Model, Multiply Hydrogen-Bonded Water Oligomers ($N = 3-20$). How Closely Can a Separable, ab Initio-Grounded Molecular Mechanics Procedure Reproduce the Results of Supermolecule Quantum Chemical Computations?

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Several high-level quantum chemical calculations have highlighted the prominent weight of nonadditivity within the total stabilization energy of multiply hydrogen-bonded complexes, such as exemplified by water oligomers (reviewed in ref 1). We have evaluated the extent to which the SIBFA (sum of interactions between fragments ab initio computed) molecular mechanics procedure[2−4] could account for nonadditivity in such complexes. This takes advantage of the separability of the energy expression into five distinct components, each of which have inherent anisotropic features. For that purpose, we have considered several representative water oligomers encompassing from $n = 3$ to $n = 20$ molecules, in cyclic and acyclic, as well as, for $n = 6$ and beyond, tridimensional cubic arrangements. Single-point ab initio SCF and MP2 supermolecular energy computations were performed in the energy-minimized structures. A decomposition of the SCF intermolecular interaction energy was done, for $n = 3-6$, using the restricted variational space approximation (RVS) due to Stevens and Fink.[5] This enabled the quantification of the relative weights of each of the two individual ab initio second-order terms, polarization and charge-transfer (E_{pol} and E_{ct}, respectively) to nonadditivity. The SIBFA procedure was found to faithfully reproduce the ab initio results, both in terms of the total ΔE's and in terms of the separate nonadditive behaviors of its own E_{pol} and E_{ct} terms. It was also able to match very closely the results of the recent density functional theory computations of Lee et al.[6] on cubic arrangements of water as occurring in ice. Thus, upon increasing n from 8 to 20, ΔE(SIBFA) was found to converge asymptotically toward a value of -11.5 kcal per molecule of water, close to the experimental binding energy of ice of -11.4. For $n = 20$ in this structure, the average dipole moment per water molecule was computed to be 2.74 D, itself very close to the value of 2.70 D in ice.

Introduction

A critical feature of multiply hydrogen-bonded complexes resides in the nonadditive character of the total binding energy.[1] Its quantitative evaluation was enabled by ab initio[7,8] and density functional theory[9,10] supermolecule computations, which were predominantly devoted to studying water oligomers.[7,9] Monte Carlo[11] and molecular dynamics[12] resorting to "classical" potential energy functions have been used to perform simulations of the liquid phase. An explicit polarization energy contribution was introduced in order to account for nonadditivity.[13] However, the need to improve such "dedicated" potentials was recently emphasized.[1,14] In addition, the extent to which these potentials can be generalized to other than oligomers of water, such as ionic complexes, remains an open issue.

Ab initio supermolecule computations are the most reliable means of computing the intermolecular interaction energy, ΔE, involving an assembly of molecules. Using energy-decomposition procedures,[5,15] the interaction energy at the SCF level, ΔE(SCF), can be decomposed into four distinct components, namely Coulomb, E_c, and exchange, E_e, at the first-order, and polarization, E_{pol}, and charge-transfer, E_{ct}, components at the second-order. Past the SCF level, Moller−Plesset computations[16] afford the correlation energy contribution, E_{corr}, which can be taken as the difference between ΔE(MP2), the intermolecular interaction energies at the MP2 level, and ΔE(SCF). A reliable molecular mechanics procedure whose objective is to reproduce the results of ab initio computations should itself be separable onto five distinct components, each of which being formulated and calibrated so as to match the features of its ab initio counterpart. It is such a requisite that has led to the inception of the SIBFA (sum of interactions between fragments ab initio computed) procedure.[2] Further refinements to this procedure were recently exposed and tested in joint molecular mechanics/ab initio supermolecule investigations of several divalent cation[3] and hydrogen-bonded complexes,[4] in which ΔE(SCF) was decomposed using the restricted variational space approximation (RVS) due to Stevens and Fink.[5] The behaviors, both radial and angular, of the components of the SIBFA binding energy were monitored against those of the ab initio ones in these complexes.

A crucial issue arises upon passing from "dimeric" complexes, to complexes involving several interacting molecules, regarding the extent of nonadditive behavior of the separate ab initio components of ΔE, particularly within the second-order energy E_2. The first kind of example is that of polycoordinated complexes of metal cations, such as Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+},[3,17] and Cu^+ and Ag^+.[18] Using the RVS procedure, E_{pol} and, to an even larger extent, E_{ct} were seen to display very sensitive nonadditive behaviors, in some cases *decreasing* in absolute magnitude upon completion of the cation's coordination. A striking illustration of anticooperativity is provided by ionic first-shell complexes of Mg^{2+} and Zn^{2+} including four or six biologically relevant ligands, such as encountered in "hard" binding sites in proteins and Zn^{2+} fingers;[17] the individual behaviors of E_{pol}(SCF) and E_{ct}(SCF) could be reproduced by their SIBFA counterparts.[17] The second kind of example is provided by multiply hydrogen-bonded water oligomers, for

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which the *increase*, in the most stable arrangements, of the total binding energy with respect to the sum of pairwise interactions is an indication for the onset of *cooperative* interactions.[6−10]

A very recent study by Chen and Gordon[7q] used the RVS procedure to analyze the determinants of the cooperative behavior in the model cyclic water trimers and tetramers. The present study is in line with these authors'. Our principal objective is to assess to what an extent could the SIBFA molecular mechanics procedure account for cooperativity in representative, large water oligomers as compared to ab initio computations. Were such a reproduction possible, this would indicate its adequacy for studies of a manifold of condensed-phase problems. These include cooperativity in the complexes of anionic ligands with a row of successive H-bond donors,[10b] as well as solvation of a variety of molecules and molecular complexes, whether neutral or ionic.

Computational Procedure

Ab Initio Computations. As in our previous studies,[3,4,17−19] the ab initio basis set used is the coreless effective potential (CEP/4-31 G) basis set derived by Stevens et al.,[20] supplemented on the heavy atoms by two diffuse, uncontracted 3d orbitals, the exponents of which were given in ref 19. This basis set will be denoted as SBK thereafter. The energy decompositions are done using the reduced variational space analysis (RVS) developped by Stevens and Fink,[5] interfaced in the Gamess package.[21] This analysis enables the deconvolution of the total ab initio SCF interaction energy, ΔE(SCF), into its individual components E_1, E_{pol}, and E_{ct}, and therefore to monitor their individual nonadditive character upon increasing the number of intervening water monomers. The basis set superposition error[22] was computed with the virtual orbital space.[23]

Computation of the Intermolecular Interaction Energies. The intermolecular interactions are computed with the SIBFA (sum of interactions between fragments ab initio computed) procedure,[2] which is formulated and calibrated on the basis of ab initio SCF supermolecule computations and extended to intramolecular (conformational) energy computations.[2,24] Refinements to SIBFA were recently presented[3,4] along with systematic comparisons with the results of ab initio computations on a series of divalent cation−ligand complexes using the RVS procedure. An important requisite is the ability of this procedure to reproduce the individual components of the SCF interaction energy and not just the total interaction. This alone can ensure for transferability of the procedure and the prospect of accounting for nonadditivity in complexes involving more than two molecules.

In the SIBFA procedure, the intermolecular interaction energy term, ΔE, is computed as a sum of five separate contributions:

$$\Delta E = E_{\mathrm{MTP}} + E_{\mathrm{rep}} + E_{\mathrm{pol}} + E_{\mathrm{ct}} + \mathrm{E}_{\mathrm{disp}} \qquad (1)$$

E_{MTP} denotes the electrostatic (multipolar) energy contribution, computed with multipoles (up to quadrupoles) derived from the ab initio SCF wave function of the constitutive fragments and distributed on the atoms and bond barycenters using the procedure developed by Vigné-Maeder and Claverie.[25] The multipole−multipole interaction energy encompasses six terms, from monopole−monopole up to quadrupole−quadrupole.

E_{rep} is the short-range repulsion energy, computed as a sum of bond−bond, bond−lone pair, and lone pair−lone pair interactions in order to account for its anisotropic character. Thus in the case ot two interacting molecules, A with bonds AB and lone pairs L_α, and C with bonds CD and lone pairs L_γ, E_{rep} is expressed as

$$E_{\mathrm{rep}} = \mathrm{C}_1\Big(\sum_{\mathrm{AB}}\sum_{\mathrm{CD}} \mathrm{rep}(\mathrm{AB},\mathrm{CD}) + \sum_{\mathrm{AB}}\sum_{\mathrm{L}\gamma} \mathrm{rep}(\mathrm{AB},\mathrm{L}_\gamma) + \sum_{\mathrm{L}\alpha}\sum_{\mathrm{CD}} \mathrm{rep}(\mathrm{L}_\alpha,\mathrm{CD}) + \sum_{\mathrm{L}\alpha}\sum_{\mathrm{L}\gamma} \mathrm{rep}(\mathrm{L}_\alpha,\mathrm{L}_\gamma)\Big) \qquad (2)$$

This formulation takes into account the explicit hybridization nature of the bonds, in addition to that of the lone pairs. Each of the four terms under the summation sign of eq 2 depends upon a functional, S, of the overlap such as, for example,

$$\mathrm{rep}(\mathrm{AB},\mathrm{CD}) = N_{\mathrm{occ}}(\mathrm{AB})\, N_{\mathrm{occ}}(\mathrm{CD})\, S^{**\,2}(\mathrm{AB},\mathrm{CD})/D_{\mathrm{AB,CD}} \qquad (3)$$

where N_{occ}(AB) and N_{occ}(CD) denote the occupation numbers of bonds AB and CD: 2 for doubly occupied bonds and lone pairs, one for π-type lone pairs. $D_{\mathrm{AB,CD}}$ is the distance between the barycenters of bonds AB and CD. This assumes, conforming to the earlier proposals by Murrell et al.,[26] a dependence of E_{rep} proportional to $S^{**\,2}/R$, rather than $S^{**\,2}$.

Within the context of Slater-like orbitals, and in the general case of all four atoms having sp hybrids on their valence electrons with hybridization coefficients c_{s} and c_{p}, the functional, S(AB,CD), of the overlap between bonds AB and CD can be expanded into up to 16 atom−atom terms as in the following equation. In this equation, I designates in succession atoms A and B of bond AB, whereas J designates the other atom of this bond. K designates in succession atoms C and D of bond CD, whereas L designates the other atom of this bond.

$$S(\mathrm{AB},\mathrm{CD}) = \sum_{I=\mathrm{A,B},J=\mathrm{B,A}}\sum_{K=\mathrm{C,D},L=\mathrm{D,C}}\big(c_{\mathrm{s}I}c_{\mathrm{s}K}\langle 2\mathrm{s}_I 2\mathrm{s}_K\rangle + c_{\mathrm{p}I}c_{\mathrm{s}K}\langle 2\mathrm{p}_{\sigma I}2\mathrm{s}_K\rangle \cos(IJ,IK) + c_{\mathrm{p}K}c_{\mathrm{s}I}\langle 2\mathrm{p}_{\sigma K}2\mathrm{s}_I\rangle \cos(KL,KI) + c_{\mathrm{p}I}c_{\mathrm{p}K}\langle 2\mathrm{p}_{\sigma I}2\mathrm{p}_{\sigma K}\rangle \cos(IJ,IK)\cos(KL,KI)\big) \qquad (4)$$

Let us consider the representative pair of atoms A and C. For simplicity, and within the context of our own earlier treatment,[2d] the following relationship between the p and s contributions to the ligand−metal overlap is assumed:

$$\langle 2\mathrm{p}_{\sigma\mathrm{A}}2_{\mathrm{sC}}\rangle = m_{\mathrm{AC}}\langle 2\mathrm{s}_{\mathrm{A}}2_{\mathrm{sC}}\rangle \qquad (5)$$

in which m_{AC} is a proportionality factor, which can be obtained by calculating the overlap functions between A and M with standard Slater orbitals using the formulas derived by Mulliken, Roothan, and co-workers.[27] For a given pair of atoms, its value is tabulated in the program, as it can be shown to be fairly constant in the zone of relevant interatomic distances (see ref 2d for details). A related proportionality relation holds between the $\langle 2\mathrm{p}_{\sigma\mathrm{A}}2\mathrm{p}_{\mathrm{sC}}\rangle$ and $\langle 2\mathrm{s}_{\mathrm{A}}2\mathrm{s}_{\mathrm{C}}\rangle$, the proportionality ratio now being 2.

$\langle 2\mathrm{s}_{\mathrm{A}}2_{\mathrm{sC}}\rangle$ can be approximated by a exponential of the distance, r_{AC}, between A and C, modulated by the geometric means of the effective radii of A and C:

$$\langle 2\mathrm{s}_{\mathrm{A}}2_{\mathrm{sC}}\rangle = M_{\mathrm{AC}}\exp(-\alpha\rho_{\mathrm{AC}}) \qquad (6)$$

$$\rho_{\mathrm{AC}} = r_{\mathrm{AC}}/4\sqrt{W_{\mathrm{A}}W_{\mathrm{C}}} \qquad (7)$$

and

$$M_{\mathrm{AC}} = \sqrt{K_{\mathrm{AC}}(1 - Q_{\mathrm{A}}/N^{\mathrm{A}}{}_{\mathrm{val}})\,(1 - Q_{\mathrm{C}}/N^{\mathrm{C}}{}_{\mathrm{val}})} \qquad (8)$$

Q_{A} and Q_{C} denote the net charges of atom A and C, and $N^{\mathrm{A}}{}_{\mathrm{val}}$ and $N^{\mathrm{C}}{}_{\mathrm{val}}$ are the number of their valence electrons. W_{A} and W_{C} are the effective radii of atoms A and C. K_{AC} is a proportionality factor between A and C, which has values tabulated according to the atomic numbers of A and C.[2−4,28]

Equation 8 takes into account the effect of the electronic populations on atoms A and C on the short-range repulsion energy.[28] α is a constant having the value of 12.35.[28]

This treatment can be easily extended to the bond−lone pair and lone pair−lone pair repulsion terms, the tip of, for example, the lone pair L_α enabling the definition of the angles (L_α,CD) and (L_α,DC) needed in the expressions above, and the distances $D_{A,BC}$ intervening in the denominator being those computed between atom A and the midpoint of bond CD.[3a,c]

E_{pol} is the polarization energy contribution, computed with distributed, anisotropic polarizabilities on the individual molecules. The polarizabilities are distributed on the centroids of the localized orbitals (heteroatom lone pairs and bond barycenters) using a procedure due to Garmer and Stevens.[29]

Considering centroid P belonging to ligand A and endowed with a polarizability tensor $\alpha_P(i,j)$, the electric field $E_P(j)$ of component j exerted on P will give rise to an induced dipole of component i and is expressed as

$$\mu_P{}^{ind}(i) = \alpha_P(i,j)\, E_P(j) \qquad (9)$$

If B denotes every molecule that interacts with A in an intermolecular complex, and Q, every multipole-bearer on B that will give rise to an electric field on P,

$$E_P(j) = \sum\nolimits_{B\to A} \sum\nolimits_{Q\epsilon B} E_{Q\to P}(j) \qquad (10)$$

the polarization energy of P is then computed as

$$E_{pol}(P) = -0.5 \sum\nolimits_i E_P(i)\, \mu_P{}^{ind}(i) \qquad (11)$$

For reasons discussed in our previous papers,[3a,c] it is necessary to reduce the electrostatic field. Such a reduction, which is imperative in the context of cation−ligand interactions,[3a] was retained in the more general context. It also has precedents in water simulations.[11] Thus, as in ref 3a,

$$E_{Q\to P} = (1 - S(P,Q))E°_{Q\to P} \qquad (12)$$

in which $E°$ denotes the electrostatic field generated on $P \in A$ by $Q \in B$, and S(Q,P) is a Gaussian screening functional:

$$S(Q,P) = Q_Q E \exp(-F(R_{PQ}{}^{**\,2})/(V_P + V_Q)) \qquad (13)$$

where R_{PQ} is the distance between Q and M, Q_Q is the monopolar charge of Q, V_P and V_q are the effective radii of P and Q, and E and F are parameters which are transferable between ligands containing the same type of ligating atoms (i.e. sp^3, sp^2, or anionic oxygens; sp^2 or sp^3 nitrogens, etc.). The field polarizing each molecule is computed with the permanent multipoles and the induced dipoles of all the other molecules in an iterative fashion.

E_{ct} is the charge-transfer energy contribution. An expression for E_{ct} was derived in our previous papers[2d,30] starting from the formula due to Murrell et al.:[31]

$$E_{ct} = -2 \sum\nolimits_{\alpha\epsilon A} \sum\nolimits_{\beta^*\epsilon} B(1/\Delta E_{\alpha\beta^*}) \int \rho_{\alpha\to\beta^*}(r)\, V^B(r)\, dr \qquad (14)$$

in which $\rho_{\alpha\to b^*}(r)$ is the overlap transition density, $V^B(r)$ is the electrostatic potential generated by molecule B, the electron acceptor, on molecule A, the electron donor, and $\Delta E_{\alpha\beta^*}$ is the energy involved in the electron transfer from orbital α in molecule A to orbital β^* in molecule B. In our treatment, the electron donors from A are restricted to its sole lone pairs, since these are the most exposed ones, as well as having the smallest ionization potentials. The virtual orbitals on the acceptor molecule are limited to the set of bond orbitals ϕ_{*BH} restricted to the bonds linking a hydrogen atom and the corresponding heavy atom B. We furthermore assume for ϕ_{*BH} the simplified form (antibonding):

$$\phi_{*BH} = h - b \qquad (15)$$

in terms of the atomic orbitals h on H and b on B, and we reduce b to its 2s B component (see ref 2d for discussion). This leads to the following expression for E_{ct}:

$$E_{ct} = -2C \sum\nolimits_{L\alpha} N_{occ}(\alpha)((T_{\alpha\beta^*})^{**\,2}/\Delta E_{\alpha\beta^*}) \qquad (16)$$

C is a constant which was calibrated in ref 4 in order to reproduce the value of E_{ct}(SCF) at equilibrium distance in the linear water dimer and is transferable to the case of all noncationic metal acceptors; $N_{occ}(\alpha)$ is the occupation number of lone pair α.

$T_{\alpha\beta^*}$ is a function of (a) the overlap between the hybrids on orbital L_α and ϕ^*_{BH}. It is expressed in a manner similar to E_{rep} (see ref 2d for details); (b) the electrostatic potential exerted on A by all the other interacting molecules. With respect to our original treatments of refs 2d and 30 three important modifications were introduced in light of a series of ligand−cation interactions and were retained to treat hydrogen-bonding interactions. They are commented in detail in ref 3a,c.

The first modification is the incorporation, in the expression of the total electrostatic potential sensed by A, of the contribution due to the dipoles induced on the electron acceptors, along with that of the permanent multipoles.

The second modification is an increase of the ionization potential of A, $I_{L\alpha}$, by the predominantly positive electrostatic potential exerted on this atom by all the other molecules in the complex, along with a reduction of the electron affinity of the electron acceptor, A_{β^*}, by the predominantly negative electrostatic potential due to its surrounding ligands. These potentials are those due to the permanent multipoles and the induced dipoles of the interacting molecules.

$$\Delta E_{\alpha\beta^*} = (I_{L\alpha} + \sum\nolimits_C V_{C\to A}) - (A_{\beta^*} + \sum\nolimits_C V_{C\to B}) \qquad (17)$$

The third modification is an expansion of the effective radius of the electron donor A, involved in the expression of the overlap dependence of the numerator $T_{\alpha\beta^*}$. This effective radius undergoes an increase proportional to the electric field it senses and in the direction of the electron acceptor.

These modifications, which introduce a coupling between E_{ct} and E_{pol}, were instrumental to account for the nonadditive behavior of E_{ct} in a series of polyligated complexes of divalent cation complexes refs 2, 17, and Deerfield et al., to be published). An important issue of the present study is the extent to which the *cooperative* behavior of the charge-transfer term in the ab initio computations, as contrasted to its *anticooperative* behavior in the metal cation oligoligates, can be accounted for.

E_{disp} is the dispersion energy component, for which an improved representation is due to Hess et al.[32] and Creuzet et al.[33] It is computed as a $C_6/Z^{**\,6}$, $C_8/Z^{**\,8}$, and $C_{10}/Z^{**\,10}$ expansion, where $Z = R_{IJ}/\sqrt{W'_I W'_J}$, R_{IJ} is the distance between I and J, W'_I and W'_J are the effective radii used for E_{disp}, and C_6, C_8, and C_{10} are empirical coefficients. Each of these terms is reduced by an exponential damping factor having the form

$$E_{damp(n)} = (1/R^{**\,n})L_{IJ} \exp(-a_{damp}(n)\, D(I,J)) \qquad (18)$$

L_{IJ} is an atom-specific parameter used for the dispersion energy, n has the values 6, 8, or 10, $a_{damp}(n)$ and $b_{damp}(n)$ are empirical coefficients, and $D(I,J)$ is a function of the interatomic distance

R_{IJ} and of the effective radii W'_I and W'_J:

$$D(I,J) = ((W'_I + W'_J)b_{\mathrm{damp}(n)}/R_{IJ}) - 1 \tag{19}$$

Furthermore, an explicit exchange−repulsion term is added to E_{disp}:

$$E_{\mathrm{exch-disp}} = L_{IJ}(1 - Q_I/N_{\mathrm{val}}(I))(1 - Q_J/N_{\mathrm{val}}(J))C_{\mathrm{exch}} \exp(-\beta_{\mathrm{exch}} Z) \tag{20}$$

As in our formulation of E_{rep}, Q_I and Q_J denote the net charge of atoms I and J, and $N_{\mathrm{val}}(I)$ and $N_{\mathrm{val}}(J)$ are the number of their valence electrons. C_{exch} and β_{exch} are empirical coefficients. Finally, directionality effects are accounted for by introducing additional interactions involving fictitious atoms at the barycenters of the heteroatom lone pairs, affected by an empirical multiplicative factor, C_{lp}. The values of the reduced effective radii W' on the lone-pair-bearing atoms and those of the fictitious atoms are the same as in the original derivation of SIBFA,[2a] where they were used for the computation of the intramolecular repulsion energy. The values of the empirical parameters presently used in this formulation of E_{disp} were given in refs 4 and 32. They were initially derived in order to fit the value of the correlation energy in hydrogen-bonded dimers, as resulting from symmetry-adapted perturbation theory.[32−34]

Geometry, Basis Set, and Minimization Procedure. The ab initio SCF computations on the individual molecules, necessary to derive the distributed multipoles and polarizabilities, also used the SBK basis set. As in our previous studies, the internal bond lengths ($d_{\mathrm{O-H}} = 0.975$ Å) and valence angles ($\theta(\mathrm{H-O-H}) = 104.5°$) were kept frozen.

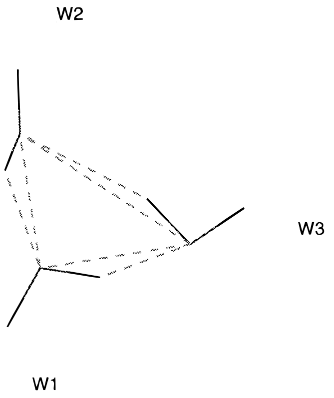
Energy minimization on the intermolecular variables (six per water molecule) was done using the Merlin[35] polyvalent minimizer. Vibrational energy corrections will not be taken into account at the present stage.

Calibration. We have rescaled the expression of the exchange-repulsion component of E_{disp}, in light of recent results obtained with the symmetry-adapted perturbation theory (SAPT).[32,34] This was done simply by using a larger value of the multiplicative constant C_{exch}, of 408 instead of 240. For the linear water dimer, this prevents too steep an increase of E_{disp} for short intermolecular distances ($d(\mathrm{O-O}) < 2.70$ Å), while enabling this component to reproduce the corresponding SAPT values to within 0.2 kcal/mol in the interval of O−O distances 2.75−3.20 Å. (N. Gresh, S. Creuzet, J. Langlet, work in preparation). At the 2.95 Å equilibrium distance, E_{disp} has a value of −1.6 kcal/mol. We retained the same calibration as in ref 4 for the other components of ΔE(SIBFA).

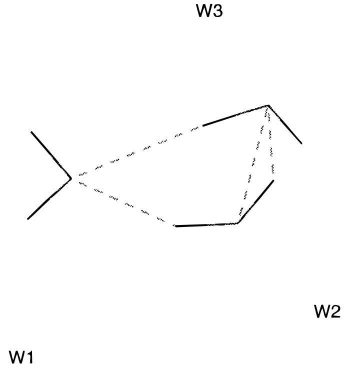
Computation of the Continuum Solvation Energies. The solvation energies are computed using the Langlet et al. continuum procedure.[36] Within this procedure, the solvation energy is computed as the following sum:

$$E_{\mathrm{solv}} = E_{\mathrm{cav}} + E_{\mathrm{el}} + E_{\mathrm{pol}} + E_{\mathrm{dr}} \tag{21}$$

E_{cav} is the cavitation energy, calculated as a sum of contributions from intersecting atoms, centered on the solute atoms, using a Reiss−Pierotti formula (ref 37, and references therein). E_{el} is the solute−solvent electrostatic energy. The electrostatic potential generated by the solute is computed with the help of the same distributed multipoles as in the expression of E_{MTP}. The dipoles, which are induced on the polarizable centers of the solute molecules, are taken into account in the computation of E_{el} along with the permanent mutipoles. At this stage, however, the additional dipoles induced on the solute molecules because of the reaction field of the solvent are not taken into account. Such a refinement will be introduced in later treatments (Langlet, J., work in progress). E_{pol} is the solute polarization energy, and E_{dr} is the dispersion−repulsion contribution. As discussed in ref 37, this procedure enables one to compute both the “free energy” term, denoted as ΔG_{solv} below, and its enthalpic contribution, denoted as ΔH_{solv} below. The integrated SIBFA/continuum procedure was recently applied in an investigation of the interactions between polar amino acid side chains in water and organic solvents,[38] to study the conformational behavior of alanine-based oligopeptides in water and organic solvents,[24] to perform energy balances for the binding of two metallopeptidase inhibitors within the active site of native and mutated thermolysin,[39] and to investigate the effect of solvation on the conformation of intermediates involved in organic synthesis.[40]



Cyclic water trimer (a)



Water trimer in structure (b)

Figure 1. Cyclic water trimer in structures a and b.

Results and Discussion

We will consider in succession water oligomers made out of 3, 4, 5, 6, and 8 water molecules. Representative complexes will be considered, along with the model cyclic ones. For $n = 8$, a “cubic” arrangement will be considered. For $n = 12$, 16, and 20, we consider only the cubic structures and compare our results to the DFT results of Lee et al.[6] We will denote by ΔE_0(SIBFA) the intermolecular energies computed using the SIBFA procedure without the E_{disp} contribution. Because the BSSE correction will be shown to be very small with the SBK basis set (see below), it will not be taken into account in our comparisons of the molecular mechanics and ab initio results.

***n* = 3.** Two competing trimers were considered, both stabilized by the same number of H-bonds (see Figure 1a,b). The first is the cyclic structure, in which each water molecule acts as an H-bond donor to one of its neighbors and as an H-bond acceptor to the other one. This is the structure shown

TABLE 1: Values of the ab Initio and the SIBFA Binding Energies and of Their Components in Two Representative Water Trimers

(a) Cyclic Water Trimer
$d_{O1-O2} = 2.88$ Å, $d_{O1-O3} = 2.86$ Å, $d_{O2-O3} = 2.86$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
trimer	−11.1	−4.8	−3.7	−2.6	−6.5	−17.6	−0.5
1−2	−2.9	−1.4	−0.8	−0.8	−2.2		
1−3	−3.5	−1.7	−0.7	−0.7	−2.3		
2−3	−3.4	−1.6	−0.9	−0.9	−2.2		
summed	−9.8	−4.7	−2.4	−2.4	−6.7		
δE_{nad}	−1.3	0.0	−1.3	−0.2	−0.2		

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^a$	E_{ct}	E_{disp}	ΔE	E_{solv}
trimer	−11.0	−4.7	−3.8	−3.1	−2.5	−5.3	−16.3	−15.9[b] −7.5[c]
1−2	−2.8	−1.3	−0.7		−0.7	−1.7		
1−3	−3.3	−1.7	−0.8		−0.8	−1.8		
2−3	−3.3	−1.7	−0.8		−0.8	−1.8		
summed	−9.4	−4.7	−2.3		−2.3	−5.3		
δE_{nad}	−1.6	0.0	−1.5		−0.2	0.0	−1.6	

(b) Central Oxygen Bidentate
$d_{O1-O2} = 3.00$ Å, $d_{O1-O3} = 3.00$ Å, $d_{O2-O3} = 2.99$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
trimer	−7.1	−4.0	−1.5	−1.5	−5.0	−12.1	−0.5
1−2	−3.3	−2.1	−0.6	−0.6	−1.6		
1−3	−2.9	−1.7	−0.5	−0.5	−1.8		
2−3	−1.1	−0.1	−0.5	−0.5	−1.7		
summed	−7.3	−3.9	−1.7	−1.7	−5.1		
δE_{nad}	0.2	0.0	0.2	0.2	−0.1		

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^a$	E_{ct}	E_{disp}	ΔE	E_{solv}
trimer	−7.0	−4.1	−1.4	−1.3	−1.5	−4.1	−11.1	−19.3[b] −10.6[c]
1−2	−3.4	−2.2	−0.6		−0.5	−1.3		
1−3	−2.9	−1.6	−0.7		−0.6	−1.3		
2−3	−1.1	−0.3	−0.5		−0.4	−1.5		
summed	−7.4	−4.1	−1.8		−1.5	−4.1		
δE_{nad}	0.4		0.4		0.0			

[a] Without the effect of the induced dipoles. [b] ΔH. [c] ΔG.

to be the most stable one by both ab initio[7] and DFT[6,8] computations and also the structure whose existence was experimentally demonstrated.[41] The three hydrogens that are not involved in the H-bonding network are about 60° tilted with respect to the ring plane. In the second trimer, one water molecule acts a simultaneous H-bond acceptor to both neighbors, through its bidentate-bound O. The compared ab initio and SIBFA results are reported in Table 1. It shows the following results.

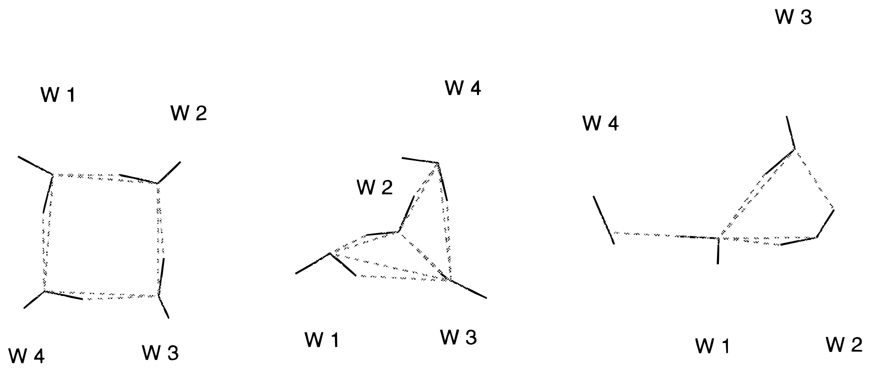
(1) Trimer a is preferred over trimer b by 4 and 5.5 kcal/mol at the SCF and MP2 levels, respectively. The values of ΔE(SIBFA) are very close to the corresponding ab initio values.

(2) In both the ab initio and the SIBFA computations, E_1 provides the smallest (0.8 kcal/mol) contribution to the a versus b preference. E_{pol} contributes more than twice as much, and both E_{ct} and E_{corr}/E_{disp} favor a over b.

(3) Whereas the onset of a stabilizing, nonadditive contribution to ΔE, δE_{nadd}, is evident in the case of trimer a (−1.3 kcal/mol), this is not the case for trimer b. On the contrary, a slight *destabilizing* contribution (0.2 kcal/mol) of δE_{nadd} occurs for it, and it is noteworthy that this can also be accounted for by the SIBFA computations.

(4) For the cyclic trimer a, the values of ΔE(SCF) and ΔE_0(SIBFA) of −11 kcal/mol, as well as those of δE_{nadd} amounting to −1.3 and −1.6 kcal/mol in the two approaches, are very close to those computed by other authors using high-level Gaussian basis sets, namely ΔE(SCF) in the −11.0−12.7 kcal/mol range and δE_{nadd} in the range −1.0−1.3 kcal/mol.[7] In both the ab initio and the SIBFA computations, E_{pol} is the principal contributor to nonadditivity, whereas E_{ct} contributes only −0.2 kcal/mol out of −1.5. This is consistent with the results of Chen and Gordon,[7q] who derived a similar value in their RVS computations using an augmented correlation-consistent polarized valence double-ζ basis set (aug-cc-pVDZ). The values of ΔE(MP2) and ΔE(SIBFA) of −17.6 and −16.3 kcal/mol, respectively, are themselves very close to the −16.6 kcal/mol one computed at the uncorrected MP2[7k] level and of −16.3 kcal/mol computed at the MP4[7p] level, as well as to the values resulting from nonlocal density functional theory computations of refs 6 and 9a,d, which are in the range −15.2−18.5 kcal/mol (without the zero-point energy correction). However, they are larger in absolute values than the DFT value of −13.8 kcal/mol computed by Xantheas with a Becke−Lee−Yang−Parr (B-LYP) functional and an aug-cc-pVDZ basis set.[9c]

(5) With respect to the water dimer case, in which the equilibrium O−O distance is 2.95 Å, a shortening of the three O−O bond distances (2.86 Å) is seen in trimer a, but not in trimer b. Such a shortening is more pronounced than in the recent study by Chen[7q] giving O−O distances of 2.93 Å,[7o] done at the SCF level. This translates the effect of the E_{disp} contribution in SIBFA, increasing the mutual interwater attractions. More important shortenings than ours (d(O−O) = 2.80 Å), on the other hand, were reported in the MP2 and MP4 calculations of Xantheas and Dunning[7g] and Klopper et al.,[7p]



Cyclic water tetramer Water tetramer, conf. b Water tetramer, conf. c

Figure 2. Water tetramer in structures a−c.

TABLE 2: Values of the ab Initio and the SIBFA Binding Energies and of Their Components in Three Representative Water Tetramers

(a) Cyclic Water Tetramer
$d_{O1-O2} = 2.83$ Å, $d_{O2-O3} = 2.80$ Å, $d_{O3-O4} = 2.82$ Å, $d_{O1-O4} = 2.80$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
tetramer	−17.5	−4.2	−7.9	−5.3	−10.4	−27.9	−1.1	2−3	−3.4	−0.4	−1.4	−1.3	−2.6		
			−10.1[a]					2−4	−1.5	−1.4	−0.0	−0.0	−0.3		
1−2	−3.0	−0.7	−1.1	−1.2	−2.4			3−4	−2.5	−0.0	−1.2	−1.2	−2.5		
1−3	−1.4	−1.3	−0.0	−0.0	−0.3			summed	−14.5	−4.0	−5.0	−4.9	−10.6		
1−4	−2.7	−0.2	−1.3	−1.2	−2.5			δE_{nad}	−3.0	0.2	−2.9	−0.4	−0.2		

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}
tetramer	−18.5	−4.2	−9.4	−7.0	−5.0	−9.1	−27.6	−20.0[c]	2−3	−3.0	−0.6	−1.3		−1.1	−2.3		
								−9.9[d]	2−4	−1.4	−1.4	−0.0		−0.0	−0.2		
1−2	−2.6	−0.6	−1.0		−1.0	−2.0			3−4	−2.4	−0.1	−1.3		−1.1	−2.2		
1−3	−1.3	−1.3	−0.0		−0.0	−0.2			summed	−13.4	−4.3	−5.2		−4.3	−9.1		
1−4	−2.7	−0.3	−1.3		−1.1	−2.2			δE_{nad}	−5.1	0.0	−4.1		−0.7	0.0		

(b) W1 Bound to W2, and W2, W3, W4 Make a Cyclic Trimer
$d_{O1-O2} = 2.81$ Å, $d_{O2-O3} = 2.76$ Å, $d_{O3-O4} = 2.99$ Å, $d_{O2-O4} = 2.85$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
tetramer	−14.2	−5.2	−5.2	−3.8	−10.4	−24.6	−1.0	2−3	−2.6	−0.4	−1.1	−1.1	−2.5		
			−6.5[a]					2−4	−1.4	−0.7	−0.4	−0.3	−1.6		
1−2	−2.8	−0.7	−1.1	−1.0	−2.2			3−4	−3.1	−1.1	−1.0	−1.0	−2.3		
1−3	−2.6	−0.7	−1.1	−1.0	−1.6			summed	−12.6	−4.9	−4.0	−3.8	−10.9		
1−4	−0.1	0.1	−0.1	−0.1	−0.7			δE_{nad}	−1.6	−0.3	−1.2	−0.0	−0.5		

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}
tetramer	−13.6	−4.8	−5.2	−4.2	−3.6	−9.1	−22.7	−19.6[c]	2−3	−2.4	−0.5	−1.0		−0.9	−2.2		
								−9.9[d]	2−4	−1.6	−0.9	−0.3		−0.3	−1.3		
1−2	−2.7	−0.7	−1.0		−0.9	−2.0			3−4	−2.8	−1.1	−0.9		−0.9	−2.0		
1−3	−2.2	−1.7	−0.3		−0.2	−1.1			Summed	−11.6	−4.7	−3.6		−3.2	−9.2		
1−4	0.1	0.2	−0.1		−0.0	−0.6			δE_{nad}.	−2.0	0.0	−1.6		−0.4	0.0		

(c) W1 Bound to W4 through One H, and Bidentate Bonded through Its O to W3 and
W4 $d_{O1-O2} = 2.86$ Å, $d_{O1-O3} = 2.86$ Å, $d_{O1-O4} = 2.84$ Å, $d_{O2-O3} = 3.1$ Å

Ab initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
tetramer	−11.0	−3.4	−4.3	−3.3	−8.2	−19.2	−0.9	2−3	−0.2	0.4	−0.3	−0.3	−1.4		
			−5.3[a]					2−4	−0.7	−0.4	−0.0	−0.0	−0.1		
1−2	−2.9	−0.9	−1.1	−0.9	−2.0			3−4	−0.4	−0.7	−0.0	−0.0	−0.0		
1−3	−2.8	−0.7	−1.1	−1.1	−2.2			summed	−10.4	−3.3	−3.7	−3.4	−8.2		
1−4	−3.4	−1.0	−1.2	−1.1	−2.5			δE_{nad}	−0.6	0.0	−0.6	0.0	0.0		

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}
tetramer	−11.7	−3.4	−5.1	−4.1	−3.3	−7.2	−18.9	−24.2[c]	2−3	−0.2	−0.5	−0.2		−0.2	−1.2	−1.2	
								−13.2[d]	2−4	−0.7	−0.7	0.0		−0.0	−0.1	−0.8	
1−2	−2.9	−1.0	−1.0		−0.9	−1.9	−4.7		3−4	−0.4	−0.4	0.0		−0.0	−0.1	−0.5	
1−3	−2.8	−0.7	−1.1		−1.0	−1.9	−4.6		summed	−10.4	−3.4	−3.7		−3.2	−7.3	−17.7	
1−4	−3.4	−1.1	−1.4		−1.1	−2.1	−5.6		δE_{nad}	−1.2	0.0	−1.3		0.0	0.0	−1.1	

[a] Computed with the Kitaura-Morokuma procedure. [b] Without the effect of the induced dipoles. [c] ΔH. [d] ΔG.

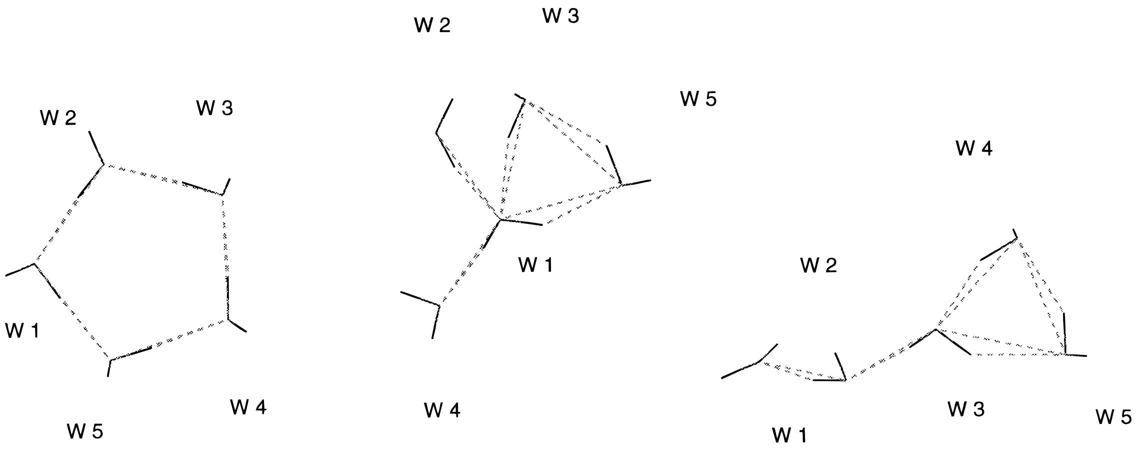
respectively, and the DFT ones of Estrin et al.[9d] An experimental value of 2.88 Å was reported in the recent paper of Liu et al.[42]

(6) Solvation effects, as computed using the continuum procedure, favor configuration b over a, and the energy difference of 3.4 kcal/mol reduces from 5.2 to 1. 8 kcal/mol the SIBFA energy difference favoring a.

***n* = 4.** Along with the cyclic tetramer a, the following two arrangements have been considered (see Figure 2a−c): (b) One water molecule acts as an H-bond acceptor to a neighboring one, itself engaged in the formation of a cyclic trimer with the remaining two other ones. (c) The external water molecule acts as an H-bond acceptor to one neighbor. The latter is again engaged in a cyclic trimeric arrangement with the two other waters, but now as a simultaneous H-bond acceptor from them, as in the case of alternative cyclic trimer b investigated above.

The results are reported in Table 2, which shows the following.

(1) The energy ordering is a > b > c, the energy differences with respect to a being 3.3 and 8.7 kcal/mol at the MP2 level, and 4.9 and 8.7 kcal/mol with the SIBFA computations. The SIBFA results can match the ab initio ones to <1 kcal/mol at



Cyclic water pentamer Water pentamer, conf. b Water pentamer, conf. c

Figure 3. Water pentamer in structures a−c.

both the SCF and MP2 levels, except with tetramer b at the MP2 level, which gives a discrepancy of 1.9 kcal/mol.

(2) A further shortening of the O−O distance has occurred (d(O−O) = 2.82 Å) in the cyclic tetramer. Concomitantly, a further reduction of the numerical weight of E_1 has occurred, which now contributes only 23% of ΔE(SCF) and ΔE_0(SIBFA) and 15% of ΔE(MP2) and ΔE(SIBFA). The O−O distance shortening is more pronounced than that obtained in the SCF computations by Chen and Gordon[7q] (2.88 Å), again due to the effect of E_{disp}. A value of 2.74 Å was recently reported in the DFT computations of Xantheas[9c] and the DFT ones of Estrin et al.[9d] An experimental value of 2.78 Å was reported.[42] The weight of E_1 is more accented in the Chen and Gordon computations, amounting to 41% of ΔE(SCF) in their aug-cc-pDVZ augmented correlation consistent polarized basis set. This is due, to a large part, to our 0.06 Å shorter O−O distances, $E_{\mathrm{rep}}/E_{\mathrm{exch}}$ increasing steeply for distances becoming smaller than the equilibrium distance (2.95 Å) found at the dimer level. In the case of the linear water dimer, large basis sets[4,7n,34,43] provide a value of E_1 close to −2.00 kcal/mol and values of both E_{pol} and E_{ct} in the range −0.8 to −1 kcal/mol.

(3) The preference in favor of a over b is due to both E_{pol} and $E_{\mathrm{ct},}$ whereas E_1 favors b over a. Nonadditivity is also the largest in cyclic tetramer a, having values of −3.0 and −5.1 kcal/mol in the ab initio and SIBFA computations, respectively. Within E_2, it is E_{pol} that displays the largest nonadditive character, that of E_{ct} being more modest (−0.4 and −0.7 kcal/mol in the ab initio and SIBFA computations, respectively). On the other hand, E_{pol} has a smaller nonadditivity (−0.5 kcal/mol) in the cyclic tetramer investigated by Chen and Gordon with an aug-cc-pVDZ basis set.[7q] Both E_1 and E_{corr}, on the other hand, remain additive.

(4) We observe that the value of E_{pol}(SIBFA) computed by taking into account the induced dipoles is close to that of E_{pol}(SCF) computed with the Kitaura−Morokuma procedure, while that of E_{pol}(SIBFA) taking only into account the permanent multipoles is closer to the RVS value. This feature will be observed for all the investigated water oligomers. Within the RVS procedure, this stems from the fact that each individual molecule in the complex is polarized by the undistorted electronic distributions of its congeners, since these have their vacant molecular orbitals frozen by the process.

(5) E_{solv} has the largest value for tetramer c, being virtually identical for a and b. Adding up E_{solv} to ΔE(SIBFA) leads to a inversion of the relative stabilization energies of tetramers c and b, favoring the former by 1 kcal/mol, and reduces from 8.7 to 4.5 kcal/mol the SIBFA preference in favor of a.

(6) For tetramer a, the values of ΔE(SCF) and ΔE_0(SIBFA) of −17.5 and −18.5 kcal/mol, respectively, are close to the HF value of −20.6 kcal/mol published by Xantheas.[7k] The values of ΔE(MP2) and ΔE(SIBFA) of −27.9 and −27.6 kcal/mol, respectively, are close to the MP2 value of −29.1 kcal/mol uncorrected for BSSE of Xantheas[7k] and the DFT values of −28.9, −30.2, and −32.4 kcal/mol obtained by Laasonen et al.,[9a] Lee et al.,[6] and Estrin et al.,[9d] respectively. They are larger in absolute values than the DFT value of −25.4 kcal/mol with the B-LYP functional.[9c] Tetramers a and b have their equivalents in conformations 4C and 4T earlier investigated by Kim et al.[7d] using a dedicated polarizable potential denoted as CCD. The respective CCD stabilization energies of 4C and 4T are −31.1 and −23.2 kcal/mol, respectively. This results in a larger energy difference (7.9 kcal/mol) than computed by MP2 or SIBFA (3.2 and 4.9 kcal/mol, respectively).

***n* = 5.** Similar to n = 4, two water pentamers were investigated in addition to the cyclic one, a (see Figure 3a−c). Our purpose in considering such alternative structures was to determine which are the energy components that could favor a over its partly acyclic competitors, and to what an extent could bulk solvation, as computed with the continuum, affect this energetical preference. All three pentamers are stabilized by the same number of H-bonds. In b, the central water molecule, W1, is involved in four simultaneous H-bonds. It acts as an H-bond acceptor, through its O, from both W2 and W3, and as an H-bond donor to both W4 and W5. W1, W3, and W5 are involved in the formation of a cyclic trimer. In c, W1, W2, and W3 make up a linear array, whereas W3, W4, and W5 make a cyclic trimer, a recurring motive in the energy minimizations. The results, reported in Table 3, show the following.

(1) Cyclic pentamer a is preferred over pentamers b and c by a large energy difference, in the range 8−10 kcal/mol in terms of ΔE(MP2) and ΔE(SIBFA), whereas c is favored over b by a small margin (0.8 kcal/mol). As in the tetramer case, E_{solv} is more in favor of structures b and c, but the energy differences with respect to (a) of 2.3 and 1.6 kcal/mol are much smaller than the corresponding differences of ΔE. Whereas b and c become equalized in term of their summed ΔE(SIBFA) + ΔH_{solv}, a remains favored over both by 8.3 kcal/mol. The inherent stability of the cyclic pentamer structure is illustrated by its frequent occurrence in the vicinity of hydrophobic groups of proteins[44] and nucleic acids.[45]

TABLE 3: Values of the ab Initio and the SIBFA Binding Energies and of Their Components in Three Representative Water Pentamers

(a) Cyclic Water Pentamer
$d_{\mathrm{O1-O2}} = 2.77$ Å, $d_{\mathrm{O2-O3}} = 2.78$ Å, $d_{\mathrm{O3-O4}} = 2.76$ Å, $d_{\mathrm{O4-O5}} = 2.76$ Å, $d_{\mathrm{O4-O1}} = 2.76$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
pentamer	−23.2	−1.8	−12.7	−8.6	−14.5	−37.7	−1.2	2−4	−1.0	−1.0	−0.0	−0.0	−0.0		
			−16.4[a]					2−5	−0.9	−0.8	−0.0	−0.0	−0.1		
1−2	−2.7	0.4	−1.5	−1.5	−2.6			3−4	−2.6	0.5	−1.6	−1.6	−2.7		
1−3	−1.1	−1.0	0.0	−0.0	−0.1			3−5	−2.5	−0.8	−0.0	−0.0	−0.1		
1−4	−0.9	−0.9	0.0	−0.0	−0.1			4−5	−2.6	0.6	−1.6	−1.6	−2.8		
1−5	−2.6	0.6	−1.6	−1.6	−2.8			summed	−15.6	−1.5	−7.8	−7.7	−14.0		
2−3	−2.0	0.9	−1.5	−1.4	−2.7			δE_{nad}	−7.2	−0.3	−4.9	−0.9	−0.5		

SIBFA

	ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}
pentamer	−26.3	−2.1	−16.6	−11.7	−7.6	−13.1	−39.4	−24.7[c]	2−4	−1.0	−1.0	0.0		0.0	−0.1	−1.1	
								−12.8[d]	2−5	−0.8	−0.8	0.0		0.0	−0.1	−1.0	
1−2	−2.6	0.3	−1.7		−1.3	−2.5	−5.1		3−4	−2.6	0.4	−1.7		−1.3	−2.5	−5.2	
1−3	−1.1	−1.0	0.0		0.0	−0.1	−1.2		3−5	−0.8	−0.8	0.0		0.0	−0.1	−1.0	
1−4	−0.9	−1.0	0.0		0.0	−0.1	−1.0		4−5	−2.5	0.5	−1.7		−1.3	−2.6	−5.1	
1−5	−2.6	0.5	−1.7		−1.3	−2.5	−5.2		summed	−16.9	−2.1	−8.4		−6.4	−13.0	−30.3	
2−3	−2.0	0.8	−1.6		−1.2	−2.4	−4.4		δE_{nad}	−9.3	0.0	−8.2		−1.2	0.0	−9.1	

(b) W1 Bound to W4 through One H, Bidentate Bound to W2 and W3 through Its O, and a Cyclic Trimer Is Made between W1, W3, and W5
$d_{\mathrm{O1-O4}} = 2.85$ Å, $d_{\mathrm{O1-O2}} = 2.98$ Å, $d_{\mathrm{O1-O3}} = 2.83$ Å, $d_{\mathrm{O1-O5}} = 2.82$ Å, $d_{\mathrm{O3-O5}} = 2.91$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
pentamer	−18.1	−7.0	−6.4	−4.7	−11.8	−29.9	−1.1	2−4	−0.6	−0.6	−0.0	−0.0	−0.0		
			−8.0[a]					2−5	−0.1	−0.1	−0.0	−0.0	−0.1		
1−2	−3.2	−1.8	−0.8	−0.6	−1.5			3−4	−0.6	−0.6	−0.0	−0.0	−0.0		
1−3	−2.5	−0.2	−1.2	−1.2	−2.6			3−5	−3.5	−2.2	−0.6	−0.6	−2.0		
1−4	−3.3	−1.0	−1.2	−1.1	−2.4			4−5	0.6	0.6	−0.0	−0.0	−0.1		
1−5	−3.2	−1.4	−1.0	−0.9	−2.6			summed	−16.3	−6.8	−5.0	−4.6	−12.1		
2−3	0.1	0.5	−0.2	−0.2	−0.9			δE_{nad}	−1.8	−0.2	−1.4	−0.1	−0.3		

SIBFA

	ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}
pentamer	−18.4	−6.8	−7.2	−5.8	−4.4	−10.0	−28.4	−27.0[c]	2−4	−0.7	−0.6	−0.0		−0.0	−0.1	−0.8	
								−14.3[d]	2−5	−0.1	−0.1	−0.0		−0.0	−0.1	−0.2	
1−2	−3.0	−1.8	−0.6		−0.6	−1.4	−4.4		3−4	−0.6	−0.6	−0.0		−0.0	−0.1	−0.7	
1−3	−1.2	−0.2	−1.0		−1.0	−2.1	−4.3		3−5	−3.2	−2.1	−0.6		−0.6	−1.6	−4.8	
1−4	−3.5	−1.1	−1.3		−1.0	−2.0	−5.5		4−5	0.6	0.6	−0.0		−0.0	−0.0	0.6	
1−5	−3.2	−1.4	−1.0		−0.8	−1.8	−5.0		summed	−15.4	−6.7	−4.7		−4.1	−9.9	−25.4	
2−3	0.4	0.6	−0.1		−0.1	−0.8	−0.4		δE_{nad}	−2.9	0.0	−2.4		−0.3	0.0	−2.9	

(c) W1, W2, and W3 in a Linear Array, W3, W4, and W5 in a Cyclic Trimer Arrangement:
$d_{\mathrm{O1-O2}} = 2.90$ Å, $d_{\mathrm{O2-O3}} = 2.86$ Å, $d_{\mathrm{O3-O4}} = 2.78$ Å, $d_{\mathrm{O4-O5}} = 2.87$ Å, $d_{\mathrm{O3-O5}} = 2.91$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE		ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
pentamer	−19.3	−7.6	−6.8	−4.9	−11.5	−30.8	−1.1	2−4	−0.4	−0.3	−0.0	−0.0	−0.1		
			−8.4[a]					2−5	0.7	0.7	−0.0	−0.0	−0.1		
1−2	−3.2	−1.5	−0.9	−0.8	−1.9			3−4	−2.3	0.1	−1.2	−1.2	−2.5		
1−3	−1.2	−1.2	0.0	−0.0	−0.2			3−5	−3.6	−2.2	−0.6	−0.7	−1.9		
1−4	−0.2	−0.2	0.0	−0.0	−0.0			4−5	−3.4	−1.6	−0.9	−0.9	−2.3		
1−5	0.2	0.2	0.0	−0.0	−0.0			summed	−16.9	−7.2	−4.8	−4.8	−11.4		
2−3	−3.5	−1.2	−1.2	−1.2	−2.4			δE_{nad}	−2.4	−0.4	−2.0	−0.1	−0.0		

SIBFA

	ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}		ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}
pentamer	−19.6	−7.6	−7.5	−6.0	−4.6	−9.5	−29.1	−26.3[c]	2−4	−0.3	−0.3	−0.0		−0.0	−0.1	−0.4	
								−13.5[d]	2−5	0.6	0.6	−0.0		−0.0	−0.0	−0.6	
1−2	−2.9	−1.3	−0.8		−0.8	−1.7	−4.6		3−4	−2.3	−0.0	−1.3		−1.0	−2.0	4.5	
1−3	−1.2	−1.2	−0.0		−0.0	−0.2	−1.4		3−5	−3.5	−2.2	−0.7		−0.6	−1.5	−5.0	
1−4	−0.0	−0.0	−0.0		−0.0	−0.0	−0.0		4−5	−3.2	−1.7	−0.8		−0.8	−1.8	−5.0	
1−5	0.2	0.2	−0.0		−0.0	−0.0	0.2		summed	−16.3	−7.5	−4.7		−4.2	−9.5	−25.8	
2−3	−3.5	−1.4	−1.1		−1.0	−2.0	−5.5		δE_{nad}.	−3.3	0.0	−2.7		−0.4	0.0	−3.3	

[a] Computed with the Kitaura−Morokuma procedure. [b] Without the effect of the induced dipoles. [c] ΔH. [d] ΔG.

(2) A further shortening of the O−O distances (d(O−O) = 2.77 Å) has occurred in the cyclic pentamer. Even shorter distances of 2.71 Å were recently reported from the DFT computations of Xantheas[9c] and Estrin et al.[9d] for this pentamer. An experimental value of 2.76 Å was reported.[42] In the cyclic pentamers located in the vicinity of the crambin protein and of a drug−nucleic acid complex, the d(O−O) distances are 2.80 Å.[44,45] A remarkable feature of the cyclic pentamer a resides in the very small weight of E_1 within the total binding energies. It thus amounts to −1.8 and −2.1 kcal/mol in the ab initio and SIBFA computations, respectively, namely, only 4.7 and 5.3% of the ΔE(MP2) and ΔE(SIBFA). Its values are much higher in pentamers b and c, for which it amounts to −7.0 and −7.6 kcal/mol. As such, the cyclic water pentamer is preferentially stabilized with respect to alternative strucures b and c, *exclusively* due to the second-order contributions. We also note that at the SCF level, δE_{nadd} can alone account for the preference in favor of the cyclic versus b pentamer. These features are fully accounted for in the SIBFA computations. Some nonadditive character of E_{ct} also starts to build up in pentamer a, although significantly more modest (−1 kcal/mol) than that of E_{pol} (−4.9 and −8.3 kcal/mol in the ab initio and SIBFA computations, respectively), whereas the numerical values of E_{ct} amount to 65 and 47% of those of E_{pol} in these respective computations. E_{corr} has a much smaller nonadditive behavior (−0.5 kcal/mol), consistent with previous ab initio results resorting to large basis sets.[7]

(3) The values of ΔE(SCF) and ΔE_0(SIBFA) of −23.2 and −26.3 kcal/mol are close to the values of −27.3 and −25.9 kcal/mol computed by Xantheas without and with the BSSE corrections.[7k] δE_{nadd} amounts to −5.7 kcal/mol in his computations, which is, however, smaller than our SCF value of −7.2 kcal/mol.

(4) The SIBFA computations seem to amplify the nonadditive character of E_{pol}, as compared to the ab initio computations. This downgrades somewhat the agreement of ΔE_0(SIBFA) with respect to ΔE(SCF) for the cyclic pentamer (−26.3 versus −23.2 kcal/mol, respectively), but this is recovered to some extent at the MP2 level, since E_{disp} has systematically smaller values (by 0.8−2 kcal/mol) than E_{corr}. Nevertheless, E_{pol}(SIBFA) has, to within <1 kcal/mol in all three pentamers, very similar values to E_{pol}(SCF) as computed with the Kitaura−Morokuma procedure. Finally, the ΔE(MP2) and ΔE(SIBFA) values of −37.7 and −39.4 kcal/mol are close to the −40.2 and −42.4 kcal/mol ones resulting from the DFT computations of Lee et al.[6] and Estrin et al.,[9d] respectively. They are larger than the DFT value of −33.7 kcal/mol using a B-LYP functional.[9c] The CCD computations of ref 7d give a value of −42.1 kcal/mol, close to ΔE(SIBFA).

***n* = 6.** There are three low-energy structures for the water hexamer, which have been investigated both theoretically[7,9] and experimentally:[46] the cyclic (a), the prism (b), and the cage (c) ones (see Figure 4a−c). They are stabilized by 6, 9, and 8 hydrogen bonds, respectively. The energy analysis is reported in Table 4, which shows the following.

(1) The prism and the cage structures have very close stabilization energies, and the cyclic hexamer comes third. This is consistent with the theoretical results of Kim et al.[7n] and Liu et al.[46] The energy separation between the cyclic hexamer and the prism and cage ones is, however, larger in the present ab initio computations than in refs 7n and 46. The values of ΔE(SIBFA) are close to those of ΔE(MP2), but give rise to a slightly smaller energy separation between the cyclic versus prism and cage structures. The total energy values rank as follows:

	prism(b)	cage(c)		cyclic (a)
ΔE_0(SCF)	-29.3	-29.5	>	-26.3
ΔE_0(SIBFA)	-33.0	-32.3	>	-29.6
ΔE(MP2)	-54.0	-53.4	>	-44.0
ΔE(SIBFA)	-51.6	-50.2	>	-46.2

(2) In the cyclic hexamer, the d(O−O) distances are shortened to 2.75 Å. As a consequence, E_1 has drastically diminished values (−0.3 kcal/mol in both the ab initio and the SIBFA computations), *so that the stabilization of the cyclic hexamer is due exclusively to the second-order contributions*. Nonadditivity accounts for −7.5 and −12.0 kcal/mol in the ab initio and SIBFA computations, respectively. ΔE_0(SIBFA) differs by 3.2 kcal/mol from ΔE(SCF). ΔE(SIBFA) differs from ΔE(MP2) by a lesser amount, 2 kcal/mol out of 45, than computed at the uncorrelated level. The value of ΔE_0(SIBFA) of −29.5 kcal/mol is smaller than the HF values of −34.1 and −32.4 kcal/mol without and with the BSSE correction, as computed by Xantheas.[7k] The value of ΔE(SIBFA) of −46.1 kcal/mol for this hexamer is very close to the MP2 value of Mhin et al.[7i] of −45.8 kcal/mol and to the DFT values of −48.8 and −45.6 kcal/mol computed by Lee et al.[6] and by Laasonen et al.,[9a] respectively. These are larger in absolute values than the DFT value of −41.8 kcal/mol using a B-LYP functional,[9c] but smaller than the DFT value of −52 kcal/mol computed by Estrin et al.[9d] and the CCD one of −51 kcal/mol.[7c]

(3) In both the prism and the cage hexamers, the average d(O−O) distances are 2.85 Å. This is the same value as found in the recent study by Liu et al. using the diffusion Monte Carlo method.[46] The values of E_1(SCF) amount to −5.6 and −6.3 kcal/mol in the prism and cage structures, respectively, and are, again, closely reproduced by the SIBFA values. Despite the larger number of hydrogen bonds, nonadditivity has a lesser amplitude than in the cyclic structure. It is slightly larger in the prism structure than in the cage one. In all three hexamers, we observe the persistently close match of E_{pol}(SIBFA) to E_{pol}(SCF) computed with the Kitaura−Morokuma procedure on one hand and that of E_{pol}(SIBFA) computed with the sole permanent multipoles to that of E_{pol}(SCF) computed with the RVS procedure on the other hand.

Evaluation of the Weight of the Three-Body Term within the Total Nonadditivity Energy $\boldsymbol{\delta E_{\mathrm{nadd}}}$. We wished to evaluate the weight of the three-body term within the total nonadditivity energy and how well would SIBFA compare with the ab initio computations in this respect. For that purpose, we have focused on the cyclic water tetramers and pentamers, which for $n = 4$ and 5 are endowed with the largest values of δE_{nadd}. Because even slight departures from symmetry might alter the energetical equivalence of successive water dimers and trimers, we have recomputed the binding energies of all distinct water trimers within these two oligomers (four for $n = 4$, and 10 for $n = 5$). From these values, we subtracted the summed binding energies of the dimers, with each dimer occurring twice in the four trimers making up the tetramer and three times in the 10 trimers making up the pentamer. The results are reported in Table 5. This table shows that in both the ab initio and SIBFA computations, and notwithstanding the rounding-off errors, nonadditivity due to the three-body term has values matching those of the global nonadditivity to within 0.3 kcal/mol. This implies that, in such water oligomers, the four-body terms (and higher order terms for $n = 5$ and beyond) should provide a negligible contribution to nonadditivity. This conclusion is consistent with previous theoretical computations.[7k,m,o]

***n* = 8.** Two different configurations were considered, which are represented in Figure 5: a cyclic octamer (a) and a three-dimensional, cubiclike structure b. The energy results are

TABLE 4: Values of the ab Initio and the SIBFA Binding Energies and of Their Components

(a) In the Cyclic Water Hexamer: All O−O Distances between Successive Waters Are at 2.75 Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
hexamer	−26.3	−0.3	−15.6	−10.5	−17.7	−44.0	−2.0
			−20.1[a]				
1−2	−2.5	0.8	−1.6	−1.6	−2.7		
1−3	−1.0	−1.0	0.0	−0.0	−0.1		
1−4	−0.7	−0.7	0.0	−0.0	−0.0		
1−5	−0.7	−0.7	0.0	−0.0	−0.0		
1−6	−2.1	1.1	−1.6	−1.6	−2.6		
2−3	−1.7	1.6	−1.6	−1.6	−2.6		
2−4	−0.8	−0.8	−0.0	−0.0	−0.1		
2−5	−0.2	−0.2	−0.0	−0.0	−0.0		
2−6	−1.0	−1.0	−0.0	−0.0	−0.1		
3−4	−2.4	0.8	−1.6	−1.6	−2.7		
3−5	−0.5	−0.5	−0.0	−0.0	−0.1		
3−6	−0.7	−0.7	−0.0	−0.0	−0.0		
4−5	−1.4	1.4	−1.5	−1.4	−2.7		
4−6	−2.5	−2.1	−0.2	−0.2	−0.8		
5−6	−0.6	2.3	−1.5	−1.4	−2.6		
summed	−18.8	0.1	−9.6	−9.4	−17.0		
δE_{nad}	−7.5	−0.4	−6.0	−1.1	−0.7		

SIBFA

	ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}
hexamer	−29.6	−0.4	−19.9	−14.1	−9.2	−16.6	−46.2	−28.8[c]
								−15.5[d]
1−2	−2.3	0.7	−1.7		−1.3	−2.6	−4.9	
1−3	−1.0	−1.0	−0.0		−0.0	−0.1	−1.2	
1−4	−0.7	−0.7	−0.0		−0.0	−0.1	−0.8	
1−5	−0.7	−0.7	−0.0		−0.0	−0.1	−0.8	
1−6	−2.1	0.9	−1.7		−1.3	−2.6	−4.7	
2−3	−1.6	1.4	−1.7		−1.3	−2.6	−4.2	
2−4	−0.8	−0.8	−0.0		−0.0	−0.1	−0.9	
2−5	−0.2	−0.2	−0.0		−0.0	−0.0	−0.3	
2−6	−1.0	−1.0	−0.0		−0.0	−0.1	−1.1	
3−4	−2.3	0.7	−1.7		−1.3	−2.6	−4.9	
3−5	−0.5	−0.5	−0.0		−0.0	−0.1	−0.6	
3−6	−0.7	−0.7	−0.0		−0.0	−0.1	−0.8	
4−5	−1.2	1.6	−1.6		−1.2	−2.4	−3.6	
4−6	−2.3	−2.1	−0.2		−0.1	−0.8	−3.1	
5−6	−0.4	1.9	−1.2		−1.1	−2.5	−2.9	
summed	−17.5	−0.5	−9.8		−7.6	−16.8	−34.8	
δE_{nad}	−12.0	0.0	−10.1		−1.6	0.0	−11.3	

(b) In the Water Hexamer, Prism Structure:
$d_{\mathrm{O1-O2}} = 2.86$ Å, $d_{\mathrm{O1-O3}} = 3.09$ Å, $d_{\mathrm{O1-O4}} = 2.76$ Å, $d_{\mathrm{O2-O3}} = 2.77$ Å,
$d_{\mathrm{O2-O5}} = 2.92$ Å, $d_{\mathrm{O3-O6}} = 2.67$ Å, $d_{\mathrm{O4-O5}} = 2.94$ Å, $d_{\mathrm{O4-O6}} = 2.92$ Å, $d_{\mathrm{O5-O6}} = 2.79$ Å

Ab initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
hexamer	−29.3	−5.6	−14.0	−9.8	−20.5	−54.0	−2.2
			−18.0[a]				
1−2	−1.6	0.2	−0.9	−1.0	−2.3		
1−3	−2.7	−2.2	−0.2	−0.2	−1.1		
1−4	−2.8	0.2	−1.5	−1.5	−2.7		
1−5	0.0	0.0	0.0	0.0	−0.2		
1−6	−1.1	−1.1	0.0	0.0	−0.2		
2−3	−0.8	1.9	−1.3	−1.3	−2.5		
2−4	0.1	0.1	0.0	−0.1	−0.4		
2−5	−3.5	−1.8	−0.8	−0.8	−2.0		
2−6	−1.4	−1.3	0.0	−0.1	−0.3		
3−4	−1.0	−1.0	0.0	−0.1	−0.3		
3−5	−1.5	−1.4	0.0	−0.1	−0.3		
3−6	−1.7	2.6	−2.0	−2.2	−3.0		
4−5	−0.6	0.4	−0.5	−0.5	−1.7		
4−6	−3.1	−1.8	−0.7	−0.6	−1.7		
5−6	−2.2	0.2	−1.2	−1.2	−2.5		
summed	−23.9	−5.8	−8.6	−9.7	−21.2		
δE_{nad}	−5.4	0.2	−5.4	−0.1	0.7		

SIBFA

	ΔE_0	E_1	E_{pol}	E_{pol}[b]	E_{ct}	E_{disp}	ΔE	E_{solv}
hexamer	−33.0	−5.9	−18.4	−13.3	−8.7	−18.6	−51.6	−23.6[c]
								−11.9[d]
1−2	−1.7	0.0	−1.0		−0.8	−1.8	−3.5	
1−3	−2.6	−2.2	−0.2		−0.2	−0.9	−3.5	
1−4	−2.9	0.0	−1.6		−1.2	−2.4	−5.2	
1−5	0.0	0.0	0.0		0.0	−0.1	−0.1	
1−6	−1.1	−1.1	0.0		0.0	−0.2	−1.3	
2−3	−0.9	1.3	−1.2		−1.0	−2.4	−3.2	
2−4	0.0	0.1	−0.0		−0.0	−0.3	−0.2	
2−5	−3.5	−1.9	−0.9		−0.7	−1.7	−5.2	
2−6	−1.4	−1.3	0.0		0.0	−0.3	−1.6	
3−4	−1.0	−1.0	0.0		0.0	−0.2	−1.2	
3−5	−1.4	−1.4	0.0		0.0	−0.2	−1.7	
3−6	−1.4	2.5	−2.3		−1.6	−3.1	−4.3	
4−5	−0.5	0.4	−0.5		−0.4	−1.5	−2.0	
4−6	−3.0	−1.8	−0.6		−0.5	−1.5	−4.5	
5−6	−2.2	0.3	−1.4		−1.0	−2.1	−4.3	
summed	−23.6	−6.1	−9.7		−7.8	−18.8		
δE_{nad}	−9.4	0.0	−8.7		−0.9			

(c) In the Water Hexamer, Cage Structure:
$d_{\mathrm{O1-O2}} = 2.76$ Å, $d_{\mathrm{O1-O4}} = 3.00$ Å, $d_{\mathrm{O1-O5}} = 2.91$ Å, $d_{\mathrm{O2-O3}} = 2.81$ Å,
$d_{\mathrm{O3-O4}} = 2.71$ Å, $d_{\mathrm{O3-O5}} = 3.02$ Å, $d_{\mathrm{O4-O6}} = 2.79$ Å, $d_{\mathrm{O5-O6}} = 2.77$ Å

Ab Initio

	ΔE_{SCF}	E_1	E_{pol}	E_{ct}	E_{corr}	ΔE_{MP2}	BSSE
hexamer	−29.5	−6.3	−13.7	−9.5	−19.9	−53.4	−2.2
			−17.6[a]				
1−2	−2.7	0.2	−1.4	−1.4	−2.6		
1−3	−1.1	−1.0	0.0	−0.0	−0.4		
1−4	−3.0	−1.9	−0.5	−0.5	−1.6		
1−5	−2.3	−0.6	−0.9	−0.8	−4.4		
1−6	0.1	0.0	−0.0	0.0	−0.2		
2−3	−2.4	0.0	−1.2	−1.2	−2.5		
2−4	−1.4	−1.3	0.0	0.0	−0.3		
2−5	0.0	0.0	0.0	0.0	−0.3		
2−6	0.0	0.0	0.0	0.0	0.0		
3−4	−2.1	1.5	−1.7	−1.9	−2.9		
3−5	−2.9	−1.8	−0.5	−0.5	−1.6		
3−6	−1.3	−1.2	−0.0	−0.1	−0.3		
4−5	−0.6	−0.4	−0.1	−0.1	−0.7		
4−6	−2.2	0.4	−1.6	−1.3	−2.4		
5−6	−2.5	0.2	−1.4	−1.4	−2.6		
summed	−24.4	−5.9	−9.3	−9.2	−22.8		
δE_{nad}	−5.1	−0.4	−4.4	−0.3	2.9		

TABLE 4 (Continued)

SIBFA

	ΔE_0	E_1	E_{pol}	$E_{pol}{}^b$	E_{ct}	E_{disp}	ΔE	E_{solv}
hexamer	−32.3	−6.3	−17.3	−12.7	−8.7	−17.9	−50.2	−24.6[c] −12.3[d]
1−2	−2.7	0.1	−1.6		−1.2	−2.4	−5.0	
1−3	−1.0	−0.9	−0.1		0.0	−0.3	−1.3	
1−4	−2.8	−1.9	−0.5		−0.4	−1.2	−4.1	
1−5	−2.4	−0.7	−0.9		−0.8	−1.7	−4.1	
1−6	0.1	0.1	−0.0		0.0	−0.1	−0.1	
2−3	−2.3	0.0	−1.3		−1.0	−2.1	−4.3	
2−4	−1.3	−1.3	0.0		0.0	−0.2	−1.6	
2−5	0.1	0.1	0.0		0.0	−0.3	−0.2	
2−6	0.0	0.0	0.0		0.0	0.0	−0.1	
3−4	−1.9	1.4	−1.9		−1.4	−2.8	−4.6	
3−5	−2.6	−1.8	−0.5		−0.4	−1.3	−4.0	
3−6	−1.2	−1.2	0.0		0.0	−0.2	−1.4	
4−5	−0.5	−0.4	−0.1		0.0	−0.6	−1.1	
4−6	−2.3	0.2	−1.4		−1.1	−2.3	−4.5	
5−6	−2.6	0.0	−1.4		−1.1	−2.3	−4.9	
summed	−23.4	−6.3	−9.7		−7.4	−17.8		
δE_{nad}	−8.9	0.0	−7.6		−1.3			

[a] Computed with the Kitaura−Morokuma procedure. [b] Without the effect of the induced dipoles. [c] ΔH. [b] ΔG.

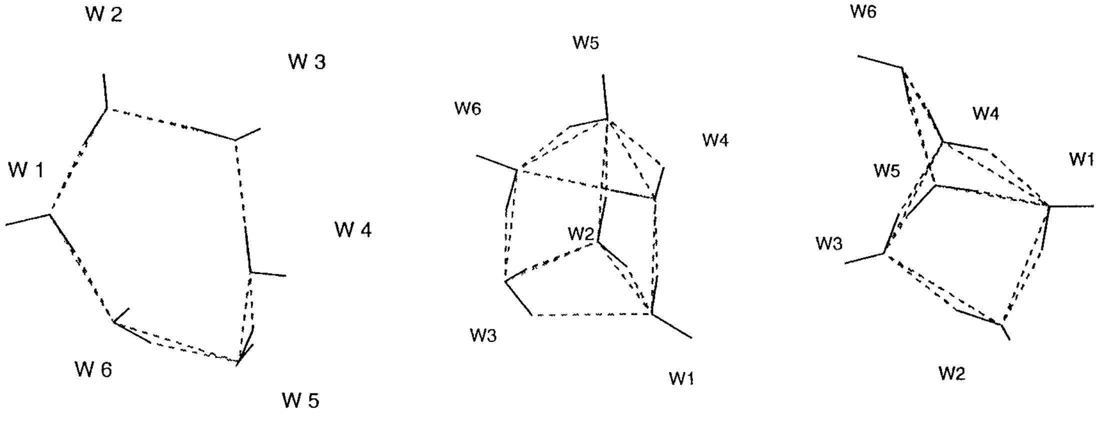
TABLE 5: Cyclic Water Tetramer and Pentamer. Evaluation of the Weight of the Three-body Term within the Total Non-additivity Energy

(a) Water Tetramer

	E_1		E_{pol}		E_{ct}	
trimer	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA
1−2−3	−2.5	−2.5	−3.2	−3.3	−2.5	−2.2
1−2−4	−2.4	−2.3	−3.1	−3.4	−2.5	−2.2
1−3−4	−1.5	−1.6	−3.3	−3.7	−2.6	−2.3
2−3−4	−1.8	−2.1	−3.4	−3.7	−2.7	−2.4
summed	−8.2	−8.5	−13.0	−14.3	−10.3	−9.1
summed binary interactions	−8.0	−8.6	−10.0	−10.4	−9.8	−8.6
resulting nonadditivity	0.2	0.0	−3.0	−3.9	−0.5	−0.5
total δ E_{nadd} (Table 3)	0.2	0.0	−2.9	−4.1	−0.4	−0.7

(b) Water Pentamer

	E_1		E_{pol}		E_{ct}	
trimer	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA
1−2−3	0.3	0.1	−3.8	−4.3	−3.1	−2.7
1−2−4	−1.5	−1.5	−1.7	−2.0	−1.6	−1.3
1−2−5	0.1	−0.1	−3.9	−4.6	−3.3	−2.8
1−3−4	−1.4	−1.5	−1.8	−2.0	−1.6	−1.4
1−3−5	−1.3	−1.4	−1.8	−2.0	−1.7	−1.4
1−4−5	0.3	0.1	−4.0	−4.7	−3.3	−2.8
2−3−4	0.4	0.2	−3.8	−4.4	−3.1	−2.7
2−3−5	−0.8	−0.9	−1.7	−1.9	−1.5	−1.3
2−4−5	−1.2	−1.3	−1.8	−2.0	−1.7	−1.4
3−4−5	0.3	0.0	−4.0	−4.7	−3.3	−2.8
summed	−4.8	−6.3	−28.3	−32.6	−24.2	−20.6
summed binary interactions	−4.5	−6.3	−23.4	−24.6	−23.1	−19.2
resulting non-additivity	−0.3	0.0	−4.9	−8.0	−1.1	−1.4
total δE_{nadd} (Table 4)	−0.3	0.0	−4.9	−8.3	−0.9	−1.2



Cyclic water hexamer

Water hexamer, prism

Water hexamer, cage

Figure 4. Water hexamer in (a) the cyclic, (b) the prism, and (c) the cage structures.

reported in Table 6. No energy decomposition was carried out for the SCF computations, since these exceed the amount of storage space needed to store the integrals in the RVS computations. The SIBFA computations show the cubic structure to be preferred by 14.6 kcal/mol (−77.8 versus −63.2) over the cyclic octamer. Such a preference is due to both E_1 (−8.7 versus

TABLE 6: Binding Energies in Two Distinct Water Octamers

(a) Cyclic Octamer

SIBFA

ΔE_0	E_1	E_{pol}	E_{pol}[a]	E_{ct}	E_{disp}	ΔE	E_{solv}
−41.4	−0.1	−28.7	−20.0	−12.6	−21.8	−63.2	−39.0[b] −21.6[c]

Ab Initio

ΔE_{SCF}	ΔE_{MP2}
−41.7	−64.9

(b) Cubic Structure

SIBFA

ΔE_0	E_1	E_{pol}	E_{pol}[a]	E_{ct}	E_{disp}	ΔE	E_{solv}
−49.7	−8.7	−27.0	−19.8	−14.0	−28.1	−77.8	−27.5[b] −13.5[c]

Ab Initio

ΔE_{SCF}	ΔE_{MP2}
−53.0	−84.2

[a] Without the effect of the induced dipoles. [b] ΔH. [c] ΔG.

−0.1 kcal/mol) and E_{disp} (−28.1 versus −21.8 kcal/mol), whereas E_{pol} and E_{ct} have mutually compensatory preferences in favor of a and b, respectively. The solvation energy computed with the continuum procedure favors the cyclic octamer over the cubic structure. The energy difference ($\delta\Delta H$ = 11.5 kcal/mol) reduces to 3.1 kcal/mol, the preference in favor of the latter. Such a finding provides an incentive for prospective Monte Carlo simulations at ambient temperature, to evaluate the extent of coexistence, or of statistical prevalence, of competing water oligomeric structures in the liquid state.

For both octamers, the ΔE_0(SIBFA) values are close to the corresponding values of ΔE(SCF). On the other hand, however, whereas ΔE(SIBFA) remains very close to ΔE(MP2) for the cyclic octamer (−63.2 versus −64.9 kcal/mol, respectively), it is smaller by 6.5 kcal/mol out of 80 in the cubic structure. We note here that the ΔE(SIBFA) values of −77.8 and −63.2 kcal/mol are very close to the DFT values of −76.0 and −61.8 kcal/mol recently published by Laasonen et al.[9a] This −77.8 kcal/mol value for the cubic octamer is also very close to that of −77.1 of the DFT computations of Lee et al.[6] and to the CCD value of −79.2 kcal/mol.[7d] It is intermediate between the MP2 values of −86.9 and −70.6 kcal/mol computed by Kim et al.[7m] without and with the BSSE correction. The O−O distances in the cubic octamer range between 2.72 and 2.90 Å. The average distance of 2.83 Å is 0.05 Å larger than the average distance of 2.78 Å obtained for the D 2d octamer in the DFT computations of Estrin et al.[9d]

***n* = 12, 16, 20.** Our investigation of these higher order oligomers of waters was limited to the cubic structures, since these correspond to the lowest binding energies of water clusters which were derived in the DFT computations of Lee et al.[6] The SIBFA energy results reported below relate to structures which were energy-minimized starting from cubic structures initially generated with the help of a computer graphics program.[47] These are represented in Figure 6. The results of our energy computations are reported in Table 7. This table also regroups the results obtained for the best water oligomers derived in this study, for $n = 3$ up to $n = 20$. In addition to the values of ΔE(MP2) and ΔE(SIBFA) and its components, we also report the values of ΔE(SIBFA)/n, the binding energy per water molecule, and the corresponding ΔE(DFT)/n value published by Lee et al.[6] It is seen that ΔE(SIBFA)/n closely matches ΔE(DFT)/n. As it was mentioned by these authors,[6] extrapolation of $\Delta E/n$ for larger values of n should converge asymptotically toward a value of −11.5 kcal/mol, the binding energy of ice at 0 °C. This also appears to be the case with ΔE(SIBFA)/n.

Let us consider the $n = 20$ water oligomer. Comparisons with results from liquid-phase simulations are to be made with some caution, since our energy-minimized structure is an icelike one and should await the outcome of actual Monte Carlo simulations using SIBFA. We would like, however, to mention its following three features:

(1) The O−O Bond Lengths. These are all in the range 2.72−2.98 Å. This range of distances is somewhat longer than the 2.60−2.86 Å one optimized for this type of structure in the DFT computations of ref 9a. The smallest distances, between 2.72 and 2.80 Å, are those connecting the two rows of water decamers. The average distance is 2.84 Å. The value reported for ice is 2.74 Å (ref 42, and references therein).

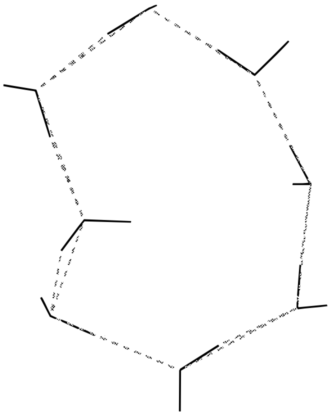
(2) *The Dipole Moment, μ, per Water Molecule.* A value of 2.74 D is computed, very close to the recently computed theoretical value of 2.76 D[42] and to the experimental value of 2.70 D for ice Ih (ref 48, and references therein). Within this 2.74 D value, the contribution of the induced dipole moments amounts to 0.8 D. The contribution from the permanent dipole moment amounts to 1.97 D, as computed using the set of distributed multipoles derived from the SCF wave function with the SBK basis set. Because of the absence of electronic correlation, this value is 0.12 D larger than the experimental value of 1.85 D. This overestimation is, nevertheless, much smaller than the one incurred with comparable large basis set computations at the Hartree−Fock level. The value of μ computed for ice should provide an upper bound to that of water in the liquid state at 0 °C. The latter has 0.1−0.3 D smaller values than ice and is estimated to lie in the 2.4−2.6 D range.[48] Monte Carlo simulations at room temperature will be necessary to ensure that such a reduction will occur using the SIBFA procedure. In this respect, three recent quantum chemical simulations are worth mentioning: (i) the DFT Car−Parinello simulation of Laasonen et al. carried out on a box of 32 water molecules, yielding a value of 2.66 D;[9b] (2) the combined DFT/classical MD simulation of Wei and Salahub using a nonlocal density correction, yielding values in the range 2.47−2.62 D;[49] and (3) the combined MP2/continuum computations of Rivail et al., yielding a value of 2.38 D.[50] It is to be noted that, by contrast, several water models with "classical" potential energy functions along with an explicit polarization energy contribution yield values of μ in the 2.8−2.9 D range:[13d,h,l] such values exceed those derived by ab initio computations and are actually larger than in ice. This is possibly due to an overestimation of the relative weight of E_{pol} within ΔE in these procedures (see below).

(3) The Weight of the Separate Energy Components within ΔE(SIBFA). The two largest contributors to ΔE(SIBFA) are E_{disp} (−82.2 kcal/mol out of −220.9) and E_{pol} (−71.3 kcal/mol). Within E_{pol}, the contribution of the induced dipoles amounts to −18.2 kcal/mol, i.e., 25%. Let us observe that the nonadditive character of E_{pol}, in addition to such a contribution, also stems from the vectorial addition of the polarizing field exerted on any one molecule by all the other ones in the oligomer. E_{pol} contributes to 32% of ΔE(SIBFA). A much larger weight (47%) was found in the simulations of Ahlstrom et al.[13e] The first-order term E_1 has the weakest overall contribution to ΔE(SIBFA), limited to 14%. The fact that the values of E_{ct} surpass those of E_1 in the higher water oligomers results from the shortening of the O−O bonds upon increasing n, which is

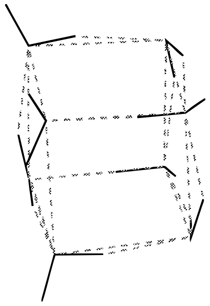
TABLE 7: Evolutions, as a Function of the Number, *n*, of Water Molecules, of the SIBFA and ab Initio Binding Energies, and of the Average Binding Energy Per Water Molecule

n	ΔE_{MP2}	$\Delta E_{\mathrm{SIBFA}}$	E_1	E_{pol}	$E_{\mathrm{pol}}{}^a$	E_{ct}	E_{disp}	$\Delta E/n$	$\Delta E_{\mathrm{DFT}}/n^e$
3^b	−17.6	−16.3	−4.7	−3.8	−3.1	−2.5	−5.3	−5.4	−5.6
4^b	−27.9	−28.1	−3.6	−10.1	−7.4	−5.2	−9.2	−7.0	−7.6
5^b	−37.7	−39.3	−2.1	−16.6	−11.4	−7.6	−13.0	−7.9	−8.0
6^b	−44.0	−46.2	−0.4	−19.9	−14.1	−9.2	−16.0	−7.7	−8.1
6^c	−54.0	−51.6	−5.9	−18.4	−13.3	−8.7	−18.6	−8.6	
8^d		−77.8	−8.7	−27.0	−19.8	−13.9	−28.2	−9.7	−9.6
12^d		−125.2	−16.6	−41.2	−30.6	−21.6	−45.8	−10.4	−10.1
16^d		−173.1	−23.2	−56.5	−42.0	−29.5	−63.9	−10.8	−10.4
20^d		−220.9	−30.1	−71.3	−53.1	−37.5	−82.0	−11.0	−10.6

[a] Computed in the absence of the induced dipoles. [b] Cyclic structure. [c] Prism structure. [d] Cubic structure. [e] Reference 6.

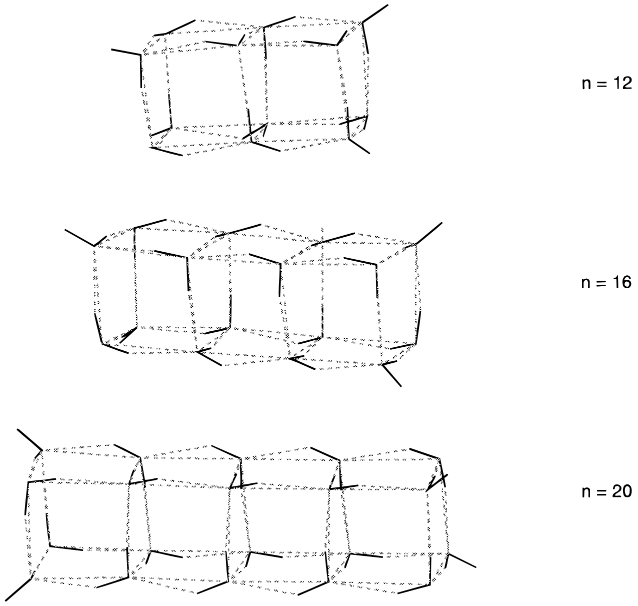


Water octamer in cyclic structure (a)



Water octamer in cubic structure (b)

Figure 5. Water octomer in (a) the cyclic structure and (b) the cubic structure.



Cubic water structures

Figure 6. Cubic structures of water oligomers with (a) $n = 12$, (b) $n = 16$, and (c) $n = 20$.

detrimental to E_1. The nonadditive character of E_{ct} being less accented than that of E_{pol} results in E_{ct} having a smaller weight (17%) than that of E_{pol}, whereas both terms had virtually identical weights in the water dimer. This emphasizes the fact that E_{pol} and E_{ct} may not be lumped together in a single energy contribution and the need for a distinct formulation of E_{ct}.

Conclusions

In this paper, we have evaluated the extent to which the SIBFA molecular mechanics procedure could account for the cooperative nature of multiply hydrogen-bonded complexes, an outstanding example of which is provided by structured water oligomers in cyclic ring and cubic structures. For that purpose, similar to our previous investigations which bore on the mono- and polyligated complexes of divalent cations,[3] as well as on neutral and ionic hydrogen-bonded systems,[4] we have undertaken a joint study in which the SIBFA results in well-defined minimized structures were recomputed by ab initio SCF/MP2 computations, and energy decomposition of ΔE(SCF) was carried out using the RVS procedure. We have also compared our results to those of SCF/MP2 as well as DFT computations carried out by other authors on the cyclic and cubic structures. As in our earlier studies[3,17,19] and that of Chen and Gordon,[7q] the RVS procedure enabled us to trace back the origin of the nonadditive behavior of ΔE. Consistent with the recent results by these authors, these calculations showed, in these oligomers, E_{pol} to be the principal term responsible for the nonadditivity. E_{ct} has a more modest nonadditive behavior, starting to build up only upon increasing the number of waters ($n > 4$). Such a behavior offers a striking contrast to the anticooperative one observed in some polycoordinated complexes of Zn^{2+},[17] for which an extreme case consisted in complexes encompassing two anionic ligands in the cation's first coordination shell. In such complexes, E_{ct} was the energy component with the most sensitive behavior, actually decreasing by up to a factor of 2 with respect to the monoligated case.

For the cyclic ring structures, the SIBFA computations were able to account for the increased compression occurring upon increasing n. Thus, the d(O−O) distances shorten from 2.95 Å in the dimer to 2.86, 2.82, 2.76, and 2.75 Å for $n = 3-6$, respectively. This results in a progressively diminishing weight of E_1 within ΔE and, concomitantly, to an increase of the weight of nonadditivity and the preferential stabilization of these ring structures over competing ones for $n = 3-5$. Notably, for $n = 5$, E_1 is reduced to −1.8 kcal/mol and is virtually nullified (−0.3 kcal/mol) for $n = 6$. Such structures are thus only stabilized thanks to the second-order terms. For $n = 5$, the cyclic structure was found to be considerably more stable (ca. 10 kcal/mol) than partially acyclic ones, despite the significantly better values of E_1 in these. Bulk solvation energy, as computed with the Langlet et al. continuum procedure, was found to favor such alternative structures only by modest amounts, leaving out the cyclic ring structure with a substantial energy preference (>7 kcal/mol) over them. Such a privileged stability can certainly be related to the frequent occurrence of pentameric ring structures, as observed in the immediate vicinity of proteins[44] and nucleic acids.[45] We note in this connection that local concentrations of correlated, five-membered rings of water molecules could be transiently oberved in simulations of liquid water.[51]

For $n = 6$, the two three-dimensional structures, prism and cage, are very close energetically to one another and are more stable than the cyclic hexameric one. This is in agreement with previous ab initio computations.[7n,46] Upon increasing n to 8, the energetical preference favoring the cubic structure over the cyclic one further increases. The energy difference of 14.6 kcal/mol is the same as the one obtained by DFT computations,[9a] the values of ΔE(SIBFA) being, themselves, close to within 1.5 kcal/mol out of 70 to these ΔE(DFT) values. For both $n = 6$ and 8, we have observed that the ab initio and SIBFA energy preferences favoring the three-dimensional structures over the cyclic ones stem from E_1 and E_{corr}(ab initio) or E_{disp}(SIBFA), whereas E_{pol} and E_{ct} had smaller, and opposite, preferences. This contrasts with the weights of these individual components in the competing structures found with $n < 6$ and underlines the need for a separable expression of ΔE. When bulk solvation is taken into account using the continuum procedure, the energy difference between the two octamers is reduced to 3.1 kcal/mol. This suggests that Monte Carlo computations may result in an equilibration of various competing structures, as contrasted to the situation at 0 °C.

For $n = 12$, 16, and 20, we considered exclusively three-dimensional cubic structures. We have compared the values of $\Delta E(\mathrm{SIBFA})/n$, the value of the binding energy per water molecule, to the corresponding DFT values that were recently published by Lee et al.[6] A very good agreement was observed. $\Delta E(\mathrm{SIBFA})/n$ was seen to converge toward a value of −11.5 kcal/mol, the experimental value in ice. For $n = 20$, the value of the average dipole moment, μ, was computed to be 2.74 D, close to the experimental value of 2.70 D in ice. This is an upper bound to the value of μ in the liquid phase, which should be 0.1−0.4 D smaller (ref 48, and references therein).

The encouraging results obtained in this study should stimulate further applications of the SIBFA procedure to theoretical studies in which cooperativity plays a very important role, as highlighted in recent papers.[6−10] Along with the results on polycoordinated complexes of divalent cations, themselves obtained jointly with ab initio computations,[3,17] they also legitimize the use of SIBFA in simulations of complex systems, such as the binding of inhibitor drugs within the active site of enzymes.[39] These results should also provide an incentive for Monte Carlo simulations to assess the accuracy with which the principal experimental observables (radial and angular distribution functions, average dipole moment, etc.) could be accounted for. Because this procedure is not exclusively dedicated to water simulations, it could also be used, in such simulations, to investigate the solvation of a wide variety of solutes and molecular complexes, possibly including those of metal cations as well. The use of the Langlet et al. continuum reaction field procedure, instead of a complete water bath, could be used to limit the number of water molecules, thereby reducing the number of intermolecular variables (6 per water molecule) and allowing for a more complete exploration of them. In another vein, energy-minimized structures derived from SIBFA could be used to provide initial starting points for further simulations by DFT computations. In return, additional comparisons with high-level quantum chemical studies can provide a basis for rescaling, or for further refinements, of individual components of ΔE, if these turned out to be necessary. These would be easily manageable on account of the separable character of the procedure.

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