Improved Formulas for the Calculation of the Electrostatic Contribution to the Intermolecular Interaction Energy from Multipolar Expansion of the Electronic Distribution

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We have, within the framework of the molecular mechanics method SIBFA, improved the formulation of the Coulomb (electrostatic) energy contribution to the intermolecular interaction energy. This was done by integrating "overlap-like" terms into two components of the multipolar development used to calculate this contribution in SIBFA. The calibration of the new component is done on five water dimers by fitting this augmented electrostatic contribution to the corresponding E_c term. Several tests are done on (i) representative neutral and ionic hydrogen-bonded complexes; (ii) the complexes of metal cations (Cu(I) and Cu(II)) with a neutral or an anionic ligand; and (iii) a representative stacked complex. The improvement brought by the new formulation reduces the difference between the ab initio (E_c) and molecular mechanics (E_{MTP}*) values by almost an order of magnitude when compared to the values of E_{MTP} calculated using the standard method.

Introduction

In molecular systems containing charged and/or polar groups, the electrostatic forces are, to a large extent, responsible for the geometrical arrangement and for a large fraction of the interaction energy between the different entities.[1] When using molecular mechanics for the study of such systems, it is therefore of primary importance to use a reliable procedure to compute the electrostatic contribution to the system energy. Among the two most widely used approaches toward this end, one resorts to atom-centered charges,[2] and possibly also bond-centered dipoles,[3] or off-centered charges,[4] that are derived by fitting to the ab initio molecular electrostatic potential. The other approach resorts to multipoles derived from the ab initio molecular wave function of the molecule considered.[5] These generally encompass monopoles, dipoles, and quadrupoles, but they can be extended to higher orders, namely octupoles and hexadecapoles. While the best accuracy may be expected from their distributions on atoms as well as bond centers,[5,6] multipoles derived from least-squares fitting to the ab initio molecular electrostatic potential (MEP) are centered only on atoms. A 2- to 3-fold reduction in relative error results in that case from the use of higher order multipoles (up to quadrupoles) with respect to expansions limited to point charges.[4]

The use of ab initio distributed multipoles is necessary to account for the anisotropic features of the electrostatic potential and constitutes an important asset of several polarizable molecular mechanics potentials.[7] Thus, it was shown that such a distribution is able to account for the larger dimerization energies of formamide than alanine dipeptide,[8] in agreement with ab initio results[9] (using a localized MP2 computational procedure[10]), while all available classical procedures that used atom-centered point charges provided the inverse preferences.[9] On the other hand, the ab initio MEP embodies, in addition to multipolar terms, effects due to charge penetration.[11] In the case of the multipole−multipole approximation of the electrostatic energy, such an overlap-like term has to be introduced to account for charge penetration. Thus, we can indicate that, in the SIBFA procedure,[7f] the electrostatic term, denoted as E_{MTP}, is systematically less attractive than the corresponding Coulomb term, E_c, that can be obtained from intermolecular interaction energy-decomposition procedures,[1,12] and the difference between the two terms increases upon decreasing the intermolecular distance. Moreover, there can exist configurations in which E_{MTP} is invariably repulsive while the electrostatic term, E_c, can have attractive values.[13] Even though such configurations are likely to be scarcely populated, similar situations can occur in intramolecular (conformational) calculations where juxtaposed fragments are constrained by the covalent bonds connecting them and cannot rearrange freely. Therefore, a close and consistent reproduction of the first-order component of ΔE_{int} could be ensured solely through a reduction of the repulsive term, E_{rep}(SIBFA), with respect to its ab initio exchange-repulsion counterpart, E_{ex}.[6,14] While the need to have an explicit representation of such effects has been recognized, very few attempts were published so far.[6b,15]

To remedy these shortcomings, and in line with ref 15, the search for an overlap-like term, that would best complement the pure multipolar expression of the electrostatic interaction energy (E_{MTP}), appears desirable. The aim of the present study consists of the derivation and calibration of an expression to be added to the genuine E_{MTP}. The resulting electrostatic contribution, E_{MTP}*, should enable us to reproduce as closely as possible the exact value of the Coulomb contribution given by energy-decomposition procedures in a diversity of situations. For that purpose, we investigate in this work a number of complexes as test cases. To evaluate the reliability of E_{MTP}*, we compare its evolution to that of E_c as a function of both distance and orientation. The complexes that we retain are those

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TABLE 1: Contributions to the Multipolar Electrostatic Interaction Energy (kcal/mol) for Selected Complexes at Equilibrium Distance

complex	mono−mono	mono−dip.	mono−quad	dip.−dip.	dip.−quad	quad− quad
$(H_2O)_2$ linear	−3.3	−2.6	−1.1	−0.5	−0.1	−0.3
$(HCONH_2)_2$ linear	−7.3	−2.8	1.6	0.1	−0.7	0.6
$Cu^{2+}-H_2O$	−46.2	−27.9	0.9	0.0	0.0	0.0
$HCOO^--H_2O$ monodentate	−11.3	−4.9	−0.3	−0.1	−0.7	0.6
$H_3CNH_3^+-H_2O$	−12.5	−7.6	0.1	−0.2	−0.1	0.0

TABLE 2: Table of Atom-type Effective Radii

atom-type	H	O(water)	O(carbonyl)	C	N(pyrrole-like)	N(pyridine-like)	N(ammonia-like)	Cu
effective radius (Å)	1.24	1.44	1.5	1.4	1.65	1.8	1.7	1.37

involving two hydrogen-bonded neutral molecules, those involving one neutral molecule and an anionic or a cationic one, and the complex between an anionic molecule and a cationic one. The comparisons are extended to the complexes formed between either a monovalent (Cu(I)) or a divalent metal (Cu(II)) and a neutral or an anionic ligand, and to a representative stacked complex.

Methods

The ab initio coulomb/electrostatic energy value, E_c, is calculated with either RVS[16] or CSOV[17] algorithms for intermolecular interaction energy decomposition, as implemented in GAMESS[18] and HONDO,[19] respectively. The CSOV method has to be used in the case of open shell systems. The basis set retained for these computations is the DZPV2 one.[20]

In the SIBFA computations, the E_{MTP} contribution is calculated using distributed multipoles, up to quadrupoles. The multipoles are derived from the ab initio molecular orbital wave function of the molecule considered, and they are distributed on its atoms and the barycenters of its chemical bonds by the procedure derived by Vigné-Maeder and Claverie.[5a]

Thus, E_{MTP} is computed as a sum of six terms:

$$E_{MTP} = E_{mono-mono} + E_{mono-dip} + E_{mono-quad} + E_{dip-dip} + E_{dip-quad} + E_{quad-quad} \quad (1)$$

To take account of the short-range electrostatic penetration effect, we have chosen to modified two terms in the calculation of E_{MTP}. Both are dominant and related to monopole interaction, as can be seen from the values of Table 1. Therefore, the first modification deals with the monopole−monopole energy term.

The monopole−monopole energy is given by

$$E_{mono-mono} = q_i q_j / r \quad (2)$$

where r is the distance between the two monopoles q_i and q_j.

Only one term appears in the equation. In our modified formulation (noted $E_{mono-mono}$*), which tends to mimic the ab initio corresponding quantity, three terms are calculated: the core−core repulsion, the core−electron attraction, and the electron−electron repulsion.

For two interacting centers i and j, the modified monopole−monopole energy takes the form

$$E_{mono-mono}^* = [Z_i Z_j - \{Z_i(Z_j - q_j)(1 - \exp(-\alpha_j r)) + Z_j(Z_i - q_i)(1 - \exp(-\alpha_i r))\} + (Z_i - q_i)(Z_j - q_j)(1 - \exp(-\beta_i r))(1 - \exp(-\beta_j r))](1/r) \quad (3)$$

Z_i and Z_j are the number of valence electrons of the two atoms concerned. In the case of the monopoles located on bonds, Z is equal to zero.

α_i and β_i are parameters depending on the effective van der Waals radii r_{vdw} and are given by

$$\alpha_i = \gamma / r_{vdwi} \quad \text{and} \quad \beta_i = \delta / r_{vdwi}$$

respectively, γ and δ being two constants equal to 4.42 and 4.12, respectively. For bond monopoles the r_{vdw} values are taken equal to the arithmetic mean between those of the atoms forming the bond. We see from the above formula that when r increases the new expression tends to the classical form which is accurate at long range (where the multipolar approximation is justified).

The second modification deals with the monopole−dipole energy term, which is given by the following equation:

$$E_{mono-dip} = -\mu_j \xi \quad (4)$$

where ξ, the electric field created by the monopole q_i at point j, is equal to

$$\xi = q_i \mathbf{r}_{ij} / r_{ij}^3 \quad (5)$$

with $\mathbf{r}_{ij}$ being the vector along r, directed from i to j.

Following the idea used for the monopole−monopole term, we have modified only the formula giving ξ to obtain $E_{mono-dip}$*.

$$E_{mono-dip}^* = -\mu_j \xi^* \quad (6)$$

with

$$\xi^* = \{Z_i - (Z_i - q_i)(1 - \exp(-\eta r))\} \mathbf{r}_{ij} / r_{ij}^3 \quad (7)$$

in which η is given by

$$\eta = \chi / [(r_{vdwi} + r_{vdwj})/2] \quad (8)$$

with χ being a constant equal to 2.40. As in the case of the monopole−monopole term, the modified expression tends to the classical one with increasing value of r.

The electrostatic interaction energy calculated using these formulas, E_{MTP}*, is given by

$$E_{MTP}^* = E_{mono-mono}^* + E_{mono-dip}^* + E_{mono-quad} + E_{dip-dip} + E_{dip-quad} + E_{quad-quad} \quad (9)$$

γ, δ, and χ were fit so that E_{MTP}* reproduces E_c on the five water dimers reported in this study.

The atom-type specific effective radii r_{vdw} were readjusted starting from the ones used in SIBFA for the repulsion energy in order to improve this reproduction for the studied complexes at their SIBFA equilibrium distances. Their values are listed in Table 2.

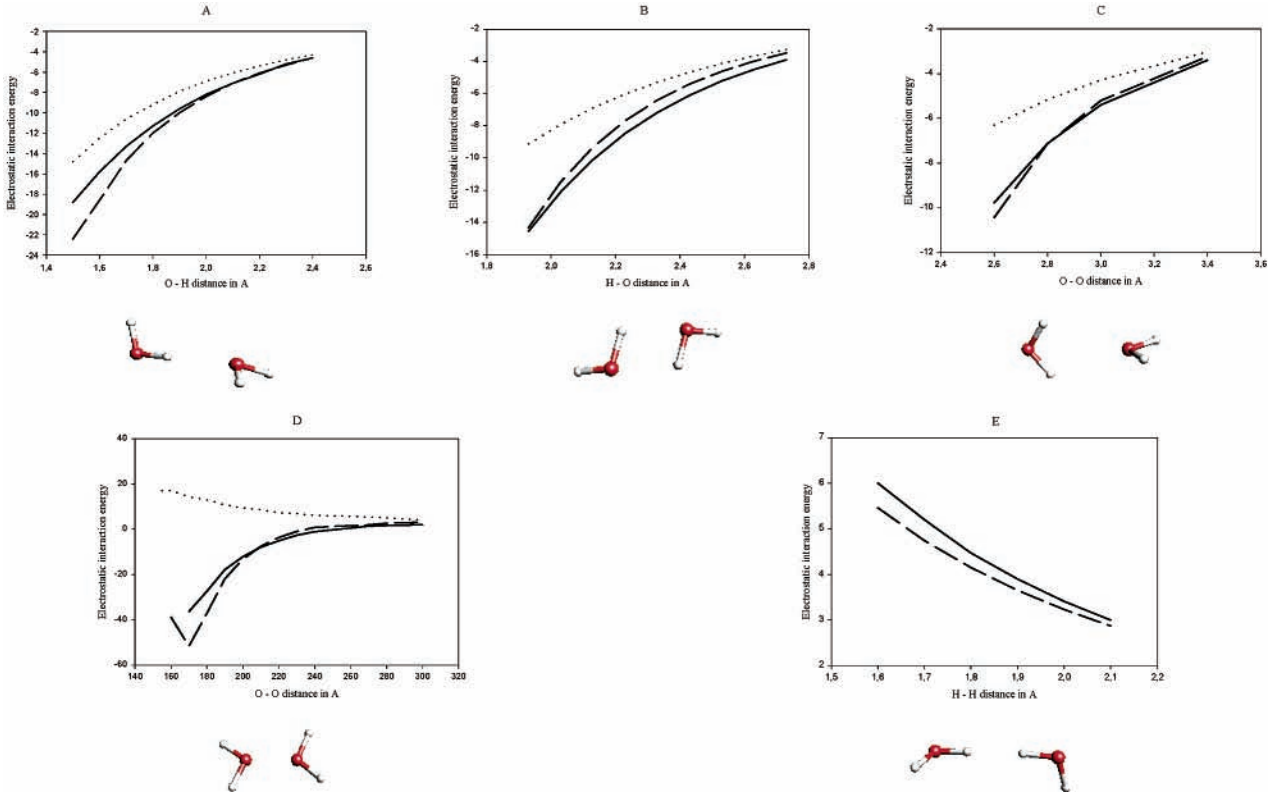

Figure 1. Variations, for water dimers, of the electrostatic interaction energy (values in kcal/mol) calculated from ab initio HF wave functions (E_c), from distributed multipoles (E_{MTP}), and from the modified formulas (E_{MTP}*) as a function of the intermolecular distance.

Results and Discussion

1. Water Dimer. Inclusion of the attractive exponential terms, yielding a closer numerical match of E_{MTP}* with E_c, can be expected to provide variations that differ in magnitude according to the orientation of the second monomer with respect to the first. It was therefore essential to ensure that such improvements occur in a balanced fashion and do not lead to any overestimation of E_c by E_{MTP}* in a particular complex, biasing the interaction energy. For that purpose, we have first considered the three standard hydrogen-bonded water dimers, namely linear, cyclic, and bifurcated. Such investigations of the orientation dependencies of the corrections to E_{MTP} have to our knowledge never been reported before. We have for these complexes reported in Figure 1A−C the evolutions of E_c, E_{MTP}*, and E_{MTP} as a function of the relevant H−O or O−O distances of approach. We see that the energy lowering has similar amplitudes for the three complexes. They are equal to −1.2, −1.1, and −1.1 kcal/mol, respectively, at equilibrium distances obtained from standard SIBFA calculations, and they enable a satisfactory match to E_c. Thus, the respective values of E_{MTP}* and E_c are equal to −8.2 and −8.4 kcal/mol in Figure 1A, −5.2 and −4.6 kcal/mol in Figure 1B, and −5.2 and −5.4 kcal/mol in Figure 1C. We then considered two extreme cases, namely the approach of the two molecules either through their O atoms (Figure 1D) or through one of their H atoms (Figure 1E). The behavior of E_c in the first of these two complexes is particularly noteworthy. Thus, while E_c has positive values in the range of O−O distances corresponding to "common" intermolecular distances (>2.6 Å), it becomes increasing less repulsive upon O−O distance shortening and actually becomes *negative* at O−O distances less than 2.5 Å. By contrast, E_{MTP} remains positive at all distances. The behavior of E_c can obviously only be interpreted by the predominance of the attractive "overlap-dependent" terms at short distances. As expected, its attractive values at O−O distances inferior to 2.5 Å are overcompensated for, in the total interaction energy, by a concomitantly very repulsive exchange contribution. Although the occurrence of such complexes is unlikely, their consideration constitutes a test for the validity of the exponential corrections. This is illustrated in Figure 1D, showing that E_{MTP}* reproduces E_c with a mean error of 1 kcal/mol in the 2.5−3.0 Å range of O−O distances, which corresponds to the most commonly encountered equilibrium distances in hydrogen-bonded complexes. In fact, further shortenings do not result in significantly larger differences between E_{MTP}* and E_c. Thus, even at the unrealistic 2.0 Å O−O distance, such an error remains confined to 1 kcal/mol. In marked contrast, E_{MTP} being dominated by the electrostatic repulsion between the two oxygen atoms increases monotonically upon shortening the O−O distance. For the complex where one H atom of the second water approaches one H atom of the first (Figure 1E), we find that the exponential correction is very negligible. In this case, E_c as well as E_{MTP} and E_{MTP}* are repulsive and monotonically increase upon shortening the H−H distance (down to 1.60 Å). The H−H distances encountered in intermolecular interactions are larger than 1.8 Å. At 1.8 Å, the difference between E_c and E_{MTP}* is 0.3 kcal/mol.

The five water dimers investigated above were those used to calibrate the exponential-dependent terms. It was nevertheless instructive to observe that only three parameters have afforded a satisfactory reproduction of the E_c values in all five arrangements at varying distances.

2. Formamide Dimer. We have investigated three types of geometry. The first two are the linear and the cyclic hydrogen-bonded dimers. For the former a previous study[1b] provided an estimation of the importance of the penetration energy at the equilibrium distance. With the basis set used by these authors it amounts to 20% of E_c. We report in Figure 2A and B the evolutions of E_c as a function of the H−O distance. Again, the

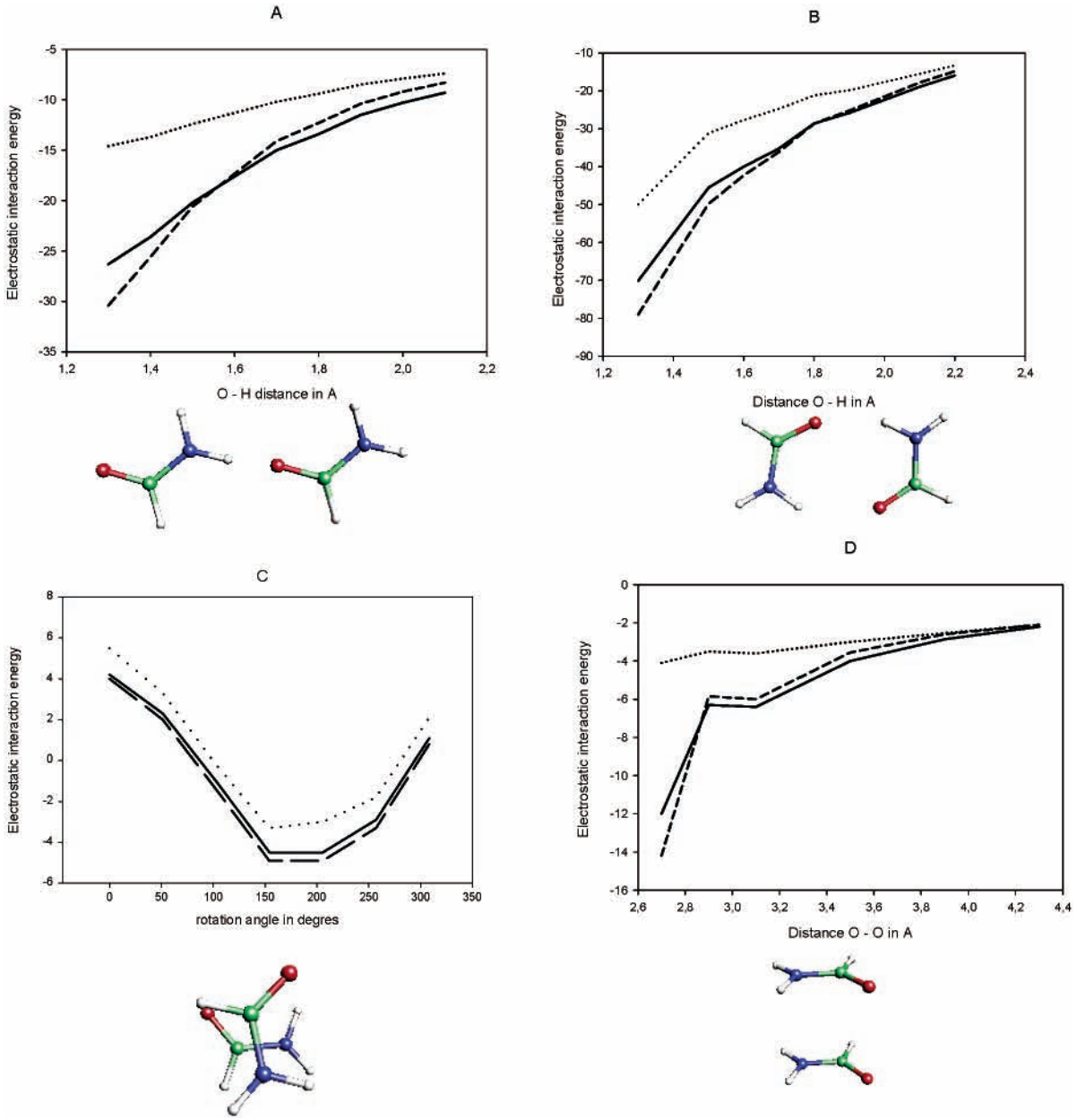

Figure 2. Variations, for formamide dimers, of the electrostatic interaction energy (values in kcal/mol) calculated from the ab initio HF wave function (E_c), from distributed multipoles (E_{MTP}), and from the modified formulas (E_{MTP}*) as a function of the intermolecular distance (A, B, and D) and molecular orientation.

amplitudes of the exponential corrections differ according to the complex. At equilibrium distances, they amount to 3.0 and to 4.5 kcal/mol for the linear and cyclic dimers, respectively. E_{MTP}* in both cases reproduces closely E_c with errors of 1 kcal/mol out of 10 and 25 for these dimers at equilibrium distances. In the linear dimer at equilibrium distance, the overlap-like term contributes 20% of E_{MTP}*, fully consistent with previous results.[1b]

To evaluate how the improvement brought to E_{MTP} translates in a completely different type of complexes, we next considered a complex in which the two formamides are interacting through vertical stacking. Such a complex can be considered as a representative of stacking complexes, which play a very important role in the stabilization of biological complexes and supramolecular assemblies. The complex investigated was generated with the help of computer graphics. In a first step, the plane of the second formamide was set parallel to that of the first at a z vertical separation of 3.3 Å, each atom of the second formamide eclipsing the corresponding one of the first when viewed perpendicular to the z axis. Then seven rotations of the second formamides were done until this molecule performed a complete rotation in its plane. The corresponding variations of E_c, E_{MTP}, and E_{MTP}* are represented in Figure 2C. The numerical amplitude of the exponential-dependent term is smaller (1.2−1.9 kcal/mol) than that in the hydrogen-bonded complexes (Figure 2A and B) above. E_{MTP}* matches E_c to within 0.2−0.4 kcal/mol while the difference between E_{MTP} and E_c fluctuates between 0.8 and 1.5 kcal/mol. The angular behavior of E_{MTP}* closely follows that of E_c. The complex with the lowest E_c has the carbonyl O of each formamide brought over the trans NH group of the other. The second formamide was then held in its initial orientation, and variations in the interplanar separation z were done. The variations of E_c, E_{MTP}, and E_{MTP}* are represented in Figure 2D. E_{MTP}* is seen to be closely reproduced (to within 0.4 kcal/mol) throughout E_c until z is equal to 2.9 Å. This shows that the radial dependencies of the

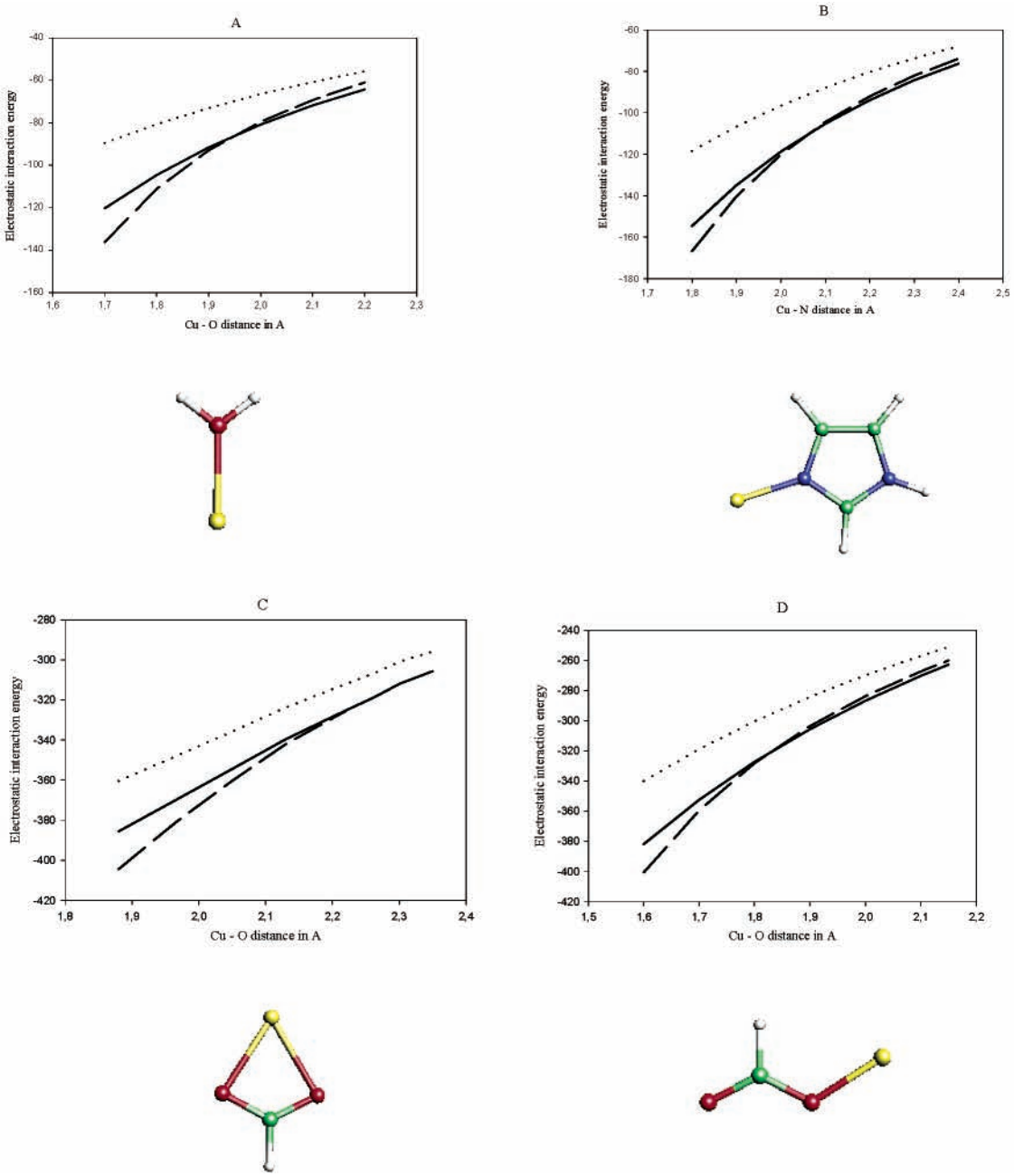

Figure 3. Variations, for Cu(II) complexes, of the electrostatic interaction energy (values in kcal/mol) calculated from ab initio HF wave functions (E_c), from distributed multipoles (E_{MTP}), and from the modified formulas (E_{MTP}*) as a function of the cation−ligand distance.

exponential term are correctly accounted for, considering the fact that, in such a complex, a maximum of atoms "see" one another. At very short interplanar distances (z < 2.9 Å), E_c shows an indentation, and this is also the case with E_{MTP}* while again E_{MTP} has a monotonic behavior as a function of z.

3. Cu(II) Complexes. We have reported in Figure 3 the radial evolutions of E_c, E_{MTP}*, and E_{MTP} as a function of the cation−ligand distances of approach for the complexes of Cu(II) with water, imidazole, and formate. For formate we consider both mono- and bidentate arrangements. In all investigated cases, E_{MTP}* closely reproduces E_c. The least satisfactory case is the bidentate copper(II)−formate complex, for which at equilibrium distance (1.97 Å) the difference between E_{MTP}* and E_c is 11 kcal/mol out of 380. By contrast, E_{MTP} differs from E_c by 53 kcal/mol.

4. Other Complexes. We conclude by the study of two positively charged complexes (Cu(I) interacting with water and methylammonium interacting with water), one negatively charged complex (formate interacting with water), and a neutral complex between a methylammonium and formate.

For the copper(I)−water complex (Figure 4A), E_{MTP}* differs from the ab initio E_c value, at the d_{CuO} SIBFA equilibrium distance of 2.0 Å, by 6 kcal/mol out of 56 as contrasted to 23 kcal/mol in terms of E_{MTP}. In the case of Cu(I), we notice, at large distances, a faster convergence of E_{MTP}* to E_{MTP} than that in the case of Cu(II). For the methylammonium−water complex (Figure 4B) we chose to calculate the electrostatic interaction energy for the approach of the oxygen of the water molecule to one hydrogen of the ammonium group. From a distance 1.5−2.3 Å, the maximum deviation of E_{MTP}* compared to E_c is equal to 1 kcal while at the equilibrium distance E_{MTP} differs from E_c by 5 kcal/mol.

To complete the study of water complexes, we have considered the interaction of a water molecule with a formate in

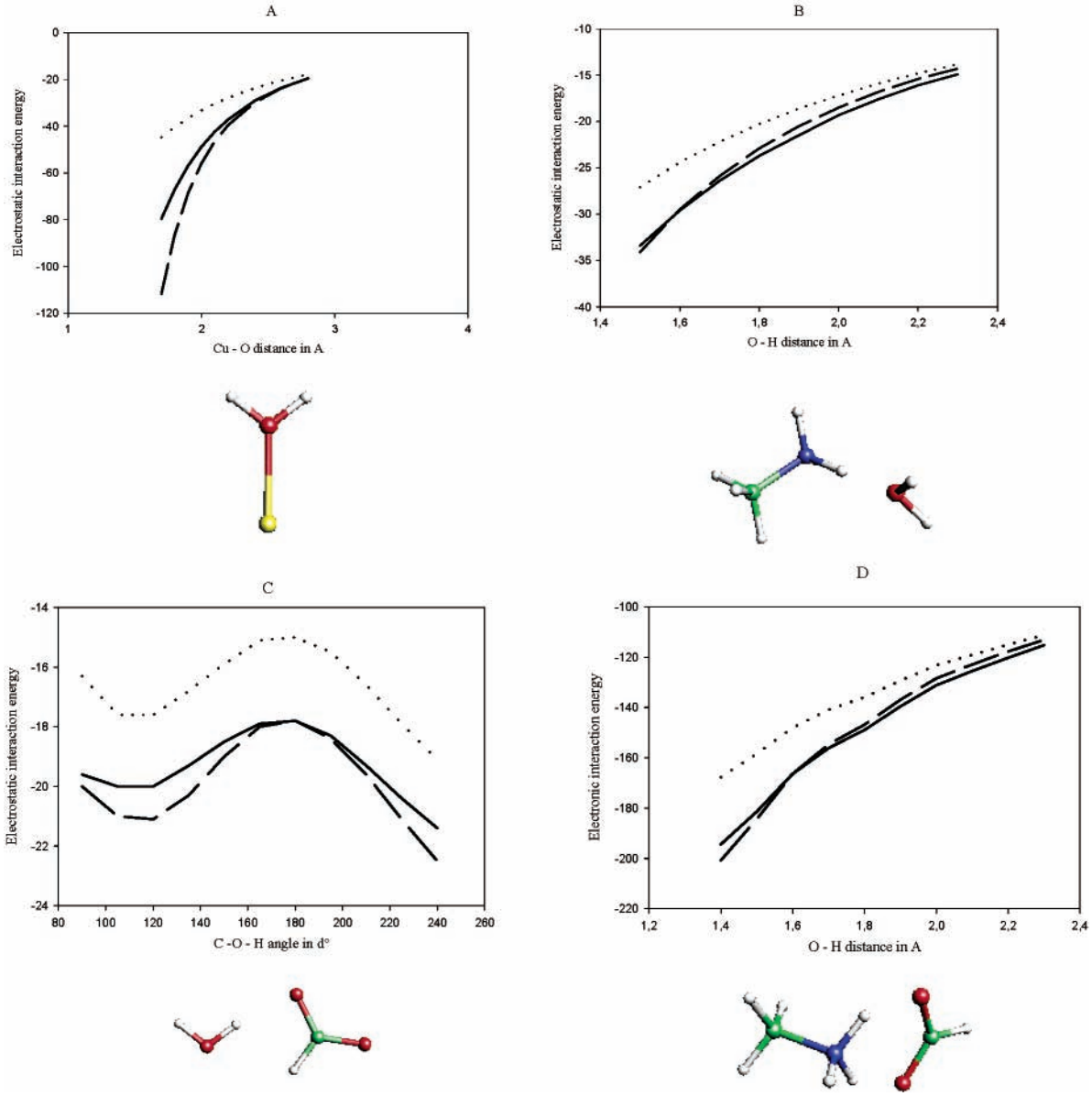

Figure 4. Variations of the electrostatic interaction energy (values in kcal/mol) calculated from ab initio HF wave functions (E_c), from distributed multipoles (E_{MTP}), and from the modified formulas (E_{MTP}*) as a function of the intermolecular distance (A, B, and D) and molecular orientation (C) for complexes containing one or two charged species.

TABLE 3: Values of E_c, E_{MTP}*, E_{MTP}, E_{pen}(HF), and E_{pen}(SIBFA) in Representative Complexes

complex	E_c	E_{MTP}*	E_{MTP}	E_{pen}(HF)	E_{pen}(SIBFA)
water dimer (linear)	−9.9	−9.2	−7.9	−2.0	−1.3
water dimer (cyclic)	−6.4	−7.1	−5.3	−0.9	−1.6
water dimer (bifurcated)	−7.1	−7.1	−5.2	−1.9	−1.9
formamide dimer (linear)	−10.5	−11.4	−8.5	−2.0	−2.9
formamide dimer (cyclic)	−25.2	−25.8	−19.8	−5.4	−6.0
formamide dimer (stacked)	−6.0	−6.4	−3.6	−2.4	−2.9
methylammonium−water (linear)	−25.9	−26.4	−22.2	−3.7	−4.1
formate−water (linear)	−18.4	−18.3	−15.5	−2.9	−2.8
formate−methylammonium (bridge)	−154.6	−156.0	−140.9	−13.7	−15.1
copper(I)−water	−56.0	−49.9	−33.3	−22.7	−16.6
copper(II)−formate (bridge)	−381.0	−369.9	−348.1	−32.9	−21.8

monodentate binding mode (Figure 4C). The electrostatic interaction energy has been evaluated following the evolution of the angle formed by one CO bond of the formate and the hydrogen of the water molecule in interaction with the oxygen (for a fixed O−H distance of 1.8 Å). E_{MTP}* differs from E_c by 1.1 kcal at the equilibrium distance (as compared to 3.7 kcal/mol for E_{MTP}). The average difference is equal to 0.6 kcal/mol.

Finally, we chose to consider the bidentate methylammonium−formate complex (Figure 4D). We have varied the distance between the two formate oxygens and two hydrogens of the ammonium group. At the equilibrium distance of 2 Å, E_{MTP}* differs by less than 2.3 kcal/mol, out of −131.1 kcal/mol, from E_c. For distances between 1.4 and 2.0 Å the difference between E_{MTP}* and E_c fluctuates and equals approximately 2%

of the ab initio electrostatic energy (6−12% in the case of E_{MTP}). Let us denote by E_{pen}(SIBFA) the E_{MTP}* − E_{MTP} difference and by E_{pen}(HF) the corresponding E_c − E_{MTP} difference. Table 3 collects, for the most representative complexes at their SIBFA equilibrium distances, the values of E_c, E_{MTP}*, and E_{MTP} and those of E_{pen}(HF) and E_{pen}(SIBFA). This shows the close correspondence between E_c and E_{MTP}*, on one hand, and between E_{pen}(HF) and E_{pen}(SIBFA) on the other hand.

Concluding Remarks

In this work we have refined the expression of the electrostatic interaction contribution of the SIBFA polarizable mechanics procedure. This was done by adding two "overlap-like" terms to the pure multipolar expression of the electrostatic interaction energy (E_{MTP}). This term was fit so that, in representative complexes, the augmented contribution, E_{MTP}*, could reproduce the quantum-chemical Coulomb energy contribution, E_c, from the RVS/CSOV energy-decomposition procedures on the corresponding complexes. We found that only a limited number of parameters was necessary for that purpose. These were the α_i and β_i terms entering the exponentials that modulate, respectively, the electron−nucleus and the electron−electron components of the "overlap-like" term, and the γ_i term in the exponential modulating the monopole−dipole component. The other parameters were effective van der Waals radii on the atoms according to their chemical types, whether aliphatic or conjugated, and these were found to be close to the corresponding radii used for the repulsion energy term. The validation of E_{MTP}* was done on several hydrogen-bonded complexes involving ionic or polar molecules, and representative cation−ligand complexes. These tests were extended to a study of the stacked complex between two formamide molecules, in which each monomer presents a maximized surface of overlap with the other. We found E_{MTP}* to have numerical values very close to those of E_c, even for distances of approach that were much shorter than the equilibrium distance. There were two examples that we think are worth mentioning. The first is a water dimer, in which each monomer approaches the other through its O atom. This complex was found to give rise to a *negative* E_c at very short O−O distances of approach, and this feature was successfully accounted for by E_{MTP}*, while E_{MTP} lacking the "overlap-like" terms was repulsive at all distances. The occurrence of such an extreme complex is highly unlikely on account of the very strong repulsive O−O overlaps. However, situations in which two like atoms are constrained to approach could frequently present themselves in intramolecular interactions, because of constraints imposed by the structures, while such constraints are not present in intermolecular interactions. The effects of the interactions could be hidden, unfortunately, because there are no energy decompositions possible upon computing actual intramolecular interactions. The other example was that of two formamides interacting through vertical stacking, for which E_{MTP}* successfully reproduced both angular and radial features of E_c, even for small interplanar z distances of 2.8 Å.

As a continuation of this work, we will calibrate E_{rep} so that it fits the corresponding values of the exchange component E_{exch} from energy-decomposition procedures. In this way, a complete term-to-term identification of both E_c and E_{exch} could be obtained, not just that of their sum, as done by the present SIBFA calibration.

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