Representation of Zn(II) Complexes in Polarizable Molecular Mechanics. Further Refinements of the Electrostatic and Short-Range Contributions. Comparisons with Parallel *Ab Initio* Computations

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Abstract: We present refinements of the SIBFA molecular mechanics procedure to represent the intermolecular interaction energies of Zn(II). The two first-order contributions, electrostatic (E_{MTP}), and short-range repulsion (E_{rep}), are refined following the recent developments due to Piquemal et al. (Piquemal et al. J Phys Chem A 2003, 107, 9800; and Piquemal et al., submitted). Thus, E_{MTP} is augmented with a penetration component, E_{pen}, which accounts for the effects of reduction in electronic density of a given molecular fragment sensed by another interacting fragment upon mutual overlap. E_{pen} is fit in a limited number of selected Zn(II)–mono-ligated complexes so that the sum of E_{MTP} and E_{pen} reproduces the Coulomb contribution E_c from an *ab initio* Hartree–Fock energy decomposition procedure. Denoting by S, the overlap matrix between localized orbitals on the interacting monomers, and by R, the distance between their centroids, E_{rep} is expressed by a S^2/R term now augmented with an S^2/R^2 one. It is calibrated in selected monoligated Zn(II) complexes to fit the corresponding exchange repulsion E_{exch} from *ab initio* energy decomposition, and no longer as previously the difference between ($E_c + E_{\text{exch}}$) and E_{MTP}. Along with the reformulation of the first-order contributions, a limited recalibration of the second-order contributions was carried out. As in our original formulation (Gresh, J Comput Chem 1995, 16, 856), the Zn(II) parameters for each energy contribution were calibrated to reproduce the radial behavior of its *ab initio* HF counterpart in monoligated complexes with N, O, and S ligands. The SIBFA procedure was subsequently validated by comparisons with parallel *ab initio* computations on several Zn(II) polyligated complexes, including binuclear Zn(II) complexes as in models for the Gal4 and β-lactamase metalloproteins. The largest relative error with respect to the RVS computations is 3%, and the ordering in relative energies of competing structures reproduced even though the absolute numerical values of the *ab initio* interaction energies can be as large as 1220 kcal/mol. A term-to-term identification of the SIBFA contributions to their *ab initio* counterparts remained possible even for the largest sized complexes.

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Introduction

Zn(II) is a cation of fundamental importance in structural and molecular biology, acting both as a cofactor of numerous metalloenzymes[1] and as a key structural element in the architecture of Zn-finger and related proteins.[2] It is also used in the construction of several supramolecular structures.[3] Although *ab initio* quantum chemistry (QC) is the most accurate procedure for the computation of intermolecular interactions, it could not be applied presently to systematically investigate very large complexes (>200 atoms) and perform detailed investigations of the potential energy hypersurfaces. QM/MM approaches at varying levels of theory are being used for metalloprotein simulations[4] in which the cation-binding site is computed by QC while its periphery is computed by standard molecular mechanics (MM) approaches. Anisotropic polarizable molecular mechanics (APMM) methods could be a viable alternative to QM/MM if the energy potential were of sufficient

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This article includes Supplementary Material available from the authors upon request or via the Internet at http://www.interscience.wiley.com/jpages/0192-8651/suppmat accuracy, and this has been a major incentive for the refinements of the SIBFA (Sum of Interactions Between Fragments *Ab Initio* Computed) method.[5] The separability of the APMM interaction energy into individual contributions can be essential for an accurate reproduction of the QC interaction energies and the transferability of the potential energy function to other complexes than those that were used for the calibration. A major asset towards the development, calibration, and validation of separable APMM potentials consists into the availability of QC energy-decomposition procedures, in which the Hartree–Fock (HF) interaction energy ΔE(HF) is decomposed into its separate contributions: Coulomb (E_c) and exchange (E_{exch}) in first-order, and polarization (E_{pol}) and charge-transfer (E_{ct}) in second-order, each of which has an APMM counterpart. We resort to the Restricted Variational Space Analysis (RVS) procedure,[6] which can be used to investigate complexes between more than one two interacting molecules. We have in previous publications presented the results of parallel QC and SIBFA computations.[7] These bore on polyligated Zn(II) complexes,[7a-b] conformation-dependent divalent cation binding by glycine and the glycine zwitterion,[7c] mercaptocarboxamides,[7d] and triphosphate.[7e] SIBFA was applied to study complexes of inhibitors with thermolysin,[8] and β-lactamase[9] metalloenzymes, the complexes of Zn(II) and Zn(II)–pentahydrates with nucleic acid bases and guanosine mononucleotide,[10] and towards *de novo* predictions of the conformation of 18-residue long Zn-fingers.[11] The parameters used in these studies have not been modified since our 1995 and 1997 papers.[5b,5d] On the other hand, the realm of SIBFA has recently been extended to other transition metal cations, namely Cu(I)[12] and Cu(II).[13] This has necessitated to include energy contributions that are specific to these cations, namely quadrupole polarizability and cation-to-ligand charge transfer for Cu(I) and ligand-field effects in the case of open-shell Cu(II). Although for polyligated Zn(II) complexes SIBFA was shown to afford a reproduction of QC interaction energies with relative errors <3%, there were two limitations. The first was the impossibility of directly identifying the SIBFA electrostatic multipolar contribution E_{MTP} with the Coulomb contribution E_c. The second was the exaggerated anticooperative nature of the SIBFA charge-transfer contribution E_{ct} compared to its *ab inito* counterpart in polyligated Zn(II) complexes.[7a–b] We will present in this article refinements to remedy these shortcomings.

E_c is sytematically more attractive than E_{MTP}, due to the presence of attractive penetration terms that translate the reduction of the electronic density on a given monomer, A, that is sensed by another interacting monomer, B, when the densities of A and B begin to overlap in the vicinity of equilibrium distance. This has recently led us[14] (Piquemal et al., submitted) along with other authors[15] to augment E_{MTP} with an explicit "penetration" contribution E_{pen}. Using the formulation by Piquemal et al.,[14] E_{pen} was calibrated in a limited set of hydrogen-bonded complexes in such a way that the sum $E_{\mathrm{MTP}} + E_{\mathrm{pen}}$ matches E_c upon performing distance variations. Tests were subsequently performed in several H-bonded and stacked complexes[14] exploring both distance and angular variations. The SIBFA repulsion energy E_{rep} could therefore be calibrated to reproduce directly E_{exch} rather than, as previously, the difference between ($E_c + E_{\mathrm{exch}}$) and E_{MTP}. The possibility of reaching a more detailed term-to-term identification of each SIBFA contribution to its QC counterpart should enable to more accurately reflect the physics of the interaction. Concerning E_{ct}, we will seek for an alternative calibration so that it matches equally well E_{ct}(RVS) than the original calibration, yet reduces its anticooperative character in polyligated complexes of Zn(II). We will compare first the results of the so-reformulated SIBFA to the QC RVS ones in monoligated Zn(II) complexes with representative neutral and anionic N, O, and S-containing ligands. We will then extend the comparisons to polyligated Zn(II) complexes. Mononuclear Zn(II) complexes are those with water molecules and varying ($n = 4-6$) first-shell coordination numbers, and those with imidazole and methanethiolate ligands ($n = 3$–4) as models for Zn-fingers. Binuclear complexes are those found in Gal4[16] and β-lactamase.[17] Comparisons with corresponding results that used the previous formulation show that a closer reproduction of E_1(RVS) by E_1(SIBFA) has taken place, and that E_{ct}(SIBFA) can now more closely match E_{ct}(RVS) in polyligated complexes, so that as a consequence, prior to including the dispersion contribution, ΔE(SIBFA) can reproduce ΔE(RVS) with further improved accuracy. For consistency with our previous work,[5,6–12] the comparisons are done with respect to QC results using the CEP 4-31G(2d) basis set. At the uncorrelated level, we believe that this is amply justified by the consistencies between the CEP 4-31G(2d) computations and those using more extended basis sets, such as 6-311+G(2d,2p),[7a,7c] 6-311G**,[7a] and DZP or TZP.[12] Such agreements bore on either the energy trends as a function of the nature of the different complexes, or on the actual numerical values of ΔE(HF). We find in the general case the CEP 4-31G(2d) results to be intermediate in magnitude between the 6-311+G(2d,2p) and the 6-311G** ones.[7a] The issue at the correlated level is less clearcut, because of the inherent limitations of the MP2 approach with finite basis sets, even such as the 6-311G** or 6-311+G(2d,2p) ones. The use of ΔE(MP2) with the CEP 4-31G(2d) basis set as a target value is justified by the very close matches obtained with this basis set at the MP2 level and from the latter type of basis sets[7a] (results presented below). In an ensuing article (Antony et al., following article of this issue), the binding of thiomandelate and captopril, two mercaptocarboxylate inhibitors of a Zn–metallo–β-lactamase, were investigated in diverse competing arrangements within the enzyme binding site. Up to 20 complexes were compared in terms of their interaction energies. The evolutions of the intermolecular interaction energies using the CEP 4-31G(2d) basis set were found to be fully consistent with the corresponding ones with the 6-311G** basis set, at both uncorrelated and correlated levels. This provides a further justification for the use of the CEP 4-31G(2d) basis set to validate the SIBFA results. The diverse polyligated Zn(II) complexes reported in this and in the following article show that a closer match to the QC results is enabled than with the former SIBFA formulation and calibration.

Procedure

Ab Initio *Computations*

The *ab initio* computations used the Coreless Effective Potential (CEP) 4-31G+(2d) basis set developed by Stevens et al.[18] The decomposition of the *ab initio* SCF interaction energy was done using the Restricted Variational Space Approximation (RVS) of Stevens and Fink.[6] This procedure gives the first-order (E_1) Coulomb (E_c) and short-range exchange-repulsion (E_e) components and the second-order (E_2) polarization (E_{pol}) and charge-transfer (E_{ct}) components. The effects of basis set superposition error (BSSE) are calculated using the counterpoise method involving the virtual orbitals.[19] The contribution of correlation to the binding energy (E_{corr}), was evaluated using the MP2 procedure.[20] The RVS computations were performed with the GAMESS software.[21]

The DFT computations used the B3LYP functional[22] and the LACV3P** Gaussian basis set, which is equivalent to the 6-311G** set on the nonmetal atoms.[23] The LMP2 computations are based on the approach developed by Saebo et al.[24] and resorted to the LACV3P** basis set. The DFT and LMP2 computations used the Jaguar 5.0 software.[25] The MP2 calculations used the Gaussian 03 software.[26]

SIBFA Computations

The intermolecular interaction energy was computed is a sum of five components: electrostatic multipolar (E_{MTP}), short-range repulsion (E_{rep}), polarization (E_{pol}), charge-transfer (E_{ct}), and dispersion (E_{disp}). The multipoles (up to quadrupoles) were distributed on the atoms and the bond barycenters using a procedure developed by Vigné–Maeder and Claverie.[27] The anisotropic polarizabilities were distributed on the centroids of the localized orbitals (heteroatom lone pairs and bond barycenters) using a procedure due to Garmer and Stevens.[28] The expression of each contribution was detailed in our previous article.[5] We present here only the refinements to E_{MTP}, E_{rep}, and E_{ct}. The Zn(II) polarization energy had been previously neglected in our previous SIBFA computations studies on account of its very small values in polyligated Zn(II) complexes. For completeness purposes, it was explicitly included in the present study and, consistent with our previous work devoted to the Cu(I) cation,[12] we have also included the contribution due to quadrupole polarizability. Such a contribution, included to handle the Cu(I) and Zn(II) metal cations, could be included for other metal cations as well. Ligand-field effects that were recently embodied[13] constitute another additional contribution, specific to transition-metal cations with nonsinglet spin multiplicity.

Introduction of a Penetration Contribution, E_{pen}

Let us denote by q_i and q_j the monopoles centered on two atoms belonging to two interacting monomers, r, their distance, and Z_i and Z_j, the number of valence electrons of the two atoms concerned. Although the standard monopole–monopole interaction is expressed as $E_{\mathrm{mono\text{–}mono}} = q_i \cdot q_j/r$, the modified monopole–monopole is expressed under the form of three terms, denoting the nucleus–nucleus, electron–nucleus, and electron–electron interactions:

$$E_{\mathrm{mono\text{–}mono*}} = [Z_iZ_j - \{Z_i(Z_j - q_j)(1 - \exp(-\alpha_j \cdot r)) - Z_j(Z_i - q_i)(1 - \exp(-\alpha_i \cdot r))\} + (Z_i - q_i)(Z_j - q_j)(1 - \exp(-\beta_i \cdot r))(1 - \exp(-\beta_j r))]*(1/r)$$

α_i and β_i are parameters, depending on effective radii P_{wi}, and are given by $\alpha_i = \gamma/P_{wi}$ and $\beta_i = \delta/P_{wi}$, where γ and δ are two constants calibrated in ref. 14 to 4.42 and 4.12, respectively. For bond monopoles, the P_{wi} values are taken equal to the arithmetic mean between those of atoms forming the bond.

The second modification bore on the monopole-dipole component, which is given by:

$$E_{\mathrm{mono\text{–}dip}} = -\mu_j\xi$$

where ξ is the electric field created by the monopole i at point j, and is equal to $\xi = q_i r_{ij}/r_{ij}^3$, r_{ij} being the vector along r, directed from i to j. Then

$$E_{\mathrm{mono\text{–}dip}}{}^* = -\mu_j\xi^*, \text{ with } \xi^* = \{Z_i - (Z_i - q_i)(1 - \exp(-\eta r))\}r_{ij}/r_{ij}^3$$

$\eta = \chi/((P_{Wi} + P_{wj})/2)$, χ being a constant equal to 2.4.

Therefore,

$$E_{\mathrm{MTP}}{}^* = E_{\mathrm{mono\text{–}mono}}{}^* + E_{\mathrm{mono\text{–}dip}}{}^* + E_{\mathrm{mono\text{–}quad}} + E_{\mathrm{dip\text{–}dip}} + E_{\mathrm{dip\text{–}quad}} + E_{\mathrm{quad\text{–}quad}}$$

The parameters γ, δ, and χ were previously fit so that $E_{\mathrm{MTP}}{}^*$ reproduces E_c on the water dimer in five different orientations:[14] linear, bifurcated, cyclic, with direct approach of the O of the first monomer towards that of the second, or of one H of the first monomer towards another H from the other (see ref. 14 for details). The penetration correction for the monopole–dipole term was found to be much smaller in magnitude than that of the monopole–monopole one. Thus, for Zn(II)–water at equilibrium distance, it amounts to −1.0 kcal/mol compared to −7.0 for monopole–monopole; for bidentate Zn(II)–formate at equilibrium distance, it amounts to 1.8 kcal/mol as opposed to −20.0 for monopole–monopole. Higher order terms, such as monopole–quadrupole, could be anticipated to provide further decaying contributions. They were thus not included in the present treatment, and should be accounted for implicitly in the calibration.

Refinement of the Short-Range Repulsion Energy

In the general case, E_{rep} is expressed as sum of bond–bond, bond–lone pair, and lone pair interactions. Its detailed expression was given in previous articles.[5] Denoting by R_{IJ} the distance between the centroids of localized orbitals such as I and J (chemical bonds or lone pair hybrids), and by S a representation of the overlap between such interacting bonds and/or lone pairs, the corresponding repulsion energy

$$E_{\mathrm{rep}}(I, J) = N_{\mathrm{occ}}(I)N_{\mathrm{occ}}(J)S^2(I, J)/R_{IJ},$$

is now augmented, following an early proposal by Murrell and Teixeiras–Dias,[29] with a S^2/R^2 term, so that:

$$E_{\mathrm{rep}}(I, J) = N_{\mathrm{occ}}(I)N_{\mathrm{occ}}(J)[C_1S^2(I, J)/R_{IJ} + C_2S^2(I, J)/R_{IJ}^2)]$$

where $N_{\mathrm{occ}}(\mathrm{I})$ and $N_{\mathrm{occ}}(\mathrm{J})$ are the occupation numbers of the corresponding orbitals I and J, and C_1 and C_2 are multiplicative constants determined by fitting E_{rep} to E_{exch} on the five above-mentioned water dimers[5] (Piquemal et al., submitted). For cation–ligand interactions, E_{rep} is limited to bond–cation and lone pair–cation interactions. A more detailed expansion is recalled as Supporting Information 1. Each exponential of the cation–atom distance in the expression, S, is multiplied by a factor such as $K_{\mathrm{Zn\text{-}A}}$, dependent on Zn and the center A. The values of the $K_{\mathrm{Zn\text{-}A}}$ parameter, along with that of the effective radius of Zn, R_{wZn}, were fit to reproduce the variation of E_{exch} with the distance of Zn with respect to its ligating atom in model N, O, and S-containing ligands, namely imidazole, water and formate, and methanethiolate. The addition of an S^2/R^2 component should confer more flexibility to E_{rep}, allowing for steeper increases at short intermolecular distances, as well as for a faster damping at large distances.

Representation of π Lone Pairs

To compute E_{rep} and E_{ct}, SIBFA uses a representation with localized lone pairs. This is unambiguous for sp,^{3} sp,^{2} and sp hybrids, endowed with occupation numbers of 2, but in the case of π lone pairs, there can be some alternative choices. We denote by L a fictitious atom denoting the tip of a lone pair and Z the heavy atom (C, N, O, S) that bears it. Then the location of the lone pair can be described using internal coordinates R_{L}, θ_{L}, and ϕ_{L}, R_{L} being the distance between L and Z, θ_{L} the "valence" angle Y–Z–L, and ϕ_{L} the "dihedral" angle X–Y–Z–L, X and Y being the two atoms preceding Z. In the standard representation, π lone pairs have $\theta_{\mathrm{L}} = 90°$, and $\phi_{\mathrm{L}} = \pm 90°$. π lone pairs exert little or no effects on E_{rep} and E_{ct} in cation–ligand complexes at, or in the vicinity of, equilibrium, the interactions occurring along, or close to, the directions of saturated lone pairs, so that alternative choices for π localization may not be critical. On the other hand, our recent studies on stacked formamide dimers (Piquemal et al., submitted), where a maximum of atoms of each monomer can overlap with those of the other monomer magnifying the effect of π lone pairs, have led us to test alternative locations and then use Zn(II) as a probe over the ligand plane. We give in Appendix A the choice adopted for formate, formamide, and imidazole.

The Charge-Transfer Contribution

We have previously[5a–b] derived the following expression for E_{ct}:

$$E_{\mathrm{ct}} = -2C_{\mathrm{st}} \sum_{\mathrm{L}\alpha} N_{\mathrm{occ}}(\alpha)((T^*_{\alpha\beta})^{**}2/\Delta E^*_{\alpha\beta})$$

where β^* denotes the empty orbital on the electron acceptor B, C_{st} is a constant, $\Delta E^*_{\alpha\beta}$ is a function of the difference between the ionization potential $\mathrm{IP}_{\mathrm{L}\alpha}$ of the electron donor A and electron affinity of the electron acceptor B, $E^*_{\mathrm{A}\beta}$, with both $\mathrm{IP}_{\mathrm{L}\alpha}$ and $E^*_{\mathrm{A}\beta}$ modulated by the electrostatic potentials that A and B separately undergo in the complex (see ref. 5b for details). We have detailed in ref. 5b the expression of the numerator $T^*_{\alpha\beta}$ (then denoted as $I^*_{\alpha\mathrm{M}}$ and with M^* replacing β^*). To outline the specific calibration changes brought for Zn(II), we would like simply to recall here that $T^*_{\alpha\beta}$ is a function of (a) an exponential of an effective electron–donor distance $\rho_{\mathrm{AM}}{}^* = R_{\mathrm{AM}}/4\mathrm{sqrt}(U_{\mathrm{A}}U^*_{\mathrm{M}})$, where R_{AM} is the distance between A and M, and U_{A} and U^*_{M} effective radii used for the donor and acceptor, respectively; (b) an angular-dependent term, which is a function of the C_s and C_p lone-pair hybridization and the cosine of the angle, centered at A, between the lone pair direction and that of the segment linking A to M; (c) a factor, denoted as N^*_{AM}, which is a function of two terms: the "self-potential" of M, on the one hand, and of the potentials exerted on the donor and on the acceptor, on the other hand. The first is expressed as $D_{\mathrm{M}}F_{\mathrm{M}}$, where the self-potential F_{M} has the expression:

$$F_{\mathrm{M}} = \zeta_{\mathrm{M}} Z_{\mathrm{M}}/(nS_{\mathrm{M}} + 1)$$

where ζ_{M} and Z_{M} are the Slater exponent of the first vacant orbital of M and the nuclear charge of M ($n = 4$, $Z_{\mathrm{M}} = 2$ for Zn(II)). D_{M} is a calibration factor.

Calibration of the Method

We give in Appendix B the values of the parameters used for the calibration. The parameters for non-Zn atoms were previously determined in our study on hydrogen-bonded and stacked complexes (Piquemal et al., submitted). They are given here along with the Zn parameters for completeness. We have followed the same approach as in our original article.[5b] Thus, the monoligated complexes of Zn with the following ligands were used for the Zn parameters: water and imidazole as representatives of neutral O and N, the cation lying along the external bisector of the H–O–H or the C–N–C angle; hydroxyl, formate, and methanethiolate as representatives of anionic O and S. For the formate complex denoted as "bidentate," Zn(II) lies along the internal bisector of the O–C–O angle, being equidistant to the two anionic oxygens. For the hydroxy and methanethiolate complexes the H–O–Zn and C–S–Zn angles are 109.5°, close to the preferred values in such complexes.[5b] We have performed 0.1 Å variations of the Zn heteroatom distances and we have fitted the Zn parameters so that each individual contribution matches as closely as possible its RVS counterpart. Upon performing radial variations, the angular variables are fixed. The internal geometries of the ligands are frozen. Concerning E_{ct}, we found that several pairs of C_{st} and D_{M} values gave similar results in the monoligated complexes, an increase of D_{M} necessitating a decrease of C_{st}. Considering the strong nonadditive character of E_{ct} in polyligated complexes, we have chosen to select the combination that allowed for the best match to E_{ct}(RVS) upon passing from the monoligated $(\mathrm{Zn{-}{-}H_2O})^{2+}$ complex to the hexahydrated $[\mathrm{Zn(H_2O)_6}]^{2+}$ one, with increases of D_{M} reducing the anticooperative character and conversely. For E_{ct}, the only changes with respect to the original Zn calibration were thus on C_{st}, D_{M}, and U^*_{M} and the I factor. Their definitions and values are given in Supporting Material S1 and in Appendix B, respectively. All polyligated Zn(II) complexes, except $[\mathrm{Zn(H_2O)_6}]$,[2] were thus part of the test set. The monoligated Zn–formamide and Zn–formate in the nonbisecting positions described below were also part of the test set. Although the ligand parameters are transferable to study interactions that do not involve Zn(II), the present Zn(II) parameters (effective radii, $K_{\mathrm{Zn\text{-}X}}$ parameters for E_{rep} and $L_{\mathrm{Zn\text{-}X}}$ parameters for E_{disp})

Table 1. Zn(II)—Formate Complex

	Angle						
	090°	105°	120°	135°	150°	165°	180°
E_c	−305.2	−313.9	−315.9	−312.9	−308.2	−304.8	−304.4
E_{exch}	84.8	77.7	72.4	66.4	61.0	57.3	55.6
$\boldsymbol{E_1}$	**−220.4**	**−236.3**	**−243.5**	**−246.4**	**−247.2**	**−247.5**	**−248.8**
E_{pol}(RVS)	−68.3	−63.1	−62.1	−62.9	−64.0	−64.5	−64.4
E_{ct}(RVS)	−24.6	−25.1	−24.7	−22.7	−20.3	−18.6	−18.3
$\boldsymbol{\Delta E}$	**−316.0**	**−327.3**	**−333.1**	**−334.9**	**−334.2**	**−333.2**	**−334.0**
E^*_{MTP}	−311.3	−315.5	−316.7	−314.6	−311.3	−308.9	−309.4
E^*_{rep}	91.1	69.7	61.4	55.9	51.1	47.5	46.2
$\boldsymbol{E_1}$**(SIBFA)**	**−220.1**	**−245.8**	**−255.2**	**−258.8**	**−260.2**	**−261.4**	**−263.2**
E_{pol}(SIBFA)	−64.0	−61.1	−60.8	−61.6	−62.7	−63.4	−63.4
E_{ct}(SIBFA)	−18.5	−20.5	−20.9	−20.2	−18.8	−17.4	−17.0
$\boldsymbol{\Delta E}$**(SIBFA)**	**−302.6**	**−327.3**	**−336.8**	**−340.6**	**−341.8**	**−342.4**	**−343.7**

Evolution as a function of the Zn–O–C angle of E_1(RVS), E_2(RVS), E_1(SIBFA), and E_2(SIBFA) and of their individual contributions, and of ΔE(RVS) and ΔE(SIBFA) in the absence of the E_{disp} contribution. The Zn—O distance is set at 1.8 Å.

are not transferable to another cation, even to isoelectronic Cu(I). On the other hand, they could be used as starting points for Cu(I) calibration in the framework of the reformulated SIBFA procedure.

Energy minimizations done to optimize in the test set the polyligated complexes were done with the Merlin package.[30]

Results and Discussions

The compared RVS and SIBFA computations are reported in Tables 1–2 and Supporting Material S2–S5 for the monoligated Zn(II) complexes and in Tables 3–6 and Supporting material S6 for polyligated Zn(II) complexes. For polyligated complexes, two QC values are given for E_{pol}. The first value, E_{pol}(RVS), gives the energy computed from the RVS analysis, each monomer being relaxed, in turn, while the orbitals of the others are frozen. This does not allow for the onset of higher than second-order terms exerted on each monomer due to relaxation of the other monomers' orbitals. The second value, E_{pol}(HF), is a value indirectly obtained upon subtracting from the total ΔE(HF), without removing the BSSE error, the sum of E_1 and E_{ct}. This should afford an estimate of the effects of crossrelaxation of the orbitals on the polarization energy. Tables 3–6 also give the values of E^*_{ct}(RVS), in which we subtracted from E_{ct}(RVS) the BSSE correction. This is an estimate, assuming tentatively that the BSSE correction should solely apply to E_{ct}. Correspondingly, we give for the SIBFA polarization contribution two values: E_{pol}(SIBFA), resulting from the

Table 2. Interaction Energies (kcal/mol) for Complexes of Zn(II) with the Cation in a Position Perpendicular to the O or the C Carbon Atom of (a) Formamide; (b) Formate

	(a) Formamide				(b) Formate			
	Zn over O *d* Zn–O = 1.90 Å		Zn over C *d* Zn–C = 2.20 Å		Zn over O *d* Zn–O = 1.80 Å		Zn over C *d* Zn–O = 2.0 Å	
	RVS	SIBFA	RVS	SIBFA	RVS	SIBFA	RVS	SIBFA
E_c/E^*_{MTP}	−66.3	−65.6	−3.9	−3.9	−308.4	−306.0	−242.7	−242.9
$E_{\mathrm{exch}}/E_{\mathrm{rep}}$	46.9	43.3	13.6	16.6	76.7	65.5	31.6	40.1
$\boldsymbol{E_1}$	**−19.4**	**−22.3**	**9.7**	**12.8**	**−231.8**	**−240.5**	**−211.1**	**−202.9**
E_{pol}(lig)	−59.5	−51.9	−53.1	−47.7	−63.9	−58.0	−62.8	−68.3
E_{pol}(Zn(II))	−1.4	−3.3 (−2.0)	−0.2	−0.7 (−0.5)	−2.7	−8.8 (−4.4)	−0.5	−3.2 (−0.6)
E_{ct}(lig)	−15.4	−10.1	−10.0	−9.7	−22.2	−18.2	−16.9	−16.6
E_{ct}(Zn(II))	−0.6	0.0	−0.3	0.0	−0.9	0.0	−0.8	0.0
$\boldsymbol{\Delta E}$	**−98.2**	**−88.1**	**−54.5**	**−46.1**	**−324.3**	**−329.2**	**−293.7**	**−293.8**

Values in parentheses correspond to the contribution to Zn polarization due to its quadrupole polarizability.

Table 3. Interaction Energies (kcal/mol) for Complexes of Zn(II) with Three Ligands: Neutral (Imidazole) or Anionic (Methanethiolate)

	$[\mathrm{Zn\ (imidazole)_3}]^{2+}$		$[\mathrm{Zn(CH_3S)}]^{-1}$	
	Ab initio	SIBFA	*Ab initio*	SIBFA
E_c/E_{MTP}	−303.0	−314.9	−664.5	−658.5
$E_{\mathrm{exch}}/E_{\mathrm{rep}}$	138.5	145.7	128.4	116.9
$\boldsymbol{E_1}$	**−164.5**	**−169.2**	**−536.1**	**−541.7**
$E_{\mathrm{pol}}(\mathrm{RVS})/E^*_{\mathrm{pol}}$	−157.8	−157.1	−95.6	−102.1
$E_{\mathrm{pol}}(\mathrm{HF})/E_{\mathrm{pol}}$	−132.5	−130.1	−75.7	−82.9
E_{ct}	−40.0	−29.2	−51.0	−45.2
$E_{\mathrm{ct*}}$	−37.7		−46.4	
BSSE	−2.3		−4.6	
$\boldsymbol{\Delta E}$	**−335.3**	**−328.5**	**−658.8**	**−669.7**
$\boldsymbol{\Delta E(\mathrm{MP2})/\Delta E_{\mathrm{tot}}}$	**−373.7**	**−366.1**	**−695.1**	**−725.9**
$\delta E(\mathrm{MP2})/E_{\mathrm{disp}}$	−38.4	−37.6	−36.3	−56.1
$\boldsymbol{\Delta E(\mathrm{HF/6\text{-}311G^{**}})^{a}}$	**−332.4**		**−639.9**	
$\boldsymbol{\Delta E(\mathrm{LMP2})^{a}}$	**−339.6**		**−656.2**	
$\delta E(\mathrm{LMP2})^{a}$	−7.2		−16.3	
$\boldsymbol{\Delta E(\mathrm{HF/6\text{-}311{+}G^{**}})^{b}}$	**−331.9**		**−649.2**	
$\boldsymbol{\Delta E(\mathrm{MP2})^{b}}$	**−363.1**		**−699.2**	
$\delta E(\mathrm{MP2})^{b}$	−31.2		−50.0	
$\boldsymbol{\Delta E(\mathrm{HF/6\text{-}311{+}{+}G}(3df, 3pd))}$	**−332.8**		**−650.9**	
$\boldsymbol{\Delta E(\mathrm{MP2})^{b}}$	**−367.5**		**−691.7**	
$\delta E(\mathrm{MP2})^{b}$	−34.7		−41.2	

[a] LACV3P**, with effective core potential on Zn(II).
[b] Full electron basis set on Zn(II).

summed polarization energies of each monomer by the electrostatic field exerted by the permanent multipoles and induced dipoles of the other monomers; and E^*_{pol} (SIBFA) resulting from the summed monomer polariztion energies by the fields due to the sole permanent multipoles of the others. We give on the same lines of results the values and E_{pol}(HF) and E_{pol}(SIBFA) on the one hand, and those of E_{pol}(RVS) and E^*_{pol}(SIBFA) on the other hand.

Table 4. Interation Energies (kcal/mol) for Complexes of Zn(II) with Four Ligands: Neutral (Imidazole) or Anionic (Methanethiolate)

	$[\mathrm{Zn(imidazole)_4}]^{2+}$		$[\mathrm{Zn(imidazole)_2(CH_3S)_2}]$		$[\mathrm{Zn(CH_3S)_4}]^{2-}$	
	Ab initio	SIBFA	*Ab initio*	SIBFA	*Ab initio*	SIBFA
E_c/E_{MTP}	−371.4	−390.1	−655.7	−660.4	−632.4	−623.6
$E_{\mathrm{exch}}/E_{\mathrm{rep}}$	161.8	172.7	152.0	149.3	107.1	91.3
$\boldsymbol{E_1}$	**−209.9**	**−217.4**	**−503.6**	**−511.0**	**−525.3**	**−532.3**
$E_{\mathrm{pol}}(\mathrm{RVS})/E^*_{\mathrm{pol}}$	−170.8	−168.9	−113.0	−119.0	−68.0	−65.3
$E_{\mathrm{pol}}(\mathrm{HF})/E_{\mathrm{pol}}$	−132.6	−127.3	−87.6	−91.7		−49.8
E_{ct}	−40.9	−29.6	−46.5	−39.1	−42.9	
$E_{\mathrm{ct*}}$	−37.6		−39.6		−37.0	−45.3
BSSE	−3.3		−5.1		−5.9	
$\boldsymbol{\Delta E}$	**−379.8**	**−374.3**	**−632.7**	**−641.9**	**−612.4**	**−627.4**
$\boldsymbol{\Delta E(\mathrm{MP2})/\Delta E_{\mathrm{tot}}}$	[a]	**−422.1**	**−694.4**	**−702.2**	**−654.1**	**−689.9**
$\delta E(\mathrm{MP2})/E_{\mathrm{disp}}$		−47.9	−61.7	−60.3	−41.7	−62.5
ΔE(HF/LACV3P)**	**−380.0**		**−622.7**		**−596.7**	
$\boldsymbol{\Delta E(\mathrm{LMP2})}$	**−390.3**		**−641.9**		**−607.7**	
$\delta E(\mathrm{LMP2})$	−10.3		−19.8		−11.0	

[a] Unconverged.

Table 5. Interaction Energies (kcal/mol) in the β-Lactamase Binding Sites

	a		*b*		*c*		*d*	
	Ab initio	SIBFA	*Ab initio*	SIBFA	*Ab initio*	SIBFA	*Ab initio*	SIBFA
E_c/E_{MTP}	−1351.8	−1373.4	−1346.3	−1367.1	−1330.7	−1364.7	−1321.0	−1345.4
$E_{\mathrm{exch}}/E_{\mathrm{rep}}$	362.3	393.9	344.3	370.0	350.4	390.5	375.9	398.8
$\boldsymbol{E_1}$	**−989.5**	**−979.5**	**−1002.0**	**−997.2**	**−980.4**	**−974.2**	**−945.1**	**−946.6**
$E_{\mathrm{pol}}(\mathrm{RVS})/E^*_{\mathrm{pol}}$	−223.9	−224.6	−203.3	−202.0	−209.9	−215.7	−252.9	−250.6
$E_{\mathrm{pol}}(\mathrm{HF})/E_{\mathrm{pol}}$	−184.9	−165.4	−173.6	−151.8	−185.6	−171.9	−216.9	−199.5
$E_{\mathrm{pol}}(\mathrm{Zn(II)})$	−6.1	−3.6	−6.0	−3.0	−7.8	−4.5	−8.0	−3.7
E_{ct}	−56.8	−43.4	−57.2	−45.9	−60.9	−45.1	−75.2	−51.7
$E_{\mathrm{ct}*}$	−35.7		−36.5		−40.1		−56.3	
BSSE	−21.1		−20.7		−20.8		−19.0	
Δ*E*	**−1210.2**	**−1188.5**	**−1212.1**	**−1194.8**	**−1206.0**	**−1191.2**	**−1218.8**	**−1197.9**
Δ*E*(MP2)/Δ$\boldsymbol{E_{\mathrm{tot}}}$	**−1327.6**	**−1304.6**	**−1324.3**	**−1305.6**	**−1313.5**	**−1299.3**	**−1325.7**	**−1309.5**
$\delta E(\mathrm{MP2})/E_{\mathrm{disp}}$	−117.4	−116.1	−112.2	−110.8	−107.5	−107.1	−106.9	−111.6
Δ*E*(HF/LACV3P)**	**−1241.0**		**−1242.6**		**−1237.4**		**−1248.3**	
Δ*E*(LMP2)	**−1270.5**		**−1270.6**		**−1270.2**		**−1272.5**	
$\delta E(\mathrm{LMP2})$	−29.5		−28.0		−32.8		−24.2	
Δ*E*(B3LYP/LACV3P)**	**−1292.1**		**−1292.7**		**−1284.9**		**−1296.6**	

a–c: Standard complexes from the *B. fragilis* binding site; *d:* Complex derived from HF energy minimization. In *a–c,* the Zn–Zn distances are 3.0, 3.5, and 3.8 Å, respectively. In *d,* the Zn–Zn distance is 4.8 Å.

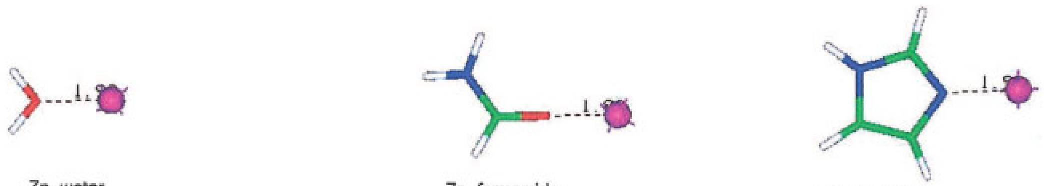
Monoligated Complexes

We have monitored Zn(II) binding to three representative neutral ligands: water, formamide, and imidazole, and to three representative anionic ligands: formate, hydroxy, and methanethiolate. The complexes are represented in chart I. Tables S2 and S3 compare the corresponding *ab initio* and SIBFA interaction energy values and components at optimized Zn–ligand positions, which except for Zn(II)–formamide were used to calibrate the Zn effective radii used for E_{pen}, E_{rep}, E_{pol}, E_{ct}, and E_{disp}, and the $K_{\text{L-Zn}}$ and $L_{\text{L-Zn}}$ pair-wise repulsion and dispersion Zn(II) parameters (L = N, O, or S). Tables S2 and S3 show Δ*E*(SIBFA) to reproduce closely the values of Δ*E*(RVS). There is also a good reproduction of the individual components of Δ*E*(RVS), namely E_c, E_{exch}, E_{pol}, and E_{ct} by their respective SIBFA counterparts E_{MTP}*, E_{rep}, E_{pol}, and E_{ct}. The weights of the second-order terms, E_{pol} and E_{ct}, are significant, as previously emphasized.[5a–b] Thus, for all three neutral ligands at equilibrium distances, E_{pol} alone has a larger magnitude than E_1, and the magnitude of E_{ct} in the anionic ligand complexes is substantial, amounting to approximately −50 kcal/mol in Zn(II)–methanethiolate. With the anionic ligands, E_{pol}(Zn)

Table 6. Interaction Energies (kcal/mol) in the Zn(II)-Binding Site of the Phospho-Mannoisomerase Metalloenzyme Encompassing a Zn-Binding Ligand Consisting of (a) Hydroxamate; (b) Formate; (c) Dianionic Phosphate

	a: Hydroxamate		b: Formate		c: Dianionic phosphate	
	Ab initio	SIBFA	*Ab initio*	SIBFA	*Ab initio*	SIBFA
E_c/E_{MTP}	−711.9	−744.8	−705.6	−732.3	−913.5	−936.3
$E_{\mathrm{exch}}/E_{\mathrm{rep}}$	144.1	147.1	152.6	152.2	182.0	189.9
$\boldsymbol{E_1}$	**−567.8**	**−596.9**	**−553.0**	**−580.1**	**−731.4**	**−746.4**
$E_{\mathrm{pol}}(\mathrm{RVS})/E^*_{\mathrm{pol}}$	−99.4	−82.5	−99.6	−81.3	−94.1	−82.5
$E_{\mathrm{pol}}(\mathrm{HF})/E_{\mathrm{pol}}$	−88.2	−68.3	−86.9	−66.3	−91.8	−74.0
E_{ct}	−26.6	−22.1	−28.3	−22.2	−28.3	−25.1
$E_{\mathrm{ct}*}$	−18.1		−20.5		−19.1	
BSSE	−8.5		−7.8		−9.2	
Δ*E*	**−674.1**	**−687.3(−651.2[a])**	**−660.4**	**−665.9(−642.8[a])**	**−842.3**	**−845.5(−833.2[a])**
Δ*E*(MP2)/Δ$\boldsymbol{E_{\mathrm{tot}}}$	**−729.8**	**−736.0(−701.0[a])**	**−714.4**	**−711.6(−690.2[a])**	**−903.1**	**−895.2(−890.4[a])**
$\delta E(\mathrm{MP2})/E_{\mathrm{disp}}$	−55.7	−48.8	−54.0	−45.8	−60.8	−51.0
Δ*E*(HF/LACV3P)**	**−700.3**		**−683.0**		**−867.3**	

[a] Using the E_{MTP} and E_{rep} formulation and the E_{ct} calibration of refs. 7a and 34.



Zn–water Zn–formamide Zn–imidazole

Zn–formate, bridge Zn–hydroxy Zn–methanethiolate Zn–formate, external

Zn–formamide perpendicular through O Zn–formamide perpendicular through C Zn–formate, perpendicular through O Zn–formate, perpendicular through C

Chart 1.

has a larger magnitude than its RVS counterpart. This stems from the quadrupole polarizability. Alternative calibration with screening of the field exerted on the cation did not modify such a shortcoming. Such overestimations were previously encountered with monoligated Cu(I)–anionic ligand complexes.[12] The overestimation is, in fact, smaller with Zn(II), because the components of its quadrupole polarizability are about four times smaller than the corresponding Cu(I) polarizability components derived from the same basis set as for Zn(II). We also found such an overestimation to be much less important in the case of the polyligated Zn(II) complexes (see below). In such complexes, the fields polarizing the cation, and their derivatives as well, tend to mutually compensate, resulting into significantly diminished E_{pol}(Zn) values.

The least agreement in terms of ΔE relates to the bidentate Zn(II)–formate complex, the error being of 9 kcal/mol out of 380, namely 3%, due to an overestimated value of E_{rep} (84.3 kcal/mol) with respect to E_{exch} (71.8 kcal/mol), insufficiently compensated for by a lesser overestimation of E_{MTP} compared to E_c (−362.1 vs. −358.5 kcal/mol, respectively). Nevertheless, it could be anticipated that in actual polyligated Zn complexes that involve this ligand,[7a–b,31] due to increased Zn–O$^-$ distances resulting from repulsive ligand–ligand interactions, such an overestimation should be reduced.

As an estimate of the basis set dependency of the RVS results, we have also recomputed the HF interaction energies in the same positions with the LACV3P** basis set. For the latter computations, we did not remove the BSSE correction, which the CEP 4-31G(2d) results show to be very small, namely <2%. The values of ΔE(RVS) using the CEP 4-31G(2d) basis set are close to those of ΔE(HF) with the LACV3P** basis set. The sole exception is the Zn–hydroxy complex, for which the LACV3P** basis set gives a 10 kcal/mol larger in magnitude ΔE than the CEP 4-31G(2d) basis set.

At the correlated level, ΔE_{tot}(SIBFA) with the dispersion energy contribution, E_{disp}, can correctly reproduce, at equilibrium distance, δE(MP2) with the CEP 4-31G(2d) basis set, namely the gain in interaction energy upon passing from the HF to the MP2 level. On the other hand, the ΔE gains at the LMP2 level with the LACV3P** basis set are significantly smaller. In one case, Zn–formamide, ΔE(LMP2) is actually smaller in magnitude than ΔE(HF).

It was necessary to evaluate the extent to which the reformulated E_{MTP*} and E_{rep} SIBFA contributions can each reproduce their RVS counterparts E_c and E_{exch}, away from equilibrium distances. We have reported in Tables S4 the values of these contributions and those of E_1, ΔE(RVS) and ΔE(SIBFA) upon performing upon variations of the Zn–ligand distance, $d_{Zn\text{-}L}$, in four complexes: Zn–water, Zn–imidazole, Zn–formate, and Zn–methanethiolate. The corresponding evolutions of SIBFA and RVS E_{pol}, E_{ct}, and δE(MP2) or E_{disp} are given as Supporting Information S5. For all complexes, the agreement between ΔE(SIBFA) and ΔE(RVS) obviously improves upon progressive lengthening of $d_{Zn\text{-}L}$. For Zn–water, it is poorer when $d_{Zn\text{-}L}$ becomes by 0.2 Å less than equilibrium distance, both E_{pol} and E_{ct}(SIBFA) increasing slower in magnitude than their RVS counterparts.

For Zn–imidazole, the agreement between SIBFA and RVS ΔE values also downgrades when $d_{\text{Zn-L}} < 0.2$ Å than equilibrium distance, but this is now due to the steeper increase of E_{rep} than E_{exch}. For the bidentate Zn–formate complex, an agreement of <3% relative error occurs only at, and past, equilibrium distance. A better agreement is found in Zn–methanethiolate on the other hand. The very close match of E_{MTP}* to E_C in both formate and methanethiolate complexes is noteworthy. Concerning the second-order components (Table S5), and as noted in our original article,[5b] the decay of E_{ct} in both anionic complexes as a function of distance is shallow. In fact, in the methanethiolate complex, E_{ct}(RVS) starts to *increase* in magnitude upon increasing the Zn–L distance past equilibrium distance ($d_{\text{Zn-S}} > 2.2$ Å), a feature also observed with E_{ct}(SIBFA).

We have also monitored the angular dependencies of ΔE(RVS) and ΔE(SIBFA) in the Zn–monodentate complex, upon varying by 15° increments the θ = C—O—Zn angle (Table 1), the starting position having the Zn—O bond *cis* to the H—C bond, the distance between Zn and the ligating O being 1.8 Å. This test is more stringent than in our original article,[5b] where the corresponding Zn—O distance was 2.0 Å, and because we now aim at a term-to-term identification of both E_1(SIBFA) contributions to their RVS counterparts, not just E_1(SIBFA) to E_1(RVS). With the exception of $\theta = 90°$, the agreement between ΔE(SIBFA) and ΔE(RVS) is with a relative error of <3%, and both energies have the same θ dependency. This is, however, due in part to some compensation of errors, a 5% overestimation of E_1 being compensated for by somewhat smaller E_{pol} and E_{ct} SIBFA values than their RVS counterparts. The very close match of E_{MTP}* to E_c is again noteworthy throughout all θ values investigated.

The radial dependencies of δE(MP2) reported in Table S5 are much more complex than could be accounted by E_{disp} which has essentially a $1/R^n$ (n = 6, 8, 10) dependency. Thus, with the Zn–neutral ligand complexes, its radial decay is very shallow, and it starts to slowly increase in magnitude at very large distances, as in Zn–imidazole for $d_{\text{Zn-N}} = 2.2$ Å. With anionic ligands, it either displays a very slow increase in magnitude at and past equilibrium distance (as in Zn–formate), or a flat behavior with an eventual modest increase in magnitude >0.4 Å past equilibrium (as in Zn–methanethiolate). Such radial behaviors are similar to those of E_{ct}(RVS). They could indicate convergence towards other states upon inclusion of correlation, with one electron transferred from the anion to Zn. Such states, however, would not be stabilized in polyligated complexes, in which the summed fields of the ligands stabilize preferentially the dipositive Zn charge.

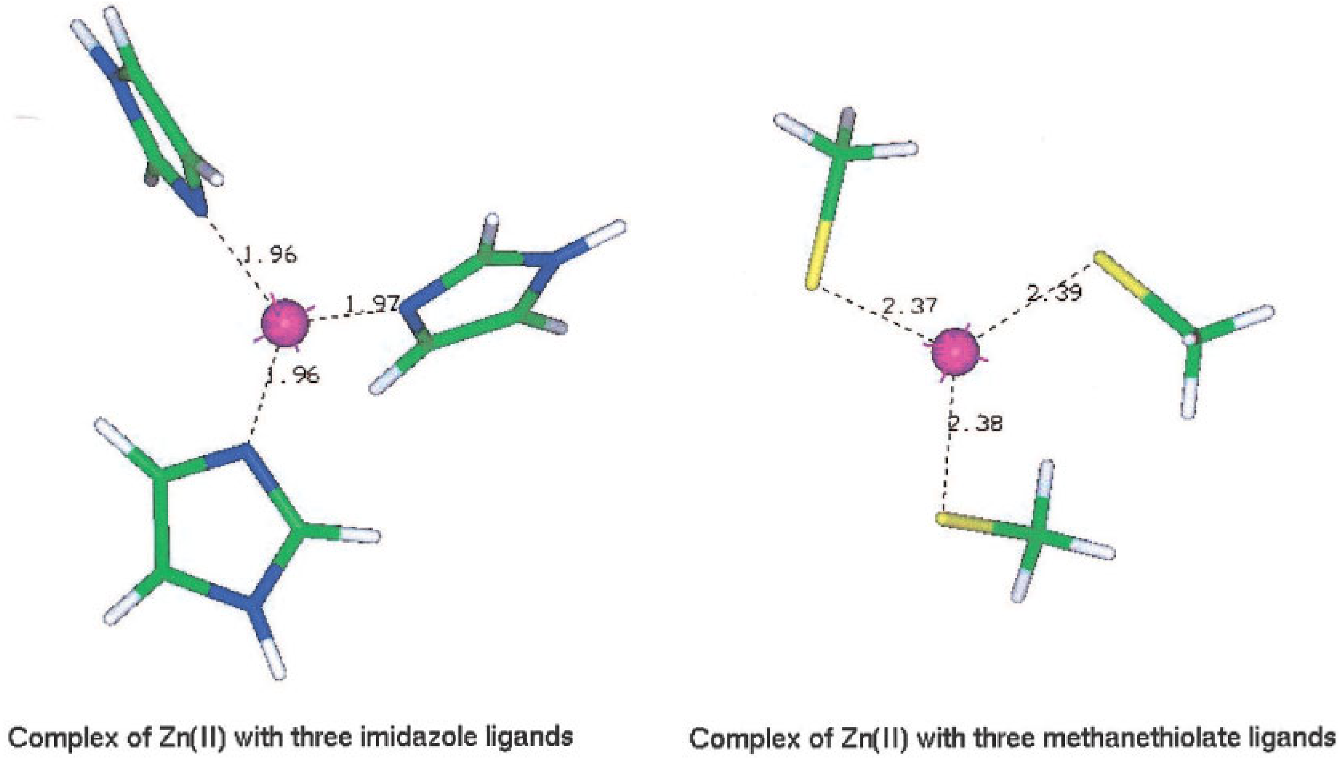
We have finally, for both Zn–formamide and Zn–formate, also investigated positions where Zn(II) is perpendicular to the ligand plane, over either an oxygen or over the carbon atom with the corresponding Zn–O–C or the Zn–C–O angles set at 90° and the Zn–O or Zn–C distances optimized (Table 2). Although on account of their significantly diminished interaction energies with respect to the minimum, such extreme binding positions are unlikely to be ever encountered in Zn–complexes of interest, we used them as probes for the representation of the interactions that take part above the rings of conjugated ligands. This enabled us to evaluate the validity of resorting to "localized" π lone pairs to represent such interactions, regarding the E_{rep}, E_{pol}, and E_{ct} contributions. As seen in Table 2, a representation of π lone pairs as "bent" lone pairs enables E_{rep} to satisfactorily reproduce E_{exch} in such modes of binding. In the case of Zn–formamide, this is in keeping with the results previously obtained for E_{rep} in stacked formamide dimers, in which a maximum of atoms from each monomer overlap with the atoms from the other monomer (Piquemal et al., submitted). We found, on the other hand, that such a representation resulted into underestimated values of E_{ct}(SIBFA) compared to E_{ct}(RVS), and we retained instead for this contribution our former representation[5b] in which the π lone pairs of the heteroatom are perpendicular to the ligand plane. We have empirically retained the former representation for E_{ct} as it could allow for an expansion and enhanced overlap of the high-lying, electron-donating π orbitals, upon approach of an electron-deficient atom above the conjugated plane. Concerning the SIBFA E_{pol} contribution, the centroids of the C═O and C—N bond polarizabilities are those obtained by the Garmer–Stevens procedure following a Boys localization procedure. This results into a representation of the C═O and C═N bond centroids similar to that in terms of "bent" π lone pairs above and below the ligand plane. Table 2 shows that ΔE(SIBFA) can closely reproduce ΔE(RVS) in Zn–formate in both perpendicular complexes, the agreement on the individual contributions being similar to those obtained in the in-plane mono- and bidentate complexes. ΔE(SIBFA) reproduces less well ΔE(RVS) in Zn–formamide. This is due to the largest part to E_{pol}(SIBFA), which is underestimated with respect to E_{pol}(RVS). This could indicate some limitations inherent to a representation of the polarizabilities of conjugated molecules by localized bond polarizabilities, although these appear only in particular modes of binding that are significantly less favorable energetically than the standard modes of approach. Stacking interactions occurring perpendicular to the ring planes involve either neutral molecules or molecules that have singly charged moieties as contrasted to the dipositive Zn(II) charge. They occur at significantly larger distances (>3.0 Å) than the presently considered 1.8–2.2 Å range for Zn interactions. It is thus highly likely that the shortcomings in E_{pol} representation should be of limited impact.

Polyligated Complexes

Mononuclear Zn(II) Complexes

Complexes of Zn(II) with Six Water Molecules

We have reinvestigated the complexes of Zn(II) with six waters in three arrangements: (a) $[\text{Zn}(\text{H}_2\text{O})_{6)}]^{2+}$, in which the cation is complexed with six inner-shell water molecules in a regular octahedral arrangement; (b) $[\text{Zn}(\text{H}_2\text{O})_5((\text{H}_2\text{O})]^{2+}$, in which it is bound by five inner-shell waters in a trigonal bipyramidal arrangement and one outer shell water; and (c) $[\text{Zn}(\text{H}_2\text{O})_4((\text{H}_2\text{O})_2]$,[2] in which it is bound by four inner-shell waters in a tetrahedral arrangement, and two outer-shell molecules. These arrangements have been previously investigated by parallel SIBFA and QC computations.[7b] We wished to evaluate the effects the present refinements on E_{MTP}, E_{rep}, and E_{ct}, on ΔE(SIBFA) as well as on the individual contributions. Table S6 shows, conforming to our previous results, that the ordering (a) > (b) > (c), is identical to the QC one, that it involves small (2%) (a)–(b) or (b)–(c) ΔE differences, and that such differences result from compensations between large energy differences of first



Complex of Zn(II) with three imidazole ligands

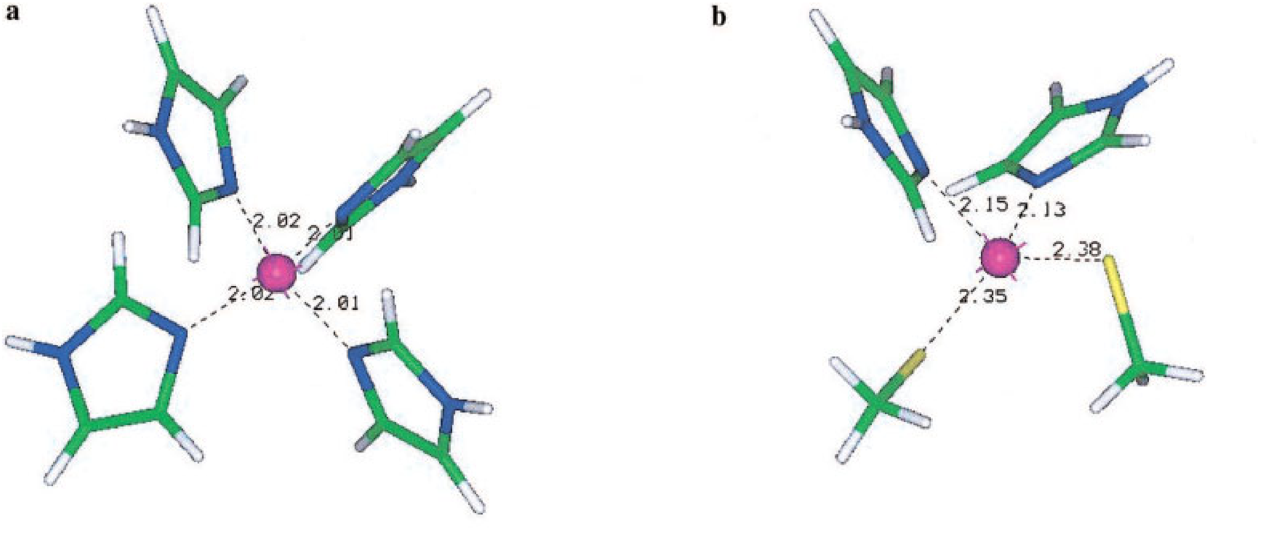
Complex of Zn(II) with three methanethiolate ligands

Figure 1. Representation of the complexes of Zn(II) with: (a) three imidazole ligands; (b) three methanethiolate ligands. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

versus second-order contributions. Thus, E_1 increasingly favors the complexes with the largest coordination numbers, while conversely, both E_{pol} and E_{ct} favor the complexes with the smallest coordination numbers. Regarding the first-order components, examination of Table S5 shows E_1(SIBFA) to much more accurately reproduce E_1(RVS) than was the case with the previous SIBFA formulation. Thus, E_1(RVS) amounts to −209.1, −191.9, and −174.9 kcal/mol in complexes (a)–(c), respectively. The corresponding SIBFA values are −213.0, −193.6, and −174.8. In our previous formulation, these values ware actually lower, amounting to −218.2, −198.9, and −179.6 kcal/mol, respectively. E_{ct}(SIBFA) is much closer to E_{ct}(RVS) than previously. Thus, E_{ct}(RVS) amounts to −20.7, −24.5, and −28. kcal/mol in (a)–(c), and E_{ct}(SIBFA) to −21.8, −24.6, and −27.4 kcal/mol, while the previous calibration gave smaller values of −14.6, −18.6, and −22.5 kcal/mol, respectively. Therefore, even though our former formulation gave ΔE values virtually identical to the present one, it involved some underlying compensation of errors, with slightly overestimated E_1 values and slightly underestimated E_{ct} ones. Table S6 also highlights the very close agreement obtained between the CEP 4-31G(2d) results and those from the 6-311+G** basis set, with an all-electron representation of Zn(II), taking place at both HF and MP2 levels. Thus, for complexes (a)–(c), ΔE(MP2) amounts to −345.3, −341.0, and −337.4 kcal/mol, respectively, with the CEP 4-31G(2d) basis set. The corresponding 6-311+G** basis set values are −342.4, −339.8, and −337.2 kcal/mol. We have further expanded the basis set to 6-311G++(3df,3pd). The ΔE values at the HF level are closer to the CEP 4-31G(2d) ones than the 6-311+G** set. On the other hand, the energy gains at the MP2 level are similar in both 6-311G++(3df,3pd) and 6-311+G** basis sets, and by 6-9 kcal/mol out of 25 smaller in magnitude than with the CEP 4-31G(2d) basis set.

Complexes of Zn(II) with Three Imidazole or Three Methanethiolate Ligands

Energy-minimization of the [Zn (imidazole)$_3$]$^{2+}$ and the [Zn(CH$_3$S)$_3$]$^{-1}$ complexes resulted into the structures reported in Figure 1, and the values of the SIBFA and QC interaction energies are reported in Table 3. A close agreement of ΔE(SIBFA) and its contributions to their RVS counterparts can be noted. Again, the results for [Zn(CH$_3$S)]$^{-1}$ indicate a significant improvement in the reproduction of ΔE(RVS) compared to our previous formulation. Thus, the value of −542.2 kcal/mol for E_1(SIBFA) is much closer to the −536.1 value than the −517.2 kcal/mol of ref. 7b. E_{ct}(SIBFA) has a value of −45.2 close to the −51.0 one of E_{ct}(RVS), while E_{ct}(SIBFA) from our previous calibration was significantly reduced (−31 kcal/mol) owing to an exaggerated anticooperativity. ΔE(SIBFA) now amounting to −669.5 kcal/mol, is correspondingly much closer to the ΔE(RVS) value of −658.8 kcal/mol than the previous ΔE(SIBFA) value of −629.2 kcal/mol. On the other hand, as mentioned in refs. 7a–b, E_{disp}(SIBFA) is an additive contribution, whereas as analyzed



Complex of Zn(II) with four imidazole ligands

Complex of Zn(II) with two imidazole and two methanethiolate ligands

Figure 2. Representation of the tetraligated complexes of Zn(II) with: (a) four imidazole ligands; (b) two imidazole ligands and two methanethiolate ligands. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in refs. 7a–b, the gain in correlation upon passing from the HF to the MP2 level is nonadditive, being anticooperative in Zn(II)-polyligated complexes with anionic ligands. As a consequence, E_{disp} has a larger magnitude than δE(MP2) (−56.1 vs. −36.3 kcal/mol). Recent energy decompositions of H-bonded[32] and cation–ligand complexes[33] performed at the correlated (DFT) level indicated that upon passing from the HF to the DFT level, a significant contribution to energy stabilization was due to the actual E_{ct} contribution. We are accordingly elaborating an alternative calibration of SIBFA, in which the multipoles and polarizabilities are derived from DFT density matrices, with E_{pen}, E_{rep}, and E_{ct} rescaled so as to reproduce E_c, E_{exch}, and E_{ct} from such correlated energy-decomposition analyses, while E_{disp} is rescaled to reproduce the differences between ΔE(MP2) and ΔE(DFT). The results will be reported in a future study. Consistent with the Zn(II) hexahydrate complexes, we note again close agreements between the CEP 4-31G(2d) and the 6-311+G** basis set with an all-electron representation of Zn(II). Thus, the CEP 4-31G(2d) values of ΔE(HF) are −335.3 and −658.8 kcal/mol for the Zn(II) complexes with three imidazoles and three methanethiolates, respectively. The corresponding 6-311+G** values are −331.9 and −649.2 kcal/mol. These values are not significantly modified upon passing to the 6-311++G(3df,3pd) basis set, with which they amount to −332.8 and −650.9 kcal/mol, respectively. There are larger differences between QC values upon passing to the MP2 level. Thus, for $[\mathrm{Zn(imidazole)_3}]^{2+}$, and similar to the Zn(II) hexahydrate complexes, the ΔE gain due to MP2 is larger with the CEP 4-31G(2d) basis set than with either 6-311+G** and 6-311++G(3df,3pd) sets, by 7.2 and 3.7 kcal/mol, respectively. By contrast, such a gain is smaller in the case of $[\mathrm{Zn(CH_3S)_3}]^-$. δE(MP2) now amounts to −36.3, −50.0, and −41.2 kcal/mol with the CEP 4-31G(2d), the 6-311+G** and the 6-311++G(3df,3pd) sets, respectively. Thus, for both complexes at the MP2 level, passing to the largest basis set would seem to improve the agreement with the CEP 4-31G(2d) basis, but this could be fortuitous to some extent, with some BSSE at the correlated level compensating, for this basis, for the reduced number of basis functions and lesser polarizability.

Tetraligated Complexes of Zn(II) with Imidazole or Methanethiolate Ligands

We have energy-minimized three complexes: (a) $[\mathrm{Zn(imidazole)_4}]^{2+}$, (b) $[\mathrm{Zn(imidazole)_2(CH_3S)_2}]$, and (c) $[\mathrm{Zn(CH_3S)_4}]^{2-}$ as models for the interactions involving Zn(II) in the core of Zn-finger proteins. In line with ref. 7b, this also enables to probe the evolution of ΔE(SIBFA) and its contribution as a function of the total charge of its ligands [0, −2, and −4 in (a)–(c), respectively] and how well they reproduce the corresponding evolutions of their RVS counterparts. The results are reported in Table 4. Complexes (a) and (b) are represented in Figure 2a–b. For all three complexes, ΔE(SIBFA) and its contributions correctly reproduce their RVS counterparts. The largest relative error in ΔE(SIBFA) vs. ΔE(RVS) is for complex (c), 15 kcal/mol out of 612, namely 2.5%. An illustration of the anticooperative character of E_{ct}(RVS) is given by the Zn(II) complex with four methanethiolates. Thus, while in the monoligated Zn–$\mathrm{CH_3S}$ complex, E_{ct}(RVS) amounted to −55 kcal/mol at a 2.5 Å Zn–S distance, its value is actually reduced to −42 kcal/mol in the tetraligated complex. The corresponding

SIBFA values are −54 kcal/mol and −45.3 kcal/mol, consistent with the trends from RVS. With its previous SIBFA calibration, E_{ct} was significantly more reduced in this tetraligated complex, then amounting to −28.5 kcal/mol and ΔE(SIBFA) was underestimated with respect to ΔE(RVS) (−577.7 vs. −618.3 kcal/mol, while the present value is −627.7 kcal/mol).

Binuclear Zn(II) Complexes

Gal4 Model

Gal4 is a binuclear Zn-finger, having six cysteinate residues complexing two Zn(II) cations, that are at 3.5 Å from one another. We had previously[7b] performed energy-minimization of a model for the Gal4 binuclear core made out of two Zn(II) cations and six methanethiolate ligands. The values of reformulated ΔE(SIBFA) for this structure, namely, −1289.3 kcal/mol, is now much closer to ΔE(RVS) (−1272.3 kcal/mol) than previously (−1221.8 kcal/mol). This is due essentially to E_{ct}(SIBFA) that now amounts to −86.3 kcal/mol compared to −92.1 for E_{ct}(RVS) while the previous E_{ct}(SIBFA) value was of −58.4 kcal/mol. An additional gain stems from the polarization contribution with the newer screening adopted for methanethiolate. Thus, E^*_{pol} and E_{pol} amount to −193.3 and −140.3 kcal/mol, respectively, close to the corresponding E_{pol}(HF) and E_{pol}(RVS) values of −198.6 and −141.2 kcal/mol. As a reflection of the near-complete symmetry around each Zn(II) cation, E_{pol}(Zn) sums to −0.4 kcal/mol, due nearly exclusively to the quadrupole polarizability.

β-Lactamase.

β-Lactamase is an enzyme that hydrolyzes penicillins and related compounds, and is responsible for the acquired resistance of bacteria against antibiotics.[34] A high-resolution three-dimensional structure of the metallo-β-lactamase from the *B. Fragilis* strain[17a] shows two Zn(II) cations at a distance of 3.5 Å from one another. The first Zn(II) is ligated by three His residues and the hydroxy anion. The second Zn(II) is complexed by three anionic residues: a cysteinate, an aspartate, the hydroxy ion, and by one His and a water molecule. We had in ref. 35 performed SIBFA energy minimization of the X-ray structure, upon constraining the Zn–Zn distance at 3.0, 3.5, and 3.8 Å. The corresponding structures are denoted *a–c*, with *b* represented in Figure 3a. These computations indicated a shallow Zn–Zn distance dependence of the interaction energy. These energy minima were subsequently reprocessed using Hartree–Fock gradient-energy minimizations at the same constrained distances. The QC computations confirmed the shallow dependence of ΔE_{int}. with a minimum at the Zn–Zn distance of 3.5 Å. They had also derived in addition a novel alternative structure, denoted as *d* with the two Zn–Zn cations now at 4.78 Å. The three His-bound Zn(II) cation is bound to the water ligand instead of the hydroxy, as a consequence of a proton transfer that took place in the course of minimization. Such a transfer amounts to breaking and forming a chemical bond, which is beyond the reach of present molecular mechanics approaches. As a consequence of proton transfer, this Zn(II) cation only binds through water to two anionic ligands: hydroxy and formate. The other Zn(II) cation, on the other hand, is bound to all three anionic ligands as well as to a His residue. Yet despite the significant differences with respect to the canonical structure, the optimized values of ΔE(HF) are very close in structures *a* and *d*. This raises some concern regarding the ability of molecular mechanics to account for such an equalization. We have accordingly restarted SIBFA energy minimizations, upon starting from the HF-derived minima. Because internal coordinates are presently fixed in SIBFA energy minimizations, we retained the standard SIBFA internal geometries of all ligands with the corresponding multipoles and polarizabilities. At the converged energy minima, single-point RVS energy decompositions were done. The compared SIBFA and RVS results are reported in Table 5. The Zn–Zn distance in *d* is 4.38 Å (Fig. 3b). The BSSE correction with the CEP 4-31G(2d) appears small (20 kcal/mol out of 1200) and relatively constant in all four structures. It stems predominantly (12 kcal/mol) from the hydroxy ligand. The RVS results on the SIBFA-optimized geometries appear consistent with the energy-minimized HF ones from ref. 35, which were done with the CEP 4-31G basis set without the two 3d polarization functions on heavy atoms but in full Cartesian space. They indicate *d* to be more stable than *b* by a very small energy difference (6.8 kcal/mol out of 1200), namely 0.6%, similar to the 4 kcal/mol amount derived in ref. 34 and they confirm the shallow nature of ΔE in the 3.0–3.8 Å range of Zn–Zn distances, in which ΔE(RVS) varies by 6 kcal/mol out 1200, namely <1%. ΔE(HF) with the LACVP3** basis set has identical trends as with the CEP 4-31G(2d) basis set. Comparing *b* and *d*, Table 5 shows the very small ΔE(RVS) difference to result from large differences between opposing trends in E_1 and $E_{ct} + E_{pol}$. Thus, due to both E_c and E_{exch}, E_1 favors *b* over *d* by 57 kcal/mol, while due to both E_{pol} and E_{ct}, the summed second-order terms favor *d* over *b* by 64 kcal/mol. The preference of both second-order terms for *d* was unanticipated because in such a structure, one Zn(II) cation has all three anionic ligands bound directly to it. The anticooperative character of both contributions in such arrangements was exemplified above with the $[Zn(CH_3S)_3]^{-1}$ and $[Zn(CH_3S)_4]^{2-}$ complexes, and could have led, in fact, to a greater reduction of both E_{pol} and E_{ct} in *d* than *b*. In addition, the second Zn(II) cation is in *d* bound to no anionic ligand that it would polarize and that it would stabilize through the charge-transfer contribution. On the other hand, due to through-water Zn-binding to formate and hydroxy, some *cooperative* interactions past first order could act to stabilize *d* over *b*. How then would polarizable molecular mechanics account for the trends from RVS analysis? Table 5 shows that ΔE(SIBFA) is in close agreement with ΔE(RVS) for all four structures, being underestimated by <22 kcal/mol out of 1200, namely 2%. Among structures *a–c*, *b* is the most stable, conform to the RVS results. ΔE(SIBFA) is also more favorable for *d* than *b*, again conforming to the RVS results, although the energy difference of 3.1 kcal/mol out of 1200 is possibly marginal. Most importantly, the RVS trends in E_1, on the one hand, and of E_{pol} and E_{ct} on the other hand, are correctly accounted for in SIBFA. Thus, both E_1 contributions, E_{MTP} and E_{rep}, favor *b*, while both E_2 contributions favor *d*, conforming to their RVS counterparts. One remaining shortcoming relates to E_{ct}(SIBFA), which, although favoring *d* over *a–c*, has reduced magnitudes with respect to E_{ct}(RVS) throughout, the relative underestimation being more notable in *d* than *a–c*. This could be qualitatively illustrated by the fact that subtracting the BSSE correction from E_{ct}(RVS) giving E_{ct*}(RVS) results into E_{ct}(SIBFA) now being larger in magnitude than E_{ct*} in *a–c* but not in *d*. Nevertheless, the remaining E_{ct} underestimation does not appear to significantly affect the agreement between the SIBFA and the RVS results.

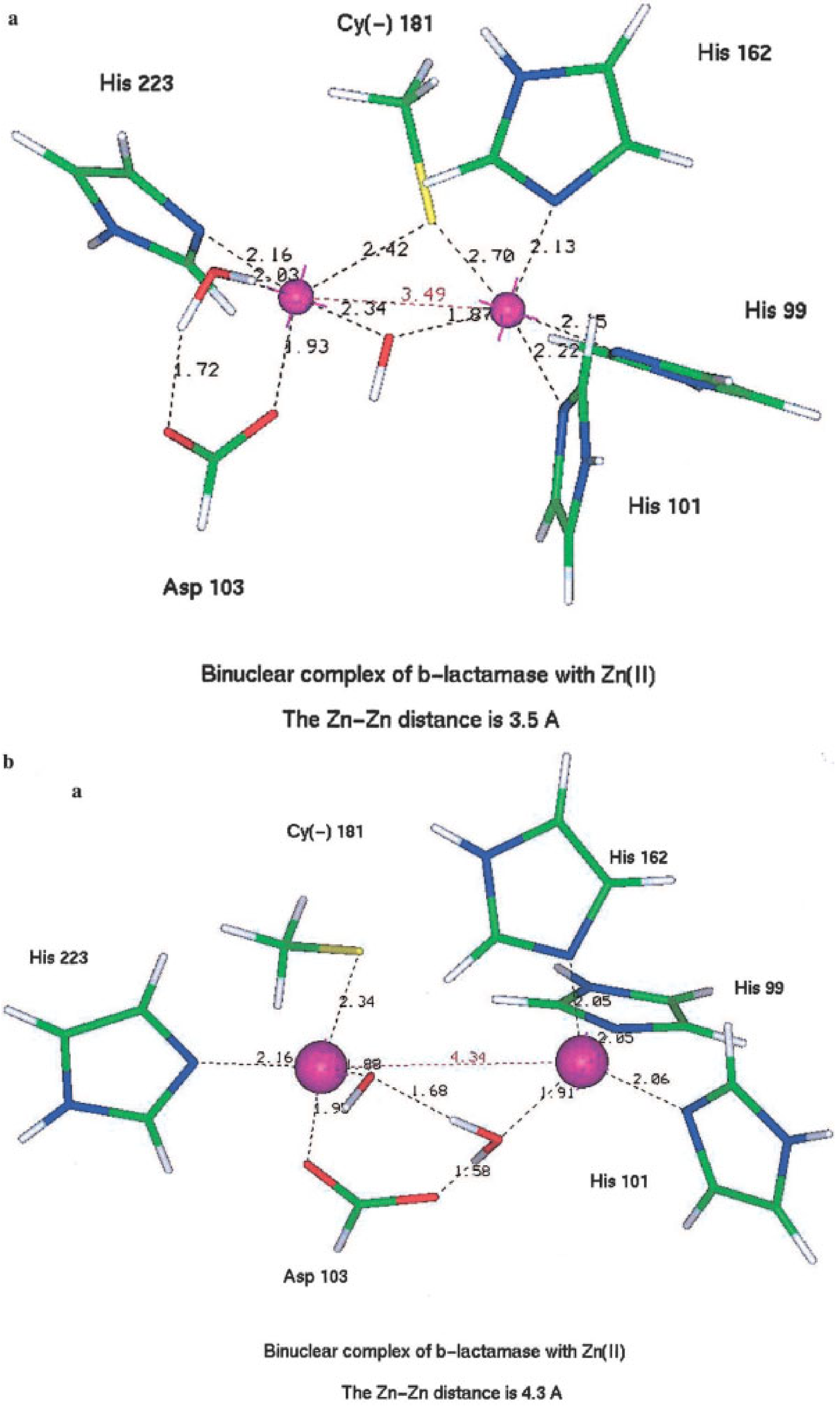
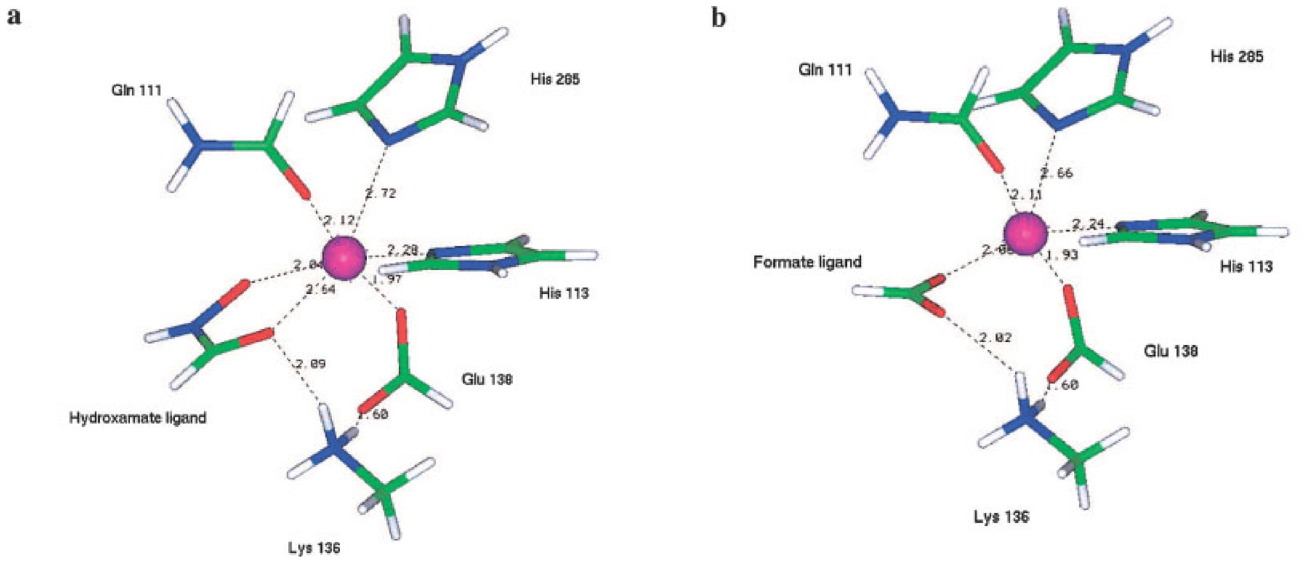
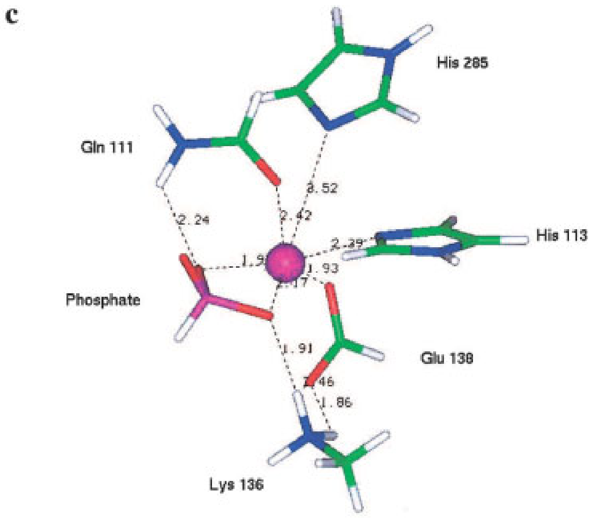


Figure 3. Representation of the complexes of two Zn(II) cations in the binding site of metallo-β-lactamase. (a) X-ray derived structure, with a Zn–Zn distance of 3.5 Å; (b) structure derived by HF energy-minimization with a Zn–Zn distance of 4.3 Å. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Complex of the hydroxamate ligand with Zn(II) and the active site of phosphomannoisomerase

Complex of the formate ligand with Zn(II) and the active site of phosphomannoisomerase



Complex of the phosphate ligand with Zn(II) and the active site of phosphomannoisomerase

Figure 4. Representation of the complexes of the binding cavity of phosphomannoisomerase with the anionic moities of inhibitors: (a) hydroxamate; (b) formate; (c) dianionic phosphate. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The relative total energies rank as follows (in kcal/mol): (a) for uncorrelated calculations, or for SIBFA without the E_{disp} contribution:

d	<	b	<	a	<	c	
0.0		6.7		8.6		12.8	Δ*E*(HF,CEP 4-31G(2d))
0.0		5.7		7.3		10.9	Δ*E*(HF, LACV3P**)
d	<	b	<	c	<	a	
0.0		3.1		6.7		9.4	Δ*E*(SIBFA)

The relative inversion of c vs. a stabilities by SIBFA involves a difference of 2.7 kcal/mol out of 1200.

For correlated calculations, or for SIBFA including the E_{disp} contribution, a, b, and d come closer together, as well as c with Δ*E*(LMP2, LACVP3P**). A preferential stabilization of a (Zn–Zn distance of 3.0 Å) over c (Zn–Zn distance of 3.8 Å) is found throughout.

a	≤	d	<	b	<	c	
0.0		1.9		3.3		14.1	Δ*E*(MP2, CEP 4-31G(2d))
d	≤	b	=	a	≈	c	
0.0		1.9		2.0		2.3	ΔE(LMP2, LACV3P**)

d	$<$	b	$<$	a	$<$	c	
0.0		3.9		4.5		11.5	ΔE(B3LYP, LACV3P**)
0.0		3.0		4.6		9.9	ΔE_{tot}(SIBFA)

The numerical values of ΔE_{tot}(SIBFA) are intermediate between those of ΔE(MP2, CEP 4-31G(2d)) and those of ΔE(B3LYP, LACV3P**), and their trends are similar to those of ΔE(B3LYP, LACV3P**). Nevertheless, it is possible that differences of 5 kcal/mol out of 1300 may be at the limit of the attainable precision even for QC computations at the correlated level and finite basis sets.

The reformulation of E_{MTP} and E_{rep} and the recalibration of E_{ct} translate into a closer reproduction of QC results than with the previous SIBFA version that was used in refs. 7a and 34. Thus, with this previous version and for complexes *a–d*, the values of ΔE are -1192.5, -1191.2, -1189.2, and -1186.7 kcal/mol, respectively. Even though the numerical values are close to the corresponding HF ones with the CEP 4-31G(2d) basis set, an inversion in the relative stabilities of *d* vs. *b* is therefore observed for the previous version, with *d* less favored than *b* by 5 kcal/mol, while it is favored by 7 kcal/mol by ΔE(HF), and by 3 kcal/mol in the new SIBFA version. Although such inversions involve relative energy differences of $<1\%$, which are certainly within the margins of error of SIBFA, we observe a much greater imbalance of effects than in the newer formulation. Thus, the values of E_1 are much larger in magnitude than their RVS or new SIBFA counterparts (-1028.2 and -973.2 kcal/mol for *b* and *d*, respectively, compared to -1002.0 and -945.1 from RVS), while conversely, the corresponding E_{ct} values are much smaller (-17.3 and -21.8 kcal/mol compared to -57.2 and -75.2 kcal/mol from RVS).

A single-point SIBFA energy computation on these β-lactamase complexes requires about half a second on one IBM sp^3 processor. The corresponding H-F or DFT computation time is about 5 h, while an HF + MP2 computation requests over 35 h. This implies that for simulations on inhibitor–protein complexes, SIBFA would be considerably faster than even QM/MM procedures. We have also recomputed complexes *a–d* using the semiempirical PM3 method,[36] using the Gaussian 03 software. The interaction energies of *a–d* have the values -1177.9, -1178.7, -1147.6, and -1163.0 kcal/mol. These values are underestimated with respect to the ΔE(HF/CEP 4-31G(2d)) values by about 5%. With respect to the QC results, there now occurs an inversion in the relative stabilities of *d* and *b, d* being being destabilized by 15 kcal/mol with respect to *b*. Other comparisons with semiempirical results were given in previous articles.[7a,7c] There are no Zn(II) parameters available for the polarizable ff02 force field in AMBER 7.0,[37] so that no comparisons can be done with this force-field regarding the β-lactamase complexes. We have reported comparisons with AMBER in a recent study in the case of complexes of pentahydrated Mg(II) with 5′ guanosine monophosphate.[10b]

Binding Interactions in the Active Site of a Metalloenzyme

Phosphomannoisomerase (PMI) catalyzes the reversible isomerization of D-mannose 6-phosphate and of D-fructose 6-phosphate (ref. 37, and references therein). It is a target for the development of anti-infectious agents. Among these, inhibitors with two anionic end moieties (phosphate and hydroxamate, or phosphate and formate) were found to be endowed with nanomolar inhibitor potencies.[38] The complexes of PMI with such inhibitors in competing orientations in the binding site have been modeled with SIBFA (Gresh et al., in preparation), and we have performed further validation calculations by parallel QC computations on models extracted from the active site. As an example, we report in Table 6 an analysis by RVS and MP2 of the corresponding complexes of the hydroxamate, formate, and bisanionic phosphate moieties with Zn(II) and the end side chains of Glu 113, Lys 136, Gln 111, His 113, and His 285. A very close agreement is found between SIBFA and QC computations, the trends being again clearly reproduced and the relative error being $<2\%$, although as in β-lactamase some compensations of error still occur, with in particular E^*_{MTP} being larger in magnitude than E_c and E_{pol}(SIBFA) being smaller in magnitude than its Q–C counterpart. As with β-lactamase, the numerical agreement with QC results is less good upon using the previous SIBFA formulation. Thus, the corresponding SIBFA values of ΔE of -651.2, -642.8, and -833.2 for complexes *a–c*, respectively, have a lesser agreement with the corresponding HF-(CEP 4-31G(2d)) ones of -674.2, -660.4, and -842.3 than with those with the newer formulation, namely -687.3, -665.9, and -845.5 kcal/mol, respectively. This is also the case concerning the ΔE(MP2) vs. ΔE_{tot}(SIBFA) values (see Table 6). PM3 computations give underestimated ΔE values, amounting to -574.1, -574.4, and -773.7 kcal/mol for *a–c*, respectively.

Conclusions

The explicit inclusion in the SIBFA procedure of a penetration contribution, E_{pen}, to the electrostatic multipolar contribution E_{MTP}, has enabled the summed $E_{MTP} + E_{pen}$ contribution, E_{MTP}*, to closely reproduce the Coulomb energy contribution E_c from *ab initio* energy-decomposition in a diversity of Zn–mono- and polyligated complexes. The short-range repulsion contribution E_{rep}, now augmented with an S^2/R^2 component, could then be recalibrated to reproduce the exchange-repulsion E_{exch} rather than to fit the difference between ($E_c + E_{exch}$) and E_{MTP}. The different validation tests reported in this study have shown E_1(SIBFA) to reproduce more closely its counterpart from the RVS energy-decomposition, E_1(RVS), than it did upon using its previous formulation and calibration. We have also recalibrated E_{ct} by simply rescaling the Zn(II) self-potential term and the Zn-multiplicative factor. We have also modified for imidazole and methanethiolate the ligand-specific factors, E and F, that screen the polarizing field. Although these changes did not modify significantly the radial behavior of E_{pol} and E_{ct} in monoligated complexes, an improved reproduction of E_{pol}(RVS) and E_{ct}(RVS) obtained in polyligated complexes.

One of the most critical tests for APMM procedures relates to binuclear complexes of divalent metal cations, in which the two dipositive charges are close (3–4 Å) to each another, giving rise to considerable enhancements of nonadditivity. This was exemplified in this study by models of two Zn(II)-binding proteins, Gal4 and metallo-β-lactamase. Thus, upon modeling the Zn-binding core of the latter, two competing arrangements have been derived. The first closely corresponded to the X-ray structure but had a very shallow energy dependence upon the Zn–Zn distance in the 3–4 Å range. The best structure (denoted as *b*) had a Zn–Zn distance of 3.5 Å. The second (denoted as *d*), originally derived by HF energy minimization, had the two Zn(II) cations further apart ($d_{\text{Zn-Zn}}$ = 4.4 Å), one Zn(II) cation bound by all three anionic ligands, while the other was solely complexed by neutral ligands and, through its water ligand, to two anionic ones. Despite the very different Zn complexation modes obtained, the QC interaction energies were extremely close (6 kcal/mol out of 1200), the RVS analysis showing this near-equalization to result from compensations between large energy differences at the level of the individual components. Thus, while E_1 favored the X-ray related structure *b* by approximately 57 kcal/mol, E_2 conversely favored structure *d* by an opposite amount of 64 kcal/mol. The SIBFA results were fully consistent with the QC ones, regarding the ΔE near-equality of *b* and *d*, the opposing trends in energy contributions, the shallow nature of ΔE in the 3–4 Å range, and the actual magnitudes of ΔE and individual contributions.

One issue to be addressed in future studies should also aim at a better representation of the gain due to correlation, which occurs upon passing from the HF level to the DFT or to the MP2 levels. It is likely that the present dispersion contribution under the form of a $1/R^n$ (n = 6, 8, 10) development should be rescaled, and that multipoles and polarizabilities derived from correlated (DFT or MP2) should be used to compute E_{MTP}, E_{pol}, and E_{ct}, to account for the effects of correlation on electronic distribution. In our previous study we had observed that for simple nonconjugated ligands, namely water and methanethiolate, E_{MTP} using correlated multipoles did not differ much from E_{MTP} using HF-derived multipoles.[7b] Nevertheless, a rescaling of E_{rep}, E_{pol}, and particularly E_{ct} needs to be considered in light of recent results from energy decompositions done at the DFT level.[32,33] E_{disp} will accordingly be rescaled to reproduce the remaining energy gain found upon passing from DFT to MP2 levels. Such studies are presently underway.

The reformulated SIBFA procedure will be applied in studies of inhibitor–protein complexes. One such study is devoted to the complexes of β-lactamase and mercaptocarboxylate inhibitors, D- and L-thiomandelate and D and L-captopril. Its results will be presented in a forthcoming article.

Acknowledgments

The *ab initio* computations were performed on the computers of the Centre de Ressources Informatiques de Haute Normandie (CRIHAN), France, and of the Centre d'Informatique National de l'Enseignement Supérieur (CINES, France).

Appendix A: Values of the R_L, θ_L, ϕ_L Internal Coordinates and of the Occupation Numbers N_{occ} for the π Lone Pairs in Formamide, Formate, and Imidazole

There are two π lone pairs on the atoms of the conjugated/aromatic ligands, above and below the plane (whence the sign alternation for ϕ_L). The determination of the value of ϕ_L was done with the help of computer graphics, in such a way that the two fictitious atoms defining the location of the tip of each π lone pair be located above and below the bond that connects its bearer, Z, and a heavy atom that is chemically bonded to it. The internal cordinates are defined according to the connectivity which is: formamide: H_1–C_2–O_3–N_4; formate: H_1–C_2–O_3–O_4; imidazole: H_1–C_2–N_3–C_4–N_5–C_6, N_5 denoting the protonated N atom. R_L values in Å, θ_L and ϕ_L in degrees.

		R_L	θ_L	ϕ_L	N_{occ}
Formamide					
	C_2	0.50	120°	±60°	0.25
	O_3	0.50	60°	±90°	0.75
	N_4	0.50	60°	±90°	1.0
Formate					
	C_2	0.50	90°	±90°	0.00
	O_3	0.50	60°	±90°	1.00
	O_4	0.50	60°	±90°	1.00
Imidazole					
	C_2	0.50	120°	±60°	0.50
	N_3	0.50	60°	±90°	0.50
	C_4	0.50	600°	±90°	0.50
	N_5	0.50	120°	±30°	1.00
	C_6	0.50	60°	±90°	0.50

Appendix B: Values of the Effective Radii (in Å) for E_{pen} (P_W), E_{rep} (R_W), E_{pol} (P_{lW}), E_{ct} (T_W), E_{disp} (D_W) and Values of Other Zn Parameters

The non-Zn parameters were determined from a previous study (Piquemal et al., submitted) on hydrogen-bonded and stacked complexes and additional complexes such as imidazole–water, and complexes involving the benzene ring and/or the methane group (Gresh, unpublished). Atoms with no lone pairs are not considered as electron donors and their T_W has not to be defined.

Effective Radii

Atom type	P_W	R_W	P_{lW}	T_W	D_W
Hydrogen					
Polar	1.30	1.24	1.20	/	1.20
Apolar in conjugated molecules	1.80	1.45	1.70	/	1.20
Carbon					
C(sp^3)	1.605	1.70	1.90	/	1.70
C(sp, conjugated as in formate or formamide):	1.605	1.55	1.90	1.70	1.725
C(sp, aromatic in heterocyclic molecules as in imidazole)	1.605	1.725	1.90	1.70	1.725
C(sp, aromatic in aromatic molecules as in benzene)	1.80	1.80	1.90	1.70	1.80
Nitrogen					
N(unprotonated in conjugated rings)					

Atom type	P_W	R_W	P_{lW}	T_W	D_W
	1.50	1.77	1.77	1.65	1.425
N(protonated in conjugated rings)					
	1.45	1.65	1.77	1.65	1.75
Oxygen					
O(sp^3)	1.41	1.448	1.448	1.50	1.285
O(sp^2 in formamide)	1.44	1.48	1.48	1.45	1.26
O(sp^2 in formate)	1.44	1.48	1.48	1.85	1.26
O(in hydroxy)	1.41	2.15	1.48	2.075	1.725
O(sp^3 in hydroxamate)[a]					
	1.40	1.455	1.48	1.675	1.425
O(in dianionic phosphate)[a]					
	1.40	1.60	1.448	2.30	1.260
Sulfur					
S (anionic)	1.445	1.90	1.925	2.45	2.40
Phosphorus					
P	1.20	1.80	1.80	/	1.80
Zn(II)	1.225	1.265	1.15	/	1.245

[a] Details on the calibration of these two atoms along with validation tests are provided in a forthcoming article.

Values of the $k_{Zn\text{-}L}$ and $l_{Zn\text{-}L}$ Multiplicative Constants of E_{rep} and E_{disp} (X = H, C, N, O, S)

X	H	C	N	O	P	S
$K_{Zn\text{-}X}$	8.6	8.6	9.1	10.1	10.3	10.3
$L_{Zn\text{-}X}$	3.7	8.0	8.0	4.0	12.0	12.0

For E_{rep}, the values of the α_1 and α_2 exponent of the exponential are 9.44 (for the S^2/R component) and 14.00 (for the S^2/R^2 component). The corresponding multiplicative factors C_1 are 44,000 and 45,000. These α and C values are the same as in our study of H-bonded complexes (Piquemal et al., submitted).

Charge-Transfer Contribution

Multiplicative factor for Zn(II): C_{st}: 0.61. Value of the calibration factor D_M: 4.0. Value of the effective acceptor radius of Zn(II) U_M^*: 2.51. Value of the I intervening in the increase of the effective radius T_W of the electron donor as a function of the magnitude of the field undergone by the donor: 1. (see ref. 5b for details). The value of the J factor is 0. In the calibration used in our preceeding study,[5b] the values of C_{st}, D_M, U_M^*, I and J were, respectively, 2.71, 2.50, 2.0, 3.75, and 0.0. For H atoms that can act as electron-acceptors, the values of U_M^* are 1.7 Å (polar) and 1.2 Å (apolar).

Polarization

In SIBFA, the field polarizing a given molecule or molecular fragment is screened by a Gaussian function, which has a multiplicative factor E, and an exponent F, specific for that fragment and initially calibrated for it[5b] so that the radial variations of E_{pol}(SIBFA) match the corresponding ones of E_{pol}(RVS) in its complexes with Zn(II) as a probe. We found that for imidazole, E and F values of 0.62 and 1.60 gave an equally good match than the previous pair of separate E values of 0.66 and 0.90 (for lone pair and bond polarizabilities, respectively) and F values of 1.95 and 1.40 (lone pairs and bonds) and an improved nonadditive behavior of E_{pol}(SIBFA) in polyligated complexes. Along the same lines, we selected for methanethiolate E and F values of 0.70 and 1.70 instead of the previous dedoubled E values of 0.68 and 0.88 (lone pair and bond polarizabilities) and F value of 1.65. All other molecular fragments retained the same E and F values as in the original article.[5b] The default values of E and F are 0.68 and 1.40. We limited the number of iterations that increase the effective radius of the polarizable distribution as a function of the induced dipole moment along the direction of polarization (see ref. 5b for details) to one instead of the default value of 5.

*Zn(II) Polarizabilities Using the 6-31G Basis Set and the CADPAC Software**

Dipole polarizability (atomic units**3) $\alpha_i = 1.65$. If i, j, k, and l denote in turn each of the x, y, and z coordinates, the values (atomic units**5) of the quadrupole polarizabilities are the following: $P_{iiii} = 0.9471$; $P_{ijij} = 0.7104$; $P_{iijj} = -0.4736$, the other elements being null. The energy contribution to the field gradients G_{ij} and G_{kl} is

$$E_{polQ} = -(1/6)T \sum_{ijkl} P_{ijkl} G_{ij} G_{kl}$$

where T is a multiplicative factor with the value 10.0, fit so that E_{pol}(Zn(II)) reproduces the values of its RVS counterpart for the $Zn(H_2O)^{2+}$ and $Zn(OH)^{+}$ complexes at their equilibrium distances.

Supplementary Material

S1. Formulation of E_{rep}, E_{pol}, E_{ct} and E_{disp} for cation-ligand interactions. S2–S5. Additional results for monoligated Zn(II) complexes. S6. Interaction energies for complexes of Zn(II) with six water molecules.

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