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Modeling Copper(I) Complexes: SIBFA Molecular Mechanics versus ab Initio Energetics and Geometrical Arrangements

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SIBFA parametrization is extended to the closed-shell Cu(I) cation. This parametrization introduces the cation polarization up to quadrupolar effects and the metal−ligand charge transfer. The results obtained are compared to the corresponding ab initio quantum-chemical quantities given by intermolecular interaction energy decomposition and MP2 runs. Mono- and polycoordinated complexes of Cu(I) with O-, S-, and N-containing ligands are considered. An extension to systems containing two and three Cu(I) cations, found in copper metalloenzyme active sites, such as cytochrome C oxidase and hemocyanin, and supramolecular systems, is reported. The results obtained show that in such cases SIBFA is able to give geometrical arrangements in reasonable agreement with experimental data and interaction energy values close to those given by ab initio computations. With respect to MP2 results, covering interaction energy range of ≈400 kcal/mol, the interaction energy rms amounts to 7.6 kcal/mol.

Introduction

The involvement of the Cu(I) cation in several enzymatic reactions[1−5] has initiated numerous experimental studies on structural and functional models of mono- and binuclear Cu(I) enzymes.[6] In supramolecular chemistry, Cu(I) is often a key factor in the stabilization of supramolecular complexes.[7−9] In synthetic chemistry, Cu(I) complexes have been recently used as catalysts in enantioselective reactions.[10]

High-level quantum-chemical investigations provide essential information on the electronic, structural, and energetic properties of Cu(I) complexes.[11−14] However, such computations become hardly tractable for systems of more than 100 atoms. Larger ones can only be handled by semiempirical or molecular mechanics procedures. For the latter, there exist conventional force-fields to handle Cu(I) complexes,[15] but they do not embody the polarization and charge-transfer terms, whose magnitude can be quite important.[16] A correct reproduction of ΔE, the intermolecular interaction energy, can be of primary importance for studies of substrate/inhibitor binding to metalloenzyme active sites. To have reliable molecular mechanics results it is essential to be able to obtain not only the value of the total ab initio ΔE value but also those of its individual contributions given by ab initio energy-decomposition of ΔE. This alone can ensure the quality of the results for other complexes than those for which the procedure was initially parametrized. It also allows that further refinements be done on the individual components without affecting the others. This is the essential objective in the formulation and calibration of the SIBFA (sum of interactions between fragments ab initio computed) polarizable molecular mechanics procedure.[17] Recent studies from our laboratories devoted to polycoordinated complexes of Zn(II) have been able to give a reasonable agreement between the structures obtained from SIBFA and ab initio computations for a model of β-lactamase active site as well as for the interaction energies calculated for models of thermolysin active site and Gal4.[17e,g] Cu(I) parametrization requires us to include its relaxation energy within ΔE, that is, the terms originating from Cu(I) polarization and Cu(I)-to-ligand charge-transfer, whereas they are negligible in the case of isoelectronic Zn(II).[16] Therefore, in addition to the calibration of $E_{\mathrm{rep}}/E_{\mathrm{disp}}$ terms concerning this cation, explicit formulas and parameters for $E_{\mathrm{pol}}(\mathrm{Cu})$ and $E_{\mathrm{ct}}(\mathrm{Cu})$ are implemented in the present work.

After calibration of the various necessary parameters on small systems, computations were carried out on a variety of larger molecular assemblies such as Cu(I) polyhydrates, dinuclear copper complexes encountered in metalloenzyme active sites and Cu-stabilized supramolecular systems. Comparisons with results using the semiempirical PM3(tm)[18] and ZINDO[19] methods, as well as with the nonpolarizable UFF[15a] molecular mechanics method, were also done for representative mono- and polyligated Cu(I) complexes. This comparison will provide information of the validity domain of the results that we will obtain for the systems of interest to us such as Cu(I) copper enzymes active site models, functional models, and their complexes with different inhibitors. Finally, it is worth noting that Cu(I) complexes should also be relevant for some Cu(II) metalloenzymes, because as exemplified by galactose oxidase and superoxide dismutase, the transient existence of Cu(I) was put forth during the catalytic cycle.[20]

Computational Procedures

Ab Initio Calculations. The ab initio computations use three basis sets. The first is the coreless effective potential (CEP

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4-31G(2d)) basis set derived by Stevens et al.,[21] supplemented on the heavy atoms by two, uncontracted 3d orbitals, the exponents of which were given previously.[22] This was the basis set used for refining and testing the SIBFA procedure.[17] Two additional sets, all-electron bases, are the DZVP2 polarized split-valence set of Godbout et al.[23] and the TZVP built from the triple-valence set of Ahlrichs et al.[24] to which were added the polarization functions proposed for the DZVP2 basis. The energy decompositions are performed using the reduced variational-space analysis (RVS) developed by Stevens and Fink,[25] interfaced in the Gamess package.[26] This procedure is related to the original Morokuma procedure[27] and to the constrained space orbital variation of Bagus et al.[28] It enables us to deconvolute the total ab initio HF interaction energy ΔE_{HF} into its components and, in its present implementation, can be performed on complexes encompassing up to 10 molecules. The energy components are Coulomb (E_c) and exchange (E_{exch}) in the first-order energy (E_1) and polarization (E_{pol}) and charge transfer (E_{ct}) in the second order (E_2). An interesting feature of the RVS procedure is that the last two components are given for each entity of the complex.

In the tables given below, E_1 is the sum of E_c and E_{exch}. E_2 is the sum of E_{pol} and E_{ct}. ΔE is the value of the HF intermolecular interaction energy, as computed with the RVS procedure with the basis set superposition error using the virtual orbitals.[29] As commented below, ΔE is not equal to the sum of E_1 and E_2. E_{corr} is the MP2 intermolecular correlation energy, and ΔE_{tot} is the sum of ΔE and E_{corr}. Unless otherwise specified, the reported ab initio results are those with the CEP 4-31G(2d) basis set. The DFT results reported were obtained using Gaussian98[30] and the B3LYP hybrid functional.[31] The complete optimization carried out for six of the systems considered in this study altogether with the single-point computation on the largest of them have been carried out using Jaguar 4.0 with the LACVP** basis set and the B3LYP functional.[32]

SIBFA Calculations. Within the SIBFA procedure, the intermolecular interaction energy ΔE is computed as a sum of five separate contributions:

$$\Delta E_{tot} = E_{MTP} + E_{rep} + E_{pol} + E_{ct} + E_{disp}$$

E_{MTP} denotes the electrostatic (multipolar) energy contribution, computed with distributed multipoles derived from the ab initio HF wave function of the constitutive fragments.[33] E_{rep} is the short-range repulsion energy, computed as a sum of bond−bond, bond−lone pair, and lone pair−lone pair interactions. E_{pol} is the polarization energy contribution which uses, on the individual fragments, distributed anisotropic polarizabilities derived by a procedure by Garmer and Stevens.[34] A Gaussian screening of the polarizing field is used. The field polarizing each molecule takes into account the permanent multipoles plus the dipoles induced on all of the other molecules in an iterative fashion. E_{ct} is the charge-transfer energy contribution, in which a coupling with the polarization is accounted for.[17] E_{disp}, the dispersion energy contribution, is computed as a sum of $1/R$,[6] $1/R$,[8] and $1/R$[10] terms.[35] A thorough description of the various terms appearing in the above formula is given in ref 17a,c−e. For consistency reasons with the RVS computations, the ab initio HF computations on the individual molecules, necessary to derive the distributed multipoles and polarizabilities, were done with the CEP 4-31G(2d) basis set. The quadrupolar polarizability tensor of Cu(I) was derived from a triple-ζ calculation using Roos's ANO[36] (21s,15p,10d,6f,4 g) → (8s,7p,5d,3f,2 g) basis set (Angyan, J.; private communication). Energy-minimization (using the *Merlin* package[37]) was performed on the set of the six intermolecular variables defining the position of each molecule in the complex.

Standard internal geometries are used to construct the constitutive fragments. These geometries are not modified upon a conformational change. This is equivalent to the rigid rotor approximation. The distributed multipoles and polarizabilities on the constitutive fragments undergo matrix rotations but no changes in their intensities. In the case of Cu(I) binding by flexible ligands, intramolecular polarization effects are accounted for by computing the fragment−fragment interactions as actual intermolecular interactions, occurring simultaneously with the Cu(I)−ligand and ligand−ligand interactions. Such a procedure was recently shown to reproduce correctly the intermolecular interaction energies of the Zn(II) cation with highly polarizable and flexible ligands, such as the glycine zwitterion,[38] anionic mercaptocarboxamides,[39] and pyrophosphate (Gresh et al., to be published).

We provide as Supporting Information the refinements brought to E_{pol} altogether with Cu(I) parameters. The refinements to E_{pol} were brought by introducing the dipolar and quadrupolar polarizabilities for the polarization energy of the Cu(I) cation, denoted as $E_{pol}(M)$ below. Those to E_{ct} consist of including penetration effects in the monopolar component of the electrostatic potentials felt by the electron donors and acceptors.

Denoting by Z_B the atomic number of atom B with which A is interacting, by q_B its atomic monopole, by R_{AB} the distance between A and B, by C_s and D_s respectively the coefficient and the exponent of the exponential and by W_B the van der Waals radius of atom B, the total electrostatic potential can be expressed as

$$V_{B\rightarrow A} = (Z_B - P_{elB})/R_{AB}$$

in which

$$P_{elB} = (Z_B - q_B)(1 - R'_{AB} C_s \exp(-D_s R'_{AB}))$$

depends on the electronic population of B and

$$R'_{AB} = R_{AB}/W_B$$

is a reduced interatomic distance.

The values of C_s and D_s were calibrated to 0.09 and 3.5, respectively, to fit the radial evolution of E_{ct} ab initio value in the monoligated complexes of Cu(I) with water and formate anion. In addition, an explicit contribution from $E_{ct}(M)$, the cation → ligand charge transfer, is also introduced. Its derivation is given in the Supporting Information.

In the tables given hereafter, E_1 is the sum of E_{MTP} and E_{rep}. E_2 is the sum of E_{pol} and E_{ct} and ΔE is the sum of E_1 and E_2, and ΔE_{tot}, the total interaction energy, is the sum of ΔE and E_{disp}. It is to be noted that, apart from the introduction of the Cu(I) parameters, no recalibration of the method was done.

Results and Discussion

A. Cu(I) Complexes with O and S Ligands. 1. Monoligated Complexes. The results concerning the oxygenated ligands are reported in Table 1, which lists the values of the ab initio and SIBFA energies and their components at equilibrium distances.

For both H_2O and formamide, the SIBFA computations closely reproduce the results of the CEP 4-31G (2d) computations, at both uncorrelated and correlated levels. E_1 has a modest weight within ΔE_{tot}, namely, 15 and 33% for the water and formamide complexes (RVS) and 15 and 40% (SIBFA). In these

TABLE 1: Values (kcal/mol) of the Intermolecular Interaction Energies and Their Components in the Complexes of Cu(I) with O-Containing Ligands for the Cu(I)−Ligand Distance (Given in Å) Optimized at the MP2 Level

							Cu$^+$−HCOO$^-$			
	Cu$^+$−OH$_2$		Cu$^+$−formamide		Cu$^+$−CH$_3$O$^-$		bridge		monodentate	
	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA
E_1	−5.3	−5.4	−17.9	−22.3	−117.5	−110.4	−133.0	−131.7	−99.7	−104.9
E_{pol}(L)	−9.8	−12.5	−15.1	−16.1	−18.2	−27.5	−16.1	−17.0	−15.4	−19.7
E_{pol}(M)[a]	−5.2	−2.8	−5.2	−2.3	−15.3	−21.0	−4.5	−9.0	−10.9	−19.3
		(−1.9)		(−1.0)		(−11.1)		(−4.5)		(−11.2)
Epol	−15.0	−15.3	−20.3	−18.4	−33.5	−48.8	−20.6	−26.1	−26.3	−39.0
E_{ct}(L)	−4.7	−4.8	−4.6	−4.0	−12.6	−12.6	−7.4	−9.7	−11.1	−10.4
E_{ct}(M)	−1.9	−1.8	−2.2	−1.3	−4.1	−2.2	−1.7	−0.6	−2.5	−1.9
E_{ct}	−6.6	−6.6	−6.8	−5.3	−16.7	−14.8	−9.1	−10.3	−13.6	−12.3
E_2	−21.6	−21.9	−27.1	−23.7	−50.2	−53.6	−29.7	−36.4	−29.9	−51.3
ΔE	−28.6	−27.3	−46.7	−46.0	−173.2	−173.8	−164.9	−167.6	−143.4	−156.1
E_{disp}	−9.4	−9.3	−7.2	−9.8	−24.1	−19.1	−14.7	−13.4	−20.5	−15.3
ΔE_{tot}	−37.9	−36.6	−53.9	−55.7	−197.3	−192.2	−179.6	−181.0	−163.9	−171.2
ΔE_{tot}[b]		−38.0				−196.9		−184.0		−173.8
d(Cu−O)[c]	1.9		1.9		1.7		2.13		1.8	
	(2.0)				(1.8)		(2.03)		(1.7)	

[a] The value in parentheses is that of the quadrupolar polarization of Cu(I). [b] Value of ΔE_{tot}(SIBFA) at the SIBFA-optimized distance. [c] The value in parentheses is the SIBFA-optimized Cu(I)−ligand distance.

two complexes, cation relaxation contributes −7.1 and −7.4 kcal/mol to ΔE(RVS) and −4.6 and −3.6 kcal/mol (SIBFA) at the MP2 optimized distance of 1.9 Å. For Cu(I)−H_2O, at this distance, ab initio and SIBFA ΔE_{tot} values of −37.9 and −36.6 kcal/mol, respectively, are close to the respective MP2 and CCSD(T) values of −38.9 and −37.2 kcal/mol by Hoyau and Ohanessian[40] using a 6-311G (2d,2p) basis set on H and O and Wachter's (14s11p5d/8s6p3d) basis set on Cu.[40] They are also close to the experimental value of −37.5 ± 0.5 kcal/mol.[40] For Cu(I)−formamide, the ab initio and SIBFA ΔE_{tot} values of −53.9 and −55.7 kcal/mol are close to their −53.4 (CCSD(T)) value[38] and to the DFT value of −56.2 kcal/mol derived by Luna et al.[11f] with a hybrid B3LYP functional and the 6-311+G-(2df,2p) basis set. The need for polarization and charge-transfer contributions to ΔE_{tot} is highlighted by comparison of Cu(I)−H_2O binding energy using the MMF94 force field[15c] with the corresponding ab initio results. This force field gives a ΔE value of −23.9 kcal/mol instead of −37.9, and a Cu−O equilibrium distance is 2.23 Å instead of 1.9 Å. For a 2.23 Å distance, SIBFA gives a value of ΔE_{tot} of −34.2 kcal/mol, whereas the sum of the sole E_1 and E_{disp} contributions is of −21.9 kcal/mol, a value very close to that obtained using MMF94 systematics.

The values reported in Table 1 concerning anionic ligands correspond to geometric arrangements depicted in Figure 1. It is observed from the tabulated values that for all three complexes ΔE_{tot}(SIBFA) can reproduce ΔE_{tot}(MP2) with a relative error <5% at the MP2 optimized distances. In Cu(I)−methoxy, cation relaxation contributes by −19.4 and −23.2 kcal/mol to ΔE_{tot} in the MP2 and SIBFA calculations, respectively. In Cu(I)−formate, its contribution to the monodentate complex stability is more than twice that in the bidentate complex (−13.4 versus −6.2 from ab initio and −21.2 versus −9.6 kcal/mol from SIBFA). The electrostatic energy contribution is by contrast larger in the bidentate complex than in the monodentate one. Inclusion of the Cu(I) relaxation terms in SIBFA appears necessary to allow for a good agreement with the ab initio results. Presently, however, one notes that although for neutral ligands E_{pol}(M) is somewhat underestimated in the SIBFA compared to the ab initio corresponding values a reverse situation occurs with anionic ligands. E_{ct}(M) in SIBFA is somewhat underestimated with respect to the ab initio computations in the Cu(I) complexes with anionic ligands and also seems to be more orientation-dependent.

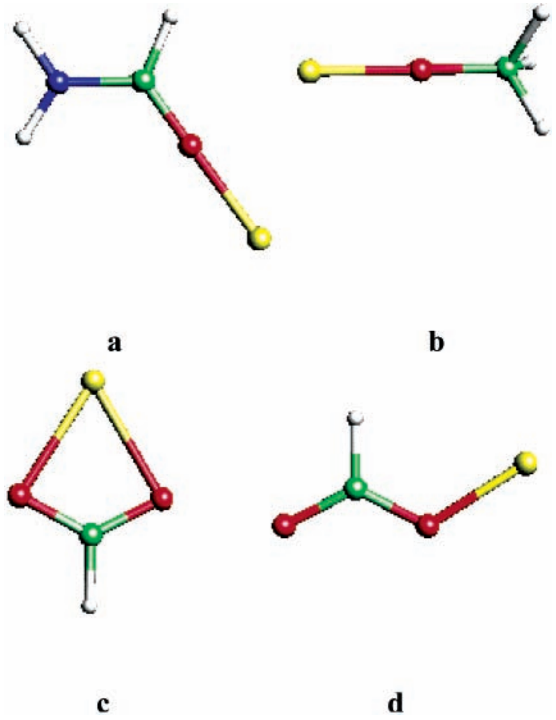

Figure 1. Geometrical arrangements of the Cu+ complexes with (a) formamide, (b) CH_3O^-, (c) bridge $HCOO^-$, and (d) monodentate $HCOO^-$.

The radial evolutions of the binding energies and their components are reported in Tables 1S and 2S for the complexes of Cu(I) with water and with formate in the bidentate position, respectively. It can be seen that the evolutions of the ab initio energies and their components are correctly reflected by their SIBFA counterparts.

It was necessary to ensure that the agreement found in the distance variations would hold upon performing angular variations of the approach of Cu(I) to the methoxy and formate anions. For that purpose, we performed 15° variations of the θ =C−O−Cu$^+$ angle, with the O−Cu distance being held at representative distances found in polycoordinated complexes of Cu(I). This investigation was extended to the methanethiolate−Cu(I) complex, with the S−Cu distance being held at 2.10 Å. The results comparing the ab initio and SIBFA interaction

TABLE 2: Angular Dependence of ΔE_{tot} (kcal/mol) Cu(I) Complexes with Methoxy, Formate, and Methanethiolate Anions

complex	method							
θ		90	105	120	135	150	165	180
$Cu^+-CH_3O^-$ [a]	Ab initio	−186.3	−197.1	−202.1	−201.1	−201.2	−197.0	−195.3
	SIBFA	−179.9	−187.5	−190.4	−194.0	−195.6	−195.0	−193.7
Cu^+-HCOO^- [b]	Ab initio	−148.9	−159.3	−167.9	−164.4	−162.3	−161.4	−161.2
	SIBFA	−146.9	−168.9	−171.3	−170.3	−169.5	−168.6	−168.5
$Cu^+-CH_3S^-$ [c]	Ab initio	−187.1	−190.6	−188.4	−182.3	−174.4	−167.6	−164.6
	SIBFA	−198.8	−198.4	−195.1	−189.7	−182.6	−177.1	−175.1

[a] The Cu−O distance is held at 1.85 Å. [b] The Cu−O distance is held at 1.80 Å. [c] The Cu−S distance is held at 2.10 Å.

TABLE 3: Values (kcal/mol) of the Intermolecular Interaction Energies and Their Components in the $Cu(I)-(OH_2)_n$ and $Cu(I)-(OH^-)_2$ Complexes ($n = 2$, 4, and 6) for the Cu(I)−O Distance (Given in Å) Optimized at the MP2 Level

	$Cu^+-(OH_2)_2$		$Cu^+-(OH^-)_2$		$Cu^+-(OH_2)_4$						$Cu^+-(OH_2)_6$	
					planar		alternate		pyramidal			
	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA
E_1	−7.8	−9.4	−184.3	−184.3	−55.3	−58.3	−53.4	−56.5	−49.4	−53.0	−65.3	−73.2
$E_{pol}(L)$	−16.9	−19.9	−12.1	−23.6	−12.0	−15.0	−12.0	−17.6	−18.1	−17.5	−12.9	−11.1
$E_{pol}(M)^a$	−14.3	−7.3 (−7.3)	−28.3	−22.0 (−22.0)	−4.3	−3.1 (−3.1)	−4.4	−3.1 (−3.1)	−5.8	−0.1	−3.2	0.0
E_{pol}	−31.2	−27.2	−40.4	−45.6	−16.3	−18.2	−16.4	−18.2	−23.9	−20.5	−16.1	−14.3
$E_{ct}(L)$	−9.4	−7.6	−11.4	−11.5	−4.8	−6.4	−4.7	−6.4	−5.7	−7.2	−4.6	−7.4
$E_{ct}(M)$	−4.0	−4.2	−6.1	−14.3	−3.0	−3.0	−3.0	−3.0	−4.5	−4.2	−5.7	−5.2
E_{ct}	−13.4	−11.8	−17.5	−25.8	−7.8	−9.4	−7.7	−9.4	−10.2	−11.4	−10.3	−12.6
E_2	−44.6	−39.0	−57.9	−71.4	−24.1	−27.6	−24.1	−27.6	−34.1	−31.9	−26.4	−26.9
ΔE	−57.3	−48.4	−251.6	−257.2	−83.2	−85.6	−81.4	−84.0	−83.0	−82.0	−91.1	−96.8
E_{disp}	−22.7	−18.8	−44.9	−34.1	−17.9	−19.7	−17.9	−24.6	−21.4	−22.8	−32.1	−32.9
ΔE_{tot}	−80.0	−67.2	−295.6	−291.3	−101.1	−105.3	−99.3	−105.6	−104.4	−104.8	−123.3	−129.7
$\Delta E_{tot}{}^b$		−69.5				−106.3		−106.4				
$d(Cu-O)^c$	1.9 (2.0)		1.8		2.2 (2.1)		2.2		2.1		2.2	

[a] The value in parentheses is that of the quadrupolar polarization of Cu(I). [b] Value of ΔE_{tot}(SIBFA) at the SIBFA-optimized distance. [c] The value in parentheses is the SIBFA-optimized Cu(I)−ligand distance.

energies are reported in Table 2. The angular behaviors of the individual components of ΔE_{tot} are given as supporting material in Tables IIIS, IVS, and VS.

For Cu(I)−methoxy, ΔE_{tot}(SIBFA) can match with a relative error of <6% ΔE_{tot}(MP2). These energies have their minimum at 150° and 120° respectively, with a shallow variation in the region of θ values between 120° and 150°. Thus ΔE_{tot}(ab initio) varies by 1 kcal/mol out of 200 in this 30° interval, whereas ΔE_{tot}(SIBFA) varies by 4.5 kcal/mol. This flat angularity is seen for all of the components of the ab initio energy in a broader 105−165° interval. For Cu(I)−formate, ΔE_{tot} from both ab initio and SIBFA computations has a shallow minimum at 120°, with the values given by the two methods differing by <6% over the whole range of θ values explored. Both procedures show that E_1 has a small preference for $\theta = 180°$. It is worth mentioning that $E_{pol}(M)$ in SIBFA has pronounced variations because of the quadrupolar polarizability contribution. Nevertheless, such a behavior does not downgrade the agreement in terms of the total energies

2. Polyligated Complexes. *O Ligands.* To evaluate the extent of nonadditivity in the polycoordinated complexes of Cu(I), we have considered some representative complexes. In all of these complexes, the polarizing field is null at the Cu(I) site because of the cancellation of the ligand field vectors in the cavity center. Therefore, $E_{pol}(M)$ should stem from the field gradients and possibly higher-order derivatives. For each of the considered arrangements, the energy was optimized by stepwise 0.1 Å variations of the Cu−O distance. The corresponding results are displayed in Table 3, and the arrangements are displayed in Figure 2.

For the $Cu(I)-(OH_2)_2$ complex (Figure 2a), ΔE_{tot}(SIBFA) is by 12.8 kcal/mol out of 80 underestimated with respect to ΔE_{tot}(ab initio) at the MP2 optimized distance. This downgraded agreement is due essentially to $E_{pol}(M)$ (−14.3 versus −7.3 kcal/mol from ab initio and SIBFA, respectively). At this point, it is worth recalling that within SIBFA this term stems exclusively from the quadrupolar polarization of Cu(I), because the field is null, whereas the field gradient is nonzero.

In $Cu(I)-(OH^-)_2$ (Figure 2b), the SIBFA computations reproduce the ab initio ones with a relative error of 2% at both uncorrelated and correlated levels. $E_{pol}(M)$ from RVS computations is enhanced by a factor of 2 with respect to its value for the $Cu(I)-(OH_2)_2$ complex. A much larger enhancement would have been anticipated owing to the effect of two anionic charges on the field gradient. In the present case, $E_{pol}(M)$ from SIBFA (−22.0 kcal/mol) is closer to its ab initio counterpart (−28.3 kcal/mol) than in $Cu(I)-(OH_2)_2$. $E_{ct}(M)$ from SIBFA is much larger than from ab initio (−14.3 versus −6.1 kcal/mol), but this comes from a preexisting exaggeration at the level of the monoligated $Cu(I)-OH^-$. This is the sole case for which an exaggeration of $E_{ct}(M)$ is observed in SIBFA results. $E_{ct}(M)$ could be reduced by reducing the acceptor effective radius of O in hydroxy, but because we want to keep the number of adjustable parameters to a minimal, this was not done here.

In the $Cu(I)-(OH_2)_4$ complexes, the three competing arrangements (Figure 2c−e) differ by 3% at the MP2 level with a modest preference for the pyramidal arrangement. The SIBFA results numerically match the ab initio ones with a relative error of 5% but favor the planar arrangement over the pyramidal one by 1.5 kcal/mol out of 105. It is instructive to observe that such a preference is due to $E_{pol}(M)$, which has values of −3.1 and −0.1 kcal/mol in these respective arrangements in SIBFA. The SIBFA value of $E_{pol}(M)$ translates the virtually null value of the field gradient at the Cu(I) position, in the pyramidal arrangement. By contrast, $E_{pol}(M)$ from RVS has the corresponding values of −4.3 and −5.8 kcal/mol, namely, larger in

TABLE 4: Values (kcal/mol) of the Intermolecular Interaction Energies and Their Components in the Complexes of Cu(I) with Methanethiolate

	$Cu^+{-}(CH_3S^-)_2$				$(Cu^+{-}CH_3S^-)_2$			
	ab initio DZVP2	ab initio CEP 4-31G(2d)	ab initio VTZP	SIBFA	ab initio DZVP2	ab initio CEP 4-31G(2d)	ab initio VTZP	SIBFA
E_1	−169.8	−159.8	−175.6	−135.0	−274.0	−262.8	−280.8	−244.7
E_{pol}(L)	−12.0	−16.8	−13.1	−25.5	−39.3	−59.8	−41.0	−73.3
E_{pol}(M)[a]	−15.8	−14.5	−11.7	−30.2(−30.2)	−14.6	−13.6	−10.9	−28.3(−26.3)
E_{pol}	−27.8	−31.3	−24.8	−55.5	−53.9	−73.4	−51.9	−100.6
E_{ct}(L)	−13.0	−22.2	−13.7	−24.5	−32.3	−32.9	−34.1	−44.8
E_{ct}(M)	−8.7	−5.1	−3.7	−7.6	−10.3	−5.6	−6.2	−6.6
E_{ct}	−21.7	−27.3	−17.4	−32.1	−43.6	−38.5	−40.3	−51.4
E_2	−49.5	−58.6	−52.2	−87.6	−97.5	−111.9	−92.2	−152.0
ΔE	−226.5	−224.3	−223.2	−222.6	−374.6	−375.3	−373.1	−394.1
E_{disp}	−48.5	−43.5	−43.9	−35.5	−69.4	−64.2	−61.5	−49.1
ΔE_{tot}	−275.1	−267.8	−267.1	−258.2	−444.0	−439.5	−434.6	−443.1

[a] The value in parentheses is that of Cu(I) quadrupolar polarization.

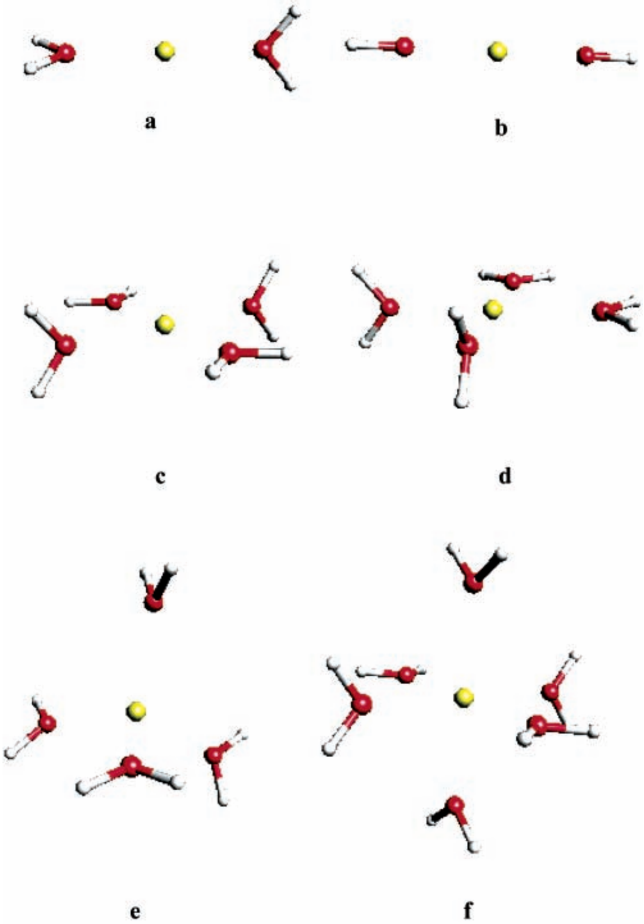

Figure 2. Geometrical arrangement of the polycoordinated complexes of Cu(I) with water and hydroxy ligands (a) $(Cu{-}(H_2O)_2)^+$, (b) $(Cu{-}(OH)_2)^-$, (c) planar $(Cu{-}(H_2O)_4)^+$, (d) alternate $(Cu{-}(H_2O)_4)^+$, (e) pyramidal $(Cu{-}(H_2O)_4)^+$, and (f) $Cu{-}(H_2O)_6)^+$.

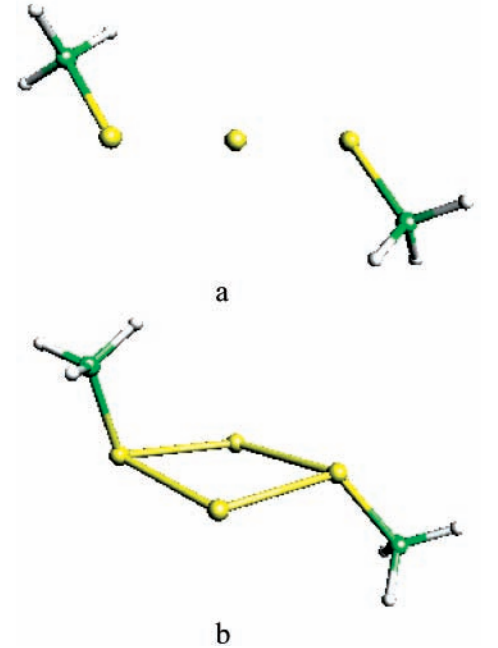

Figure 3. Geometrical arrangement of the $[Cu(CH_3S)_2]^-$ and $[Cu(CH_3S)]_2$ complexes.

the pyramidal arrangement despite the very small values of the field gradient. E_{ct}(M) from SIBFA matches its ab initio counterpart to within 0.3 kcal/mol in all three arrangements. Finally, the trends in E_1, E_{pol}(L), and E_{ct}(L), are similar in SIBFA and RVS.

For the hexahydrate complex Cu(I)−$(OH_2)_6$ complex (Figure 2f), we also have a close agreement between ΔE_{tot}(SIBFA) and ΔE_{tot}(ab initio) (−129.7 versus −123.3 kcal/mol). Although E_{pol}(M) in SIBFA is null because the field gradient itself is null, E_{pol}(M) from RVS retains a small value (−3.2 kcal/mol). E_{ct}(M) from SIBFA remains close to E_{ct}(M) from ab initio (−5.2 versus −5.7 kcal/mol) as in the other Cu(I) oligohydrate complexes.

S Ligands. Methanethiolate, the deprotonated side-chain of the cysteine residue in proteins is encountered as a Cu(I) ligand in several biological systems, such as the blue copper proteins and cytochrome *c* oxidase.[41] Two representative Cu(I)−methanethiolate complexes were investigated (Table 4 and Figure 3): (a) a mononuclear complex in which Cu(I) is sandwiched between two methanethiolates and (b) a binuclear complex having two Cu(I) cations and two methanethiolate anions derived from the crystal structure of cytochrome *c* oxidase active site in which the two S and the two Cu(I) cations lie in the same plane with both S ligands sharing the cations.[41] At this point, we have to mention that the computations are dealing with two d^{10} coppers, whereas the experimental geometry and a recent DFT study[41d] concern a mixed-valence pair.

For both complexes, the RVS calculations were carried out with three basis sets, with one of them (VTZP) having a triple-ζ valence shell. The values of ΔE_{tot} computed with the different basis sets differ by less than 3% even though the various contributions might have more spread values. For the mononuclear complex, the value of ΔE_{tot}(SIBFA) underestimates the corresponding ab initio values by 3−6%, the lowest discrepancy

TABLE 5: Values (kcal/mol) of the Intermolecular Interaction Energies and Their Components in Complexes of Cu(I) with N-Containing Ligands for the Cu(I)−Ligand Distance (Values in Å) Optimized at the MP2 Level

	Cu^+−methylamine		Cu^+−imidazole		Cu^+−pyridine	
	ab initio	SIBFA	ab initio	SIBFA	ab initio	SIBFA
E_1	−5.5	−0.6	−13.9	−13.5	−4.5	−7.5
$E_{pol}(L)$	−13.3	−20.1	−17.7	−22.6	−19.6	−23.6
$E_{pol}(M)^a$	−7.4	−12.7	−6.8	−8.7	−7.0	−6.7
		(−9.3)		(−5.4)		(−3.5)
E_{pol}	−20.7	−32.9	−24.5	−31.3	−26.6	−30.3
$E_{ct}(L)$	−11.1	−10.1	−9.6	−9.4	−10.2	−9.6
$E_{ct}(M)$	−2.3	−2.2	−2.5	−1.8	−2.6	−1.2
E_{ct}	−13.4	−12.3	−12.1	−11.2	−12.8	−10.8
E_2	−34.1	−45.2	−36.6	−42.5	−39.4	−41.1
ΔE	−42.5	−45.7	−53.2	−56.5	−46.9	−50.1
E_{disp}	−18.7	−24.4	−19.0	−18.5	−20.1	−15.0
ΔE_{tot}	−61.2	−70.1	−72.2	−75.0	−67.0	−65.1
$\Delta E_{tot}{}^b$		−72.8		−78.1		−70.7
$d(Cu-N)^c$	1.9		1.9		1.9	
	(1.8)		(1.8)		(1.8)	

[a] The value in parentheses is that of the quadrupolar polarization of Cu(I). [b] Value of ΔE_{tot}(SIBFA) at the SIBFA-optimized distance. [c] The value in parentheses corresponds to the SIBFA-optimized distance.

correponding to the triple-ζ valence set. However, there are some imbalanced effects, E_1 is underestimated by SIBFA, whereas $E_{pol}(M)$ is overestimated. Such a relative difference already preexisted in the monoligated Cu(I) complex with methanethiolate. $E_{ct}(M)$ of −7.6 kcal/mol in SIBFA is intermediate between the values obtained from ab initio calculations, −3.7−8.7 kcal/mol.

For the binuclear complex, the agreement with ab intio appears more satisfactory because the SIBFA value of ΔE_{tot} (−443.1 kcal/mol) is intermediate between those obtained from the three different basis sets (−434.6 to −444.0 kcal/mol). As for the mononuclear complex, E_1 is underestimated, whereas $E_{pol}(M)$ is overestimated.

B. Cu(I) Complexes with N Ligands. 1. Monoligated Complexes. Table 5 reports the binding energy values of Cu(I) with methylamine, imidazole, and pyridine. The latter two are widely encountered in biochemistry and supramolecular chemistry, respectively. Both ab initio and SIBFA computations give Cu(I) as more strongly bound to imidazole than to pyridine, because of the E_1 component. However, the SIBFA optimized values of ΔE_{tot} are of 5.9 and 3.7 kcal/mol larger than the corresponding ab initio ones, even though at the MP2 optimized distances such a difference is smaller (2.8 and 1.9 kcal/mol respectively). For these two complexes, Cu(I) relaxation contributes to ∼12% of ΔE_{tot}. For Cu(I)−methylamine, a good agreement at the uncorrelated level is seen between ab initio and SIBFA ΔE values (−42.5 versus −45.7 kcal/mol respectively), but it is less satisfactory at the correlated level (−70.1 versus −61.2 kcal/mol) at the MP2 optimized distance. The weights of the individual components of ΔE is not well accounted for. This may reflect a persistent difficulty in the representation of cation binding to saturated amonia like nitrogens, already encounted upon studying the binding of Zn(II) to the N ligand of neutral glycine.[38] $E_{pol}(M)$ is larger in SIBFA than in ab initio (−12.7 versus −7.4 kcal/mol), but $E_{ct}(M)$ has the same value. The value of ΔE_{tot} (ab initio) of −61.2 kcal/mol is close to the −58.1 and −59.8 kcal/mol values found in the 6-311G (2d,2p) CCSD(T) calculations by Hoyau and Ohanessian[40] and the 6-311+G(2df,2p) calculations of Luna et al.[11f] However, the corresponding optimized value of ΔE_{tot}(SIBFA) of −72.8 kcal/mol is exaggerated in that case. The radial evolutions of ΔE(MP2) and ΔE_{tot}(SIBFA) and of their components are reported in Table 6S.

2. Polycoordinated Complexes. We have investigated the following arrangements: (a) Cu(I) bound to three ammonia ligands, Cu(I) − $(NH_3)_3$; the geometrical arrangement for this system is taken from a previous ab initio study on a model of oxytyrosinase active site;[12c] (b) a model binuclear complex, made of two Cu(I)−$(NH_3)_3$ entities in a mutual disposition with a Cu(I)−Cu(I) distance of 3.5 Å, as in dinuclear copper enzyme active sites;[42] (c) Cu(I) bound to three imidazole ligands. The energy results are reported in Table 6. The ab initio computations were performed with all three basis sets.

For the mononuclear complex Cu(I)−$(NH_3)_3$, ΔE_{tot}(SIBFA) matches ΔE_{tot}(ab initio) with a relative error of 2%, although the error at the uncorrelated level is larger (8%). $E_{pol}(M)$ from SIBFA is underestimated (−2.9 versus −6.2 to −8.2 kcal/mol), whereas the numerical value of E_{ct} is correctly accounted for, namely, −3.9 kcal/mol as compared to −2.0 to −4.7 kcal/mol given by the ab initio calculations. For binuclear complex b, depicted in Figure 4a, a good accuracy is retained. Here also the match is less good at the uncorrelated level as can be seen from Table 6. Although $E_{pol}(M)$ is smaller than in the ab initio computations, $E_{ct}(M)$ in SIBFA of −4.5 kcal/mol is intermediate between the ab initio values −11.0 and −4.1 kcal/mol. Worth noting is the fact that although these basis sets yield comparable values of ΔE_{tot} and ΔE, the weights of their individual components differ more substantially.

For complex c, the relative difference between SIBFA ΔE_{tot} and ΔE_{MP2} values is small (1.2 kcal/mol) only with the largest

TABLE 6: Values (kcal/mol) of the Interolecular Interaction Energies and Their Components in Polycoordinated Complexes of Cu^+ Ammonia and Imidazole (See Text and Figure 4b,c for the Geometrical Arrangements)

	$Cu^+-(NH_3)_3$				$(Cu^+-(NH_3)_3)_2$ staggered				Cu^+-ImH_3			
	ab initio				ab initio				ab initio			
	DZVP2	CEP 4-31G(2d)	TZVP	SIBFA	DZVP2	CEP 4-31G(2d)	TZVP	SIBFA	DZVP2	CEP 4-31G(2d)	TZVP	SIBFA
E_1	−53.9	−47.1	−58.7	−42.5	−37.4	−20.3	−46.4	−10.6	−37.6	−30.7	−44.1	−39.0
$E_{pol}(L)$	−11.4	−16.9	−13.3	−17.1	−31.9	−48.1	−36.7	−53.1	−26.1	−26.5	−27.6	−25.9
$E_{pol}(M)$	−8.2	−7.0	−6.2	−2.9	−20.7	−17.8	−15.9	−11.5	−14.6	−13.4	−10.6	−6.2
				(−0.4)				(−2.3)				(−0.8)
E_{pol}	−19.6	−23.9	−19.5	−20.0	−52.6	−65.9	−52.6	−57.9	−40.7	−39.9	−38.2	−32.0
$E_{ct}(L)$	−3.6	−9.8	−2.7	−11.4	−11.9	−23.9	−9.6	−25.2	−4.8	−15.6	−3.8	−12.9
$E_{ct}(M)$	−4.7	−2.5	−2.0	−3.9	−11.0	−4.8	−4.1	−4.5	−10.0	−6.2	−4.1	−5.8
E_{ct}	−8.3	−12.3	−4.7	−15.3	−22.9	−28.7	−11.7	−29.7	−14.8	−21.8	−7.9	−18.7
E_2	−27.9	−26.2	−24.2	−35.3	−75.5	-−94.6	−64.3	−87.6	−45.5	−51.7	−46.1	−50.7
ΔE	−84.0	−84.5	−83.7	−77.8	−115.0	−112.8	−111.4	−101.3	−95.5	−93.7	−90.9	−88.1
E_{disp}	−26.9	−28.6	−21.7	−32.7	−64.5	−61.0	−48.6	−66.3	−56.2	−61.6	−42.7	−46.7
ΔE_{tot}	−110.9	−113.1	−105.4	−110.5	−179.5	−173.8	−160.0	−167.5	−151.7	−155.3	−133.6	−134.8

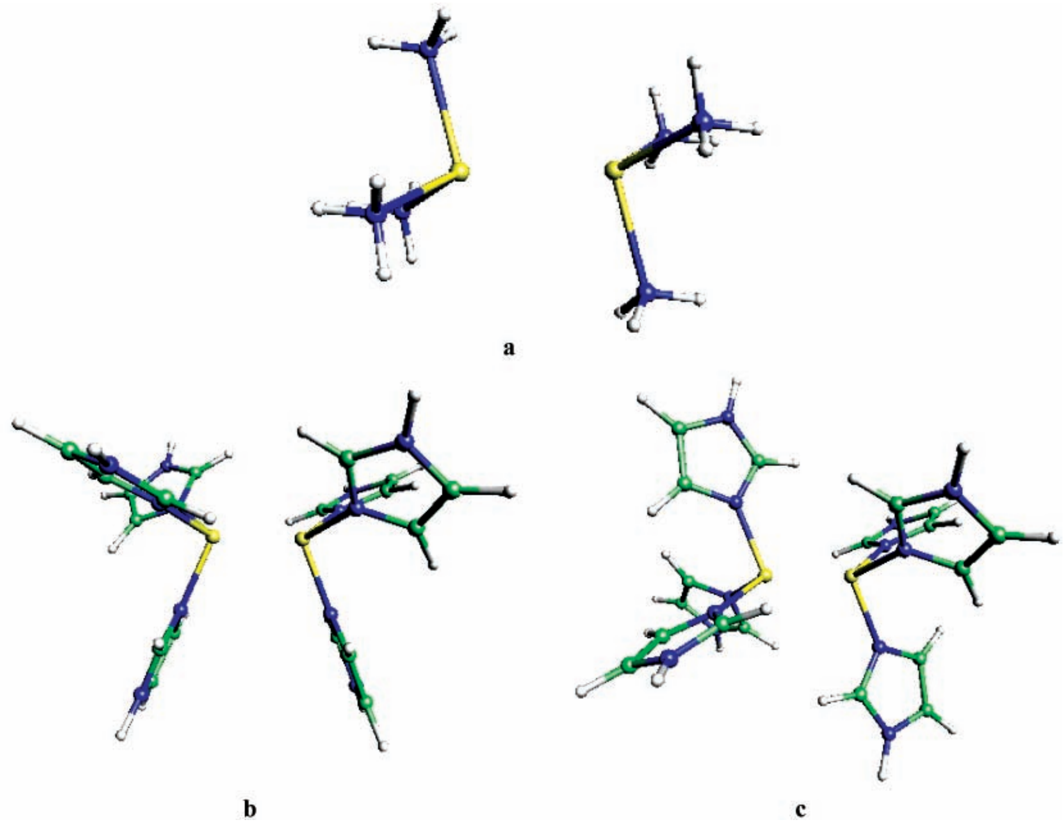

Figure 4. Representation of the polycoordinated complexes of Cu(I) with N ligands (a) staggered [Cu(I)$-$(NH$_3$)$_3$]$_2$ complex, (b) staggered [Cu(I)$-$(ImH)$_3$]$_2$ complex, and (c) eclipsed [Cu(I)$-$(ImH)$_3$]$_2$ complex.

(TZVP) basis set. More extensive comparisons with more refined ab initio computations using a larger basis set would be of interest to delineate the precision of SIBFA results for such systems, but they are presently prevented by the high cost of such computations.

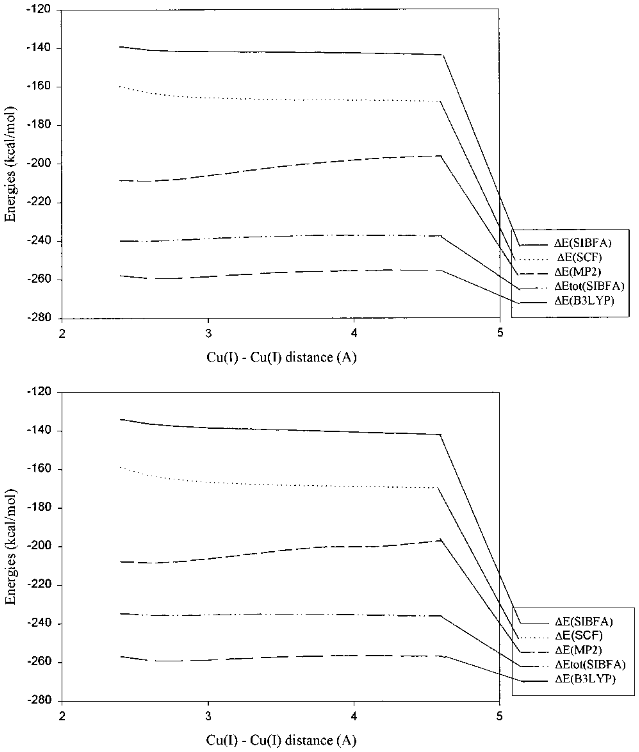

Figure 5. [Cu(I)$-$(ImH)$_3$]$_2$. Evolution of the binding energies as a function of the Cu(I)$-$Cu(I) distance: (A) staggered arrangement; (B) eclipsed arrangement.

Monitoring the Distance Dependencies in a Binuclear (Cu(I)$-$(Imidazole)$_3$)$_2$ Complex. Complexes involving two Cu(I) cations and six His residues are encountered in the active site of several copper metalloenzymes such as oxygen carriers and monoxygenases.[42] On this basis, functional models for such enzymes were recently designed, of which some are endowed with an oxidase activity.[6b,43] An important step in modeling binuclear Cu(I) active sites consists of monitoring the Cu(I)$-$Cu(I) distance dependence in model complexes. For that purpose, we considered arrangements built out of Cu(I)$-$(imidazole)$_3$ complexes with the geometrical arrangement described in ref 44 and performed stepwise variations of the Cu(I)$-$Cu(I) distance. Two arrangements were considered, in which the imidazoles of the second monomer are disposed in a staggered or in an eclipsed arrangement with respect to the first (Figure 4b,c). The Cu(I)$-$Cu(I) distance dependencies are reported in Figure 5A,B for the staggered and eclipsed arrangements, respectively. This figure reports the distance variations of ΔE and ΔE(SIBFA), plus those of ΔE(DFT), ΔE(MP2), and ΔE_{tot}(SIBFA), with the ab initio values being obtained with the DZVP2 basis set. The distance dependency of ΔE is shallow in both arrangements. Thus, a 2.0 Å increase of the Cu(I)$-$Cu(I) distance in the staggered arrangement, from 2.6 to 4.6 Å, gives by a gain of less than 6 kcal/mol of ΔE from both type of calculations. On the other hand, ΔE(DFT) and ΔE(MP2) present a shallow, but distinct, minimum, at the Cu(I)$-$Cu(I) distance of 2.6 Å. This is also the case with ΔE_{tot}(SIBFA). Such very shallow dependencies could have important implications to easen the approach of a substrate or an inhibitor to a binuclear enzyme active site, as they could allow for an opening of the site to accommodate the incoming reactant. Shallow behaviors of the β-lactamase, a bifunctional Zn(II) metalloenzyme, were also found by us by parallel ab initio and SIBFA computations.[17g,45] This enzyme, however, encompasses three anionic ligands to shield the electrostatic repulsions between the two dications. The present complexes, by contrast, are devoid of counterions.

The comparison between the HF and DFT results, as well as between ΔE(SIBFA) and ΔE_{tot}(SIBFA), shows that correlation effects and their present E_{disp} counterpart in SIBFA are necessary to stabilize, albeit weakly, the complex for the Cu(I)−Cu(I) distance of 2.6 Å. The contribution of the cation relaxation is also important. In the staggered arrangement, it amounts at this distance to −32.9 kcal/mol, namely, 14% of ΔE_{tot}(SIBFA) with E_{pol}(M) and E_{ct}(M) values of −22.0 and −10.9 kcal/mol, respectively. The ability of SIBFA to account for the distance variations of the quantum chemical binding energies is a satisfactory feature. Examination of the ΔE(SIBFA) components shows its shallow radial behavior to stem from the mutual compensations between E_1 increase because of the reduction of the Cu(I)−Cu(I) electrostatic repulsions on the one hand and from the concomitant decrease of E_{pol} on the other hand, because of a reduction of the field undergone by each individual monomer. The radial decrease of E_{disp} parallels that of the correlation energy E_{corr}, evaluated as the difference between the ΔE(HF) and ΔE(DFT)/ΔE(MP2) values. At the uncorrelated level, ΔE(SIBFA) is about 20 kcal/mol smaller than ΔE(SCF) using the DZVP2 basis set, part of which is coming from the 7.4 kcal/mol found for each mononuclear Cu(I)−(ImH)$_3$ complex. The values of ΔE_{tot}(SIBFA) for the 2.6 Å Cu−Cu distance are −240.0 and −235.5 kcal/mol, in the staggered and eclipsed arrangements, respectively. These values are intermediate between those of ΔE(MP2) of −210.0 and of ΔE(DFT) of −260.0 kcal/mol.

C. Polyligated Complexes of Cu(I) with Flexible Ligands. 1. Modeling of a Cu(I) Complex Involving a Proximal Aromatic Ring. Several examples have highlighted the involvement of Cu(I) in the stabilization of supramolecular assemblies.[9] Whenever structurally possible, its interaction with electron-rich aromatic rings could provide an additional factor to the stabilization. Thus, in the recently determined crystal structure of the Cu(I) complex with a tridentate ligand, *N*-(3-indolylethyl)-*N*,*N*-bis(6-methyl-2-pyridylmethyl)amine (Me$_2$IEP), Cu(I) is stacked over the five-membered ring of indole, at close distances to the C(2) and C(3) carbons of 2.23 and 2.27 Å respectively.[8] We have computed the binding energy of Cu(I) with Me$_2$IEP, which was built out of its constitutive fragments, trimethylamine, pyridine, indole, and methane. It was necessary to account for nonadditivity effects simultaneously involving Cu(I)−Me$_2$IEP and intra-Me$_2$IEP interactions. This is done by computing the interaction energy between the ligand fragments simultaneously with the Cu(I)−ligand ones. To avoid the polarization overestimation which occurs when the contribution of the multipoles located on the junctional bonds is not taken into account (in that case the various fragments carry a noninteger net charge), we use the procedure recently adopted by us to study the binding of Zn$^{(II)}$ with flexible ligands encompassing two ligating groups.[38,39] When using this procedure, the junctional hydrogens are located on the C atoms whence they originate. The total intermolecular interaction energy thus encompasses the Cu(I)−Me$_2$IEP intermolecular interactions as well as the mutual interactions between the pyridine, methyldiethylamine, and indole fragments. It includes in addition three "intramolecular" interaction energy terms, two between each pyridine ring and its methyl substituent and one between the amine nitrogen and its connecting methyl and ethyl groups. These are computed after redistribution of the multipoles along the junctional bonds with the procedure published in ref 46 reporting the initial derivation of the SIBFA method for flexible molecule computations. A 3-fold torsional energy contribution for rotations along the saturated C−C bonds is also added, with a height of 2.3 kcal/mol.[46] Energy-minimization was done on the dihedral angles of Me$_2$IEP and the three intermolecular variables defining the orientation of Cu(I). It was also performed on the ligand torsional angles in the absence of Cu(I), to evaluate the amount of conformational energy increase upon Cu(I)−ligand binding. Single-point ab initio HF and DFT/B3LYP computations using the DZVP2 basis set were performed at the SIBFA energy-minimized structure, which is represented in Figure 6. The SIBFA intermolecular interaction energy was computed as the difference between the energy of the complex and that of Me$_2$-IEP in the absence of Cu(I) in the same conformation. The results are reported in Table 7. The total energies were also computed relative to the energy of isolated Me2IEP, whose conformation was independently energy-minimized in the absence of Cu(I) binding (values reported in the second column of Table 7). The SIBFA results reproduce satisfactorily both HF and DFT energies, although they seem to exaggerate somewhat the difference in conformational energies found at the HF level between the Cu(I)-bound and -unbound conformations. The SIBFA Cu(I)−ligand distances are 2.10 Å to the trimethylamine N, and 2.10 and 2.21 Å to the pyridine N. The corresponding X-ray distances are 2.16, 2.01, and 2.01 Å. The Cu−C(2) and Cu−C(3) distances of 2.59 and 2.90 Å are longer than the X-ray ones of 2.23 and 2.27, and Cu(I) is displaced

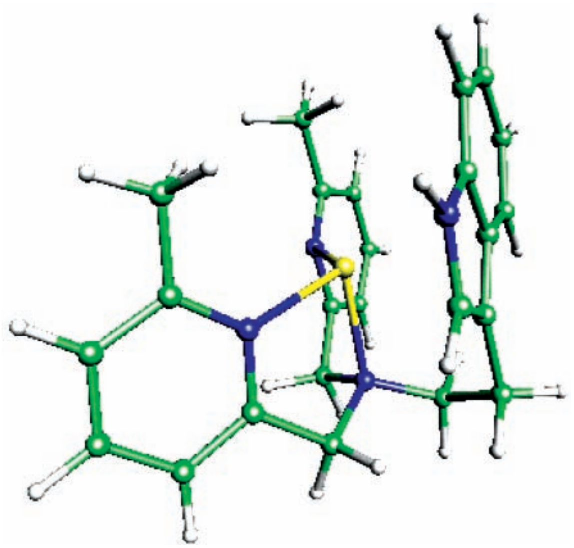

Figure 6. Representation of the energy-minimized structure of the complex of Cu(I) with Me2IEP.

TABLE 7: Interaction Energies (kcal/mol) between Cu(I) and Me$_2$IEP

	Cu(I)Me$_2$IEP[a]	Cu(I)−Me$_2$IEP[b]
E_{MTP}	−116.7	−107.6
E_{rep}	47.1	42.5
E_1	−69.5	−63.0
E_{pol}(M)	−1.3	−1.3
E_{ct}(M)	−2.6	−2.6
E_2	−40.7	−40.3
ΔE	−110.2	−103.3
E_{disp}	−49.7	−52.0
ΔE_{intra}	0.0	10.0
ΔE_{tot}	−159.9	−145.5
ΔE(HF)	−108.6	−102.9
ΔE(DFT)	−148.9	−142.0

[a] In the optimized complex. [b] Difference between the energies of the optimized complex and that of the sum of Cu(I) plus optimized Me$_2$IEP.

TABLE 8: Interaction Energy (kcal/mol) Calculated with Different Computational Procedures Available for Cu(I) (See Text)

	ab initio					
	basis I[a]	basis II[b]				
	B3LYP	MP2	PM3(tm)	ZINDO	UFF	SIBFA
Cu(I)−H_2O	−48.2	−39.1	−82.9	−166.2	−27.0	−36.6
Cu(I)−$(H_2O)_6$	−152.2	−129.0	−233.4	−702.8	−118.6	−129.7
Cu(I)−ImH	−95.0	−74.2	−135.0	−212.3	−75.3	−75.0
Cu(I)−$CHONH_2$	−76.2	−57.0	−104.0	−207.3	−35.5	−55.7
Cu(I)−CH_3S^-	−203.8	−193.5	−295.5	−306.5	−133.7	−200.1
Cu(I)−Me_2IEP	−143.3	−164.7	−299.3	−378.3	−83.3	−145.5

[a] Complexes and ligands fully optimized using the B3LYP functional and LACVP** basis set. [b] MP2 single point calculations using the DFT optimized geometries and the CEP 4-31G basis.

more toward the interior of the five-membered ring. An alternative structure in which the Cu(I) to C(2) and C(3) distances are fixed to 2.2 and 2.5 Å was found to be 8.5 kcal/mol higher in terms of total energies (shorter restraining distances yielded much higher energies). Single-point DFT/B3LYP computations using the LACVP** basis on these two conformations also favored the unconstrained conformation, although by a lesser amount (3.7 kcal/mol). DFT/B3LYP energy minimization resulted in distances between Cu(I) and C(2) and C(3) of 2.37 and 2.33 Å, respectively (interaction energies reported in Table 8 below). Such distances are only 0.1 A larger than the experimental ones. An improved match to the experimental structure may be facilitated in the ab initio computations by relaxation of the saturated valence angles of the sp^3 C and N atoms of Me_2IEP, whereas these angles are set to 109.5° in the SIBFA computations and presently not allowed to vary. With SIBFA, the procedure variation of bond angles requires a calibration of the corresponding force constants on the basis ab initio computations, compatible with the other energy terms. This is presently underway for peptides and will be generalized in the future.

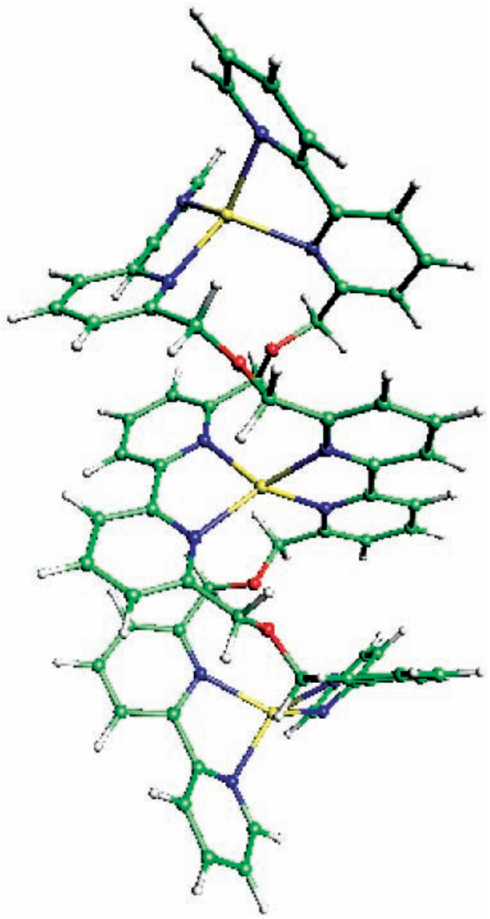

Figure 7. Representation of the energy-minimized structure of the double-stranded helicate complex of three Cu(I) with two BP3 ligands.

2. Double-Stranded Helicate Stabilized by Cu(I) Cations. Example of an Oligobipyridine Ligand. The ability of Cu(I) to nucleate the assembly of supramolecular architectures was illustrated in complexes of oligopyridine forming double-stranded helicates in its presence.[9] Thus, a molecule built out of three 2,2′-bipyridine units separated by 2-oxapropylene bridges (denoted as BP_3) was seen by X-ray crystallography to form a double helix stabilized by the binding of three Cu(I) cations, each of which complexes two pyridine nitrogens from each BP_3 ligand along the helix. The average Cu(I)−N distance is 2.02 Å. The complex bears a net positive charge of +3. In view of the predominant metal−metal electrostatic repulsion, we deemed it essential to verify whether SIBFA could account for the stability of the structure of the $[(BP_3)_2(Cu)_3]^{3+}$ complex, and its structural features. The starting conformation of each BP_3 monomer was built using torsional angles of −60° around all C−C bonds and of 180° around the C−O bonds. The second BP_3 monomer was brought in the vicinity of the first with the help of computer graphics so as to create three successive Cu(I)-binding cavities from four pyridine nitrogens, two from each monomer. A Cu(I) cation was first docked into each of the three cavities, by a first round of energy-minimization using distance restraints on the Cu(I)−N distances (four restraints per cation). To account for conjugation effects, a 2-fold torsional energy barrier was introduced for rotations along the six C−C interpyridine rings. Its amplitude was of −15 kcal/mol, fitted from comparisons with respect to ab initio computations performed by doing 30° torsional variations on bispyridine. We also used a 3-fold rotational barrier for rotations along the C−O bonds, using an amplitude of 1.5 kcal/mol.[46] Minimizations were performed on the three intermolecular variables defining the orientation of each cation in the cavity, the six intermolecular variables defining the position of the second monomer with respect to the first, and the torsional angles of each monomer. In a second round of energy-minimizations, the restraints were removed. To account for the strong nonadditivity effects in the supramolecular complex, the interaction energies were calculated, as done for Me_2IEP, by resorting to a global pseudointermolecular procedure. Thus, the Cu(I)−Cu(I), intermolecular BP_3−BP_3, intramolecular BP_3, and Cu(I)−BP_3 interactions are computed simultaneously. The total energy includes in addition the four intramolecular interaction energies of the connecting ether bridges. The total stabilization energy is computed by subtracting from the total minimized energy twice that of a BP_3 monomer independently relaxed using the same energy computational procedure as in the complex. The resulting structure for the $[(BP_3)_2(Cu)_3]^{3+}$ complex is represented in Figure 7. The averaged Cu(I)−N distances are 2.14 Å in the central cavity and 2.16 Å in the first and third ones. The smallest Cu−N distance is 2.09 Å, and the largest one is 2.23 Å. The complex has a very large stabilization energy, ΔE, of −325 kcal/mol. Its components have the following values: $E_1 = -50.2$, $E_{pol} = -89.4$, $E_{ct} = -46.4$, and $E_{disp} = -144.7$ kcal/mol. The difference between the sum of these four terms and ΔE_s is due to small variations of the intramolecular and conjugation/torsional terms in the relaxed BP_3 monomer. The summed polarization energies of the three Cu(I) cations amount to −2.5 kcal/mol, of which −1.9 kcal/mol stem from quadrupole polarizability. The summed Cu(I) to ligand charge-transfer terms amount to −13 kcal/mol. E_{pol} and E_{disp} are thus the most important contributors to ΔE, and E_1 only contributes about 17% of the total energy. This highlights the essential role of the second-order effects in stabilizing a complex having three net charges of +1 and no neutralizing counterions. ΔE is much closer to the corresponding single-point DFT/B3LYP value of −353.2 kcal/mol computed at the SIBFA-minimized conformations than the energy-minimized PM3(tm) value of −539.2 kcal/mol. By contrast, the nonpolarizable molecular mechanics UFF procedure gives a positive ΔE. If, however, we subtract from the complex total energy the summed energies of two BP3 monomers held in their conformations in the complex, a value of −409.5 kcal/mol is obtained instead of −325.3 kcal/mol. The corresponding DFT/B3LYP value is −400.9 kcal/mol instead of −353.2 kcla/mol. This indicates that the conformational energy increase of the two BP3 monomers is 84.5 kcal/mol from SIBFA and only 47.7 kcal/mol from B3LYP. To analyze the reasons for such an overestimation, we have compared the conformational energies of bipyridine in the trans and cis conformation, which relate to free and complexed BP3, respectively. DFT and SIBFA find the cis conformation to be higher in energy than the trans one by 8 and 15 kcal/mol in, respectively. The 7 kcal/mol overestimation appearing six times in the BP3 double helix can thus be identified as the factor responsible for such an overestimation. This originates principally from a corresponding overestimation by E_{MTP} of the repulsive interactions between the two pyridine nitrogens in the cis conformation, whereas E_{rep} entailed much smaller increases (3 kcal/mol out of 15). As was done in the present study for E_{ct}, and in light of such a finding, we plan to introduce an explicit penetration energy contribution in E_{MTP} as well as a further improvement to SIBFA, thus conferring an additional attractive character to this component.

Conclusions

In this study, we have proposed a parametrization of the closed-shell Cu(I) cation for SIBFA molecular mechanics computations. In line with our previous work devoted to dicationic closed-shell Mg(II), Ca(II), Zn(II), and Cd(II) divalent cations,[17] the calibration is grounded on the results of ab initio supermolecule computations using the RVS energy-decomposition analysis. In line with our previous study[16] and in contrast to the isoelectronic cation Zn(II), the relaxation of Cu(I) is found to provide a significant contribution to the total interaction energy. Numerical values for the weights of $E_{\mathrm{pol}}(\mathrm{M})$ and $E_{\mathrm{ct}}(\mathrm{M})$, the polarization and the Cu(I)-to-ligand charge-transfer energy terms, are provided by the RVS analysis. We have attempted to explicitly introduce both terms in SIBFA. $E_{\mathrm{pol}}(\mathrm{M})$ embodies two components. The first stems from the electrostatic field undergone by Cu(I), which involves its dipolar polarizability, and the second stems from the gradient of the field, which involves its quadrupolar polarizability. The expression of $E_{\mathrm{ct}}(\mathrm{M})$ is derived from earlier developments on which the formulas for $E_{\mathrm{ct}}(\mathrm{L})$, the ligand-to-cation charge-transfer, were established.

To validate our approach, computations on representative mono- and polyligated complexes of Cu(I) with O, S, and N ligands were done in parallel by the ab initio supermolecular approach with energy-decomposition. Both SIBFA results and RVS analysis do give a contribution of the cation relaxation of ∼15% in the case of neutral ligands; this percentage is smaller with anionic ones.

We have evaluated the rms deviation in terms of total SIBFA energies with respect to their MP2 counterparts reported in Tables 1−4 in which the interaction energy values vary from −38 to −444 kcal/mol. It amounts to 7.6 kcal/mol. The SIBFA optimized Cu(I)−ligand distances differ by less 0.1 Å from the corresponding value obtained from MP2 computations.

As a first step toward the study of supramolecular complexes, the SIBFA procedure was used to study the binding of Cu^+ to flexible molecules having N ligands. For *N*-(3-indolylethyl)-*N*,*N*-bis(6-methyl-2-pyridylmethyl)amine ($\mathrm{Me_2IEP}$), a complex which is still amenable to HF and DFT computations, a satisfactory agreement between SIBFA and the quantum-chemical interaction energy values is obtained at both uncorrelated and correlated levels. For a double-stranded helicate formed by two oligopyridine ligands and three Cu^+ cations, first synthesized by Lehn et al.,[9a,b] SIBFA energy-minimizations gave a stable complex, in which each Cu^+ cation is in a tetrahedral environment made of four pyridines, with each strand contributing two ligands. This stabilization takes place despite the fact that the three positive charges are not neutralized by anions. The structural characteristics of the complex are similar to the X-ray ones. The average Cu−N distance is 2.15 Å, with the X-ray one being 2.02 Å. The most important contribution to ΔE is E_{disp}, similar to the situation in the binuclear complexes of two Cu^+ cations with six imidazoles.

To compare the handling of Cu(I) interactions by SIBFA to those from other approaches, we have selected some representative complexes and performed in parallel computations using the semiempirical PM3(tm) and ZINDO procedures as well as the nonpolarizable UFF molecular mechanics, as implemented in the Gaussian 98 software. The results are reported in Table 8 and compared to DFT and MP2 computations. For each of these complexes, energy minimization was performed independently in the framework of the procedure considered except for the $\mathrm{Me_2IEP}$ complex, for which the MP2 computations were done at the DFT-minimized conformation. It is found that the DFT/B3LYP energy values using the LACVP** basis are generally larger in magnitude than the MP2 ones using the CEP 4-31G(2d) basis set used for the calibration of SIBFA. Both semiempirical approaches give overestimated values of the Cu(I) interaction energies, whereas by contrast, and except in the case of imidazole, UFF underestimates these values as can be seen from Table 8.

The CPU timings of SIBFA have enabled us to use this procedure for energy-minimization studies on models of Zn(II) metalloenzymes encompassing more than 100 residues and their complexes with inhibitors.[17e,47] The results on Cu(I) calibration, reported in this study, are overall satisfactory. They have prompted an extension to functional mimics of Cu^+ enzymes. These will be reported elsewhere.

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Supporting Information Available: Cu(I) parameters for SIBFA computations, formulas used for Cu(I) quadrupolar polarization and cation-to-ligand charge-transfer. Tables 1S−3S report the variation as a function of the Cu(I)−ligand distance, of the various components of the interaction energies in Cu(I)−H_2O, Cu(I)−formate, and Cu(I)−imidazole complexes. Tables 4S−6S report the angular variation in the Cu(I) complexes with methoxy, formate and methanethiolate anions.

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(48) ^{a}Complexes and ligands fully optimized using B3LYP functional and LACVP** basis set.

(49) ^{b}MP2 single point calculations using the DFT optimized geometries and the CEP 4-31G basis.