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Modeling Anhydrous and Aqua Copper(II) Amino Acid Complexes: A New Molecular Mechanics Force Field Parametrization Based on Quantum Chemical Studies and Experimental Crystal Data

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This paper presents the vacuum structures of aquacopper(II) bis(amino acid) complexes with glycine, sarcosine, *N,N*-dimethylglycine, and *N*-*tert*-butyl-*N*-methylglycine estimated using the B3LYP method. The differences between the B3LYP vacuum structures and experimental crystal structures suggested considerable influence of crystal lattice packing effects on the changes in the complexes' geometries. A previously developed molecular mechanics force field for modeling anhydrous copper(II) amino acidates was reoptimized to simulate these changes and predict the properties of both trans and cis anhydrous and aqua copper(II) amino acid complexes. The modeling included experimental molecular and crystal structures of 13 anhydrous and 10 aqua copper(II) amino acidates with the same atom types (Cu(II), C, H, N, and O) but various copper(II) coordination polyhedron geometries, crystal symmetries, and intermolecular interactions. The empirical parameters of the selected potential energy functions were optimized on the B3LYP vacuum copper(II) coordination geometries of three anhydrous copper(II) amino acidates and on experimental crystalline internal coordinates and unit cell dimensions of six anhydrous and six aqua copper(II) amino acid complexes. The respective equilibrium structures were calculated in vacuo and in simulated crystalline environment. The efficacy of the final force field, FFW, was examined. The total root-mean-square deviations between the experimental and theoretical crystal values were 0.018 Å in the bond lengths, 2.2° in the valence angles, 5.5° in the torsion angles, and 0.395 Å in the unit cell lengths. FFW reproduced the unit cell volumes in the range from –8.1 to 9.6%. The means of Cu to axial water oxygen distances were 2.4 ± 0.1 Å (experiment) and 2.6 ± 0.1 Å (FFW). This paper describes the ability of the molecular mechanics model and FFW force field to simulate the flexibility of the metal coordination polyhedron. The new force field proved effective in predicting the most stable molecular conformation of copper(II) amino acidato systems in vacuo.

Introduction

Copper complexes with amino acids are compounds of biological importance. They are a part of the accessible physiological pool of an essential trace element copper for most tissues.[1−3] Many low-molecular-weight copper complexes—some with amino acids and amino acid derivatives—act as antiinflammatory, antiulcer, anticonvulsant, anticancer, and/or radiation protection agents.[4] Copper(II) complexes with amino acids are also worthy of scientific interest because of their stereochemical properties. Namely, copper(II), as a Jahn−Teller center,[5,6] chelated with amino acids can adopt

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a variety of coordination geometries, from irregular square-planar, distorted planar, flattened tetrahedral, and distorted square-pyramidal to distorted octahedral, as observed in their experimental crystal structures.[7−27] Modeling the flexibility (plasticity) of the copper(II) coordination sphere with empirical molecular mechanics method is therefore a challenge.

Molecular mechanics (MM) method for transition metal complexes is still under development. A number of reviews dealing with MM for coordination compounds have been published.[28−38] The limitations and advantages of the method, especially nowadays when the development of both computers and ab initio molecular quantum mechanics methods makes ab initio methods applicable to large systems, have been addressed in a series of recent reviews.[32−38] In our earlier paper we presented different approaches to MM modeling of copper(II) complexes.[39] In addition, modeling the plasticity of the copper(II) coordination geometry using a combined MM and ligand-field theory model has been surveyed in a recent review.[33]

In an MM calculation, the effects of surrounding environment of a molecule can be either implicitly incorporated on an average basis in the parameter set or they can be calculated explicitly by including the environment in calculations.[40,41] However, either approach affects the force field parametrization.[40] Our choice has been to calculate the environmental effects explicitly,[11,39,42] that is, to develop a so-called "vacuumlike" force field applicable to both isolated systems (a gas-phase approximation) and condensed-phase simulations (by explicit accounting for the influences of surrounding environment such as crystal lattice or solution). This approach enabled us to model anhydrous four-coordinate copper(II) amino acidates with the same trans or cis CuN_2O_2 coordination polyhedron in a simulated crystal lattice and study the impact of the crystal packing forces on the changes in the copper(II) coordination sphere as well as on the overall geometry of the molecules.[11,39,42] Furthermore, it allowed us to predict conformations that a copper(II) amino acid complex might have in vacuo as an isolated system, without the influence of intermolecular interactions in the crystal lattice. The efficacy of the force fields was evaluated by comparing the calculated and the experimental crystal data, whereas the reliability of the predicted vacuum structures was verified by the structures obtained using quantum chemical methods.[11,39] The first quantum chemical calculations of the equilibrium geometry and electronic structure of the anhydrous copper(II) complexes with L-alanine, L-leucine, and L-*N*,*N*-dimethylvaline applying the hybrid density functional method B3LYP[43,44] and the natural population analysis (NPA)[45] showed that the deviations from planarity of the copper(II) coordination geometry observed in the crystal state and calculated in vacuo had to be attributed to intramolecular strain and/or crystal packing effects.[39] The last in the series of our force fields, the FF1 force field,[11] reproduced well the differences between the experimental crystalline and B3LYP in vacuo copper(II) amino acidato structures. This good reproduction proved that the changes from vacuum to crystalline structures should be sought in the crystal lattice packing preferences.

In this study, we extended the application of our MM model[11] to five- and six-coordinate copper(II) chelates, namely aquacopper(II) amino acid complexes with one or two water molecules apically bound to the copper(II) in their crystal structures. The introduction of water molecules into

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the modeled systems raised the question of how to model the interactions with water molecules. The force fields proposed along with the reported X-ray crystal structures for five-coordinate aquacopper(II) *N*-alkylated amino acidates[18−22] held the water molecule at the pyramid apex by applying valence-angle bending potentials and a harmonic bond-stretching potential between the copper and water oxygen. In contrast, as we did crystal simulations, we chose to treat equally all water molecules present in a crystallographic asymmetric unit. Thus, water molecules, placed either axially to copper(II) or being waters of crystallization, were taken as separate entities, and the interactions between the water atoms and the atoms of the copper(II) amino acid complex were modeled with the 12−6 Lennard-Jones potential plus electrostatic potential. These potentials were the only choice for describing the intermolecular interactions in simulated crystal lattice offered in the consistent force field (CFF) computer program[46−48] we used for optimization of empirical potential energy parameters.

Experimental evidence[49,50] and theoretical calculations[51] encouraged us not to assume a firm bond formation between copper and water oxygen. The X-ray absorption study of copper(II) glycinato complexes in aqueous solution showed that the axial distance between Cu(II) and water oxygen was significantly longer in these complexes than was the average Cu(II)−O(axial) distance in Cu^{2+} complexes in aqueous electrolyte solutions.[49] This finding was interpreted as an indication that the axial bonds were getting longer upon the formation of the Cu−glycine complexes and that the interaction between Cu(II) and H_2O at the axial site weakened. The measurements of electron spin resonance spectra of copper(II) complexes with L-*N*,*N*-dialkylated alanine in different solutions showed that the chelate with L-*N*,*N*-dimethylalanine retained a water molecule at the apical position independently on the type of solution, while the apical water molecule could be easily bound and released from the copper(II) coordination sphere in the complexes with L-*N*,*N*-diethylalanine and L-*N*,*N*-dipropylalanine.[50] In addition, theoretical modeling of trans and cis isomers of bis(glycinato)copper(II)•$2H_2O$ using the B3LYP method with a variety of the basis sets showed that axial Cu---OH_2 interactions competed with the forming of hydrogen bonds between water molecules and the glycinato atoms in vacuo:[51] during the geometry optimization for the trans isomer, two water molecules shifted from the coordinating axial position toward the noncoordinating position in the equatorial plane defined by copper(II) and amino acid donor atoms. However, in the cis configuration, water molecules stayed in their original axial position, still forming hydrogen bonds with amino acid atoms.[51]

This paper describes a theoretical investigation into the gas-phase and condensed-phase structure modeling of anhydrous and aqua copper(II) amino acid complexes and compares it with the available experimental and quantum chemical data. The new results of geometry optimizations performed on various aqua−copper(II) bis-chelates with glycine and glycine derivatives using the B3LYP method are presented. The FF1 force field[11] had to be reoptimized, as the initial simulations of the X-ray crystal and B3LYP vacuum structures of the aquacopper(II) amino acid complexes showed that the force field could not follow a much greater nonplanarity ("puckering") of chelate rings in the aqua than in the anhydrous class of compounds. The aim was to derive a force field that can reproduce and predict the structural data of both anhydrous and aqua trans and cis copper(II) amino acid complexes in vacuo and in the crystalline environment. This would help to develop a model and a vacuumlike force field that could be effective in simulating and predicting the properties of a whole class of compounds of our interest, that is, copper(II) complexes with amino acids, not only in the vacuum and crystal environment but also in different environments such as solutions in which biological reactions take place.

Methods

Quantum Chemistry. The ab initio quantum chemical calculations were performed using the Gaussian98 package of programs.[52] The hybrid density functional B3LYP method[43,44] was applied to studied structures, as it has been shown to yield reliable results for comparable systems.[39,51,53] As we deal with neutral copper(II) systems, we have one unpaired electron and the spin multiplicity of 2. This is why we chose the restricted open shell approach to determine electronic energies and wave functions.[54] Three different basis sets were applied, all based on the Dunning/Huzinaga full double-ζ (D95) basis[55] and Los Alamos effective core potentials (ECP) plus double-ζ basis[56−58] for copper. This combination of basis sets corresponds to the LanL2DZ basis set keyword in Gaussian98, for which reason we hereinafter refer to this approach as B3LYP/

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LanL2DZ. Further on, polarization functions[59] were added to carbon, oxygen, and nitrogen (the B3LYP/LanL2DZ(d) approach), and the largest basis set also included diffuse functions[60] on the same first row elements (the approach is named B3LYP/LanL2DZ+(d)). The importance of using ECPs when dealing with copper(II) complexes with amino acids has been emphasized by de Bruin et al.,[51] and the use of diffuse and polarization functions allows better description of hydrogen bonds. Energy minimizations were performed without any constraints with the standard algorithm ("Berny algorithm")[61] implemented in Gaussian98. For each basis set (i.e. LanL2DZ, LanL2DZ(d), and LanL2DZ+(d)) individual optimizations were performed. To make sure that every optimized geometry represented the minimum, vibrational frequency calculations were performed on them. The valence electron configuration and atomic charges, which may be a helpful tool for chemical analysis of the studied systems, particularly of the electronic features of different amino acids acting as copper(II) ligands, were computed using the NPA method.[45]

Molecular Mechanics. The conformational (strain) potential energy was calculated from the following basic formula:

$$V_{\text{total}} = \sum_{\text{bonds}} D_{\text{e}}(\mathrm{e}^{-2\alpha(b-b_0)} - 2\mathrm{e}^{-\alpha(b-b_0)}) + \frac{1}{2}\sum_{\substack{\text{valence}\\ \text{angles}}} k_\theta(\theta - \theta_0)^2 + \frac{1}{2}\sum_{\substack{\text{torsion}\\ \text{angles}}} V_\varphi(1 \pm \cos n\varphi) + \frac{1}{2}\sum_{\text{opp}} k_\chi \chi^2 + \sum_{i<j}(A_iA_j r_{ij}^{-12} - B_iB_j r_{ij}^{-6}) + \sum_{l<m} q_l q_m r_{lm}^{-1}$$

Here b, θ, φ, χ, and r are bond lengths, valence, torsion, and out-of-plane angles, and nonbonded distances. D_{e}, α, and b_0 are empirical parameters for bond stretching (a Morse function), k_θ and θ_0 for valence-angle bending, and k_χ for the out-of-plane deformational potential for the carboxyl groups. Torsional interactions are specified with V_φ and n (height and multiplicity of the torsional barrier, respectively). One torsion per bond was calculated. A and B are one-atom empirical parameters for the van der Waals interactions (a Lennard-Jones 12−6 function). q is a charge parameter. Intramolecular interactions separated by three and more bonds were considered nonbonded and calculated with the Lennard-Jones and electrostatic potentials. We chose the same potential energy functions as in our previously described MM model for tetracoordinated copper(II) amino acidates.[11] The interactions inside the copper(II) coordination sphere were modeled using the Morse potential between the copper and ligand donor atoms (two nitrogens and two oxygens), the repulsive electrostatic potential between the donor atoms, and a torsionlike potential dependent on the "torsion" angle O−N−N−O, with two minima at 0 and 180° that correspond to the cis- and the trans-planar $\mathrm{CuN_2O_2}$ configurations, respectively. It is a model without any explicit valence-angle bending potential for the angles around copper. The interactions between the water atoms and the atoms of a bis(amino acidato)copper(II) complex were calculated with the Lennard-Jones 12−6 and electrostatic potentials regardless of the water molecule position around the copper(II) complex.

All MM calculations were performed using the CFF program for conformational analysis,[46−48] which was slightly modified to cope with the electrostatic interactions among nonbonded atoms of the metal coordination polyhedron. In the CFF program, the input charge parameters are used for an assignment of fractional atomic charges. The assignment is done by a special charge redistribution algorithm, which keeps neutral the total charge of the molecules and distributes the charge values in a manner supposed to mimic ab initio results.[48] We modified the charge distribution routine of the CFF program to get the assigned fractional charges close to the charges resulting from the natural population analysis (the reason for selecting NPA charges as a guideline to the charge parameter values has been given elsewhere[39]). The conformational potential energy was minimized for an isolated molecular system (in vacuo or a gas-phase approximation) and for a molecule surrounded with other molecules in the crystal lattice (a condensed-phase approximation). The intermolecular atom−atom interactions were calculated using the same functional forms (Lennard-Jones 12−6 function and Coulombic potential) and empirical parameters as for the intramolecular nonbonded interactions. The crystal simulations were carried out by using the Williams variant of the Ewald lattice summation method[62,63] with a spherical and abrupt cutoff limit of 14 Å and convergence constants of 0.2 Å^{-1}, 0.2 Å^{-1}, and 0.0 for Coulomb, dispersion, and repulsion lattice summation terms. A detailed description of the crystal simulations is given elsewhere.[11,63] The empirical parameters of the potential energy functions were determined by combining trial and error guesses with the optimization algorithm which is a variant of the general least-squares method (the Levenberg−Marquardt algorithm).[47,48]

Experimental Crystal Data

The experimental molecular and crystal structures of 13 anhydrous and 10 aqua copper(II) amino acidates with the same atom types but various copper(II) coordination polyhedron geometry, crystal symmetries, and intermolecular interactions were selected for modeling (Table 1). Table 1 lists the molecules' abbreviations used hereinafter. The compounds are electrically neutral molecules. Amino acid donor atoms chelated to the copper(II) are the same in all complexes, that is, two oxygens and two nitrogens in the trans position in 19 molecules and in the cis position in four molecules. Twelve X-ray crystal structures of anhydrous copper(II) complexes were used for the development of MM models described earlier.[11,39] In this study we enlarged the set of experimental data with the atomic coordinates of *cis*-Cu(L-Ala)$_2$ that were obtained using single-crystal neutron diffraction techniques at low (7 K) and ambient temperature[17] and with the X-ray crystal structural data of 10 aqua−copper(II) complexes bis-ligated with amino acids and *N*-alkylated amino acids (Table 1).

The copper(II) coordination polyhedra were found to have either an irregular square-planar, a distorted planar, or a flattened tetrahedral geometry in the X-ray crystal structures of anhydrous trans copper(II) amino acidates.[11,39] In this class of compounds, copper(II) chelates with *N*,*N*-dialkylated amino acids are truly tetracoordinated and bonded only by van der Waals force in the crystals. Other trans anhydrous complexes, besides having the van der Waals interactions, are linked together via a net of N−H⋯O═C bonds and by intermolecular copper−carbonyl oxygen interactions, completing an elongated octahedron around copper. In the cis copper(II) complexes with D-alanine[16] and L-alanine,[17] the copper atom coordination environment was described as a distorted square-pyramid with N and O ligand atoms in the equatorial plane cis to each other and with the fifth coordinate position occupied by a weakly bonded carbonyl oxygen from an

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Table 1. Anhydrous and Aqua Copper(II) Amino Acid Complexes Whose Experimental Crystal Data Were Included in the Modeling

compd name	abbreviation	ref
	Anhydrous	
trans-bis(L-*N*,*N*-dimethylvalinato)copper(II)	*trans*-Cu(L-Me_2Val)$_2$	7
trans-bis(D,L-*N*,*N*-diethylalaninato)copper(II)	*trans*-Cu(D,L-Et_2Ala)$_2$	8
trans-bis(L-*N*,*N*-dimethylisoleucinato)copper(II)	*trans*-Cu(L-Me_2Ile)$_2$	9
trans-bis(D,L-*N*,*N*-dimethylvalinato)copper(II)	*trans*-Cu(D,L-Me_2Val)$_2$	10
trans-bis(L-*N*,*N*-dipropylalaninato)copper(II)	*trans*-Cu(L-Pr_2Ala)$_2$	11
trans-bis(L-alaninato)copper(II)	*trans*-Cu(L-Ala)$_2$	12
trans-bis(1-aminocyclopentanecarboxylato)copper(II)	*trans*-Cu(1-Acpc)$_2$	12
trans-bis(L-leucinato)copper(II)	*trans*-Cu(L-Leu)$_2$	13
trans-bis(D,L-2-aminobutyrato)copper(II)	*trans*-Cu(D,L-2-aBut)$_2$	13
trans-bis(L-2-aminobutyrato)copper(II)	*trans*-Cu(L-2-aBut)$_2$	14
trans-bis(α-aminoisobutyrato)copper(II)	*trans*-Cu(α-aiBut)$_2$	15
cis-bis(D-alaninato)copper(II)	*cis*-Cu(D-Ala)$_2$	16
cis-bis(L-alaninato)copper(II)	*cis*-Cu(L-Ala)$_2$	17
	Aqua	
trans-aquabis(L-*N*,*N*-dimethylvalinato)copper(II) hydrate	*trans*-Cu(L-Me_2Val)$_2$$\cdot$$2H_2O$	18
trans-aquabis(L-*N*,*N*-diethylalaninato)copper(II)	*trans*-Cu(L-Et_2Ala)$_2$$\cdot$$H_2O$	19
trans-aquabis(L-*N*,*N*-dimethylalaninato)copper(II) hexahydrate	*trans*-Cu(L-Me_2Ala)$_2$$\cdot$$7H_2O$	20
trans-aquabis(L-*N*,*N*-dimethylisoleucinato)copper(II)	*trans*-Cu(L-Me_2Ile)$_2$$\cdot$$H_2O$	21
trans-aquabis(*N*-*tert*-butyl-*N*-methylglycinato)copper(II)	*trans*-Cu(tBuMeGly)$_2$$\cdot$$H_2O$	22
trans-aquabis(*N*,*N*-dimethylglycinato)copper(II) dihydrate	*trans*-Cu(Me_2Gly)$_2$$\cdot$$3H_2O$	23
trans-diaquabis(sarcosinato)copper(II)	*trans*-Cu(Sar)$_2$$\cdot$$2H_2O$	24
trans-bis(D,L-alaninato)copper(II) monohydrate	*trans*-Cu(D,L-Ala)$_2$$\cdot$$H_2O$	25
cis-bis(glycinato)copper(II) monohydrate	*cis*-Cu(Gly)$_2$$\cdot$$H_2O$	26
cis-bis(L-isoleucinato)copper(II) monohydrate	*cis*-Cu(L-Ile)$_2$$\cdot$$H_2O$	27

adjacent molecule. For *cis*-Cu(L-Ala)$_2$, no phase transition was observed between the crystal structures determined at ambient and low (7 K) temperature.[17] The unit cells were orthorhombic at both temperatures, with cell dimensions 0.5−0.7% smaller at 7 K. The contraction of the cell and the shortening of the distance between copper and carbonyl oxygen (from 2.372 to 2.326 Å) appeared to be the most significant differences between the two structures.

The crystal structure of aquacopper(II) amino acid complexes is greatly dominated by intermolecular hydrogen bonds formed between water hydrogens and carbonyl oxygens from the surrounding molecules. When two or more water molecules are present in the crystal lattice, the copper complexes are additionally linked through a network of hydrogen bridges between water molecules and the amino acid's oxygen and nitrogen atoms. In Cu(Sar)$_2$$\cdot$$2H_2O$[24] and Cu(D,L-Ala)$_2$$\cdot$$H_2O$,[25] four donor atoms were in plane with the copper atom forming an irregular square-planar coordination geometry. Two water molecules placed centrosymmetrically above and below the coordination plane formed an elongated octahedron around the metal atom. In addition, Cu(Gly)$_2$$\cdot$$H_2O$ had octahedral coordination geometry.[26] Two glycine molecules were coordinated to copper(II) in a distorted planar cis configuration, and one water oxygen and one carbonyl oxygen atom from an adjacent asymmetric unit completed the distorted octahedron. The copper(II) coordination polyhedra of other aquacopper(II) amino acid complexes were described either as irregular or distorted square-pyramids with water oxygen (denoted as O_w throughout the paper) at the pyramid apex.

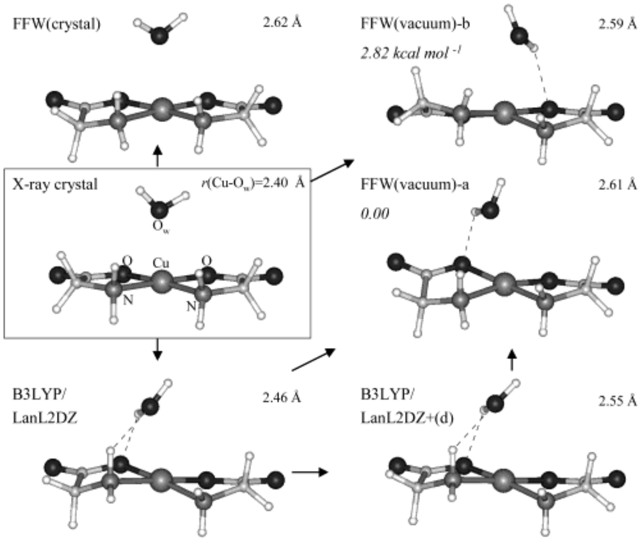

Figure 1. *cis*-Cu(Gly)$_2$$\cdot$$H_2O$: Experimental X-ray crystal structure, vacuum structures obtained using the B3LYP method, and minimum crystal and vacuum structures estimated with the new MM force field FFW. The arrows point toward minimum structures from structures whose atomic coordinates were used as starting coordinates for geometry optimization. The values given in italics are relative energies. The values expressed in Å are Cu to O_w distances. The hydrogen bonds of less than or equal to 2.5 Å are marked with broken lines.

Results and Discussion

Quantum Chemical Data. To extend our knowledge about the properties which copper(II) amino acid complexes might have in the gas phase and to achieve new data for the force field parametrization, we applied the B3LYP and NPA methods to study four aqua−copper(II) bis(glycinato) complexes: *cis*-Cu(Gly)$_2$$\cdot$$H_2O$; *trans*-Cu(Sar)$_2$$\cdot$$2H_2O$; *trans*-Cu($Me_2$Gly)$_2$$\cdot$$3H_2O$; *trans*-Cu(tBuMeGly)$_2$$\cdot$$H_2O$. The geometry optimizations were first performed at the B3LYP/LanL2DZ level of theory and continued over the B3LYP/LanL2DZ(d) to the B3LYP/LanL2DZ+(d) level. Figures 1−4 show the minimum structures of the four copper(II) chelates estimated using the B3LYP/LanL2DZ and/or B3LYP/LanL2DZ+(d) basis sets, together with their experimental X-ray crystal and MM equilibrium structures. All geometry optimizations were started from experimental crystalline atomic coordinates, except in one case (for Cu(tBuMeGly)$_2$$\cdot$$H_2O$) where an additional optimization was performed with the initial structure taken from MM calculations (Figure 4). According to the input atomic coordinates, the Gaussian98 program assigns a point group to the system and retains the point group symmetry restrictions during geometry optimiza-

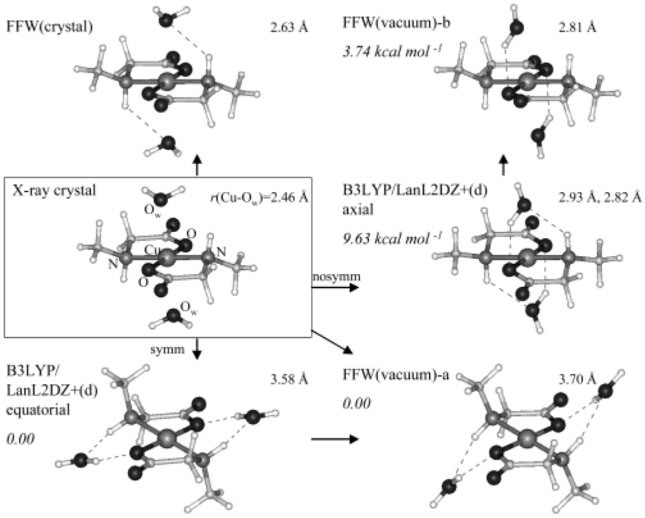

Figure 2. *trans*-Cu(Sar)$_2$·2H$_2$O: Experimental X-ray crystal structure, theoretical FFW(crystal) structure, and minimum FFW and B3LYP/LanL2DZ+(d) vacuum structures with axial and equatorial positions of water molecules to the copper(II) coordination plane. A detailed description is given in Figure 1. "Symm" means that C_i symmetry was retained, and "nosymm" that no symmetry constraint was accounted for during the geometry optimization.

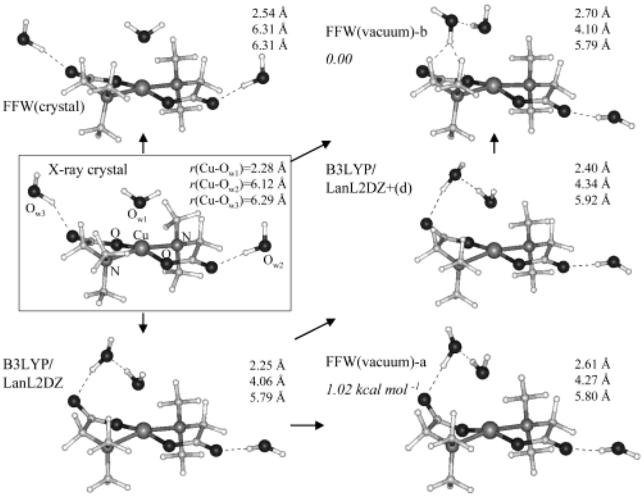

Figure 3. *trans*-Cu(Me$_2$Gly)$_2$·3H$_2$O: X-ray crystal structure, B3LYP vacuum structures, and equilibrium FFW crystal and FFW vacuum structures. A detailed description is given in Figure 1.

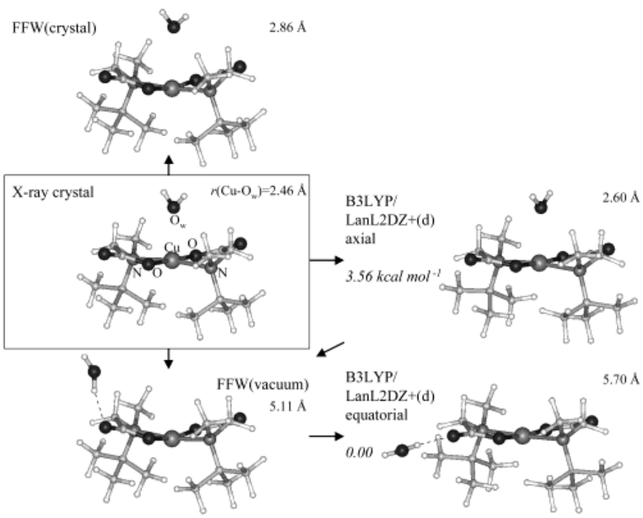

Figure 4. *trans*-Cu(tBuMeGly)$_2$·H$_2$O: Experimental X-ray crystal structure, in crystal and in vacuo FFW structures, and B3LYP/LanL2DZ+(d) minima with axial and equatorial positions of the water molecule to the copper(II) coordination plane. A detailed description is given in Figure 1.

tion. Such assignment occurred automatically to Cu(Sar)$_2$·2H$_2$O and Cu(tBuMeGly)$_2$·H$_2$O which possessed the C_i and C_2 symmetry in the crystal lattice, respectively. For them, we performed additional geometry optimizations without the symmetry restrictions, i.e., as if the systems had the C_1 symmetry, and a new minimum was obtained for Cu(Sar)$_2$·2H$_2$O denoted as B3LYP/LanL2DZ+(d) axial structure in Figure 2. Our B3LYP results confirmed the findings of de Bruin et al.[51] that the formation of hydrogen bonds between water molecules and amino acid atoms competes with the axial Cu---OH$_2$ interactions. The water molecule(s) preferred the equatorial over the axial position regardless of how many hydrogen bonds were formed between water atoms and amino acid atoms of trans copper(II) chelates with sarcosine (Figure 2) and *N*-*tert*-butyl-*N*-methylglycine (Figure 4). Water molecules stayed in the axial position in the experimental X-ray crystal structures of Cu(Sar)$_2$·2H$_2$O, but this was due to the crystal effects.

The greatest geometry differences between the B3LYP/LanL2DZ and B3LYP/LanL2DZ+(d) structures occurred in water entities, as the H−O$_w$−H angles changed from 112−114° (LanL2DZ) to 106−108° (LanL2DZ+(d)) and as the distances between Cu(II) and the axial O$_w$ lengthened by 0.194 Å on average. Shorter bond lengths in the carboxyl group yielded by LanL2DZ+(d) relative to LanL2DZ[39] and the change in the H−O$_w$−H angles obviously caused substantial differences in the chelate ring geometry between LanL2DZ and LanL2DZ+(d) structures of Cu(Me$_2$Gly)$_2$·3H$_2$O (Figure 3, Table S1).

In the four studied aquacopper(II) glycinato systems, the valence electron configuration on the atoms of the copper(II) coordination polyhedron evaluated using the NPA method with the LanL2DZ+(d) basis set is very similar to the one obtained for the three anhydrous copper(II) chelates with L-alanine, L-leucine, and L-*N*,*N*-dimethylvaline.[39] This result led us to the same conclusion as for the anhydrous copper(II) complexes:[39] a planar copper(II) coordination geometry is electronically favored for the whole class of copper(II) amino acid complexes with the CuN$_2$O$_2$ coordination polyhedron, independently of whether water molecules are present in the studied systems. The comparison between the axial and equatorial minima of Cu(tBuMeGly)$_2$ (Figure 4) further confirms this conclusion: without the water molecule in the metal first coordination sphere in the equatorial minimum, the atoms of the coordination polyhedron relaxed to the positions closer to the ideal planar configuration (as the N−Cu−N angle changed from 172.4 to 177.9° and the O−N−N−O angle from −168.1 to −177.5°) without substantial changes in the electronic structure of the complex. The NPA charges obtained for the axial and equatorial minimum differ less than 4% (the NPA charges are given in Table S2).

Force Field Parametrization. The force field FF1, developed for anhydrous tetracoordinated copper(II) amino acidates with *trans*- and *cis*-CuN_2O_2 coordination polyhedron,[11] was taken as the initial empirical parameter set for parameter optimization. To account for the inclusion of water molecules into the studied systems, the initial empirical parameter set was extended by the parameters D_e, α, and b_0 for the O_w-H bond length, k_θ and θ_0 for the $H-O_w-H$ valence angle, and A, B, and q for the nonbonded interactions of water oxygen and water hydrogen. As FF1 proved good in reproducing the bond lengths and valence angles,[11] we decided to keep unchanged the empirical parameters of the bond-stretching, valence-angle bending, out-of-plane bending, and electrostatic potential energy part of the conformational potential, V_{total}, and vary only the parameters of the torsion and Lennard-Jones potentials. The parameters were reoptimized and fitted with the aim to obtain a potential energy parameter set that could yield the best possible reproduction of experimental crystal structures and in vacuo B3LYP structures, regardless of whether water molecules were present in the studied systems. The difference in the crystal packing forces between the anhydrous copper(II) complexes with *N*-alkylated amino acids (van der Waals forces only) and other copper(II) amino acidates (the N−H···O═C hydrogen bonding plus van der Waals forces for anhydrous complexes and also hydrogen bonding with the water atoms in aqua complexes) were simulated by separating Lennard-Jones parameters for the hydrogens bonded to nitrogen, carbon, and water oxygen atoms.

The empirical parameters of the torsion and Lennard-Jones potentials were optimized with respect to the experimental data (bond lengths, valence and torsion angles, and unit cell dimensions) of the following six anhydrous and six aqua copper(II) complexes: Cu(L-Me_2Val)$_2$,[7] Cu(D,L-Et_2Ala)$_2$,[8] Cu(L-Leu)$_2$,[13] Cu(D,L-2-aBut)$_2$,[13] Cu(L-2-aBut)$_2$,[14] Cu(D-Ala)$_2$;[16] Cu(L-Me_2Val)$_2$·$2H_2O$,[18] Cu(L-Et_2Ala)$_2$·H_2O,[19] Cu(D,L-Ala)$_2$·H_2O,[25] Cu(Sar)$_2$·$2H_2O$,[24] Cu(Me_2Gly)$_2$·$3H_2O$,[23] Cu(tBuMeGly)$_2$·H_2O.[22] To ensure the planarity of the copper(II) coordination geometry for anhydrous molecules in vacuo, the parameters were also optimized with respect to the B3LYP valence angles around copper in three trans copper(II) chelates:[39] Cu(L-Me_2Val)$_2$; Cu(L-Ala)$_2$; Cu(L-Leu)$_2$. The empirical parameters were systematically tested on other seven anhydrous and four aqua crystalline structures. During the parameters' fitting process, we only had the minimum structures estimated using the LanL2DZ basis set of the aquacopper(II) bis(amino acid) complexes with glycine, sarcosine, and *N*,*N*-dimethylglycine at our disposal to check the parameters' validity in aqua copper(II) amino acidates in vacuo.

We chose several conditions to restrict the empirical parameter hyperspace in the search for the potential energy parameter set which could yield the best possible reproduction of experimental crystal data and of the geometries optimized using the B3LYP method. The conditions necessary for the force field to be considered reliable were that it had to do the following: (1) yield both trans and cis amino acid chelation to the copper(II); (2) allow for the movement of two water molecules from the axial position in Cu(Sar)$_2$·$2H_2O$ (see X-ray crystal structure in Figure 2) to the equatorial position (as obtained by the B3LYP/LanL2DZ geometry optimization) during in vacuo energy minimization, which accompanied a conformational change in Cu(Sar)$_2$ (i.e., the methyl groups on the nitrogen atoms underwent the transition from crystalline equatorial to in vacuo axial positions with respect to the chelate ring planes, Figure 2); (3) simulate the pronounced puckering of the chelate ring in Cu(Me_2Gly)$_2$·$3H_2O$ as yielded by the B3LYP/LanL2DZ geometry optimization (Figure 3); (4) keep the positions of the water molecules as close to their experimental and B3LYP positions as possible; (5) preserve the 2-fold crystallographic symmetry in the simulated crystal lattices of aquacopper(II) bis(amino acid) complexes with L-*N*,*N*-dimethylalanine, L-*N*,*N*-diethylalanine, and *N*-*tert*-butyl-*N*-methylglycine, with Cu(II) and O_w on a 2-fold axis; (6) retain the irregular square-planar copper(II) coordination geometry in the aqua systems of Cu(Sar)$_2$ and Cu(D,L-Ala)$_2$.

The aqua systems appeared to be more difficult to model than the anhydrous systems. The chelate ring geometry in the studied aquacopper(II) amino acidates were more puckered (nonplanar) than in the anhydrous copper(II) chelates. This greater deviation from the planarity may be explained by additional requirements for hydrogen bonding in the experimental crystal structures of aqua complexes. As the torsion multiplicity values of −4.0 and −2.0 for the torsions around the Cu−O and O−C bonds, respectively, in the FF1 force field could not simulate such deformations of the chelate rings, we tried different combinations of the multiplicities. The value of $n = -6.0$ for both torsions met all our requirements imposed for a reliable force field.

The final force field, named FFW, met all six requirements and still yielded the geometry reproduction of the anhydrous copper(II) amino acid complexes comparable to that of the force field FF1 (see sections below). The new empirical parameters that differ from the FF1's potential energy parameter set[11] are listed in Table 2. The assignments of the charges due to the charge parameters given in Table 2 and elsewhere[11] for the copper(II) complexes studied in this paper for the first time are presented in Table S2. The fractional atomic charges for earlier studied copper(II) amino acid complexes are given elsewhere.[11] The fractional charges assigned to the water atoms by CFF were the same in all studied systems (i.e., −1.034 e for O_w and 0.517 e for water hydrogens).

Reproduction of Experimental Crystal Data. Having obtained the new force field, FFW, we examined the ability of the MM model to reproduce molecular and crystal structures of the 23 copper(II) amino acid complexes. The experimental atomic coordinates and the unit cell lengths and angles were taken as the starting points for geometry optimization using the crystal simulator of the CFF program. Table 3 shows errors in reproducing the experimental internal coordinates and unit cell dimensions for each compound and the total root-mean-square (rms) deviations from the experimental values calculated for the anhydrous and for the aqua complexes separately and for all 23 compounds.

In comparison with the FF1 results,[11] the simulations of experimental anhydrous crystal structures using FFW are

Table 2. Potential Energy Parameter Set[a,b]

bond	D_e	α	b_0
O_w−H	53.000	3.000	0.985

angle	k_θ	θ_0
H−O_w−H	455.000	1.911

torsion	V_φ	n
−C−C−	10.905	3.000
−C−N−	6.550	3.000
−O−Cu−	2.250	−6.000
−C−K−	0.789	12.000
−O−K−	2.210	−6.000
−Cu−N−	0.090	12.000
−N−N−	16.100	−2.000

nonbonding	A	B
H(C)	80.000	3.581
H(N)	200.000	9.049
H(O_w)	5.600	0.001
C	908.358	13.828
N	1371.991	50.347
O	1175.182	65.494
Q	285.759	14.396
O_w	210.000	0.010
Cu	1135.031	45.038
K	304.173	14.666

atom	charge param q
O_w	1.234
H(O_w)	0.001

[a] Uncommon symbols: K, planar carbon atom; Q, double-bonded oxygen atom; O_w, water oxygen. [b] Units are as follows: D_e, kcal mol^{-1}; α, Å^{-1}; b_0, Å; k_θ, kcal mol^{-1} rad^{-2}; θ_0, rad; V_φ, kcal mol^{-1}; A, (kcal mol^{-1} Å^{12})$^{1/2}$; B, (kcal mol^{-1} Å^{6})$^{1/2}$; q, in electron units (the expression for electrostatic interactions has to be multiplied by 332.091 kcal mol^{-1} Å to be in kcal mol^{-1}).

slightly worse in torsion angles and slightly better in valence angles and unit cell dimensions (Table 3). For the newly introduced *cis*-Cu(L-Ala)$_2$, the fits between the experimental and FFW molecular and crystal data obtained at 7 K and ambient temperature (Table 3) are 1 order of magnitude greater than the rms deviations between the experimental structures themselves (rms(Δb) = 0.008 Å, rms($\Delta\theta$) = 0.3°, rms($\Delta\varphi$) = 0.3°, and rms(Δa,Δb,Δc) = 0.063 Å). The total rms errors for the aqua copper(II) chelates are the same in the bond lengths, larger by less than 1° in the valence angles and larger by 2° in the torsion angles than for the anhydrous compounds (Table 3).

The maximum differences calculated between the experimental and FFW internal coordinates for the anhydrous copper(II) chelates are −0.073 Å for the N−C_{alkyl} bond in Cu(D,L-Et$_2$Ala)$_2$, −8.3° for the Cu−N−C_{alkyl} valence angle in Cu(L-Me$_2$Val)$_2$, and −11.7° for the O−N−N−O torsion angle in Cu(L-Me$_2$Ile)$_2$. The corresponding maximum differences calculated between the X-ray and FFW values for the 10 aqua complexes are −0.080 Å for the N−C bond in Cu(Me$_2$Gly)$_2$·3H_2O, −10.3° for the O−Cu−O valence angle in Cu(tBuMeGly)$_2$·H_2O, and −10.4° for the O−C−C$^\alpha$−N torsion angle in Cu(Me$_2$Gly)$_2$·3H_2O when examining the trans copper(II) amino acidates and −24.7° for O−C−C$^\alpha$−N in Cu(Gly)$_2$·H_2O for the cis molecules. Cu(Gly)$_2$·H_2O had almost planar chelate rings in the X-ray crystal structure[26] (Figure 1). However, FFW yielded greater distortion of the chelate rings (FFW(crystal) in Figure 1), with the maximum absolute value of the torsion angle of 17.9° vs. experimental 8.3°. As for the second aqua cis molecule Cu(L-Ile)$_2$·H_2O, the experimental and theoretical molecular structures matched well except for the O−C═O group and an alkyl chain in one chelate ring. The reason could be a different hydrogen-bonding pattern obtained by FFW in the simulated crystal lattice: a hydrogen bonded to the nitrogen atom formed a hydrogen bond with a water's oxygen, whereas it formed the hydrogen bond with an adjacent molecule's carbonyl oxygen in the experimental lattice. The total rms($\Delta\varphi$) calculated only for 8 trans aqua complexes is 5.1°. The total rms deviations in the a, b, and c unit cell parameters are smaller within 0.2 Å for the anhydrous structures than for the aqua complexes (Table 3). Nevertheless, the largest relative deviations between experimental and theoretical unit cell lengths among the anhydrous and aqua copper(II) compounds were 7.3% in Cu(L-Me$_2$Ile)$_2$ and −9.8% in Cu(Sar)$_2$·2H_2O, respectively.

Table 4 presents the mean values and standard deviations for copper(II) coordination polyhedron bonds and angles calculated for all studied copper(II) amino acidates. The FFW means are within the standard deviations of the experimental means for almost all structural parameters presented in Table 4, except for the Cu−O_w distances and the angles of the cis molecules. The shapes of the coordination polyhedra are generally well reproduced. The exceptions are Cu(L-Me$_2$Ile)$_2$ and Cu(tBuMeGly)$_2$·H_2O. For Cu(L-Me$_2$Ile)$_2$, FFW yielded two angles of the coordination polyhedron, O−Cu−O′ and O′−N′−N−O, to deviate by 7.8 and −11.0° from their experimental values, respectively. This led to the transformation of the X-ray flattened tetrahedron into a flattened pyramid. In Cu(tBuMeGly)$_2$·H_2O, FFW moved the copper atom below the basal plane defined by the four donor atoms, while in the experimental crystal lattice the copper stood above the plane (Figure 4, X-ray crystal and FFW(crystal)). This effect is an exception, as the simulation of the distorted square-pyramidal coordination polyhedron in other aquacopper(II) amino acid complexes was good. The hydrogen-bonding pattern in the crystal lattice of Cu(tBuMeGly)$_2$·H_2O was well reproduced (the apical water formed hydrogen bridges with the C═O groups of neighboring molecules). FFW maintained the planarity of the copper(II) coordination polyhedra in crystal and in vacuo for all molecules whose amino acid donor atoms form irregular square-planar configuration to the copper(II) in the experimental crystal lattice.

To sum up, FFW is capable of simulating the flexibility (plasticity) of the copper(II) coordination sphere and of simulating the chelate ring geometries in the crystal lattice for both anhydrous and aqua copper(II) amino acid complexes.

Reproduction of Quantum Chemical Data and the Prediction of in Vacuo Geometries by FFW. As mentioned in the Force Field Parametrization section, the results obtained by the B3LYP/LanL2DZ basis set for Cu(Gly)$_2$·H_2O, Cu(Sar)$_2$·2H_2O, and Cu(Me$_2$Gly)$_2$·3H_2O were used to

Table 3. Comparison of Experimental Crystal and FFW(crystal) Structures[a] by Means of the Root-Mean-Square Deviations, Rms, in Internal Coordinates[b] and Unit Cell Constants (a, b and c, Expressed in Å) and Differences, Δ, between Experimental and Theoretical Unit Cell Angles (α, β and γ, Expressed in deg) and Volumes (V)

compd	rms(Δ*b*)	rms(Δθ)	rms(Δφ)	rms(Δa,Δb,Δc)	Δα, Δβ, Δγ	100ΔV/V_{exp}
Cu(L-Me_2Val)$_2$	0.014	2.5	4.0	0.637	0.0, 0.0, 0.0	−2.3
trans-Cu(L-Ala)$_2$	0.016	2.3	5.2	0.175	0.0, 3.2, 0.0	−2.5
Cu(L-Leu)$_2$	0.013	2.1	4.4	0.234	0.0, −1.8, 0.0	−0.6
Cu(D,L-2-aBut)$_2$	0.013	1.5	3.1	0.326	0.0, −4.0. 0.0	−8.1
Cu(1-Acpc)$_2$	0.012	1.7	4.6	0.084	0.0, 1.7, 0.0	−1.0
Cu(D,L-Et_2Ala)$_2$	0.031	2.2	1.8	0.216	4.1, 0.5, −2.9	3.2
Cu(D,L-Me_2Val)$_2$	0.010	1.6	2.7	0.054	0.0, −0.1, 0.0	1.1
Cu(L-2-aBut)$_2$	0.015	2.2	6.2	0.238	0.0, 2.6, 0.0	−3.7
Cu(α-aiBut)$_2$	0.015	1.9	3.6	0.147	0.0, −0.3, 0.0	0.0
Cu(L-Me_2Ile)$_2$	0.020	2.8	5.3	0.559	0.0, 0.9, 0.0	0.1
Cu(L-Pr_2Ala)$_2$	0.020	2.1	5.1	0.199	0.0, 0.2, 0.0	−5.7
Cu(D-Ala)$_2$	0.025	2.1	5.9	0.174	0.0, 0.0, 0.0	−5.3
cis-Cu(L-Ala)$_2$	0.010	2.1	6.6	0.164	0.0, 0.0, 0.0	−5.0
cis-Cu(L-Ala)$_2$ at 7 K[c]	0.011	2.1	6.7	0.216	0.0, 0.0, 0.0	−7.0
total	0.018	2.1	4.7	0.296		
Cu(L-Me_2Val)$_2$•$2H_2O$	0.011	1.8	4.0	0.528	4.8, −1.4, −1.1	−0.1
Cu(Me_2Gly)$_2$•$3H_2O$	0.035	2.8	6.2	0.625	0.0, 0.0, 0.0	5.9
Cu(Sar)$_2$•$2H_2O$	0.017	1.4	5.5	0.822	0.0, −0.8, 0.0	1.1
Cu(L-Et_2Ala)$_2$•H_2O	0.020	2.3	6.4	0.270	0.0, 0.0, 0.0	−0.3
Cu(tBuMeGly)$_2$•H_2O	0.021	2.7	3.7	0.360	0.0, 0.0, 0.0	−4.1
Cu(L-Me_2Ile)$_2$•H_2O	0.017	2.3	4.6	0.071	0.0, 0.0, 0.0	0.8
Cu(D,L-Ala)$_2$•H_2O	0.020	2.3	6.3	0.585	0.0, 8.7, 0.0	2.7
Cu(L-Me_2Ala)$_2$•$7H_2O$	0.008	2.1	2.5	0.474	0.0, 1.4, 0.0	9.6
Cu(Gly)$_2$•H_2O	0.018	2.1	12.8	0.438	0.0, 0.0, 0.0	4.5
Cu(L-Ile)$_2$•H_2O	0.014	3.1	7.9	0.364	0.0, 0.0, 0.0	−4.3
total	0.019	2.4	6.5	0.494		
grand tot.	0.018	2.2	5.5	0.395		

[a] The compounds are abbreviated as in Table 1 (without trans and cis characterizations, except for Cu(L-Ala)$_2$ structures). [b] Internal coordinates: bond lengths, *b* (in Å); valence angles, θ (in degrees); torsion angles, φ (in deg). Hydrogen atoms are not taken into account. [c] The structure obtained at 7 K was not taken into account when calculating total errors.

Table 4. Means and Standard Deviations of the Cu−N and Cu−O Bond Lengths and Nonbonded Axial Cu−O Distances, *r* (in Å), and of the Angles around Copper (Six Valence Angles and the Torsional O′−N′−N−O Angle in deg) for 13 Anhydrous (11 Trans and 2 Cis) and 10 Aqua (8 Trans and 2 Cis) Copper(II) Amino Acidato Complexes

	anhydrous		aqua	
coord	expt cryst	FFW(cryst)	expt cryst	FFW(cryst)
Cu−N	1.999(21)	2.003(17)	2.028(34)	2.016(15)
Cu−O	1.931(24)	1.927(4)	1.944(19)	1.930(5)
$r(Cu-O_{carbonyl})$	2.79(23)	2.72(11)	2.743	2.596
$r(Cu-O_W)$			2.40(13)	2.64(10)
trans				
N−Cu−N′	174.7(6.2)	174.4(5.9)	170.5(6.5)	173.2(5.1)
N−Cu−O	84.1(0.3)	84.2(0.2)	84.0(0.7)	83.8(0.6)
N−Cu−O′	96.0(0.5)	95.9(0.3)	95.3(1.4)	95.1(1.0)
N′−Cu−O	94.9(2.0)	95.4(1.7)	95.4(1.0)	95.3(1.0)
N′−Cu−O′	84.6(0.8)	84.7(0.9)	84.2(0.9)	83.7(1.5)
O−Cu−O′	178.7(1.8)	177.4(2.9)	171.4(7.6)	170.3(6.5)
O′−N′−N−O	176.6(9.8)	178.6(6.4)	−179.9(7.5)	180.0(6.5)
cis				
N−Cu−N′	98.7(0.1)	95.4(0.0)	95.7(1.0)	92.3(2.2)
N−Cu−O	83.7(0.1)	84.8(0.0)	84.6(0.4)	85.8(0.8)
N−Cu−O′	172.3(0.1)	176.1(0.0)	169.2(6.0)	164.5(11.5)
N′−Cu−O	171.5(0.0)	176.3(0.0)	176.6(1.5)	172.2(4.0)
N′−Cu−O′	84.6(0.0)	87.0(0.0)	85.0(0.5)	86.5(0.5)
O−Cu−O′	91.9(0.3)	92.6(0.0)	92.3(0.6)	92.8(4.6)
O′−N′−N−O	0.1(1.0)	−0.1(0.6)	5.7(3.4)	5.1(5.3)

fit and test the empirical potential energy parameter set. Energy minimizations in vacuo using FFW, which started from the B3LYP/LanL2DZ minimum structures, led to minimum geometries referred to as FFW(vacuum)-a in Figures 1−3. However, when energy minimization was started from X-ray atomic coordinates, it yielded the same FFW(vacuum)-a minimum for Cu(Sar)$_2$•$2H_2O$ (Figure 2) and new minima for Cu(Gly)$_2$•H_2O and Cu(Me_2Gly)$_2$•$3H_2O$ (in Figures 1 and 3 they are marked as FFW(vacuum)-b). These minima had higher conformational potential energy for the former and lower energy in the second system. A new ab initio geometry optimization using the larger LanL2DZ+(d) basis set yielded the equilibrium geometry of Cu(Met_2Gly)$_2$•$3H_2O$ (the B3LYP/LanL2DZ+(d) minimum in Figure 3) closer to the more stable FFW(vacuum)-b than to FFW(vacuum)-a (Table 5). In general, all FFW(vacuum) structures with the lowest potential energy were systematically closer to the minimum structures obtained using the LanL2DZ+-

Table 5. Root-Mean-Square Deviations, Rms, and Maximim Differences, Δ, Calculated between the Bond Lengths, b (in Å), Valence Angles, θ (in deg), and Torsion Angles, φ (in deg), of Two Indicated Structures in Comparison[a]

compared structs	rms(Δb)	Δb_{max}	rms($\Delta\theta$)	$\Delta\theta_{max}$	rms($\Delta\varphi$)	$\Delta\varphi_{max}$
$Cu(Gly)_2\cdot H_2O$						
FFW(vacuum)-a vs LanL2DZ+(d)	0.029	−0.080 (Cu−N)	3.2	−9.9 (N−Cu−N)	6.5	−14.2 (O−N−N−O)
LanL2DZ+(d) vs X-ray cryst	0.038	0.096 (Cu−N)	2.3	3.4 (O−K−Q)	19.7	−36.3 (K−C−N−Cu)
FFW(vacuum)-a vs FFW(cryst)	0.004	0.007 (C−H)	2.1	−7.6 (N−Cu−N)	9.8	−16.2 (O−Cu−N−C)
$Cu(Me_2Gly)_2\cdot 3H_2O$						
FFW(vacuum)-a vs LanL2DZ+(d)	0.021	−0.057 (Cu−N)	2.3	−10.0 (O−Cu−O)	9.3	−22.8 (Cu−O−K−C)
FFW(vacuum)-b vs LanL2DZ+(d)	0.020	−0.068 (Cu−N)	1.8	−7.7 (O−Cu−O)	8.0	18.5 (Cu−O−K−C)
LanL2DZ+(d) vs X-ray cryst	0.032	−0.085 (N−C)[b]	2.5	8.5 (O−Cu−O)	7.6	13.9 (K−C−N−Cu)
FFW(vacuum)-b vs FFW(cryst)	0.002	−0.005 (Cu−O)	1.0	−5.0 (N−Cu−N)	2.6	6.1 (Cu−O−K−C)
$Cu(Sar)_2\cdot 2H_2O$						
FFW(vacuum)-a vs LanL2DZ+(d) equat	0.019	−0.046 (Cu−N)	2.1	−7.0 (Cu−N−H)	6.0	9.8 (O−Cu−N−C)
FFW(vacuum)-b vs LanL2DZ+(d) axial	0.019	−0.038 (Cu−N)	1.8	−4.2 (Cu−N−C)	11.1	−16.3 (O−Cu−N−C)
LanL2DZ+(d) equat vs X-ray cryst	0.032	0.053 (K−O)	2.7	−7.5 (Cu−N−C)	36.5	±52.4 (K−C−N−Cu)
FFW(vacuum)-a vs FFW(cryst)	0.006	−0.016 (Cu−O)	0.9	3.8 (Cu−N−H)	28.7	±45.8 (K−C−N−Cu)
LanL2DZ+(d) axial vs X-ray cryst	0.029	0.052 (K−O)	1.5	2.7 (C−N−C)	8.1	13.5 (O−Cu−N−C)
FFW(vacuum)-b vs FFW(cryst)	0.004	−0.008 (Cu−O)	0.2	−0.5 (N−Cu−O)	2.8	±5.4 (H−C−N−Cu)
$Cu(tBuMeGly)_2\cdot H_2O$						
FFW(vacuum) vs LanL2DZ+(d) axial	0.032	−0.142 (Cu−N)	2.2	−9.2 (O−Cu−O)	7.9	16.6 (H−C−C−N)
FFW(vacuum) vs LanL2DZ+(d) equat	0.029	−0.125 (Cu−N)	2.1	−7.7 (O−Cu−O)	7.2	17.4 (C−C−N−Cu)
LanL2DZ+(d) axial vs X-ray cryst	0.029	0.085 (Cu−N)	1.4	−2.7 (O−Cu−O)	7.2	−13.3 (C−C−N−Cu)
LanL2DZ+(d) equat vs X-ray cryst	0.024	0.069 (Cu−N)	1.8	6.3 (N−Cu−N)	9.9	17.1 (C−C−N−Cu)
FFW(vacuum) vs FFW(cryst)	0.002	0.006 (N−C)	0.7	−5.5 (N−Cu−N)	2.8	5.3 (K−O−Cu−N)

[a] The structures are denoted as in Figures 1−4. Uncommon symbols: K, planar carbon atom; Q, double-bonded oxygen. Water molecules are not taken into comparisons. When X-ray crystal structures are compared, hydrogen atoms are not accounted. [b] The difference is caused by rather long experimentally determined bond length of 1.56 ± 0.04 Å (the B3LYP/LanL2DZ+(d) value is 1.479 Å).

(d) basis set than to the minima obtained using the smaller LanL2DZ basis set.

The predictive ability of FFW was probed on $Cu(tBuMeGly)_2\cdot H_2O$ (Figure 4), as the B3LYP calculations were performed on this system after the optimization of empirical parameters had been finished. The force field failed to reproduce the minimum with apical water in the copper(II) coordination sphere (Figure 4, LanL2DZ+(d) axial); it rather allowed the water molecule to move toward the carbonyl oxygen and form a hydrogen bond (Figure 4, FFW(vacuum)). Additional B3LYP geometry optimization using the FFW(vacuum) atomic coordinates yielded a new minimum (Figure 4, LanL2DZ+(d) equatorial) and confirmed that the system with water molecule forming a hydrogen bond would be energetically preferred to the one with H_2O in the first copper(II) coordination sphere. As the energy difference is small (3.56 kcal mol^{-1}, Figure 4), and FFW underestimated the LanL2DZ+(d) energy difference between the axial and the equatorial minimum for $Cu(Sar)_2\cdot 2H_2O$ (Figure 2), it is likely that the force field produced even smaller energy difference for $Cu(tBuMeGly)_2\cdot H_2O$, which may be the reason FFW did not keep the water molecule in the apical position in vacuo.

FFW's reproduction of the B3LYP geometries of the three anhydrous trans complexes was comparable to that of FF1;[11] it yielded almost the same copper(II) coordination polyhedron angles and slightly less accurate chelate ring torsion angles. The rms($\Delta\varphi$) deviations between B3LYP and FFW(vacuum) torsion angles are 4.8, 1.7, and 3.1° for Cu(L-Me$_2$Val)$_2$, Cu(L-Leu)$_2$, and Cu(L-Ala)$_2$, respectively. Table 5 shows rms deviations and maximal differences calculated between the internal coordinates of the FFW(vacuum) and B3LYP/LanL2DZ+(d) structures, the B3LYP/LanL2DZ+(d) and X-ray crystal structures, and the FFW(crystal) and FFW(vacuum) structures. The extent of deviations and maximum differences can give an insight into the ability of the force field to reproduce the ab initio in vacuo data and the differences between the X-ray crystal and B3LYP/LanL2DZ+(d) geometries. The differences in the FFW torsion angles were smaller between the vacuum and crystal values than between the ab initio and experimental crystal values (Table 5). However, $Cu(Gly)_2\cdot H_2O$ showed more pronounced puckering of the chelate rings in FFW(vacuum)-a than in FFW(crystal), which was analogous to the differences between the B3LYP vacuum vs X-ray crystal structure ($\Delta\varphi_{max}$ in Table 5, Figure 1). Moreover, FFW accurately reproduced the conformational change in $Cu(Sar)_2$ (Figure 2; $\Delta\varphi_{max}$ in Table 5). In other words, FFW can follow, although not to the full extent, the changes in the internal coordinates from crystalline to isolated molecular systems.

The means and standard deviations of the Cu−N and Cu−O bond lengths calculated for the four B3LYP/LanL2DZ+(d) aquacopper(II) glycinato structures with the lowest energy were 2.089 ± 0.020 Å (Cu−N) and 1.939 ± 0.016 Å (Cu−O). The respective FFW(vacuum) values were 2.014 ± 0.012 and 1.924 ± 0.003 Å. Like with the anhydrous copper(II) amino acid complexes,[39] the force field cannot reproduce the ab initio lengthening of the Cu−N bonds, while the Cu−O bond lengths are reproduced within the standard errors. This may be a good result, as the B3LYP method is known to overestimate metal−ligand distances.[64] In all $Cu(Sar)_2\cdot 2H_2O$ structures, the copper(II) and amino acid donor atoms formed an irregular square-planar coordination geometry. The square-pyramidal coordination polyhedra of three other copper(II) glycinato complexes were more

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(64) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*, 2nd ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2001.

Table 6. Selected Structural Coordinates of the Bis(glycinato)copper(II) Systems with 1−6 Water Molecules As Obtained from X-ray Diffraction and X-ray Absorption Studies and Estimated by the B3LYP Method and the FFW Force Field in Vacuo[a]

coord	X-ray diffraction[b] (cryst): H_2O cis	X-ray abs[c] (aq soln): 2 H_2O	B3LYP:[d] 2 H_2O		B3LYP:[e] H_2O cis	FFW:[e] H_2O cis	FFW: 2 H_2O		FFW: 6 H_2O	
			cis	trans			trans	cis	trans	cis
Cu−N	1.98, 2.02	1.99	2.07	2.05	2.08, 2.07	2.00	1.99	2.00	1.99	2.00
Cu−O	1.95, 1.96	1.95	1.97	1.95	1.93, 1.96	1.92, 1.93	1.92	1.93	1.93	1.93, 1.92
$r(Cu-O_{w,ax})$	2.40	2.40 ± 0.06	2.69, 2.70		2.55	2.61	2.79 (ax)	2.58	2.70	2.54, 2.65
$r(Cu-O_{w,s})$		3.3 ± 0.2		3.56			3.97 (eq)		3.88 4.29	3.54, 3.67 3.89, 5.30
X−Cu−Y	175.1, 178.0	179			175.1, 177.2	173.2, 168.6	180.0	174.0	180.0	171.7, 175.3
$r(Cu-C)$	2.83, 2.88	2.84			2.88, 2.89	2.83	2.83	2.83	2.84	2.81, 2.82
$r(Cu-K)$	2.75, 2.77	2.79			2.79, 2.82	2.72, 2.73	2.72	2.73	2.72	2.73,2.72
$r(K-Q)$	1.23, 1.24	1.24			1.23	1.22	1.22	1.22	1.22	1.22
Cu−K−Q	162.0, 164.3	168			164.0, 163.7	163.4, 162.6	161.0 (ax) 162.4 (eq)	163.3	156.9	158.0, 163.4
V_{total}							1.20 (ax) 0.00 (eq)	15.45	0.00	9.62

[a] Bond lengths and atom−atom distances, angles, and coformational strain energy V_{total} are given in Å, deg, and kcal mol^{-1}, respectively. Uncommon atomic symbols are explained in Figure 5. X−Cu−Y stands for trans valence angles, that is, N−Cu−O for cis isomers, and N−Cu−N and O−Cu−O angles for trans isomers. $O_{w,ax}$ and $O_{w,s}$ denote oxygens belonging to the axial water molecule and the copper(II) second coordination sphere, respectively. The ax and eq abbreviations refer to two trans minima; see Figure 5. [b] Reference 26. [c] Reference 49. [d] Reference 51 (values obtained by the mixed IV basis set). [e] Structures B3LYP/LanL2DZ+(d) and FFW(vacuum)-a; see Figure 1.

distorted in the FFW structures than in the LanL2DZ+(d) geometries (see $\Delta\theta_{max}$ values in Table 5). FFW also underestimated the N−Cu−N and O−Cu−O valence angles of anhydrous Cu(L-Me_2Val)$_2$ by 4.5 and 5.3°, respectively, with respect to their B3LYP/LanL2DZ(d) values.[39]

To examine the influence of the apically coordinated water molecule on the coordination geometry in Cu(Gly)$_2$, Cu(Me_2Gly)$_2$, and Cu(tBuMeGly)$_2$, FFW was used to calculate the equilibrium geometries without water molecules in the systems. The coordination polyhedron angles changed only up to 2.0° for Cu(Gly)$_2$ and Cu(tBuMeGly)$_2$. However, the shape of the copper(II) coordination polyhedron for Cu(Me_2Gly)$_2$ relaxed from a distorted square-pyramid toward a distorted planar configuration (FFW yielded the N−Cu−N and O−Cu−O angles to be 167.6 and 163.0° in the aqua system and 176.4 and 171.5° in the system without water molecules, respectively). With this respect, the force field simulation is correct inasmuch as it confirms the quantum chemical result[39] that planar copper(II) coordination geometry is electronically preferred where there are no sterical influences. Interestingly, the lack of a water molecule in the studied system allowed FFW to retain the C_2 symmetry of Cu(tBuMeGly)$_2$ in vacuo. We can conclude that the inability of FFW to hold the water molecule in the axial position to the copper(II) violates the molecule's symmetry in vacuo.

Although FFW's reproduction of the B3LYP structures of aquacopper(II) chelates was less accurate than for the anhydrous molecules (which is not surprising, since aqua systems are more complicated for modeling), the force field predicted well the structures with the lowest strain energy. In addition, it accurately reproduced the quantum chemical result[51] that the formation of hydrogen bonds between water molecules and amino acid atoms competed with the axial Cu---O_w interactions. Moreover, in most cases FFW simulated quite well the hydrogen-bonding pattern obtained by the B3LYP calculations (Figures 1−4, Table S3).

To examine the predictive ability of FFW further, we constructed the systems of cis and trans isomers of Cu(Gly)$_2$ surrounded by up to six water molecules. Their equilibrium geometries are shown in Figure 5. The selected structural coordinates of the estimated minimum structures are collected in Table 6 along with those obtained by X-ray diffraction,[26] X-ray absorption,[49] and B3LYP calculations.[51] The predicted structures can offer qualitative information about the arrangements water molecules may have around a bis(amino acidato)copper(II) complex. In *cis*-Cu(Gly)$_2$ isomers, water molecules tend to be in the axial rather than equatorial position with respect to the copper(II) coordination plane (Figure 5). By contrast, the trans isomers allow water molecules to adopt the equatorial as well as axial positions (Figure 5). FFW produced the lowest strain energy for equatorially positioned water molecules in *trans*-Cu(Gly)$_2$·2H_2O (Table 6) alike to Cu(Sar)$_2$·2H_2O (Figure 2). The

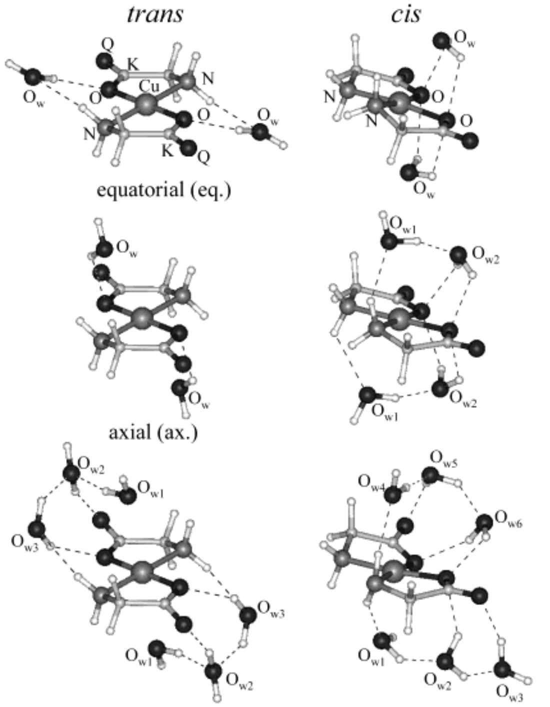

Figure 5. Structures of trans and cis isomers of Cu(Gly)$_2$ interacting with 2 H_2O, 4 H_2O, and 6 H_2O calculated with FFW in vacuo. Uncommon symbols: K, planar carbon atom; Q, carbonyl oxygen.

energy difference between anhydrous *cis*- and *trans*-$Cu(Gly)_2$ complexes obtained by FFW was 24.6 kcal mol^{-1}, with the trans isomer being more stable. The corresponding B3LYP/LanL2DZ+(d) energy difference was 13.6 kcal mol^{-1}. By addition of two and six water molecules to the studied systems, the FFW energy difference dropped to 15.5 and 9.6 kcal mol^{-1}, respectively. These energy differences are in line with the ab initio calculations,[51] which yielded the trans isomer of $Cu(Gly)_2 \cdot 2H_2O$ more stable than the cis isomer by 18 kcal mol^{-1} in vacuo and by 10 kcal mol^{-1} in a dielectric medium representing water. The FFW structural coordinates deviated substantially from the values obtained by the X-ray absorption techniques[49] for $r(Cu-O_w)$, $r(Cu-K)$, and $Cu-K-Q$ (Table 6). The comparison indicates that the predicted structures may have greater distortion of the chelate rings than the measured ones.

Conclusions

The new quantum chemical data presented in this paper proved irreplaceable when used with the experimental crystal data for the force field parametrization. The new force field, FFW, is capable of simulating the flexibility (plasticity) of the copper(II) coordination sphere as well as of the chelate ring geometries in the crystal lattice for both classes of compounds, anhydrous and aqua copper(II) amino acid complexes. The force field can, although not to the full extent, reproduce the changes in the internal coordinates between crystalline and isolated molecular systems. It simulates the result stemming from the B3LYP geometry optimizations for aquacopper(II) glycinato systems[51] that the formation of hydrogen bonds between water molecules and amino acids competes with the axial $Cu{-}{-}{-}OH_2$ interactions. It is also capable of simulating the hydrogen bonding. The MM model can be recommended for metal complexes with flexible coordination geometry, and FFW for predicting the most stable conformation of copper(II) amino acid complexes in vacuo.[65]

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Supporting Information Available: Listing of root-mean-square deviations and maximim differences calculated between internal coordinates of the B3LYP/LanL2DZ structure and B3LYP/LanL2DZ+(d) structure and of the B3LYP/LanL2DZ structure and X-ray crystal structure (Table S1), the fractional charges assigned by the CFF program using the charge parameters from Table 2 and ref 11 and charges obtained by the NPA method (Table S2), and hydrogen-bonding distances and angles in the four aquacopper(II) glycinato structures presented in Figures 1−4 (Table S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(65) The CFF program can be obtained free of charge upon request from Professor Kjeld Rasmussen (E-mail address: kjr@kemi.dtu.dk). The modified subroutines of the CFF program are available from J. S. upon request.