This provides information on the relative importance of the electrostatic, induction, and dispersive contributions to the interaction energy. Altogether our results could be particularly useful for the refinement of molecular mechanics force fields as well as comparison with other partitioning schemes used for the calibration of some molecular mechanics potentials.

## Computational Methods

**Ab Initio Calculations.** Ab initio benchmark calculations of the monoligand Zn(II) complexes examined in this work were carried out assuming the frozen core approximation in all the correlated calculations and using correlation consistent basis sets for valence electron correlation. The basis sets were constructed by employing the Dunning’s correlation consistent basis<sup>25,26</sup> on the main group atoms and the nonrelativistic all-electron basis from Balabanov and Peterson on zinc.<sup>5</sup>

Molecular geometries were optimized at the MP2/aug-cc-pVTZ level. Harmonic frequency calculations were performed to check whether the optimized geometries are local minima on the Potential Energy Surfaces (PES) and to obtain the Zero-Point Vibrational Energies (ZPVE). Electronic energies were refined by performing single-point calculations at the CCSD(T)/aug-cc-pVTZ level of theory (coupled cluster single and double excitation augmented with a noniterative treatment of triple excitations)<sup>27</sup> on the MP2/aug-cc-pVTZ optimized geometries. To estimate the effect of larger basis sets on the ab initio energies, single-point MP2/aug-cc-pVnZ ( $n=4, 5$ ) calculations were also performed on the MP2/aug-cc-pVTZ geometries.

As above-mentioned, the fundamental advantage in using a sequence of correlation consistent basis sets is the possibility of extrapolating the results toward the CBS limit and, thereby, removing basis set truncation errors. As proposed by Peterson and Puzzarini,<sup>28</sup> we used two extrapolation formulas

$$E_n = E_{\text{CBS}} + An^{-3} \quad (1)$$

$$E_n = E_{\text{CBS}} + An^{-(n-1)} + Be^{-(n-1)^2} \quad (2)$$

where  $n$  is the cardinal number of the basis set and  $E_{\text{CBS}}$ ,  $A$ , and  $B$  are fitting parameters, with  $E_{\text{CBS}}$  being the resulting estimate of the CBS limit. The average  $E_{\text{CBS}}$  value obtained from these two expressions has been reported as a conservative estimate of the actual CBS limit.<sup>5,28</sup> Herein, extrapolations using eqs 1 and 2 with the aug-cc-pVnZ ( $n=4, 5$ ) basis sets were used systematically on the MP2 correlation energies. The HF energies were not extrapolated, and the 5Z HF values were simply taken as the most accurate estimates of the HF limits.

In general, the calculation of the CCSD(T) CBS limit for all the complexes considered in this work is impractical. Then we decided to approximate the corresponding CCSD(T) CBS values by means of the following “composite” formula

$$E_{\text{CCSD(T) CBS}} \approx E_{\text{CCSD(T)/aug-cc-pVTZ}} + (E_{\text{MP2/CBS}} - E_{\text{MP2/aug-cc-pVTZ}}) \quad (3)$$

which basically summarizes the computational scheme adopted in this work for computing the high-level benchmark energies of the Zn(II) monoligand complexes.

The sensitivity of the computed binding energies and molecular properties with respect to basis set effects and/or the method employed for geometry optimization were assessed by carrying out further *ab initio* calculations for some of the Zn(II)-*L* complexes (*L*=OH<sup>−</sup>, H<sub>2</sub>O, HS<sup>−</sup>, and H<sub>2</sub>S). For these small complexes, molecular geometries were reoptimized at the CCSD/aug-cc-pVTZ level and binding energies were recomputed on the new geometries using the “composite” approximation in eq 3. Moreover, the CBS limit of the CCSD(T) energies was also estimated by means of single-point CCSD(T)/aug-cc-pVnZ (*n*=4, 5) calculations and using eqs 1 and 2. We also tested that the same CBS-limit is consistently attained from both electronic energies that included the Counterpoise (CP) correction for Basis Set Superposition Error (BSSE)<sup>29</sup> and uncorrected energies. Finally, the quality of the frozen core approximation was assessed by performing full electron correlation calculations with basis sets optimal for correlating the outer-core 3*s* and 3*p* electrons, which are generally needed to compute accurate dissociation energies involving 3*d* elements and second-row main group elements. In these calculations, we employed the aug-cc-pwVnZ basis set for Zn,<sup>5</sup> aug-cc-pV(*n*+*d*)Z for S,<sup>30</sup> and the standard aug-cc-pVnZ for H and O.

**Density Functional Calculations.** Five density functionals were selected for this study: two generalized gradient approximation (GGA) functionals, PW91<sup>31</sup> and PBE;<sup>32</sup> two hybrid functionals, B3LYP<sup>33–36</sup> and MPWLYP1M;<sup>37</sup> and one meta-GGA functional, TPSS.<sup>38</sup> The MPWLYP1M functional has been developed recently, and it consists of the modified Perdew–Wang exchange functional and the Lee–Yang–Parr (LYP) correlation functional. It has one parameter (the percentage of HF exchange) optimized for metals (though not specifically for Zn). Note that both PBE and TPSS are nonempirical functionals, whereas PW91, B3LYP, and MPWLYP1M contain explicitly empirical parameters. These functionals were used to fully optimize the geometries of the Zn(II) complexes and the isolated ligands followed by analytical frequency calculations. The default integration grid (75 radial shells and 302 angular points) was used for all the DFT calculations. For test purposes we also carried out optimizations and frequency calculations on the whole set of complexes using a larger (“UltraFine”) integration grid with 99 radial shells and 590 angular points. These test calculations have been performed using the PBE functional and the aug-cc-pVTZ basis set.

We employed different basis sets for the DFT calculations ranging from double- $\zeta$  up to triple- $\zeta$  valence quality: 6-31G(*d*), 6-31+G(*d*), 6-31+G(2*d*,*p*), 6-311+G(*d*), and aug-cc-pVTZ. The double- $\zeta$  sets consists of the Pople basis for main group atoms and first-row transition metals.<sup>39</sup> The first two selected sets include one set of *d*-type polarization functions on the main group atoms and one set of *f*-type polarization functions on Zn. The 6-31+G(2*d*,*p*) basis include two sets of *d*-type and *f*-type functions along with one set of *p*-type

functions on the hydrogen atoms. All the basis, except the smallest 6-31G(*d*), additionally include one set of *s*- and *p*-type diffuse functions on the main group atoms and one set of *s*- and *d*-type and two sets of *p*-type functions on Zn. Cartesian functions were used for the 6-31G Pople basis set. On the other hand, the 6-311+G(*d*) basis is constructed by employing the triple- $\zeta$  valence 6-311G<sup>40</sup> basis set for the main group atoms and the Wachters<sup>41</sup> and Hay<sup>42</sup> basis set for Zn with the scaling factors of Raghavachari and Trucks.<sup>43</sup> This basis includes 5 *d*-type and 7 *f*-type pure functions. For the sake of completeness, geometrical and energetic parameters were also obtained by means of the MP2 method combined with the 6-31G(*d*), 6-31+G(*d*), 6-31+G(2*d*,*p*), and 6-311+G(*d*) basis sets. Besides, the aug-cc-pVQZ basis set was used to check the basis set truncation error in the DFT calculations. This has been done on the whole set of complexes using the B3LYP and the TPSS functionals. Finally, we would like to remind the reader that the applicability of DFT to the study of molecular anions has been debated in the literature specially in the past decade. For a recent review we refer to the work of Rienstra-Kiracofe et al.<sup>44</sup> It is shown in this review that DFT, in the form of inexact functionals, in conjunction with basis sets of at least double- $\zeta$  quality including diffuse functions is applicable to anionic species. We therefore believe that the functionals and basis sets tested in this work are adequate for the study of Zn<sup>2+</sup> complexes with anionic ligands.

All of the calculations in this paper were performed with the Gaussian03 program package.<sup>45</sup> Finally, we would like to point out that we did not include solvent effects in our calculations since we are not aiming at reproducing the Zn(II) environment in biomolecular systems but rather to compare the performance of our tested functionals and basis sets.

**SAPT Analyses.** In order to analyze the nature of the bonding interactions in the Zn(II) complexes we used the Symmetry Adapted Perturbation Theory (SAPT) approach.<sup>46,47</sup> SAPT computes the interaction energy as a sum of physically meaningful contributions, namely, electrostatic, induction, dispersion, and exchange. If we group these contributions in terms arising at the noncorrelated and correlated levels we can write

$$E_{\text{int}}^{\text{HF}} = E_{\text{elst}}^{(10)} + E_{\text{exch}}^{(10)} + E_{\text{ind},r}^{(20)} + E_{\text{exch-ind},r}^{(20)} + \delta E_{\text{int}}^{\text{HF}} \quad (4)$$

$$E_{\text{int}}^{\text{corr}} = E_{\text{elst},r}^{(12)} + E_{\text{exch}}^{(11)} + E_{\text{exch}}^{(12)} + {}^tE_{\text{ind}}^{(22)} + {}^tE_{\text{exch-ind}}^{(22)} + E_{\text{disp}}^{(20)} + E_{\text{exch-disp}}^{(20)} \quad (5)$$

where  $E_{\text{int}}^{\text{HF}}$  represents the supermolecular (SP) HF interaction energy, and  $E_{\text{int}}^{\text{corr}}$  contains all the correlated contributions (up to second order, i.e., the so-called SAPT2 approach). The term  $\delta E_{\text{int}}^{\text{HF}}$  in eq 4 contains third and higher order (noncorrelated) induction and exchange-induction terms and is defined as the difference between the SAPT noncorrelated first- and second-order energy and the supermolecular HF interaction energy. We further point out that  $E_{\text{int}}^{\text{corr}}$  as defined in eq 5 is approximately equivalent to the supermolecular MP2 correlation energy.<sup>48</sup> All the contributions in eqs 4 and 5 have a clear physical interpretation:  $E_{\text{elst}}^{(10)} +$



$E_{\text{elst},r}^{(12)} = E_{\text{elst}}^{(1)}$  represents the electrostatic interaction of the charge densities of the unperturbed monomers,  $E_{\text{exch}}^{(10)} + E_{\text{exch}}^{(11)} + E_{\text{exch}}^{(12)} = E_{\text{exch}}^{(1)}$  takes into account the repulsion of the (unperturbed) charge densities of the monomers due to the Pauli exclusion principle,  $E_{\text{ind},r}^{(20)} + {}^tE_{\text{ind}}^{(22)} = E_{\text{ind}}^{(2)}$  collects the interactions of the permanent multipole moments of one monomer with the induced moments of the other,  $E_{\text{disp}}^{(20)} = E_{\text{disp}}^{(2)}$  represents the interaction of the instantaneous multipole moments of the monomers, and, finally,  $E_{\text{exch-ind},r}^{(20)} + {}^tE_{\text{exch-ind}}^{(22)} = E_{\text{exch-ind}}^{(2)}$  and  $E_{\text{exch-disp}}^{(20)} = E_{\text{exch-disp}}^{(2)}$  take into account the exchange effects associated with the induction and dispersion interactions, respectively. In this work we will group the SAPT components in two terms as follows:

$$E^{(1)} = E_{\text{elst}}^{(10)} + E_{\text{exch}}^{(10)} + E_{\text{elst},r}^{(12)} + E_{\text{exch}}^{(11)} + E_{\text{exch}}^{(12)} \quad (6)$$

$$E^{(2)} = E_{\text{ind},r}^{(20)} + E_{\text{exch-ind},r}^{(20)} + {}^tE_{\text{ind}}^{(22)} + {}^tE_{\text{exch-ind}}^{(22)} + E_{\text{disp}}^{(20)} + E_{\text{exch-disp}}^{(20)} \quad (7)$$

The first term,  $E^{(1)}$ , collects all contributions at first order with respect to the intermolecular interaction operator, whereas the second term collects all contributions at second order. We are interested in this partitioning because in this way we can separate those components arising from the interaction of the unperturbed fragments from those associated with the relaxation of the charge densities of the monomers (caused by the interaction with the partner). Thus,  $E^{(1)}$  represents the classical electrostatic interaction energy, whereas  $E^{(2)}$  collects all polarization and charge-transfer effects.

Finally, the SAPT interaction energy can be represented as

$$E_{\text{int}}(\text{SAPT}) = E^{(1)} + E^{(2)} + \delta E_{\text{int}}^{\text{HF}} \quad (8)$$

which should be roughly equivalent to the supermolecular MP2 (SP-MP2) interaction energy as commented before. For more details about this methodology see ref 49 and references therein. All SAPT calculations were performed with the SAPT2002 program.<sup>46</sup> We would finally like to remind the reader that the interaction energies are related to the bond dissociation energies ( $D_e$ ) by means of the deformation energies of the fragments, that is, the energy required to bring the fragments from their isolated geometry to the geometry they have in the complex, namely

$$-D_e = E_{\text{int}} + E_{\text{def}} \quad (9)$$

## Results and Discussion

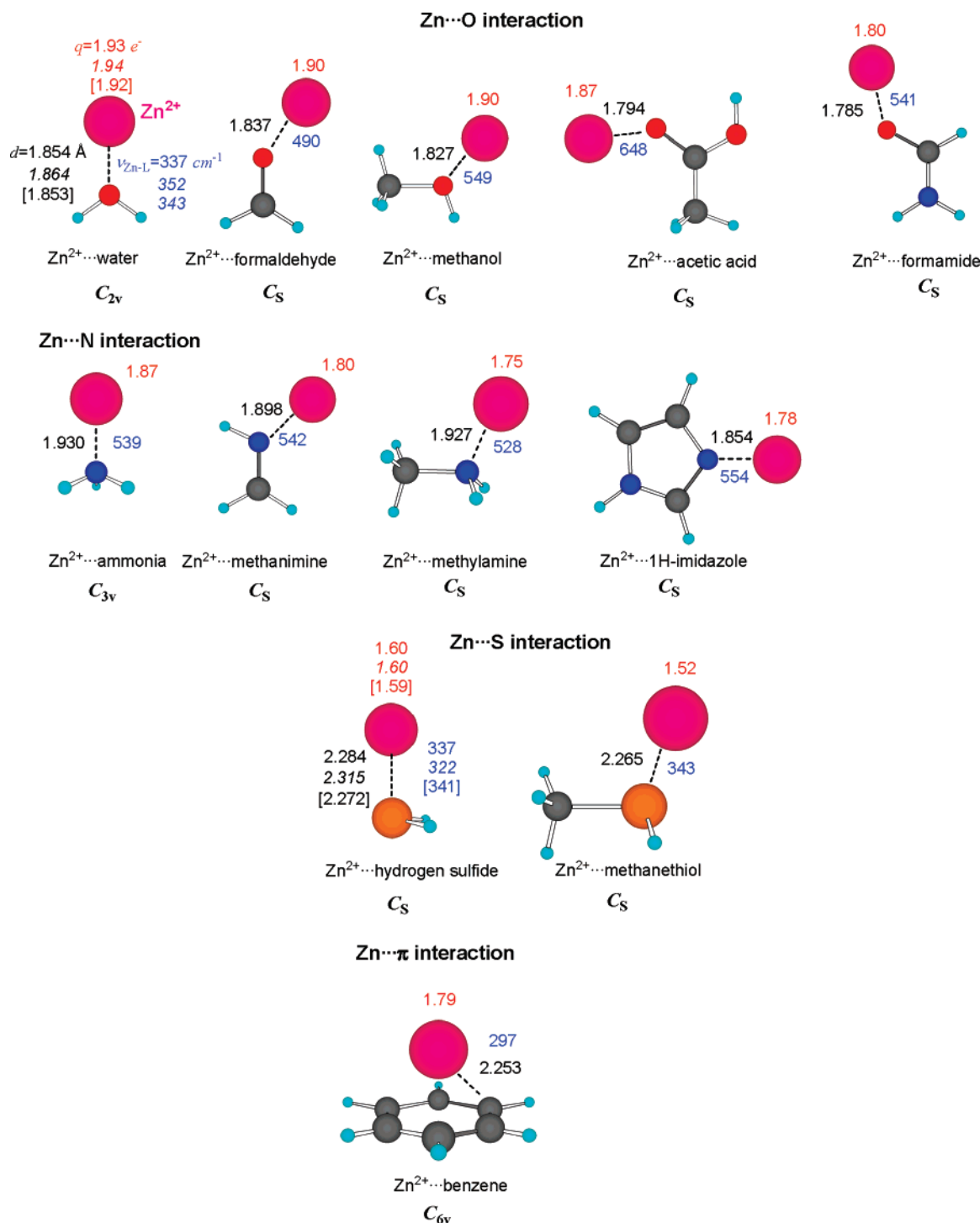
**Ab Initio Calculations.** Figures 1 and 2 show the optimized structures for the monoligand complexes formed between Zn(II) and the neutral ligands ( $L$  = water, ammonia, hydrogen sulfide, formaldehyde, methylimine, methanol, methylamine, methanethiol, acetic acid, formamide, imidazole, and benzene) and anionic ligands ( $L$  = hydroxide, hydrosulfide, methanolate, methanethiolate, acetate, and imidazolate), respectively. All the structures were characterized as energy minima on the MP2/aug-cc-pVTZ potential energy surface, excepting the  $[\text{Zn}(\text{imidazolate})]^+$  complex with  $C_s$

symmetry that corresponded to a transition structure. For each complex shown in Figures 1 and 2, the equilibrium Zn- $L$  distance involving the Zn atom and the donor atom(s) of the ligand, the Natural Population Analysis (NPA) charge<sup>50</sup> of the Zn atom, and the harmonic frequency of the stretching normal mode associated with the Zn- $L$  bond are also reported. As mentioned in the Methods section, the consistency of the computational scheme employed for computing the binding energies was tested in the case of the complexes of Zn(II) with water, hydrosulfide, hydroxide, and sulfide by using more elaborated computational schemes as well (see Table 1). We will analyze first these validation calculations, and then we will present the benchmark data for all the Zn(II) complexes.

**Validation Calculations.** To ensure that the benchmark calculations performed for the 18 Zn(II)-complexes are accurate and could replace missing experimental data, we report in Table 1 some test calculations that assess the adequacy of the various choices made in the computational scheme defined in eqs 1–3 (i.e., “composite” approximation, MP2 geometries, valence correlation, CBS extrapolation, ...). For example, by carrying out single-point CCSD(T)/aug-cc-pVnZ ( $n=4, 5$ ) calculations on the four test complexes, we found that the  $D_e$  values computed with the “composite” method are nearly identical ( $\sim \pm 0.10$  kcal/mol) to those obtained with the CCSD(T)/CBS method. We also found that the binding energies are rather insensitive to small changes on the equilibrium geometries: although the structures optimized at the CCSD/aug-cc-pVTZ level have slightly larger Zn-ligand distances by 0.01–0.03 Å than the MP2 structures, practically the same  $D_e$  values were obtained using the MP2/aug-cc-pVTZ and the CCSD/aug-cc-pVTZ optimized geometries (see Table 1). In addition, we see in Figure 1 that the NPA charges of the Zn atom computed from the MP2 and CCSD electronic densities match closely to each other ( $\pm 0.01 e^-$ ) and that the MP2 and CCSD harmonic stretching frequencies for the Zn-ligand bond are very similar.

Of particular interest can be to determine the relevance of core-valence correlation effects. The small Zn(II)- $L$  complexes and their ligands were reoptimized by carrying out full electron MP2 calculations with enlarged basis sets for explicitly including core-valence correlation effects. The resulting molecular geometries and the NPA charge of the Zn atom hardly differ from the frozen-core MP2 results. On the other hand, the changes in the “composite” binding energies,  $D_e$ , computed correlating all the electrons, with respect to the frozen core values are  $-1.11$ ,  $-0.96$ ,  $-1.25$ , and  $-1.81$  kcal/mol for  $L = \text{H}_2\text{O}$ ,  $\text{H}_2\text{S}$ ,  $\text{OH}^-$ , and  $\text{HS}^-$ , respectively. Thus, we estimate that core-valence correlation effects should range between 1 and 2 kcal/mol for the monoligand  $\text{Zn}^{2+}$  complexes. This relatively small influence of core-valence correlation could be related to the fact that binding between the Zn(II) cation and a ligand donor atom results in a small accumulation of charge in the interatomic region, that is, zinc-ligand bonds are essentially closed-shell interactions with only a partial covalent character.<sup>17</sup>

In order to assess now the reliability of the CBS extrapolation, we computed the change in the binding energies when going from MP2/aug-cc-pVQZ to MP2/aug-cc-pV5Z and

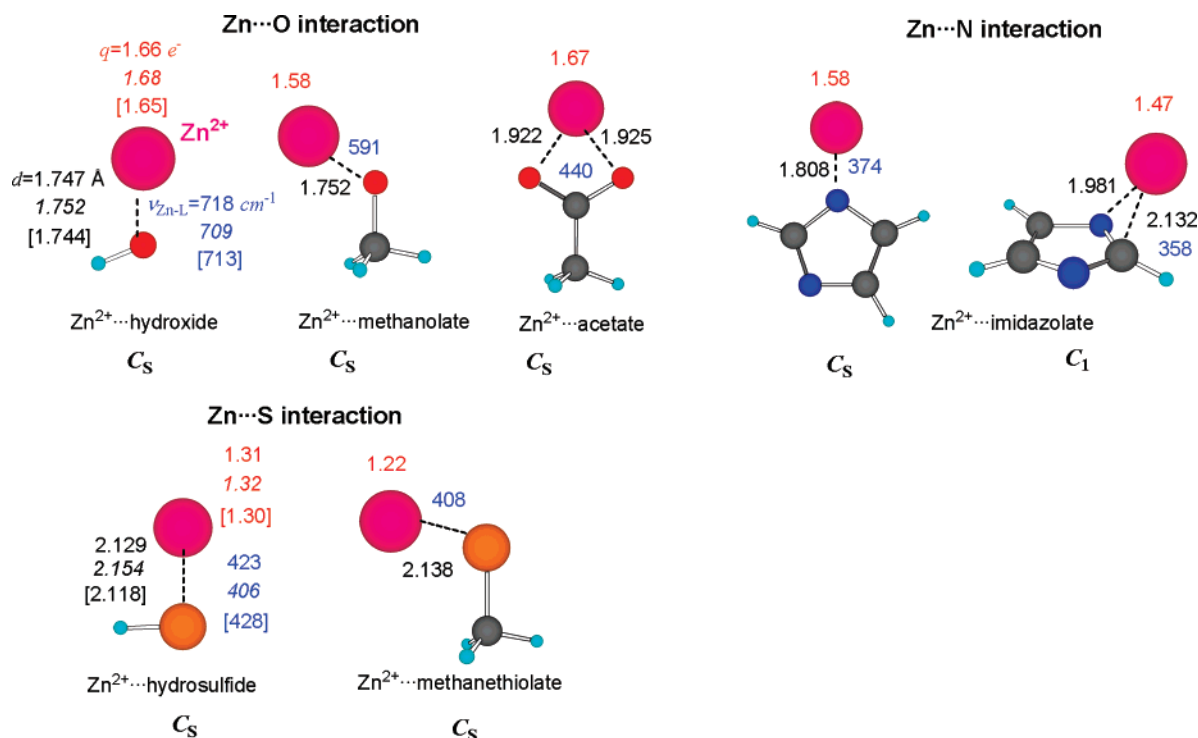


**Figure 1.** Geometrical arrangement of the studied Zn(II) complexes with neutral ligands along with the most important geometrical parameters as computed at the MP2/aug-cc-pVTZ level of theory. For water and hydrogen sulfide, CCSD/aug-cc-pVTZ and full electron MP2 data are given in italics and in squared brackets, respectively. All distances are given in angstroms.

from MP2/aug-cc-pV5Z to MP2/CBS for the set of four selected complexes. The differences are smaller than 0.50 kcal/mol (the average is 0.27 kcal/mol for the set of both neutral and anionic ligands) and 0.21 kcal/mol (average: 0.16 kcal/mol), respectively. When the core-valence correlation is taken into account, these differences are smaller than 0.73 kcal/mol and 0.13 kcal/mol, respectively. We also estimated for these four systems the CBS limit extrapolating the CP-corrected binding energies. The final “composite”  $D_e$  values are within 0.17 kcal/mol of the uncorrected ones.

Overall, we conclude that the larger factor that could affect the benchmark “composite” energies are the core-valence correlation effects which, as commented before, should be within 1–2 kcal/mol for these systems. Therefore, we believe that limiting to valence correlation effects in the benchmark calculations represents a reasonable compromise between cost and accuracy, which should be close to chemical accuracy ( $\sim 1$  kcal/mol).

**Ab Initio Benchmark Data.** Table 2 contains the ab initio binding energies for the full set of Zn(II) complexes that



**Figure 2.** Geometrical arrangement of the studied Zn(II) complexes with anionic ligands along with the most important geometrical parameters as computed at the MP2/aug-cc-pVTZ level of theory. For hydroxide and sulfide, CCSD/aug-cc-pVTZ and full electron MP2 data are given in italics and in squared brackets, respectively. All distances are given in angstroms.

**Table 1.** Binding Energies (in kcal/mol) for the Small Zn(II) Complexes Obtained with Different Ab Initio Computational Protocols

ligand	MP2/aug-cc-pVTZ	CCSD(T)/aug-cc-pVTZ	MP2/CBS <sup>a</sup>	composite method <sup>b</sup>	CCSD(T)/CBS <sup>a</sup>
Frozen Core, MP2/aug-cc-pVTZ Geometries					
water	-98.02	-97.43	-98.78	-98.19	-98.27
hydrogen sulfide	-113.05	-112.36	-114.29	-113.59	-113.55
hydroxide	-424.21	-425.16	-425.37	-426.32	-426.36
hydrosulfide	-408.48	-407.92	-410.44	-409.87	-409.68
Frozen Core, MP2/aug-cc-pVTZ Geometries, CP-Corrected Energies					
water	-97.41	-96.84	-98.67	-98.10	
hydrogen sulfide	-112.41	-111.78	-114.15	-113.52	
hydroxide	-423.08	-424.05	-425.19	-426.15	
hydrosulfide	-407.37	-406.89	-410.20	-409.73	
Frozen Core, CCSD/aug-cc-pVTZ Geometries					
water	-98.00	-97.45	-98.73	-98.18	-98.26
hydrogen sulfide	-112.95	-112.44	-114.11	-113.60	-113.55
hydroxide	-424.15	-425.19	-425.30	-426.34	-426.38
hydrosulfide	-408.37	-408.03	-410.23	-409.89	-409.69
Full Electron, MP2 Geometries, aug-cc-pwVnZ for Zn, aug-cc-pV(n+d)Z for S					
water	-98.98	-98.08	-100.21	-99.30	-
hydrogen sulfide	-115.26	-113.79	-116.01	-114.55	-
hydroxide	-426.32	-426.46	-427.43	-427.57	-
hydrosulfide	-412.16	-410.27	-413.57	-411.68	-

<sup>a</sup> Obtained from CBS extrapolation of the correlation energy based on eqs 1 and 2 and using the HF/aug-cc-pV5Z energies. <sup>b</sup> Using an additive combination of electronic energies.

are examined in this work. The “composite”  $D_e$  values in Table 2 provide the benchmark data. Nevertheless, the MP2/aug-cc-pVTZ level shows a good performance as compared with the “composite” energy calculations. In fact the computed binding energies using the MP2/aug-cc-pVTZ geometries are quite similar regardless of the correlated method (CCSD(T) vs MP2) or the basis set (see Table 2)

employed to perform the corresponding single-point calculations. With respect to the MP2/aug-cc-pVTZ energy values, inclusion of energy corrections due to higher correlated methods and larger basis sets cancel each other partially, so that the average difference between the MP2/aug-cc-pVTZ calculations and the more accurate “composite” energy values is only 0.7 kcal/mol for neutral ligands or 2.1 kcal/mol for

**Table 2.** Binding Energies (in kcal/mol) for the Zn(II) Complexes Optimized at the MP2/aug-cc-pVTZ Level Obtained with the MP2 and CCSD(T) Methods

ligand	MP2/ aug-cc- pVTZ $D_e$	CCSD(T)/ aug-cc- pVTZ $D_e$	MP2/ CBS <sup>a</sup> $D_e$	composite method <sup>b</sup> $D_e$	composite method <sup>c</sup> $D_0$
water	-98.02	-97.43	-98.78	-98.19	-96.56
ammonia	-129.08	-128.08	-129.81	-128.82	-126.11
hydrogen sulfide	-113.05	-112.36	-114.29	-113.59	-111.72
formaldehyde	-108.32	-108.62	-108.98	-109.28	-107.49
methanimine	-139.63	-138.56	-140.48	-139.42	-137.32
methanol	-116.35	-115.55	-116.83	-116.03	-115.26
methylamine	-143.50	-142.54	-144.01	-143.05	-141.10
methanethiol	-134.45	-133.95	-135.73	-135.22	-134.15
acetic acid	-132.94	-133.43	-133.61	-134.09	-133.28
formamide	-148.30	-148.76	-149.01	-149.48	-147.29
1H-imidazole	-172.87	-172.04	-173.55	-172.72	-171.34
benzene	-160.20	-157.20	-161.19	-158.19	-156.64
hydroxide	-424.21	-425.16	-425.37	-426.32	-424.14
hydrosulfide	-408.48	-407.92	-410.44	-409.87	-408.28
methanolate	-423.07	-423.46	-424.12	-424.52	-421.10
methanethiolate	-420.22	-419.73	-422.14	-421.66	-419.92
acetate	-413.31	-414.45	-414.81	-415.95	-413.97
imidazolate ( $C_S$ )	-379.09	-381.80	-380.19	-382.89	-381.93
imidazolate ( $C_1$ )	-386.96	-387.19	-384.82	-385.05	-383.98

<sup>a</sup> Obtained from CBS extrapolation of the MP2 correlation energy based on eqs 1 and 2 and using the HF/aug-cc-pV5Z energies.

<sup>b</sup> Using an additive combination of electronic energies (CCSD(T)/aug-cc-pVTZ+ MP2/CBS - MP2/aug-cc-pVTZ). <sup>c</sup> Using an additive combination of electronic energies and including MP2/aug-cc-pVTZ ZPVE energies

anionic ligands whose complexes have much larger binding energies. The largest differences arise in benzene and imidazolate ( $C_S$ ) that are within 3 kcal/mol, still in very good agreement. All these results suggest that predictions obtained at the MP2/aug-cc-pVTZ level for Zn(II) complexes should already be quite reliable. This is gratifying because both CCSD(T)/aug-cc-pVTZ and MP2/aug-cc-pVnZ ( $n=4, 5$ ) calculations are much more computationally demanding. We also note in passing that the MP2/aug-cc-pVTZ level has also been found to produce an accurate and balanced description of hydrogen-bonded and dispersion-bound complexes.<sup>51</sup>

For the neutral ligands, the optimized structures correspond to monodentate Zn(II) complexes that can be characterized by a single interatomic Zn-X distance of  $\sim 1.82, 1.90$ , and  $2.27 \text{ \AA}$  for  $X = O, N$ , and  $S$ , respectively. For a given type of donor atom, it turns out that the binding energy ( $D_e$ ) correlates well with the Zn-X distance (e.g., the linear correlation coefficient,  $r$ , between the Zn-X distances and the composite  $D_e$  values amounts to 0.987 and 0.909 for  $X = O$  and  $N$ , respectively). In the case of benzene, a typical cation- $\pi$  complex is formed in which the Zn(II) ion is equidistant with respect to the six C atoms. The metal-ligand bond in the complexes with neutral ligands implies a significant charge transfer within the  $0.07\text{--}0.48 e^-$  range according to the NPA charges. The amount of charge transfer, which depends on the electronegativity and hybridization of the donor X atom, is quite well correlated with the  $D_e$  energies ( $r \sim 0.90\text{--}0.94$ ), suggesting thus that the charge-transfer interaction plays an important role in the total

**Table 3.** Protonation Energies (PEs in kcal/mol) for Various Acid-Base Pairs Both in Their Isolated Form and in the Corresponding Zn(II) Complexes<sup>c</sup>

acid-base pair	MP2/ aug-cc- pVTZ	CCSD(T)/ aug-cc- pVTZ	MP2/ CBS <sup>a</sup>	composite method <sup>b</sup>
A/B				
H <sub>2</sub> O/OH <sup>-</sup>	-393.26	-397.15	-393.13	-397.02 (-389.01)
H <sub>2</sub> S/HS <sup>-</sup>	-353.60	-355.99	-353.38	-355.77 (-349.97)
CH <sub>3</sub> OH/CH <sub>3</sub> O <sup>-</sup>	-388.27	-391.13	-388.11	-390.98 (-381.09)
CH <sub>3</sub> SH/CH <sub>3</sub> S <sup>-</sup>	-360.25	-362.65	-360.18	-362.58 (-356.17)
CH <sub>3</sub> COOH/ CH <sub>3</sub> COO <sup>-</sup>	-352.13	-354.85	-351.90	-354.63 (-346.06)
1H-imidazol/ 1H-imida- zolate	-352.91	-356.78	-352.89	-356.76 (-348.01)
Zn-A/Zn-B				
H <sub>2</sub> O/OH <sup>-</sup>	-67.08	-69.42	-66.55	-68.89 (-61.43)
H <sub>2</sub> S/HS <sup>-</sup>	-58.17	-60.43	-57.23	-59.49 (-53.41)
CH <sub>3</sub> OH/CH <sub>3</sub> O <sup>-</sup>	-81.55	-83.23	-80.81	-82.49 (-75.25)
CH <sub>3</sub> SH/CH <sub>3</sub> S <sup>-</sup>	-74.48	-76.86	-73.76	-76.15 (-70.40)
CH <sub>3</sub> COOH/ CH <sub>3</sub> COO <sup>-</sup>	-71.76	-73.83	-70.70	-72.77 (-65.36)
1H-imidazol/ 1H-imida- zolate	-146.69	-147.03	-146.25	-146.59 (-137.42)

<sup>a</sup> Obtained from CBS extrapolation of the MP2 correlation energy based on eqs 1 and 2 and using the HF/aug-cc-pV5Z energies.

<sup>b</sup> Using an additive combination of electronic energies (CCSD(T)/aug-cc-pVTZ+ MP2/CBS - MP2/aug-cc-pVTZ). Values in parentheses include the MP2/aug-cc-pVTZ ZPVE energies. <sup>c</sup> Molecular geometries were obtained at the MP2/aug-cc-pVTZ level.

binding. It may be interesting to note that the frequency of the stretching motion of the Zn-X bond is uncorrelated with the strength of the metal-ligand bond expressed in terms of binding energies.

The strong interaction between the Zn(II) cation and the anionic ligands is reflected in the magnitude of the computed binding energies (from  $-420$  to  $-380$  kcal/mol), which is accompanied by a typical shortening of the Zn-X distances of  $\sim 0.10 \text{ \AA}$  with respect to the neutral ligands and an important charge transfer from ligand to Zn(II) ( $0.36\text{--}0.68 e^-$ ). The two complexes formed between Zn(II) and imidazolate deserve some specific comments. One of these complexes corresponds to a planar monodentate structure ( $C_S$  complex), which is characterized as a transition structure with an imaginary frequency of  $120 \text{ cm}^{-1}$  for an out-of-plane movement of the Zn-N bond. This transition structure leads to a true energy minimum ( $C_1$  symmetry), which corresponds to a bidentate Zn(II) complex that can be better described as an asymmetric  $\pi$ -complex between Zn(II) and one of the C=N double bonds. In spite of their quite dissimilar coordination geometry and electronic features, the  $C_S$  complex is only 2.05 kcal/mol above the  $C_1$  one.

Since the catalytic mode of action of many zinc-enzymes involves proton-transfer events to and from zinc-ligands (water molecules and amino acid side chains), we also derived the protonation energies (PE) of some of the ligands studied in this work at the different correlated levels of theory. According to the PE values reported in Table 3, the nature of the correlated method (CCSD(T) vs MP2) has a more pronounced effect ( $\sim 2$  kcal/mol) on the computed PEs than in the case of the Zn-L binding energies, whereas the



**Table 4.** Mean Signed Errors (MSE) and Standard Deviations (Å) in the Metal–Ligand Bond Distances of the Monoligand Zn(II) Complexes Studied in This Work with Respect to the MP2/aug-cc-pVTZ Reference Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G( <i>d</i> )	MSE	−0.017	−0.016	−0.010	−0.013	−0.018	−0.024
	SD	0.016	0.017	0.012	0.014	0.015	0.009
6-31+G( <i>d</i> )	MSE	0.032	0.034	0.029	0.032	0.027	−0.004
	SD	0.019	0.020	0.015	0.018	0.016	0.005
6-31+G(2 <i>d</i> , <i>p</i> )	MSE	0.036	0.038	0.034	0.037	0.030	0.005
	SD	0.020	0.020	0.015	0.019	0.016	0.004
6-311+G( <i>d</i> )	MSE	0.052	0.055	0.046	0.050	0.047	0.010
	SD	0.023	0.023	0.016	0.021	0.018	0.003
aug-cc-pVTZ	MSE	0.041	0.044	0.035	0.041	0.036	
	SD	0.018	0.019	0.017	0.018	0.015	

CBS limit of the MP2 PEs is very similar to the MP2/aug-cc-pVTZ values. When comparing the PEs of the isolated A/B pairs with those of their Zn-bound counterparts, we see that the Zn(II) cation decreases the PEs by 327.58, 296.56, 305.84, 285.77, 280.69, and 210.59 kcal/mol for the H<sub>2</sub>O/OH<sup>−</sup>, H<sub>2</sub>S/HS<sup>−</sup>, CH<sub>3</sub>OH/CH<sub>3</sub>O<sup>−</sup>, CH<sub>3</sub>SH/CH<sub>3</sub>S<sup>−</sup>, CH<sub>3</sub>COOH/CH<sub>3</sub>COO<sup>−</sup>, and imidazole/imidazolate acid–base pairs, respectively (composite energy values including ZPVE). Thus, the actual impact on the acid–base strength of the Zn-ligands is quite variable, the water/hydroxide pair being the most affected one, which is in consonance with the important role that zinc-bound water molecules usually have in zinc-enzymes.

**DFT Calculations.** In principle, the performance of the tested DFT functionals will be assessed by mean signed errors (MSE), i.e., the averages of the deviations with respect to the reference results including the sign of the error. We will not discuss in general mean unsigned errors (MUE) because all the functionals have shown systematic deviations either overestimating or underestimating the reference values for a given basis set. Thus, MUE do not provide any additional information. We also report standard deviations in order to describe the spread of the error distribution with respect to the mean value. Notice that for the sake of simplicity, part of the results obtained in this study are included in tables presented in the Supporting Information. These tables will be labeled with “S” when referred throughout the text.

**DFT Molecular Geometries of the Zn-L Complexes.** Table 4 collects the mean signed standard errors (MSE) and standard deviations in the Zn-ligand bond distance for the different complexes. As commented above, we will take the MP2/aug-cc-pVTZ values as the reference. The mean values were computed for the whole set of complexes since similar errors were obtained for both neutral and anionic ligands. Before discussing the data collected in Table 4, we would like to point out that, in general, we found that MP2 and DFT agree in fact in the geometry of the lowest energy structure for most of the analyzed complexes. However, in few cases, we found qualitative differences which deserve to be commented. For example, the Zn(II)-H<sub>2</sub>O complex has *C*<sub>2v</sub> symmetry at the MP2 level of theory. At the DFT level, the nature of the *C*<sub>2v</sub> stationary point depends on both the functional and the basis set. With the PBE functional and

the 6-31+G(*d*), 6-31+G(2*d*,*p*), and aug-cc-pVTZ basis sets it is a transition structure (the imaginary frequencies are 66i cm<sup>−1</sup>, 227i cm<sup>−1</sup>, and 159i cm<sup>−1</sup>, respectively). The same happens at the PW91/6-31+G(2*d*,*p*), PW91/aug-cc-pVTZ, TPSS/6-31+G(2*d*,*p*), and TPSS/aug-cc-pVTZ levels (195i cm<sup>−1</sup>, 133i cm<sup>−1</sup>, 180i cm<sup>−1</sup>, and 76i cm<sup>−1</sup> respectively). A similar situation occurs in [Zn(CH<sub>3</sub>OH)]<sup>2+</sup>. At the MP2 level with all basis sets this complex has *C*<sub>s</sub> symmetry with the zinc cation lying in the methanol symmetry plane (see Figure 1). However, at the DFT level and with all basis sets, this structure has one imaginary frequency indicating that the symmetry of the lowest energy conformation is *C*<sub>1</sub>. The imaginary frequency lies between 90 and 270 cm<sup>−1</sup> depending on the functional and the basis set, except for B3LYP that predicts values between 66 and 99 cm<sup>−1</sup>. We have nevertheless assumed a *C*<sub>s</sub> symmetry for this complex as suggested by the MP2/aug-cc-pVTZ calculation. Different MP2/aug-cc-pVTZ and DFT minimum energy structures are also predicted for [Zn(CH<sub>3</sub>COOH)]<sup>2+</sup> and [Zn(CH<sub>3</sub>COO)]<sup>+</sup>. In these two cases, however, the differences are related to the rotation of the methyl group. We considered a OCCH dihedral angle of 180 for the former and 0 for the later (see Figures 1 and 2). These are the values of the dihedral angles in the MP2/aug-cc-pVTZ equilibrium geometries. Finally, the [Zn(imidazolate)]<sup>+</sup> complex has *C*<sub>1</sub> symmetry and a Zn<sup>2+</sup>···π(C=N) interaction at all levels except MPWLYP1M and TPSS, which predict a more favorable interaction between the Zn(II) ion and the nitrogen lone pair in the *C*<sub>s</sub> complex. For comparative purposes, we considered a *C*<sub>s</sub> symmetry for this complex. We would like to point out that these imaginary frequencies are associated with a particular functional and basis set and do not depend on the integration grid. We checked this point in the water complex with the 6-31+G-(2*d*,*p*) basis set. The lowest frequency is reproduced within 6 cm<sup>−1</sup> for the five functionals. As commented above in the Methods section, we also carried out optimizations and frequency calculations at the PBE/aug-cc-pVTZ level of theory using a larger integration grid. We obtained frequencies which were similar to those calculated with the default “medium” grid. Our conclusion is therefore that the Zn<sup>2+</sup>-L interaction can be in general accurately described by a ‘medium’ integration grid.

Table 4 shows that all the tested functionals give, for a given basis set, metal–ligand distances that are larger than the MP2 ones by about 0.03–0.04 Å. The five functionals behave similarly, being B3LYP and TPSS the ones that predict shorter bond lengths. The data collected in Table 4 also reveal that the smallest 6-31G(*d*) basis set gives the lowest MSEs due to an error cancellation between the overestimation of the metal–ligand bond distances by the tested functionals and the underestimation associated with the size of the basis set. At the MP2 level with the 6-31+G-(*d*) basis, the MSE is already as small as 0.004 Å. With the tested functionals, this basis set performs also quite well predicting distances within 0.006–0.010 Å from the aug-cc-pVTZ ones. Let us also point out that metal–ligand bond distances obtained with a larger integration grid at the PBE/aug-cc-pVTZ level differ by less than 0.003 Å of the “medium” grid results (see Table S4). Finally, in order to



**Table 5.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Binding Energies of the  $[\text{Zn-L}]^{2+}$  Complexes (Neutral Ligands  $L = \text{H}_2\text{O}$ ,  $\text{NH}_3$ ,  $\text{H}_2\text{S}$ ,  $\text{H}_2\text{CO}$ ,  $\text{H}_2\text{CNH}$ ,  $\text{CH}_3\text{OH}$ ,  $\text{CH}_3\text{NH}_2$ ,  $\text{CH}_3\text{SH}$ ,  $\text{CH}_3\text{COOH}$ ,  $\text{HCONH}_2$ , 1H-Imidazole, and Benzene) with Respect to the Reference “Composite” Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	-24.20	-21.84	-16.79	-25.00	-17.11	-3.69
	SD	4.36	4.38	3.66	3.27	4.82	5.65
6-31+G(d)	MSE	-19.38	-18.07	-12.06	-18.08	-14.11	-3.32
	SD	3.14	3.15	2.37	3.37	1.80	2.17
6-31+G(2d,p)	MSE	-19.72	-18.41	-12.20	-18.39	-14.47	-1.58
	SD	3.99	4.00	2.82	3.99	2.65	1.89
6-311+G(d)	MSE	-16.03	-14.87	-8.94	-14.64	-10.02	0.73
	SD	3.45	3.51	3.02	3.81	2.06	3.17
aug-cc-pVTZ	MSE	-16.16	-15.56	-9.57	-15.14	-10.60	0.11
	SD	3.60	3.64	2.79	4.00	2.20	0.86

**Table 6.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Binding Energies of the  $[\text{Zn-L}]^+$  Complexes (Anionic Ligands,  $L = \text{OH}^-$ ,  $\text{HS}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{CH}_3\text{S}^-$ ,  $\text{CH}_3\text{COO}^-$ , and Imidazolate) with Respect to the Reference “Composite” Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	-45.83	-42.91	-34.24	-48.69	-34.76	-14.16
	SD	14.08	14.20	12.86	12.55	14.75	13.07
6-31+G(d)	MSE	-27.62	-26.17	-16.69	-27.77	-20.56	-3.05
	SD	4.49	4.49	3.06	4.69	3.81	3.58
6-31+G(2d,p)	MSE	-28.72	-27.23	-17.56	-28.74	-21.80	-1.29
	SD	4.63	4.61	3.16	4.97	3.70	2.11
6-311+G(d)	MSE	-23.06	-21.58	-12.24	-23.17	-15.02	2.70
	SD	5.27	5.19	4.00	5.59	4.07	4.32
aug-cc-pVTZ	MSE	-23.68	-22.79	-13.77	-24.33	-16.13	2.14
	SD	5.08	5.04	3.27	5.18	3.91	0.87

check the basis set truncation error we have also carried out optimizations using the B3LYP and TPSS functionals with the aug-cc-pVQZ basis set on the whole set of complexes (see Table S5). For the TPSS functional the maximum deviation from the aug-cc-pVTZ values is 0.003 Å. For B3LYP the maximum deviation is 0.002 Å except for two complexes, namely,  $\text{Zn}^{2+} \cdots \text{NH}_3$  and  $\text{Zn}^{2+} \cdots \text{ImH}$ , for which the difference between the TZ and QZ values is 0.03 and 0.02 Å, respectively. These results show that the geometries of the Zn(II) complexes are already well converged with the aug-cc-pVTZ basis set.

Regarding the rest of the geometrical parameters let us just point out that, with the exceptions already commented above, they are in general very similar with both MP2 and DFT methodologies. Furthermore, these values do not change much with the size of the basis set (except for the smallest one) and are very close to the reference aug-cc-pVTZ results.

**DFT Binding Energies of Zn-L Complexes.** Tables 5 and 6 show the mean signed errors (MSE) and standard deviations for the tested functionals and the MP2 method with the selected basis sets. Table 5 collects the results obtained for the neutral ligands, whereas Table 6 lists the results obtained for the anionic ones. We split this data because the magnitude of the binding energies for both type of ligands is quite different (see Table 3). Nevertheless, we

also list in Table S1 the mean errors calculated for the whole set of complexes.

From the data collected in Table 5, we see that all the tested functionals overestimate the binding energies. Notice that the MSEs diminish when increasing the basis set. Interestingly, we do not observe a quantitative improvement when going from 6-31+G(d) to 6-31+G(2d,p), but a clear reduction of the error is achieved with the 6-311+G(d) basis, which give results close to the aug-cc-pVTZ ones. With the aug-cc-pVTZ basis set, the deviation of the DFT values is still 10–16 kcal/mol, about 5–10% of the reference data, which correspond to the high level “composite” binding energies ( $D_e$  values in Table 2). The second conclusion that can be drawn from the data listed in Table 5 is that B3LYP and TPSS functionals perform the best, yielding MSEs that are about 33% smaller than those obtained with the other functionals.

Table 6 shows the MSEs obtained for the complexes with anionic ligands. Now, the magnitude of the deviations is larger, in agreement with the larger magnitude of the binding energies, but the conclusions are the same: all the functionals show a very similar systematic behavior, and the functionals B3LYP and TPSS perform the best. With the aug-cc-pVTZ basis, the tested functionals overestimate the binding energies by about 23 kcal/mol (14 kcal/mol and 16 kcal/mol at the B3LYP and TPSS levels, respectively) which represents about 5% of the reference “composite” value. We would like to add here that the binding energies of both neutral and anionic ligands obtained with a larger integration grid are within 0.1 kcal/mol from the ‘medium’ grid values. This shows that larger grids are in principle not required for the computation of binding energies. Besides, TPSS/aug-cc-pVQZ calculations (see Table S6) show that the TPSS/aug-cc-pVTZ binding energies are already converged within 0.4 kcal/mol. Interestingly, B3LYP/aug-cc-pVTZ energies appear to be underestimated still by 1.5–2.5 kcal/mol (see also Table S6). Notice then, that, with respect to the reference ab initio values, B3LYP/aug-cc-pVQZ binding energies are slightly more overestimated than B3LYP/aug-cc-pVTZ ones.

The MSE in the binding energies corrected for BSSE by means of the counterpoise (CP) method<sup>29</sup> are listed in Tables 7 and 8. Comparing the MSE collected in Tables 5 and 7, it is clear that all the functionals give very similar BSSE. With the smallest basis set, namely 6-31G(d), it is about 12 kcal/mol, 50% of the ‘uncorrected’ MSE. With the 6-31+G(d), 6-31+G(2d,p), and 6-311+G(d) basis sets, the BSSE is reduced to 1–2 kcal/mol, while with the aug-cc-pVTZ basis it is negligible. Since all the functionals overestimate the binding energies with MSE values larger than the BSSE, the CP-corrected energies are necessary closer to the composite results. At the MP2 level (last column in Table 7), the CP-corrected energies do not necessary get closer to the “composite” values. This is not an unexpected result because the MP2 energies are not far from the reference data. We remind the reader that the CP method does not correct for basis set incompleteness errors apart from the BSSE. Thus, it is possible that it yields too small binding energies compared to the CBS values, which do not suffer from any kind of basis set incompleteness. Table 8 shows the corre-

**Table 7.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Counterpoise (CP) Corrected Binding Energies of the  $[\text{Zn-L}]^{2+}$  Complexes (Neutral Ligands,  $L = \text{H}_2\text{O}$ ,  $\text{NH}_3$ ,  $\text{H}_2\text{S}$ ,  $\text{H}_2\text{CO}$ ,  $\text{H}_2\text{CNH}$ ,  $\text{CH}_3\text{OH}$ ,  $\text{CH}_3\text{NH}_2$ ,  $\text{CH}_3\text{SH}$ ,  $\text{CH}_3\text{COOH}$ ,  $\text{HCONH}_2$ , Imidazole, and Benzene) with Respect to the Reference “Composite” Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	-11.32	-9.18	-4.97	-12.72	-5.06	8.58
	SD	2.16	2.15	2.51	3.63	2.37	4.55
6-31+G(d)	MSE	-17.35	-16.17	-10.27	-16.25	-12.30	1.90
	SD	3.30	3.28	2.53	3.65	1.94	1.66
6-31+G(2d,p)	MSE	-18.24	-16.97	-10.82	-16.87	-13.14	1.70
	SD	4.05	4.04	3.01	4.22	2.69	1.28
6-311+G(d)	MSE	-14.62	-13.50	-7.65	-13.37	-8.71	4.94
	SD	3.56	3.59	2.94	3.90	2.12	2.24
aug-cc-pVTZ	MSE	-15.92	-15.32	-9.36	-14.91	-10.42	
	SD	3.62	3.65	2.84	4.04	2.20	

**Table 8.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Counterpoise (CP) Corrected Binding Energies of the  $[\text{Zn-L}]^+$  Complexes (Anionic Ligands,  $L = \text{OH}^-$ ,  $\text{HS}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{CH}_3\text{S}^-$ ,  $\text{CH}_3\text{COO}^-$ , and  $\text{Im}^-$ ) with Respect to the Reference “Composite” Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	-21.16	-18.53	-11.96	-24.50	-12.00	8.77
	SD	5.71	5.82	4.61	4.97	6.32	5.67
6-31+G(d)	MSE	-25.44	-24.01	-14.87	-25.76	-18.57	4.10
	SD	4.92	4.91	3.34	5.09	3.96	2.22
6-31+G(2d,p)	MSE	-26.62	-25.18	-15.81	-26.76	-19.91	3.35
	SD	4.99	4.98	3.39	5.23	3.87	1.76
6-311+G(d)	MSE	-21.77	-20.32	-11.18	-22.03	-13.81	8.97
	SD	5.62	5.54	4.19	5.88	4.30	2.99
aug-cc-pVTZ	MSE	-23.06	-22.20	-13.42	-23.75	-15.59	
	SD	5.31	5.26	3.34	5.31	4.07	

**Table 9.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Protonation Energies of the Anionic Ligands ( $L = \text{OH}^-$ ,  $\text{HS}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{CH}_3\text{S}^-$ ,  $\text{CH}_3\text{COO}^-$ , and Imidazolate) with Respect to the Reference “Composite” Values

basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	-13.27	-12.75	-14.02	-17.32	-14.21	-12.13
	SD	10.22	10.37	9.51	9.26	9.58	9.23
6-31+G(d)	MSE	6.05	6.30	4.34	2.09	3.09	6.11
	SD	1.64	1.63	1.13	1.74	1.56	1.51
6-31+G(2d,p)	MSE	2.63	2.88	0.88	-1.41	-0.21	2.01
	SD	1.21	1.22	0.76	1.21	1.06	0.93
6-311+G(d)	MSE	6.42	6.69	4.64	2.27	3.36	5.86
	SD	2.19	2.16	1.56	2.11	1.94	1.38
aug-cc-pVTZ	MSE	3.07	3.32	1.06	-1.13	0.08	2.89
	SD	2.17	2.17	1.42	2.13	1.96	0.73

sponding MSE in the CP-corrected binding energies of the complexes with an anionic ligand. The conclusions that can be drawn are the same already commented. The BSSE is about 24 kcal/mol with the smallest basis set, again approximately 50% of the ‘uncorrected’ MSE. With the larger basis, it reduces to less than 2 kcal/mol.

**DFT Protonation Energies.** In Table 9 we report the MSE and standard deviations for the protonation energies of the

**Table 10.** Mean Signed Errors (MSE) and Standard Deviations (kcal/mol) in the Protonation Energies of the  $[\text{Zn-L}]^+$  Complexes (Anionic Ligands,  $L = \text{OH}^-$ ,  $\text{HS}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{CH}_3\text{S}^-$ ,  $\text{CH}_3\text{COO}^-$ , and Imidazolate) with Respect to the Reference “Composite” Values

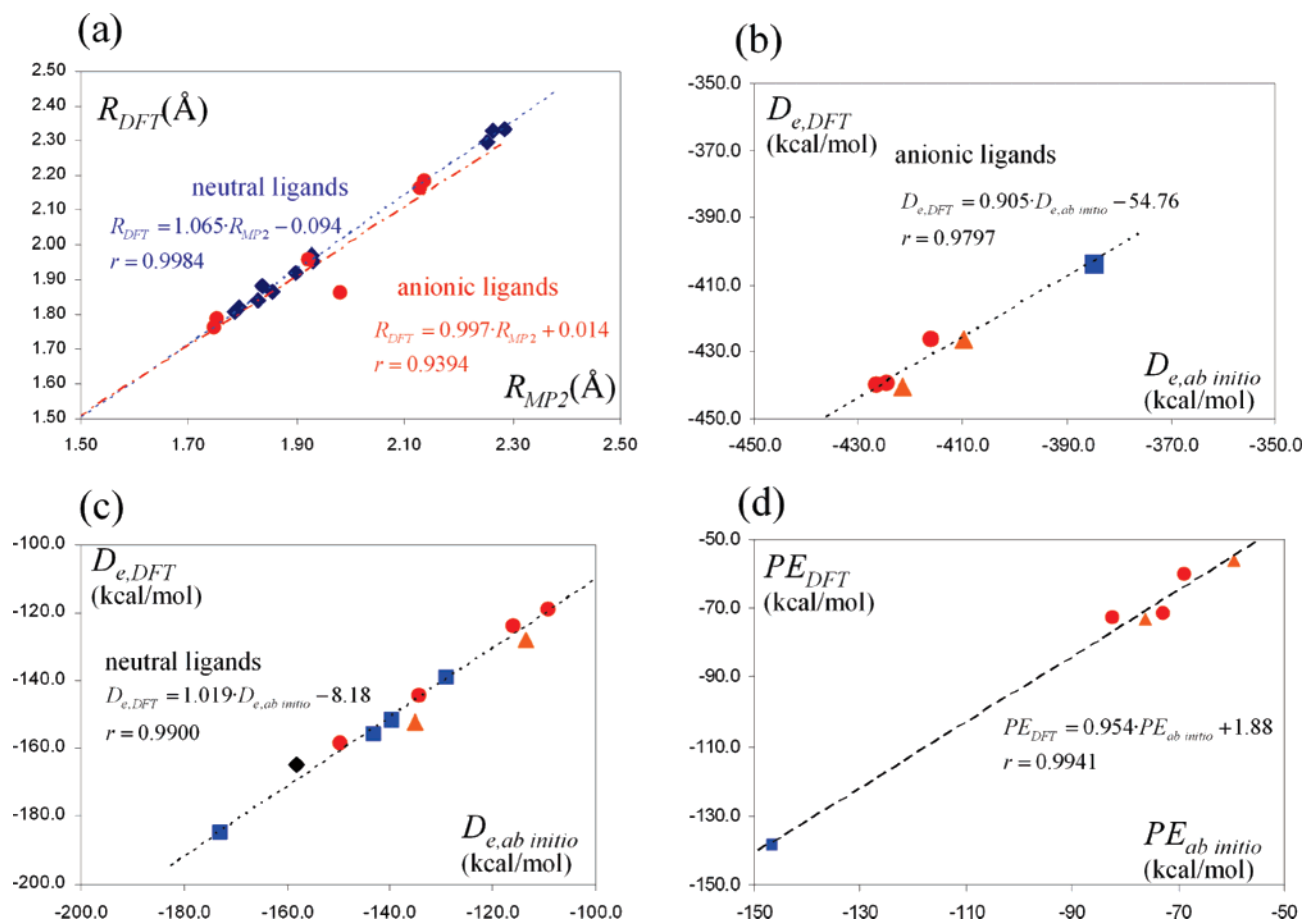
basis set		PW91	PBE	B3LYP	MPWLYP1M	TPSS	MP2
6-31G(d)	MSE	10.31	10.28	5.02	7.70	5.60	0.60
	SD	3.67	3.70	1.39	3.11	3.16	3.34
6-31+G(d)	MSE	14.27	14.41	8.73	11.24	9.84	6.37
	SD	5.17	5.28	2.66	4.55	4.24	1.89
6-31+G(2d,p)	MSE	11.36	11.48	5.73	8.16	7.17	2.52
	SD	5.82	5.91	3.26	5.11	4.93	0.40
6-311+G(d)	MSE	12.87	12.83	7.06	9.64	8.05	3.60
	SD	4.92	5.09	2.42	4.18	4.01	2.11
aug-cc-pVTZ	MSE	9.94	9.96	4.43	6.74	5.29	1.11
	SD	5.75	5.89	3.29	4.99	4.93	0.69

isolated acid–base pairs as computed with the tested functionals and the MP2 method with the selected basis sets. The results obtained for the corresponding Zn-L complexes are shown in Table 10.

In consonance with expectations, the PEs computed with the small basis set (6-31G(d)) in the absence of the Zn(II) cation contain relatively large errors ( $>12$  kcal/mol in absolute value). These results are much improved by including diffuse and/or further polarization functions in the basis set at all the methods. Particularly, the B3LYP calculations with the 6-31+G(2d,p) and aug-cc-pVTZ basis sets give PE values that are very close to the best ab initio values, with MSEs of only 0.88 and 1.06 kcal/mol, respectively. Although the performance of the rest of DFT methods and the MP2 method in the PE calculations for the free ligands is clearly worse, the magnitude of their MSEs is still lower than those associated with the Zn-ligand binding energies in Tables 4–8.

As above-mentioned, to find out whether a ligand is protonated or deprotonated when coordinated to the Zn(II) cation is an important question. Unfortunately, the quality of the PEs predicted by the DFT methods decreases significantly for the Zn-L complexes with respect to the isolated ligands as the MSEs collected in Table 10 are 3–4-fold larger than those in Table 9 for the more complete basis sets. The opposite trend arises in the MP2 calculations, whose MSE values in Tables 9 and 10 are more comparable to each other. These observations illustrate clearly the extra difficulty associated with the theoretical description of the zinc complexes. However, it is also clear that the average error in the DFT protonation energies is lower than in the metal–ligand binding energy calculations. Again we conclude that all the functionals show basically the same trends and that B3LYP and TPSS perform the best.

**Correlation between DFT and Ab Initio Data.** The MSE values collected in Tables 4–10 assess the overall accuracy of selected functionals in calculating metal–ligand distances, binding energies, and protonation energies of monoligand Zn(II) complexes with reference to the benchmark ab initio results. However, many applications of theoretical methods that are relevant to zinc enzymology involve the computation of only relative energies for ligand exchange processes and/or proton-transfer reactions. Of course, this type of calcula-



**Figure 3.** Linear regression plots of B3LYP/6-31+G(2d,p) data vs ab initio reference data: (a) zinc–ligand distances; (b) binding energies for anionic ligands; (c) binding energies for neutral ligands; and (d) protonation energies for zinc(II) complexes. Filled circles, squares, triangles, and diamond in plots (b–d) stand for oxygen-donor, nitrogen-donor, sulfur-donor, and benzene ligands, respectively.

tions can benefit from cancellation of “systematic” errors in the computed binding energies ( $D_e$ ) and protonation energies (PEs) and, in general, the lower MSE of the  $D_e$  and PEs, the larger odds of cancellation of errors in the relative energies. Nevertheless, it may be interesting to examine some linear correlation plots of DFT results vs the ab initio reference results (discriminating between the neutral and the anionic ligands; see Figure 3) in order to ascertain more clearly the differences and similarities in the systematic deviations of the computed properties. For this purpose, we chose B3LYP/6-31+G(2d,p) as the DFT level of theory because this level shows a good balance between global accuracy and computational cost.

We see in Figure 3 that the best linear correlation between DFT and ab initio data corresponds to the protonation energies of the Zn-L complexes ( $r = 0.994$ ), which is in consonance with the relatively low MSE of the B3LYP/6-31+G(2d,p) PEs. A reasonably good correlation coefficient is also obtained for the binding energies of neutral ligands ( $r = 0.990$ ) although the corresponding MSE is larger than that of the PEs. However, the linear regression fit of the binding energies is less satisfactory in the case of the anionic ligands ( $r = 0.980$ ). Similarly, the DFT zinc-ligand distances are better correlated with the ab initio data for the neutral ligands (see Figure 3a).

In terms of linear regression theory, the value of  $r^2$  from plots (a–d) in Figure 3 can be interpreted as the fraction of the total variance of the DFT data that is “explained” by the variation in the corresponding ab initio data.<sup>52</sup> For example, the uncertainty (as reflected in the variance) about a DFT PE energy value is reduced about 99.4% once we know its corresponding ab initio score and the correlation ratio ( $r^2 = 0.994$ ) between the DFT and ab initio data. Reciprocally, the variance of the DFT data that remains “unexplained” by the linear regression fits is given by  $1 - r^2$ . Assuming that this latter variability is mainly due to the nonsystematic (i.e., erratic) errors, we propose to estimate the magnitude of the nonsystematic errors in the DFT calculations by multiplying the fraction of “unexplained” variation ( $1 - r^2$ ) by 100.0 kcal/mol (an upper limit of the energy range covered by the regression analyses). In this way, we obtain that the approximate values of the nonsystematic errors for PEs,  $D_e$  for neutral ligands, and  $D_e$  for anionic ligands would be  $\sim 1.1$ ,  $\sim 2.0$ , and  $\sim 4.0$  kcal/mol, respectively, at the B3LYP/6-31+G(2d,p) level. In this scenario, both relative energies for processes involving the rupture of bonds between Zn(II) and neutral ligands and relative protonation energies of zinc-complexes, should be determined quite accurately using a hybrid DFT method combined with a flexible basis set like 6-31+G(2d,p) because the addition of the nonsystematic



**Table 11.** Contributions to the SAPT Interaction Energies (in kcal/mol) for the  $[\text{Zn-L}]^{2+}$  Complexes (Neutral Ligands) with the 6-31+G(2d,p) Basis Set

ligand	$E_{\text{elst}}^{(1)}$	$E_{\text{ind}}^{(2)}$	$E_{\text{disp}}^{(2)}$	$E_{\text{exch}}^{(1)}$	$E_{\text{exch}}^{(2)}$	$E^{(1)a}$	$E^{(2)b}$	$\delta E_{\text{int}}^{\text{HF}}$	$E_{\text{int}}(\text{SAPT})$
H <sub>2</sub> O	−88.0	−243.2	−6.5	55.7	175.3	−32.3	−74.4	10.3	−96.5
H <sub>2</sub> CO	−85.3	−270.8	−7.0	58.5	183.3	−26.8	−94.5	9.4	−111.9
CH <sub>3</sub> OH	−103.2	−313.8	−7.7	66.6	223.3	−36.6	−98.2	13.5	−121.3
CH <sub>3</sub> COOH	−115.6	−362.3	−8.6	75.5	254.8	−40.1	−116.1	14.5	−141.7
HCONH <sub>2</sub>	−129.9	−375.3	−8.7	78.0	265.0	−51.9	−119.0	15.8	−155.1
NH <sub>3</sub>	−129.2	−461.1	−9.0	82.4	360.2	−46.8	−109.9	28.4	−128.3
H <sub>2</sub> CNH	−126.7	−444.8	−9.0	79.1	333.1	−47.6	−120.7	23.6	−144.8
CH <sub>3</sub> NH <sub>2</sub>	−132.5	−477.1	−8.9	80.3	366.0	−52.2	−120.2	26.0	−146.2
1H-imidazole	−155.9	−545.7	−10.7	95.3	407.6	−60.6	−148.8	29.9	−179.5
H <sub>2</sub> S	−63.5	−375.6	−6.9	52.4	269.7	−11.1	−112.8	16.0	−107.9
CH <sub>3</sub> SH	−78.9	−433.6	−7.6	59.4	313.1	−19.5	−128.1	18.0	−129.6
benzene	−71.3	−416.9	−15.5	77.8	262.5	6.5	−169.9	3.5	−159.9

$$^a E^{(1)} = E_{\text{elst}}^{(1)} + E_{\text{exch}}^{(1)}, \quad ^b E^{(2)} = E_{\text{ind}}^{(2)} + E_{\text{disp}}^{(2)} + E_{\text{exch}}^{(2)}$$

errors would amount to  $\sim 2$ – $4$  kcal/mol. However, the DFT relative energies for ligand rearrangement processes involving anions could have a larger error of  $\sim 8$  kcal/mol. We note that these estimations are basically in agreement with the fact that, from previous computational experience in metal-containing systems,<sup>53</sup> the error on the relative energies computed by standard DFT methodologies is unlikely to exceed a range of 3–5 kcal/mol.

**SAPT Analyses.** In this section we will analyze the nature of the Zn(II)-ligand interaction by means of the Symmetry-Adapted Perturbation Theory. Table 11 collects the interaction energy components as well as the total intermolecular interaction energies for the Zn(II) complexes formed with the neutral ligands (see also Table S3 in the Supporting Information for a fully complete presentation of the SAPT data). For this analysis, we select again the 6-31+G(2d,p) basis set. We would also like to point out the fact that the interaction energies of these complexes range between 100 and 180 kcal/mol and, therefore, that the applicability of the SAPT2 methodology (that is, whether it can fully recover the SP-MP2 interaction energy) is here a matter of concern. As commented above in the Computational Methods section, terms of order higher than the second, which may well be important in these strongly bonded systems, can be obtained from a SP–HF calculation via the  $\delta E_{\text{int}}^{\text{HF}}$  term. This is an easy and computationally cheap way of including these contributions, but this approximation does not come without a price since the physically meaningful components that comprise  $\delta E_{\text{int}}^{\text{HF}}$  are of course not known. In the present case,  $\delta E_{\text{int}}^{\text{HF}}$  represents in the worst case 10% of the total interaction energy, and, therefore, we think that we can provide a fairly correct qualitative picture of the nature of the interaction in these complexes by using SAPT2. However, we have not studied the anionic ligands because the interaction energy is in these cases far too large to be fully recovered by an intermolecular perturbation method without losing the physically meaningful picture of the interaction.

The results collected in Table 11 show that the electrostatic interaction  $E_{\text{elst}}^{(1)}$  is not the largest attractive term in these complexes since it only represents 14–26% of the total attractive energy terms  $E_{\text{elst}}^{(1)} + E_{\text{ind}}^{(2)} + E_{\text{disp}}^{(2)}$ . The largest contribution to the interaction energy comes from  $E_{\text{ind}}^{(2)}$ ,

whereas the dispersion energy clearly plays a minor role in the bonding of these systems. Of course, we also have to take into account that the induction component is partially quenched by its exchange counterpart (the same happens to the dispersion component, but the exchange-dispersion term is actually rather small, see Table S3). However, we do not think that it is particularly meaningful to sum up the induction and the exchange-induction components and conclude that these systems are stabilized mainly by  $E_{\text{elst}}^{(1)}$ . After all, if the  $E_{\text{ind}}^{(2)}$  contribution were to be of a similar size of  $E_{\text{elst}}^{(1)}$ , the interaction energy would be repulsive. We think that a clearer picture of the interaction can be obtained by collecting all the components that contribute to a certain order in the intermolecular perturbation together, as described in the Computational Methods section. When using SAPT2, the two resulting terms are  $E^{(1)}$  and  $E^{(2)}$  which are also shown in Table 11. We see that in all cases  $E^{(1)}$  is smaller than  $E^{(2)}$  by more than 50%. Even in one particular case namely,  $[\text{Zn}(\text{benzene})]^{2+}$ ,  $E^{(1)}$  is repulsive. We interpret these results as indicating that the main stabilizing factor of the studied Zn(II) complexes is not the electrostatic attraction of the interacting fragments but the relaxation of the charge densities of the monomers through induction and charge transfer. This effect is far more important for the most polarizable ligands: hydrogen sulfide and methanethiol (see Table 11). The complex  $\text{Zn}^{2+} \cdots \text{benzene}$  is a particular case because in this system the zinc atom is not pointing directly toward a negative local charge concentration of the base resulting in a relatively small electrostatic attraction and a positive first-order interaction energy. One important conclusion of this analysis is therefore that any methodology which is aimed to be applied to the study of Zn(II) complexes should give a correct description of the relaxation of the charge distribution of the interacting monomers. The systematic overestimation of the bond dissociation energies by different density functionals found in this work is actually related to this fact. Indeed, recent results obtained by Piquemal et al.<sup>54</sup> for the  $[\text{Zn}(\text{imidazole})]^{2+}$  complex show that the larger interaction energy obtained with four different functionals (PW91, B3PW91, BLYP, and B3LYP) with respect to the MP2 value (13–26 kcal/mol with a DZVP2 basis set; we obtained in this work 13–22 kcal/mol with



the 6-31+G(2d,p) basis depending on the functional) is due to the overestimation of the charge-transfer effects, which is caused, in turn, by an overestimation of the imidazole polarizability.<sup>54</sup> This explanation is in complete agreement with our results, which highlight the importance of a correct description of the relaxation of the fragments' wave functions taking into account the important role played by the induction forces in the interaction of these complexes.

**Implications for Molecular Mechanics Models.** Besides its academic interest, the results of our SAPT calculations could be useful for the assessment of the so-called "non-bonded" molecular mechanics potentials that include electrostatic and van der Waals forces instead of covalent ones to maintain the Zn(II) coordination geometry during molecular dynamics simulations of zinc-enzymes. Thus, the simplest Zn(II) "nonbonded" models include merely a Coulombic term plus a Lennard-Jones term whose parameters are optimized either by fitting to ab initio interaction energies<sup>55</sup> or by reproducing relative experimental hydration free energies and the coordination number of Zn(II) in water.<sup>56</sup> However, in consonance with the importance of the induction and charge-transfer effects shown by the physically meaningful SAPT methodology, it has been found<sup>57</sup> that the "nonbonded" models should also include charge transfer from the donor atoms and local polarization of the Zn(II) ion and its ligands in order to properly describe the flexible coordination structure of the Zn(II) ions in proteins. We believe that further improvement of this or other extended "nonbonded" models<sup>24</sup> could be expected if these potentials are designed to reflect the underlying physical forces that govern the intermolecular interactions in monoligand complexes.

## Conclusions

On the basis of the ab initio benchmark calculations for the 18 monoligand Zn(II)-complexes that are examined in this work, we can draw the following conclusions and/or recommendations: (a) Given that the MP2/aug-cc-pVTZ energies are in very good agreement with the "composite" CCSD(T) ones, this could be the ab initio level of choice in order to accurately predict the binding energies and/or PEs for polyligand Zn(II) complexes. (b) All the tested DFT functionals overestimate systematically the binding energy between the Zn(II) ion and the different ligands, the B3LYP and TPSS methods performing the best. (c) The Pople's 6-31+G(2d,p) basis set combined with the DFT or MP2 methods provides a good compromise between accuracy and computational cost for the systems studied here. (d) Using a hybrid DFT or a meta-GGA method, relative energies for ligand exchange and proton-transfer processes involving neutral ligands should be determined within a 2–4 kcal/mol accuracy, but larger errors should be expected for anionic ligands.

From the SAPT calculations, we find that, in the case of neutral ligands bound to the Zn(II) ion, 90% of their interaction energy can be assigned to well-defined and physically meaningful intermolecular forces. The SAPT calculations show that induction and charge-transfer interactions have a larger contribution than the classical electrostatic attraction between the fragments. This stresses the fact that

any theoretical methodology aimed to be applied to the study of Zn(II) complexes should be able to give a good description of the relaxation of the charge densities of the monomers upon complexation.

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**Supporting Information Available:** Mean signed errors and standard deviations in the binding energies of the whole set of complexes included in this study, fully complete presentation of the SAPT data, metal–ligand bond distances obtained at the PBE/aug-cc-pVTZ level with an "ultrafine" grid, and metal–ligand bond distances and binding energies obtained with the B3LYP and TPSS functionals using a aug-cc-pVQZ basis set. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Lipscomb, W. N. N. S. *Chem. Rev.* **1996**, *96*, 2375–2433.
- (2) Bartlett, R. J. *J. Phys. Chem.* **1989**, *93*, 1697–1708.
- (3) Dunning, T. H., Jr. *J. Phys. Chem. A* **2000**, *104*, 9062–9080.
- (4) Martin, J. M. L. Ab initio thermochemistry beyond chemical accuracy for first- and second-row compounds. In *Nato ASI Symposium Volume ASIC 535, Energetics of stable molecules and reactive intermediates*; Minas da Piedade, M. E., Ed.; Kluwer Academic Publishers: Dordrecht, 1999; pp 373–415.
- (5) Balabanov, N. B.; Peterson, K. A. *J. Chem. Phys.* **2005**, *123*, 064107.
- (6) Koch, W.; Holthausen, M. C. *A Chemist's guide to density functional theory*, 2nd ed.; Wiley-VCH: New York, 2001; p 528.
- (7) Estiu, G.; Suarez, D.; Merz, K. M. J. *J. Comput. Chem.* **2006**, *27*, 1240–1262.
- (8) Weston, J. *Chem. Rev.* **2005**, *105*, 2151–2174.
- (9) Strain, M. C.; Scuseria, G. E.; Frisch, M. J. *Science* **1996**, *271*, 51–53.
- (10) White, C. A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M. *Chem. Phys. Lett.* **1996**, *253*, 268–278.
- (11) Eichkorn, K.; Treutler, O.; Öhm, H.; Häser, M.; Ahlrichs, R. *Chem. Phys. Lett.* **1995**, *240*, 283–289.
- (12) Goringe, C. M.; Bowler, D. R.; Hernández, E. *Rep. Prog. Phys.* **1997**, *60*, 1447–1512.
- (13) Elstner, M. *Theor. Chem. Acc.* **2006**, *116*, 316–325.
- (14) Jensen, K. P.; Roos, B. O.; Ryde, U. *J. Chem. Phys.* **2007**, *126*, 014103.
- (15) Diaz, N.; Suarez, D.; Merz, K. M. J. *Chem. Phys. Lett.* **2000**, *326*, 288–292.
- (16) Tiraboschi Gresh, N.; Giessner-Prettre Pedersen, L. G.; Deerfield, D. W. *J. Comput. Chem.* **2000**, *12*, 1011–1039.
- (17) Diaz, N.; Suarez, D.; Merz, K. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 4197–4208.
- (18) Yazal, J. E.; Pang, Y.-P. *J. Mol. Struct. (THEOCHEM)* **2001**, *545*, 271–274.

- (19) Frison, G.; Ohanessian, G. *J. Comput. Chem.* **2008**, *29*, 416–433.
- (20) Brothers, E. N.; Suarez, D.; Deerfield, D. W.; Merz, K. M. *J. J. Comput. Chem.* **2004**, *25*, 1677–1692.
- (21) Elstner, M.; Cui, Q.; Muni, P.; Kaxiras, E.; Frauenheim, T.; Karplus, M. *J. Comput. Chem.* **2003**, *24*, 565–581.
- (22) Gresh, N.; Garmer, D. J. *J. Comput. Chem.* **1996**, *17*, 1481–1495.
- (23) Rogalewicz, F.; Ohanessian, G.; Gresh, N. *J. Comput. Chem.* **2000**, *21*, 963–973.
- (24) Gresh, N.; Piquemal, J.-P.; Krauss, M. J. *J. Comput. Chem.* **2005**, *26*, 1113–1130.
- (25) Kendall, R. A.; Dunning, J. T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796–6806.
- (26) Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1993**, *98*, 1358–1371.
- (27) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479–483.
- (28) Peterson, K. A.; Puzzarini, C. *Theor. Chem. Acc.* **2005**, *114*, 283–296.
- (29) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.
- (30) Dunning, T. H. J.; Peterson, K. A.; Wilson, A. K. *J. Chem. Phys.* **2001**, *114*, 9244–9253.
- (31) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *57*, 14999–14999.
- (32) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *78*, 1396–1396.
- (33) Becke, A. D. *J. Chem. Phys.* **1986**, *95*, 7184–7187.
- (34) Becke, A. D. *J. Chem. Phys.* **1988**, *88*, 2547–2553.
- (35) Becke, A. D. *J. Chem. Phys.* **1988**, *88*, 1053–1062.
- (36) Lee, C.; Yang, R. G.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
- (37) Schultz, N. E.; Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 4388–4403.
- (38) Tao, J.; Perdew, J. P.; Staroverov, V. N.; Scuseria, G. E. *Phys. Rev. Lett.* **2003**, *91*, 146401.
- (39) Rassolov, V. A.; Ratner, M. A.; Pople, J. A.; Redfern, P. C.; Curtiss, L. A. *J. Comput. Chem.* **2001**, *22*, 976–984.
- (40) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4654–4655.
- (41) Wachters, A. J. H. *J. Chem. Phys.* **1970**, *52*, 1033.
- (42) Hay, P. J. *J. Chem. Phys.* **1977**, *66*, 4377–4384.
- (43) Raghavachari, K.; Trucks, G. W. *J. Chem. Phys.* **1989**, *91*, 1062–1065.
- (44) Rienstra-Kiracofe, J. C.; Tschumper, G. S.; Schaefer, H. F., III; Nandi, S.; Ellison, G. B. *Chem. Rev.* **2002**, *102*, 231–282.
- (45) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.
- (46) Bukowski, B. R.; Cencek, W.; Jankowski, P.; Jezierski, B.; Jezierska, M.; Kucharski, S. A.; Misquitta, A. J.; Moszynski, R.; Patkowski, K.; Rybak, S.; Szalewicz, K.; Williams, H. L.; Wormer, P. E. S. *SAPT2002: An Ab Initio program for many-body symmetry-adapted perturbation theory calculations of intermolecular interaction energies. Sequential and parallel versions*; 2002. See [http://www.Physics.Udel.Edu/\\_szalewic/sapt/sapt.html](http://www.Physics.Udel.Edu/_szalewic/sapt/sapt.html).
- (47) Jezierski, B.; Moszynski, R.; Szalewicz, K. *Chem. Rev.* **1994**, *94*, 1887–1930.
- (48) Chalasinski, G.; Szczesniak, M. *Mol. Phys.* **1988**, *63*, 205–224.
- (49) Misquitta, A. J.; Bukowski, R.; Szalewicz, K. *J. Chem. Phys.* **2000**, *112*, 5308–5319.
- (50) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.
- (51) Riley, K. E.; Hobza, P. *J. Phys. Chem. A* **2007**, *111*, 8257–8263.
- (52) Frank, H.; Althoen, S. C. *Statistics: Concepts and applications*; Cambridge University Press: 1994.
- (53) Siegbahn, P. E. M. *Q. Rev. Biophys.* **2003**, *36*, 91–145.
- (54) Piquemal, J. P.; Marquez, A.; Parisel, O.; Giessner-Prettre, C. *J. Comput. Chem.* **2005**, *26*, 1052–1062.
- (55) Stote, R. H.; Karplus, M. *Proteins: Struct., Funct., Genet.* **1995**, *23*, 12–31.
- (56) Babu, C. S.; Lim, C. *J. Phys. Chem. A* **2006**, *110*, 691–699.
- (57) Sakharov, D. V.; Lim, C. *J. Am. Chem. Soc.* **2005**, *127*, 4921–4929.

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