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Many-Body Exchange-Repulsion in Polarizable Molecular Mechanics. I. Orbital-Based Approximations and Applications to Hydrated Metal Cation Complexes

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We have quantified the extent of the nonadditivity of the short-range exchange-repulsion energy, $E_{\text{exch-rep}}$, in several polycoordinated complexes of alkali, alkaline-earth, transition, and metal cations. This was done by performing *ab initio* energy decomposition analyses of interaction energies in these complexes. The magnitude of $E_{\text{exch-rep}(n\text{-body}, n > 2)}$ was found to be strongly cation-dependent, ranging from close to zero for some alkali metal complexes to about 6 kcal/mol for the hexahydrated Zn^{2+} complex. In all cases, the cation–water molecules, $E_{\text{exch-rep}(\text{three-body})}$, has been found to be the dominant contribution to many-body exchange-repulsion effects, higher order terms being negligible. As the physical basis of this effect is discussed, a three-center exponential term was introduced in the SIBFA (Sum of Interactions Between Fragments *Ab initio* computed) polarizable molecular

mechanics procedure to model such effects. The three-body correction is added to the two-center (two-body) overlap-like formulation of the short-range repulsion contribution, E_{rep} , which is grounded on simplified integrals obtained from localized molecular orbital theory. The present term is computed on using mostly precomputed two-body terms and, therefore, does not increase significantly the computational cost of the method. It was shown to match closely $E_{\text{three-body}}$ in a series of test cases bearing on the complexes of Ca^{2+} , Zn^{2+} , and Hg^{2+} . For example, its introduction enabled to restore the correct tetrahedral versus square planar preference found from quantum chemistry calculations on the tetrahydrate of Hg^{2+} and $[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$. © 2011 Wiley Periodicals, Inc. *J Comput Chem* 32: 2949–2957, 2011

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Introduction

Nonadditivity is an essential feature of intermolecular interactions within multimolecular complexes. It could either enhance the intermolecular interaction energies, as in the case of several multiply H-bonded complexes, or reduce them, as in the case of several multiply coordinated complexes of metal cations.^[1,2] Energy decomposition analysis (EDA) techniques pertaining to quantum chemistry (QC)^[3–7] allow to unravel the contributions to the interaction energy which are responsible for nonadditivity. This is essential to evaluate the ability QC-derived polarizable molecular mechanics (PMM) potentials to account for it.^[1,8–10]

In recent years, several QC and PMM studies showed that it could be traced back predominantly to the second-order contributions: namely induction (polarization plus charge transfer) and dispersion. Until now, despite some QC studies,^[2,11–14] little attention was given to the study of first-order many-body effects in molecular mechanics (MM). Thus, despite some notable exceptions,^[1,10,15–20] MM techniques generally do not attempt to reproduce an individual exchange-repulsion contribution and resort instead to Lennard–Jones-like van der Waals (vdW) terms reproducing it along with dispersion and other mixed terms. Of course physics is more complex and if the Coulomb interaction is formally a two-body quantity, the exchange-repulsion contribution is not. Indeed, exchange-repulsion is associated to Pauli repulsion, and its evaluation requires the computation of a first-order (frozen) wave


function, which must respect the antisymmetry principle. To do so, the molecular orbitals (MO) of the considered final complex are built on the frozen MOs of the individual interacting fragments computed separately that are then submitted to a necessary orthogonalization. Such an orthogonalization process affects the final values of the energies, and, therefore, on the whole, the exchange-repulsion can exhibit nonadditive characters that are usually believed to be less important in the literature.^[2] But is it always the case? In a pioneering work, Lybrand and Kollman^[11] included a three-body exponential

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term to account for nonadditivity in the polyhydrated complexes of Mg^{2+} and Ca^{2+} , along with an explicit polarization contribution. Because this was performed without a direct comparison with EDA computations, it could not be possible, however, to ascribe such a term to a well-defined contribution.

The purpose of the present work, which will bear on several biologically relevant metal cations, is to seek for the nonadditivity of the repulsion energy to quantify it in hydrated metal-cation complexes (denoted as $[\text{M}(\text{H}_2\text{O})_x]^{n+}$). Indeed, if such a quantity were not negligible for metals where a large number of electrons is concentrated, its noninclusion into a PMM formalism attempting to separately reproduce all the QC features^[1,18] would be a problem for an accurate reproduction of the interaction energies. In the first part of this article, the nonadditivity of the short-range exchange-repulsion in a series of $[\text{M}(\text{H}_2\text{O})_6]^{n+}$ complexes is evaluated by EDA. The cations denoted as M are: (a) the Na^+ , K^+ , Rb^+ , Cu^+ , Ag^+ , and Au^+ monovalent cations; and (b) the Mg^{2+} , Ca^{2+} , Sr^{2+} , Zn^{2+} , Cd^{2+} , Hg^{2+} , and Pb^{2+} divalent cations. As we investigate the importance of three-body interactions versus the higher order terms, the influences of the choice of the basis sets and pseudopotentials are discussed. In the second part, an implementation of a three-body exponential term, added to the orbital overlap-based $S^2/R + S^2/R^2$ repulsion,^[18] is put forth in the context of the SIBFA PMM method.^[1] The validity of this term to account for $E_{\text{exch-rep}}$ nonadditivity is tested on several complexes of Ca^{2+} , Zn^{2+} , and Hg^{2+} .

Ab initio Evaluation of Exchange-Repulsion Many-Body Effects within Metal Cation–Water Clusters

Ab initio EDA

Scope on the computation of exchange-repulsion energies at the Hartree–Fock (HF) level, the interaction energy between two or more fragments can be decomposed into four contributions:

$$\Delta E = E_{\text{coul}} + E_{\text{rep}} + E_{\text{pol}} + E_{\text{CT}},$$

namely, Coulomb/electrostatics and exchange-repulsion at first order and polarization and charge-transfer at second order.

This study will only focus on the second of the two first-order contributions, namely the exchange-repulsion term. EDA computations were performed with the reduced variational space (RVS) procedure.^[4]

The RVS scheme constructs the final complex MO on the orbitals of the isolated monomers (which were precomputed in their respective basis set), it is then possible to select variational spaces including or excluding the virtual orbitals of a selected molecule in the construction of the “multimolecular Fock matrix” or to freeze the orbitals of a chosen monomer. From this computational procedure, one gets two types of contributions depending on the choice of the variational space namely frozen (first order) or unfrozen/relaxed (second order). We will focus here on the first order, which is the sum of the electrostatic and exchange-repulsion energies computed on

the MO of the isolated interacting entities, and corresponds to the antisymmetrized Hartree product of the isolated monomer wave functions. In that case, the occupied orbitals of all fragments remain frozen with no possibility of relaxation into the virtual orbitals. Therefore, the only effect leading to a change in the MO/SCF energies is linked to the necessary orthogonalization of the monomers MOs.

Thus, in RVS, the total exchange-repulsion is computed following a three-step procedure: (1) computation of the complex first-order energy (E_1) computed as the difference of the total Self Consistent Field (SCF) energy of the final complex built on the frozen monomer MO's and of the respective SCF energies of the isolated monomers; (2) computations of the Coulomb energy (E_{coul}); (3) computation of $E_{\text{exch-rep}}$ as: $E_{\text{exch-rep}} = E_1 - E_{\text{coul}}$.

The intermolecular three-body and higher order repulsion energies are computed as follows:

$$E_{\text{rep}}^{3\text{-body}}(\text{Comp}) = E_{\text{rep}}^{\text{tot}}(\text{Comp}) - E_{\text{rep}}^{2\text{-body}}(\text{Comp}) \quad (1)$$

$$E_{\text{rep}}^{2\text{-body}}(\text{Comp}) = \sum_{A \in \text{Comp}} \left\{ \sum_{B \neq A \in \text{Comp}} [E_{\text{rep}}^{\text{tot}}(\text{AB})] \right\} \quad (2)$$

where $E_{\text{rep}}^{\text{tot}}(\text{AB})$ is the pair repulsion energy between molecules A and B within the whole complex Comp, $E_{\text{rep}}^{\text{tot}}$ is the exchange-repulsion energy in the whole complex (Comp), and $E_{\text{rep}}^{3\text{-body}}$ is the three-body and higher terms.

The four-body and higher order repulsion terms were also calculated for some complexes. Its formulation derives from the following equations:

$$E_{\text{rep}}^{4\text{-body}}(\text{Comp}) = E_{\text{rep}}^{\text{tot}}(\text{Comp}) - E_{\text{rep}}^{2\text{-body}}(\text{Comp}) - E_{\text{rep}}^{3\text{-body}}(\text{Comp}) \quad (3)$$

and

$$E_{\text{rep}}^{3\text{-body}}(\text{Comp}) = \sum_{A,B,C \in \text{Comp}} \{E_{\text{rep}}^{\text{tot}}(\text{ABC}) - E_{\text{rep}}^{2\text{-body}}(\text{ABC})\} \quad (4)$$

with the previous definition for $E_{\text{rep}}^{\text{tot}}$ and $E_{\text{rep}}^{2\text{-body}}$, $E_{\text{rep}}^{4\text{-body}}$ being as previously the four-body and higher terms and $E_{\text{rep}}^{\text{tot}}(\text{ABC})$ the total energy of the cluster formed of the molecules A, B, and C and $E_{\text{rep}}^{2\text{-body}}$ is the total two-body energy for the complex ABC

Equations (3) and (4) can be summarized as:

$$E_{\text{rep}}^{4\text{-body}}(\text{Comp}) = E_{\text{rep}}^{\text{tot}}(\text{Comp}) - \sum_{A,B,C \in \text{Comp}} \{E_{\text{rep}}^{\text{tot}}(\text{ABC})\} + (N - 3) * \sum_{A,B \in \text{Comp}} \{E_{\text{rep}}^{\text{tot}}(\text{AB})\} \quad (5)$$

In this equation, N denotes the total number of molecules in cluster Comp.

Equation (5) is a more convenient form than eq. (3) because energy decomposition methods give the total repulsion energy for given complexes such as $E_{\text{rep}}^{\text{tot}}(\text{AB})$, $E_{\text{rep}}^{\text{tot}}(\text{ABC})$, and $E_{\text{rep}}^{\text{tot}}(\text{Comp})$.

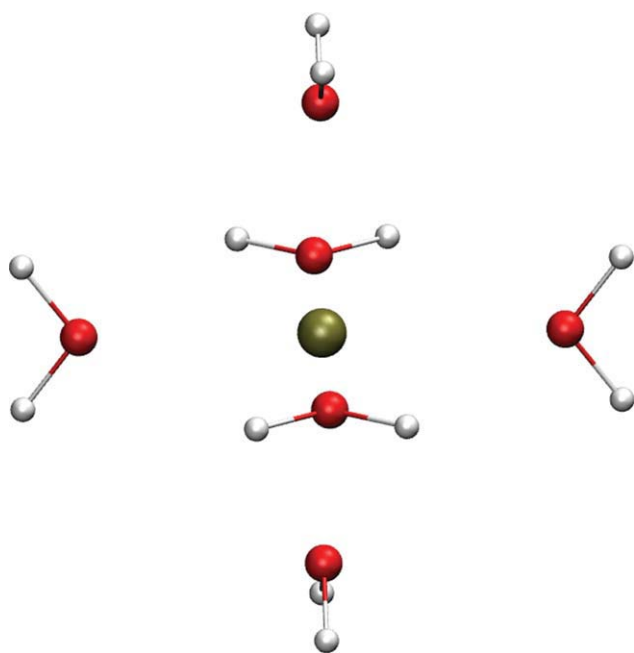


Figure 1. Representation of the $[\text{Ca}(\text{H}_2\text{O})_6]^{2+}$ in the octahedral form computed at the B3LYP/6-31++G** level.

$E_{\text{rep}}^{3\text{-body}}$ was computed for a large range of hexahydrated metal–cation complexes at the same level of theory as for the energy minimization. We will resort throughout to a notation in which the cation basis set is given first, followed, under the slash sign, by the water basis set. For Ca^{2+} and Zn^{2+} , tests were performed with other basis sets and pseudo-potentials. We adopt the notation “SBK” to denote the CEP 4-31G(2d) basis set given by Stevens et al.^[21] We have thus considered SBK/SBK, 6-31++G** (6-31G** for Zn^{2+})/6-31++G**, and 6-31++G** (6-31G** for Zn^{2+})/aug-cc-pVDZ.^[22] This enabled to quantify the importance of the pseudo-potential and of the basis set on $E_{\text{rep}}^{3\text{-body}}$. Finally, $E_{\text{rep}}^{4\text{-body}}$ was computed for Hg^{2+} and Zn^{2+} complexed by six first-shell water molecules.

Computational details. For all metal cations (Na^+ , Mg^{2+} , K^+ , Ca^{2+} , Cu^+ , Zn^{2+} , Rb^+ , Sr^{2+} , Ag^+ , Cd^{2+} , Au^+ , Hg^{2+} , and Pb^{2+}), model complexes with six water molecules were built with an octahedral geometry. They were optimized at the HF level to be consistent with the EDA computations performed at this level of theory. Such a choice ensures the practicability of the computations and a clear definition of the exchange-repulsion energy within the RVS EDA procedure.^[4] All the calculations were performed using the 6-31++G**^[23] basis set on the metal ligands. For the metal cations, they resorted either to the Stuttgart pseudo-potentials (SDD),^[24] as is the case for Cu^+ , Zn^{2+} , Rb^+ , Sr^{2+} , Ag^+ , Cd^{2+} , Au^+ , Hg^{2+} , and Pb^{2+} , or to the 6-31++G** full electron basis set, as is the case for Na^+ , Mg^{2+} , K^+ , and Ca^{2+} . Frequencies were calculated for every optimized structure to ensure that all structures could be associated to an energy minimum. For Ca^{2+} and Zn^{2+} , tests were performed with other basis sets and pseudo-potentials. We have thus considered SBK/SBK, 6-31++G** (6-31G** for Zn^{2+})/6-31++G**, and 6-31++G** (6-31G** for Zn^{2+})/aug-cc-pVDZ.^[22] This enabled to quantify the importance of the

pseudo-potential and of the basis set on $E_{\text{rep}}^{3\text{-body}}$. Finally, $E_{\text{rep}}^{4\text{-body}}$ was computed for Hg^{2+} and Zn^{2+} complexed by six first-shell water molecules. A representation of an octahedral geometry is provided in Figure 1 using the $[\text{Ca}(\text{H}_2\text{O})_6]^{2+}$ complex. In addition, the xyz coordinates of all the complexes are displayed in Supporting Information S1

Results

Repulsion energy for the different cation with six water molecules at HF/SDD/6-31+G** level

The many-body repulsion effects were computed for a broad range of cation–ligand complexes, and the values are reported in Table 1. These encompass alkali, alkaline-earth, transition,

Table 1. Values (kcal/mol) of the repulsion energy in the complexes of monovalent and divalent metal cations with six water molecules.

Metal	$E_{\text{rep}}^{2\text{-body}}$	$E_{\text{rep}}^{\text{tot}}$	$E_{\text{rep}}^{3\text{-body}}$	$E_{\text{rep}}^{3\text{-body}}$ (% $E_{\text{rep}}^{\text{tot}}$)
Na^+	36.6	36.5	−0.1	−0.3
Mg^{2+}	90.0	92.0	2.0	2.2
K^+	20.5	20.0	−0.5	−2.3
Ca^{2+}	75.9	73.5	−2.4	−3.2
Cu^+	53.1	56.4	3.3	5.8
Zn^{2+}	101.3	108.1	6.8	6.3
Rb^+	17.6	17.4	−0.2	−1.0
Sr^{2+}	65.4	63.8	−1.6	−2.5
Ag^+	47.1	49.4	2.3	4.7
Cd^{2+}	88.0	91.7	3.7	4.0
Au^+	157.6	158.6	1.0	0.7
Hg^{2+}	89.7	94.3	4.6	4.9
Pb^{2+}	56.7	59.4	2.7	4.6

$$E_{\text{rep}}^{2\text{-body}} = \sum_{\text{molecule A}} \left\{ \sum_{\text{molecule B} \neq \text{A}} [E_{\text{rep}}(\text{A}, \text{B})] \right\}$$

where $E_{\text{rep}}(\text{A}, \text{B})$ denotes the pair repulsion energy. $E_{\text{rep}}^{\text{tot}}$ is the repulsion energy of the whole complex. $E_{\text{rep}}^{3\text{-body}}(\text{Comp}) = E_{\text{rep}}^{\text{tot}}(\text{Comp}) - E_{\text{rep}}^{2\text{-body}}(\text{Comp})$ is the repulsion due to three-body and higher interactions.

and heavy metal cations. The present study highlights different characteristics from a cation to another.

We first observe that $E_{\text{rep}}^{3\text{-body}}$ is cooperative for alkaline cations, namely Na^+ , K^+ , and Rb^+ , but its magnitude is very small (from −0.3 to −1). Alkaline-earth cations exhibit both cooperative (for Ca^{2+} and Rb^{2+}) and anticooperative (Mg^{2+}) effects with values around ± 2 kcal/mol. The negative values could be due to a slight predominance of the negative “pure exchange contribution,” which is large enough to overcome the actual repulsion term as found in early QC studies.^[2]

For transition and heavy metal cations, the three-body exchange-repulsion has always positive (i.e., anticooperative) values ranking from 1.03 kcal/mol for Au^+ to 6.79 for Zn^{2+} . The cations belonging to the copper column have lower three-body effects than those belonging to the zinc column. Au^+ presents a specific case due to its preference for a linear geometry^[25] instead of the octahedral-like one adopted by the other cations investigated. Therefore, it shows very small many-body repulsion.

The nonadditivity of $E_{\text{exch-rep}}$ was also calculated in some of these arrangements but in the absence of the bound metal cation. Such arrangements had very small many-body exchange-repulsions, amounting to less than 10% of the total many-body effects found when the cation is present.

Thus, on removal of the calcium cation from $[\text{Ca}(\text{H}_2\text{O})_6]^{2+}$ complex, the water–water total exchange-repulsion amounts for 2.37 kcal/mol, whereas the two-body quantity is about 2.64 kcal/mol leading to a -0.27 kcal/mol only many-body contribution. The same test was performed at the geometry of the $[\text{Zn}(\text{H}_2\text{O})_6]^{2+}$ complex. Here, the water–water total exchange-repulsion amounts for 12.36 kcal/mol, whereas the two-body quantity is about 13.97 kcal/mol leading to a -1.6 kcal/mol only many-body contribution. In these two cases, the magnitude of the water–water total exchange-repulsion interaction depends exponentially on the water–water distances, which are higher in the case of calcium ($\text{Ca}(\text{II})$: $d(\text{O}-\text{O}) = 3.47 \text{ \AA}$; $\text{Zn}(\text{II})$: $d(\text{O}-\text{O}) = 3.02 \text{ \AA}$) as $E_{\text{exch-rep}}$ decreases exponentially with distance. Therefore, in light of the high values of the total water–cation exchange-repulsion values, the important interactions to consider for the nonadditive effects are the cation–ligand ones and the water–water interactions can be neglected.

The nature of the computed effects is complex as it is obtained as a difference between the full exchange-repulsion including all many-body effects and the sum of all additive two-body terms. The level of treatment of the system could, then, modify the magnitude of the nonadditive term calculated with the present basis set. In the following section, we investigate the influence of the calculation level on the many-body exchange-repulsion energy.

Influence of the basis set and of the pseudo-potential on $E_{\text{rep}}^{3\text{-body}}$

Calculations of the nonadditivity of the exchange-repulsion were carried out for different basis sets (double and triple zetas) for the water molecules. Results are reported in Table 2.

Cation	Method	$E_{\text{rep}}^{2\text{-body}}$	$E_{\text{rep}}^{\text{tot}}$	$E_{\text{rep}}^{3\text{-body}}$	$E_{\text{rep}}^{3\text{-body}}$ (% $E_{\text{rep}}^{\text{tot}}$)
Ca^{2+}	SDD/6-31++G**	75.9	73.49	-2.37	-3.1
	6-31++G**/6-31++G**	73.0	71.1	-1.9	-2.6
	6-31++G**/augccpvdz	66.0	64.6	-1.3	-2.0
	6-311++G**/6-311++G**	72.4	70.6	-1.8	-2.5
Zn^{2+}	SBK/SBK	82.4	87.5	5.1	6.2
	SDD/6-31++G**	101.3	108.1	6.8	6.7
	6-31G**/6-31++G**	109.9	114.8	4.9	4.5
	6-31G**/augccpvdz	95.9	100.7	4.7	4.9
	6-31G**/6-311++G**	108.4	113.3	4.9	4.5

Values (kcal/mol) of $E_{\text{rep}}^{2\text{-body}}$, $E_{\text{rep}}^{\text{tot}}$, and $E_{\text{rep}}^{3\text{-body}}$ for different full electron and pseudo-potential basis sets. SBK, SDD, and 6-31G** or 6-31++G** basis sets are used for the cations and 6-31++G**, aug-cc-pvdz, and 6-311++G** are used for water.

The basis set level appears to have little impact on the magnitude of many-body effects. Thus, for the hexahydrate complexes of both Ca^{2+} and Zn^{2+} , such magnitudes change by less than 0.5 kcal/mol. This represents less than 0.5% of the

total repulsion energy. On the other hand, representation of the metal cation by a full-electron set as contrasted to a valence set with a pseudo-potential affects more the amplitude of the three-body term. Thus, for the hexahydrate complex of Zn^{2+} , the basis set choice out of 7 can induce on this term a change of up to 2 kcal/mol. For this complex, $E_{\text{exch-rep}}$ amounts to 100 kcal/mol, so this represents a relative error of 2% for this contribution. The core-electrons in a pseudo-potential calculation are not taken into account explicitly in the antisymmetrization of the wave function, which could explain the influence of the pseudo-potential used.

To conclude, on the one hand, the choice of the basis set could appear not to be critical concerning the nonadditivity of the exchange-repulsion energy. It must be recalled, on the other hand that in the present computations, the wave functions of the frozen monomers used to construct the final dimer wave functions within the RVS procedure are computed using the monomer-centered basis elements. It was shown that the use of the dimer basis for each monomer could affect the final values of exchange-repulsion^[26] acting as a "basis set superposition error"-like effect on exchange-repulsion, which also modifies the Coulomb contribution. By construction, the present RVS computations are monomer-centered consistent with the fact that all PMM methods resort to QC-derived properties of the isolated fragments to compute intermolecular interactions, namely multipoles and polarizabilities. Therefore, this indirect basis set effect will always be present in the computation with small- and medium-sized basis sets and would only vanish upon progressing toward the complete basis set limit. Such an effect could be partially corrected by the use of a many-body PMM first-order term.

In the following section, we consider the influence of four-body and higher body repulsion terms.

Evaluation of higher order many-body effects

We have evaluated the amount of four-body and higher body repulsion terms on the hexahydrate complexes of Ca^{2+} , Zn^{2+} , and Hg^{2+} . The values reported in Table 3 never exceed 0.2%

Metal	$E_{\text{rep}}^{2\text{-body}}$	$E_{\text{rep}}^{\text{tot}}$	$E_{\text{rep}}^{3\text{-body}}$	$E_{\text{rep}}^{3\text{-body}}$ (% $E_{\text{rep}}^{\text{tot}}$)	$E_{\text{rep}}^{4\text{-body}}$	$E_{\text{rep}}^{4\text{-body}}$ (% $E_{\text{rep}}^{\text{tot}}$)
Ca^{2+}	75.9	73.5	-2.4	-3.2	0.1	0.1
Zn^{2+}	101.3	108.1	6.8	6.7	-0.3	-0.2
Hg^{2+}	89.7	94.3	4.6	4.9	0.0	0.0

of the total repulsion and can be thus considered as negligible. It is then fully justified to limit our force-field implementation to the inclusion of many-body repulsion through a three-body correction.

PMM Modeling of the Many-Body Exchange-Repulsion Term

SIBFA is a force field^[1] based on the reproduction of the individual contributions of the *ab initio* QC interaction energy.

Each SIBFA contribution is the counterpart of a QC one and could be refined on adding new physical effects independently from the other contributions. Details about its formulation can be found elsewhere.^[1,3] Concerning the first-order terms within SIBFA, the electrostatic (Coulomb) and repulsion contributions, namely E_{MTP^*} and E_{rep} , do not have nonadditivity features. E_{MTP} is computed as a sum of intermolecular multipole–multipole interactions. The multipoles (charges, dipoles, and quadrupoles) are located on the atoms and bonds centers of the molecules or molecular fragments. They are derived from their *ab initio* MO by a procedure given by Vigné-Maeder and Clavier.^[27] E_{MTP^*} is augmented by an explicit penetration term using a formulation due to Piquemal et al.^[28] As the Coulomb energy is exactly additive, we will therefore focus in this study on the sole exchange-repulsion contribution E_{rep} .

In the present formulation of SIBFA, the exchange-repulsion energy is a two-body quantity that is expressed as an approximation of the overlap between the localized molecular orbitals of the interacting molecules. The expression of the exchange-repulsion energy is detailed below.

Expression of the SIBFA two-body exchange repulsion

General formulation

Within the SIBFA formalism, the two-body exchange-repulsion energy between two interacting molecules, namely A and B, is computed as a sum of bond–bond, lone pair–lone pair, and bond–lone pair repulsions:

$$\begin{aligned}
 E_{rep} = & \sum_{p-q \text{ bond of A}} \left[\sum_{r-s \text{ bond of B}} rep(p-q, r-s) \right] \\
 & + \sum_{p-q \text{ bond of A}} \left[\sum_{L_\beta \text{ lone pair of B}} rep(p-q, L_\beta) \right] \\
 & + \sum_{L_\alpha \text{ lone pair of A}} \left[\sum_{r-s \text{ bond of B}} rep(L_\alpha, r-s) \right] \\
 & + \sum_{L_\alpha \text{ lone pair of A}} \left[\sum_{L_\beta \text{ lone pair of B}} rep(L_\alpha, L_\beta) \right] \quad (6)
 \end{aligned}$$

In this equation, $p-q$ and $r-s$ denote bonds between two adjacent atoms of molecules A and molecule B, respectively, and L_α and L_β denote a lone pair on molecules A and B, respectively (see Figure 2). We use the subscript i to denote a bond or a lone pair L_α belonging to A and subscript j to denote a bond or a lone pair belonging to B. We then have the following equations:

$$E_{rep} = \sum_{i \in A} \left[\sum_{j \in B} rep(i, j) \right] \quad (7)$$

$rep(i, j)$ was previously proposed^[29] to have a $S^2/r+S^2/r^2$ dependency, in which S denotes a representation of the intermolecular overlap between electron densities on the bonds or the lone pairs, and R denotes the distance between their respective centroids. The formulation of E_{rep} was already given in previous articles.^[18,30,31] We recast it below, as it enables to introduce the three-body correction in the proper context.

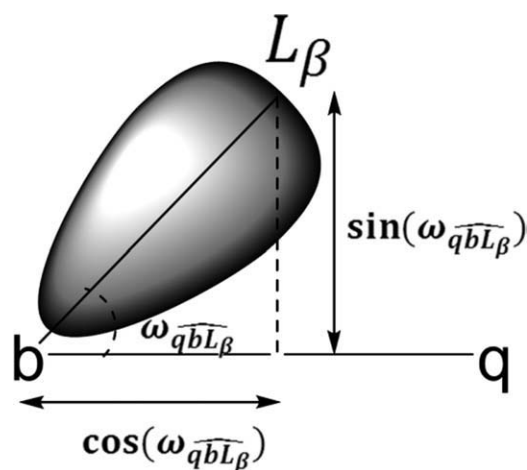


Figure 2. Visualization of different terms involved in the SIBFA interaction between an atom q of a bond named $p-q$ and a lone pair L_β of an atom b .

The bond–bond repulsion can be expressed using overlap integral-like terms (represented as S) between every atom (p , q , r , and s) involved in the interacting bonds ($p-q$ and $r-s$) as defined by Gresh et al.^[30]:

$$\begin{aligned}
 rep(p-q, r-s) = & N_{occ}(p-q)N_{occ}(r-s) \\
 & \times \left[C_1 \left(\frac{S_{p-q,r-s}^1}{R_{p-q,r-s}} \right)^2 + C_2 \left(\frac{S_{p-q,r-s}^2}{(R_{p-q,r-s})^2} \right) \right] \quad (8)
 \end{aligned}$$

with

$$S_{p-q,r-s}^i = S_{pr}^i + S_{ps}^i + S_{qr}^i + S_{qs}^i, \quad i = 1 \text{ or } 2 \quad (9)$$

Here, $R_{p-q,r-s}$ is the distance between the midpoint of the bonds $p-q$ and $r-s$. $N_{occ}(p-q)$ and $N_{occ}(r-s)$ are the occupation numbers of the bonds $p-q$ and $r-s$ (usually they are equal to 2.0), respectively.

In eq. (9), the bond/bond overlap, $S_{p-q,r-s}^i$, is developed as a sum of atom/atom overlaps, S_{pr}^i . This is based on the idea that the bond orbital can be decomposed in terms of two s -type atom-centred orbitals. S_{pr}^i is then approximated to be proportional to an exponential function:

$$S_{pr}^i = \langle 2s_p | 2p_r \rangle = M_{pr} e^{-\alpha_i \rho_{pr}}, \quad i = 1 \text{ or } 2 \text{ with } \rho_{pr} = \frac{r_{pr}}{4\sqrt{(U_p U_r)}} \quad (10)$$

where U_p and U_q are the effective radii of the atoms p and q , respectively, and r_{pr} is the distance between them. The proportionality coefficient, M_{pr} , is characteristic of the nature of the centers p and r involved:

$$M_{pr}^2 = \frac{K_{pr}}{v_p v_r} \left(1 - \frac{Q_p}{N_p^{val}} \right) \left(1 - \frac{Q_r}{N_r^{val}} \right) \quad (11)$$

where K_{pr} is a constant characteristic of the two atomic numbers of p and r , v_p and v_r are the total number of chemical bonds of p and r , respectively, N_p^{val} and N_r^{val} denote the

number of valence electrons of p and r , respectively, and Q_p and Q_r are the partial charges of p and r , respectively. For non-metal atoms (H, C, N, O, S, P), the K_{pq} values are computed as products of atomic K_p and K_q parameters. The values originally determined by Claverie^[32] were retained.

In eq. (8), the first term within square brackets depends on the multiplicative coefficient C_1 and the exponent α_1 of the exponential. The second term depends on C_2 and α_2 . These four parameters are general to all molecules and were originally fitted in ref. 18 in order for E_{rep} to reproduce the numerical values of the QC short-range exchange-repulsion, $E_{\text{exch-rep}}$, in the linear and bifurcated water dimers on performing variations of the O—H distance. The values of these parameters^[18] were retained. Modulation of E_{rep} as a function of: (a) the nature of the atoms involved, if different for O and H; (b) the basis set used, is done by the effective vdW radii (U_p and U_q) in the fitting procedure.

Finally, C_1 and C_2 of eq. (8) and of the following equations are constants obtained by fitting E_{rep} to $E_{\text{exch-rep}}$ on water dimers.^[18]

The bond-lone pair repulsion, as previously described, can be expressed using overlap integrals between atoms p and q and lone pair L_β ,

$$\begin{aligned} \text{rep}(p-q, L_\beta) &= \text{rep}(L_\beta, p-q) \\ &= N_{\text{occ}}(L_\beta) N_{\text{occ}}(p-q) \left[C_1 \frac{(S_{p-q, L_\beta}^1)^2}{R_{p-q, L_\beta}} + C_2 \frac{(S_{p-q, L_\beta}^2)^2}{(R_{p-q, L_\beta})^2} \right] \end{aligned} \quad (12)$$

with

$$S_{p-q, L_\beta}^i = S_{pL_\beta}^i + S_{qL_\beta}^i \quad (13)$$

The different notations used here are equivalent to those used for bond-bond repulsion [eq. (8)], R_{p-q, L_β} is the distance between the midpoint of p - q bond and the centroid of the lone pair L_β . The occupation number N_{occ} of a lone pair is set to 2.0 for a sp^3 -, sp^2 -, or sp -hybrid lone pair and to 1.0 or 0.5 for each lobe of a pure π lone pair.

The standard hybrid form for the orbitals is now used to estimate the considered overlap integral. The atomic orbital can be assumed to be predominantly spherical and then of s -type and directionality. A lone pair L_β of an atom b can be expressed as a sum of s - and p -type orbitals:

$$L_\beta = C_s * 2s_b + C_p * 2p_b \quad (14)$$

To further simplify this equation let us assume that the $2p$ orbital can be divided into a σ part along the direction q - b and a π part perpendicular to it:

$$L_\beta = C_s * 2s_b + C_p * [2p_{\sigma b} \cos \omega_{qL_\beta} + 2p_{\pi b} \sin \omega_{qL_\beta}] \quad (15)$$

where ω_{qL_β} is the angle between the direction of the lone pair L_β and the direction p - q (the direction of the lone pair L_β is the direction b - l where l is the centroid of the lone pair see Fig. 2).

We also propose that the atomic orbital, for example, on the q atom, is mainly spherical meaning of s -type.

Assuming the previous approximation, the overlap integral becomes:

$$\begin{aligned} \langle \chi_q | \chi_{L_\beta} \rangle &= C_{sb} \langle 2s_q | 2s_b \rangle + C_{pb} \cos \omega_{qL_\beta} \langle 2s_q | 2p_{\sigma b} \rangle \\ &+ C_{pb} \sin \omega_{qL_\beta} \langle 2s_q | 2p_{\pi b} \rangle \end{aligned} \quad (16)$$

The last integral is null for symmetry reasons. We further use the relation:

$$\langle 2s_q | 2p_{\sigma b} \rangle = m_{qb} \langle 2s_q | 2s_b \rangle$$

The proportionality coefficient m_{qb} is characteristic of the pair of atoms involved (here q and b) and is tabulated in the program. It is also important to note $m_{qb} \neq m_{bq}$ if q and b are atoms having different atomic numbers.

Equation (15) therefore simplifies as:

$$\langle \chi_q | \chi_{L_\beta} \rangle = \langle 2s_q | 2s_b \rangle (C_{sb} + C_{pb} * m_{qb} \cos \omega_{qL_\beta}) \quad (17)$$

This results into the following equation for S_{qb} :

$$S_{qL_\beta}^i = M_{qb} e^{-\alpha_i \rho_{qb}} (C_{sb} + C_{pb} * m_{qb} \cos \omega_{qL_\beta}) \quad (18)$$

In eqs. (16) and (17), C_{sb} and C_{pb} are standard hybridization coefficients for the lone pairs (0.50 and 0.866 for sp^3 , 0.577 and 0.816 for sp^2 , and 0.0 and 1.0 for π).

For nonmetal atoms, the proportionality factors m_{qb} were originally programmed from formula given for the overlap between Slater orbitals by Mulliken et al.^[33] They were found to have nearly constant values in a broad range of values encompassing equilibrium distance.^[30,34] Such values were originally derived and reported by us in Ref. [30] and are tabulated in the program.

The lone pair-lone pair repulsion is computed as previously using overlap integrals, this time, between two nonspherical orbitals localized on an atom a and an atom b :

$$\text{rep}(L_\alpha, L_\beta) = N_{\text{occ}}(L_\alpha) N_{\text{occ}}(L_\beta) \left[C_1 \frac{(S_{L_\alpha, L_\beta}^1)^2}{R_{L_\alpha, L_\beta}} + C_2 \frac{(S_{L_\alpha, L_\beta}^2)^2}{(R_{L_\alpha, L_\beta})^2} \right] \quad (19)$$

using the same notation as for eqs. (8) and (12). The same approximation as for S_{pL_β} is used for S_{L_α, L_β} :

$$\begin{aligned} S_{L_\alpha, L_\beta}^i &= M_{ab} e^{-\alpha_i \rho_{ab}} (C_{sa} C_{sb} + C_{sa} C_{pb} * m_{pb} \cos \omega_{abL_\beta} \\ &+ C_{pa} C_{sb} * m_{ab} \cos \omega_{abL_\beta} + C_{sa} C_{pb} * m_{ba} \cos \omega_{L_\alpha, ab} \\ &+ 2C_{pa} C_{pb} * \cos \omega_{abL_\beta} * \cos \omega_{L_\alpha, ab}) \end{aligned} \quad (20)$$

It is important to note that $\omega_{L_\alpha, ab}$ is centered on atom a , which is different of ω_{abL_β} centered on atom b .

Case of a metal cation The cation-bond repulsion between a bond p - q and a metal cation (Cat) is computed using the same equations as before:

$$\text{rep}(p-q, \text{Cat}) = N_{\text{occ}}(p-q) \left[C_1 \frac{(S_{p-q, \text{cat}}^1)^2}{R_{p-q, \text{Cat}}^2} + C_2 \frac{(S_{p-q, \text{Cat}}^2)^2}{(R_{p-q, \text{Cat}})^2} \right] \quad (21)$$

with $S_{p-q, \text{Cat}}^i = S_{p\text{Cat}}^i + S_{q\text{Cat}}^i$

Here, $R_{p-q, \text{Cat}}$ is the distance between the bond centroid (midpoint) and the cation, C_1 and C_2 are the same constants as previously defined, and $N_{\text{occ}}(p-q)$ is the occupation number of the bond $p-q$.

$$S_{p\text{Cat}}^i = M_{p\text{Cat}} e^{-\alpha_i \rho_{p\text{Cat}}} \quad (22)$$

with

$$\rho_{p\text{Cat}} = \frac{r_{p\text{Cat}}}{4\sqrt{(U_p U_{\text{Cat}})}} \text{ and } M_{p\text{Cat}}^2 = \frac{K_{p\text{Cat}}}{v_p} \left(1 - \frac{Q_p}{N_p^{\text{val}}} \right) \quad (23)$$

and

$$\text{rep}(L_x, \text{Cat}) = N_{\text{occ}}(L_x) \left[C_1 \frac{(S_{L_x, \text{Cat}}^1)^2}{R_{L_x, \text{Cat}}^2} + C_2 \frac{(S_{L_x, \text{Cat}}^2)^2}{(R_{L_x, \text{Cat}})^2} \right] \quad (24)$$

where N_p^{val} is the number of valence electrons of atom p and v_p is the total number of bonds and lone pairs originating from p .

For metal cations, the values of $K_{p\text{Cat}}$ are fit so that E_{rep} matches the numerical values and distance variations of E_{exch} in the monoligated complex of the cation with representative ligands: water for O, imidazole for N, and methanethiolate for S. This is the procedure that was followed in refs. 35 and 36.

The different constants and variables defined here are the same as for the bond-bond repulsion.

The cation-lone pair repulsion between a cation (Cat) and a lone-pair L_x (of an atom a) is defined in the same way as previously expressed:

$$S_{L_x, \text{Cat}}^i = M_{a\text{Cat}} e^{-\alpha_i \rho_{a\text{Cat}}} \left(C_{sa} + C_{pa} * m_{a\text{Cat}} \cos \omega_{\text{Cat}L_x} \right) \quad (25)$$

similarl to eq. (17):

The values found for the $m_{a\text{Cat}}$ concerning Zn(II) were 1.0 with C, N, and O and 1.87 with S.^[35] We have retained these values for the heavy and transition metal cations. Variations should be absorbed, here again, by the calibration of the $K_{a\text{Cat}}$ values.

All the other constants are already defined in the previous sections.

Inclusion of a three-body exchange-repulsion correction within SIBFA

The present QC results indicate that for several cations a three-body correction is needed to improve the representation of E_{rep} . Such a correction was introduced using expressions present in the two-body exchange-repulsion.

The following equations are general to any molecule, but in the present work, we limit our computations to the cation-water interactions following our *ab initio* results.

Different expressions were tested to model the three-body part ($E_{\text{rep}}^{3\text{-body}}$). Only the most successful one is presented below. It is derived from the two-body repulsion equation but, instead of the S^2/r term used for $E_{\text{rep}}^{2\text{-body}}$, uses a $S^3/r^{3/2}$ formulation:

$$E_{\text{rep}}^{3\text{-body}} = \lambda \sum_{i \in A} \sum_{j \in B} \sum_{k \in C} \left[\frac{S_{ij}}{\sqrt{r_{ij}}} * \frac{S_{jk}}{\sqrt{r_{jk}}} * \frac{S_{ik}}{\sqrt{r_{ik}}} \right] \quad (26)$$

where r_{ij} , r_{ik} , and r_{jk} are the distances between the cation i , namely fragment A, and atoms j and k belonging to fragments B and C, respectively; S_{ij} , S_{ik} , and S_{jk} have the expressions given in the previous section. λ is a scaling factor.

The three-body term is computed by using the S overlap functional and the distances between centers and, therefore, does not significantly increase the computational cost.

The two-body exchange-repulsion is computed using the previously published parameters. To avoid a full refitting of both two- and three-body contributions, we use a different α parameter to compute the S cation-ligand overlap functionals [see eqs. (21) and (24)]. The specific three-body α and λ parameters are given in Table 5.

The three-body repulsion was tested for representative complexes of Ca(II), Zn(II), and Hg(II). The coordinates of all the 18 complexes are given in Supporting Information S2. The constant λ appears to depend only on the nature of the cation involved in the complex formed and not on the nature of the different ligands. The following SIBFA energies were computed on the *ab initio*-optimized complex described in the previous part.

SIBFA Results

The preceding QC computations showed that in polyligated complexes of metal cations, such as their hexahydrates, the many-body repulsion could amount to up to 6 kcal/mol. This could have a significant impact on handling large inorganic and a fortiori bioinorganic complexes such as metalloproteins. They also showed that accounting for the three-body repulsion enabled to recover virtually the entirety of E_{rep} nonadditivity including the previously discussed basis set effects. We now evaluate the extent to which its formulation in the context of SIBFA [eq. (20)] could account for such a nonadditivity.

Parametrization. The validity of the three-body repulsion expressed in eq. (20) was tested on three cations of particular importance in inorganic and bioinorganic chemistry:

1. Zn^{2+} which in the series investigated is the cation giving rise to the largest many-body component of the repulsion;
2. Ca^{2+} for which the many-body component of the repulsion has negative values;

3. Hg^{2+} , a heavy metal cation, involved in several toxicology issues. It is presently investigated in the context of QC and of the integrated GEM/SIBFA approach.

The parametrization of the SIBFA three-body repulsion was performed on adjusting the constants α and λ to fit its

ab initio counterpart. The complexes used for the parametrization are: $[\text{Ca}(\text{H}_2\text{O})_2]^{2+}$; $[\text{Ca}(\text{H}_2\text{O})_6]^{2+}$ in an octahedral arrangement; the octahedral $[\text{Zn}(\text{H}_2\text{O})_6]^{2+}$ complex; $[\text{Zn}(\text{H}_2\text{O})_{5/1}]^{2+}$ and $[\text{Zn}(\text{H}_2\text{O})_{4/2}]^{2+}$, which have a total of six water molecules, with five and four, respectively, in the first hydration shell and one and two second-shell; $[\text{Hg}(\text{H}_2\text{O})_2]^{2+}$ and $[\text{Hg}(\text{H}_2\text{O})_6]^{2+}$ in an octahedral arrangement. The complexes used for the validation of the parameters are: $[\text{Ca}(\text{H}_2\text{O})_4]^{2+}$ in a square planar (SP)

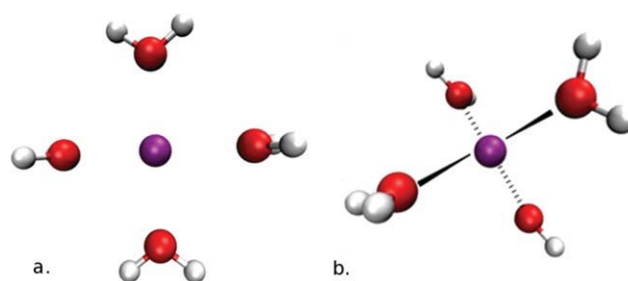


Figure 3. Representation of the $[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$ in the square planar (a) and tetrahedral (b) forms computed at the B3LYP/SDD/6-31++G** level.

	Complex	Ab initio	SIBFA
Calcium	$[\text{Ca}(\text{H}_2\text{O})_6]^{2+[\text{a}]}$	-1.17	-1.01
	$[\text{Ca}(\text{H}_2\text{O})_4]^{2+}$ SP	-0.40	-0.44
	$[\text{Ca}(\text{H}_2\text{O})_4]^{2+}$ Td	-0.46	-0.46
Zinc	$[\text{Ca}(\text{H}_2\text{O})_2]^{2+ [\text{a}]}$	0.12	-0.02
	$[\text{Zn}(\text{H}_2\text{O})_6]^{2+ [\text{a}]}$	6.93	6.40
	$[\text{Zn}(\text{H}_2\text{O})_6]^{2+} - 1$	4.91	4.27
	$[\text{Zn}(\text{H}_2\text{O})_6]^{2+} - 2$	2.94	2.22
	$[\text{Zn}(\text{H}_2\text{O})_6]^{2+} - 3$	1.41	1.08
	$[\text{Zn}(\text{H}_2\text{O})_6]^{2+} - 4$	0.77	0.59
	$[\text{Zn}(\text{H}_2\text{O})_{5/1}]^{2+ [\text{a}]}$	4.38	4.74
	$[\text{Zn}(\text{H}_2\text{O})_{4/2}]^{2+ [\text{a}]}$	1.35	3.10
	$[\text{Zn}(\text{CH}_3\text{S})_3]^-$	2.47	2.27
	$[\text{Zn}(\text{CH}_3\text{S})_4]^{2-}$	4.60	2.47
	$[\text{Zn}(\text{imidazole})_3]^{2+}$	1.53	1.66
Mercury	$[\text{Hg}(\text{H}_2\text{O})_6]^{2+ [\text{a}]}$	4.09	5.04
	$[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$ SP	4.83	4.77
	$[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$ Td	1.71	1.56
	$[\text{Hg}(\text{H}_2\text{O})_2]^{2+ [\text{a}]}$	1.01	0.27

[a] The complexes used for parametrization

Cation	α	λ
Ca^{2+}	2.00	-35
Zn^{2+}	2.13	300
Hg^{2+}	2.13	470

as well as in a tetrahedral (Td) arrangement; $[\text{Zn}(\text{H}_2\text{O})_6]^{2+} - n$ ($0 = n = 4$), derived from the octahedral $[\text{Zn}(\text{H}_2\text{O})_6]^{2+}$ complexes upon progressive removal of n water molecules; $[\text{Zn}(\text{CH}_3\text{S})_3]^-$; $[\text{Zn}(\text{CH}_3\text{S})_4]^{2-}$; $[\text{Zn}(\text{imidazole})_3]^{2+}$; and $[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$ in a SP form and in a Td geometry. The coordinate of the different complexes are given in Supporting Information S2. It is noteworthy that the parameters derived for the complexes with the water ligand oxygens enable to provide a close match of E_{rep} to $E_{\text{exch-rep}}$ in the case of the imidazole N ligand and methanethiolate S ligand.

The present SIBFA implementation uses multipoles and polarizabilities derived from the SBK basis set. The intermolecular QC computations were accordingly performed with this basis set for consistency. The sole exception concerns Ca^{2+} for which the 6-31++G** basis set was used because the large core SBK pseudo-potential does not leave out any valence electrons for it.

The compared QC and SIBFA values of the three-body E_{rep} component are reported in Table 4. The parameters optimized for each cation are reported in Table 5. For 16 of the 18 investigated complexes, the SIBFA values differ by less than

$[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$	Tetrahedral		Square planar	
	Ab initio	SIBFA	Ab initio	SIBFA
E_{rep}	78.0	81.8	132.3	126.9
E_{c}	-194.2	-196.0	-226.9	-226.6
E_1	-116.1	-114.3	-94.6	-99.7
E_2	-89.3	-86.8	-101.7	-102.8
ΔE	-205.5	-201.1	-196.3	-202.5
$\Delta E_{\text{three-body}}$	1.7	1.6	4.8	4.8
$E_{\text{rep modified}}$	78.0	83.3	132.3	131.7
$\Delta E_{\text{modified}}$	-205.5	-199.6	-196.3	-197.7

1 kcal/mol from the QC ones and have generally smaller magnitudes.

Relative stabilities of the Td and SP structures of mercury tetrahydrate $[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$. Two main competing structures can be adopted by the tetrahydrate complexes of metal cations, SP, and Td (see Fig. 3). Their binding energies are compared in the case of Hg^{2+} in Table 6. The *ab initio* results favor the Td structure by about 9 kcal/mol out of 200. This preference stems from the summed first-order (E_1) contributions. Thus, E_1 favors this structure by 21.5 kcal/mol, whereas E_2 favors the SP form by a lesser amount, namely 12.4 kcal/mol. The E_1 preference stems from a significantly smaller (54 kcal/mol) E_{exch} value in the Td structure. Table 5 shows that the SIBFA contributions can match closely their *ab initio* counterparts, except for the E_{rep} contribution in the SP structure, which is 5.4 kcal/mol smaller than $E_{\text{exch-rep}}$. The larger short-range repulsions in SP than in Td structures are due to the greater proximities of the ligands in the former, particularly for the pairs of ligands coming at right angles to one another. This could imply that for these, $\text{O}_w\text{—Hg—O}_w$ three-body effects would have a more destabilizing effect than in the Td structure. This is indeed confirmed by consideration of the $\Delta E_{\text{three-body}}$ term. Thus, both QC and SIBFA results yield values of 4.8 kcal/mol in the SP structure as contrasted to 1.6–1.7 kcal/mol in the Td one.

Addition of such a term to $\Delta E(\text{SIBFA})$ appears to restore the correct Td over SP preference.

Conclusions

EDA analyses have quantified the extent of many-body nonadditivity of E_{exch} in polycoordinated complexes of a series of alkali, alkaline-earth, transition, and heavy metal cations. The magnitude of the many-body repulsion was shown to be strongly cation-dependent and other than three-body effects were found to be negligible. This was exemplified in the series of hexahydrate complexes. Thus, it could be either significant, as in the case of Zn^{2+} (6 kcal/mol out of 108) or close to 0 kcal/mol as in the case of Na^+ , K^+ , or Rb^+ . The size of the basis set did not appear to be very important but the utilization and nature of the pseudo-potential on metal cations could change by up to 2 kcal/mol the nonadditivity of $E_{\text{exch-rep}}$. In addition, the inherent error due to the choice of the monomer basis set within the RVS EDA computation was discussed. It was also shown that higher than three-body terms could be neglected as they never change the repulsion energy by more than 0.2%.

We have accordingly implemented a three-body repulsion in the SIBFA potential and tested it on several complexes of Ca^{2+} , Zn^{2+} , and Hg^{2+} . Such a term is computed using already present two-body terms and therefore does not increase the computational cost.

In 17 of the 19 complexes investigated, $\Delta E_{\text{three-body}}(\text{SIBFA})$ was found to differ from $\Delta E_{\text{three-body}}(\text{QC})$ by less than 1 kcal/mol. Accounting for this contribution could be important on comparing the relative stabilities of the competing arrangements of the polycoordinated complexes of a metal cations. This was shown in the present study concerning the Td versus SP arrangements of $[\text{Hg}(\text{H}_2\text{O})_4]^{2+}$. The SIBFA three-body correction reproduced very closely its *ab initio* counterpart in both arrangements. Its inclusion in the total SIBFA interaction energy enabled to restore the Td versus SP preference consistent with the QC computations. Future works will deal with (1) the inclusion of correlation effects with our many-body formalism through density functional theory^[26,37] or post-HF methods^[7]; (2) alternative formulations based on density overlap.^[1,15]

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