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Modeling Cu^{2+}-Aβ complexes from computational approaches

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Amyloid plaques formation and oxidative stress are two key events in the pathology of the Alzheimer disease (AD), in which metal cations have been shown to play an important role. In particular, the interaction of the redox active Cu^{2+} metal cation with Aβ has been found to interfere in amyloid aggregation and to lead to reactive oxygen species (ROS). A detailed knowledge of the electronic and molecular structure of Cu^{2+}-Aβ complexes is thus important to get a better understanding of the role of these complexes in the development and progression of the AD disease. The computational treatment of these systems requires a combination of several available computational methodologies, because two fundamental aspects have to be addressed: the metal coordination sphere and the conformation adopted by the peptide upon copper binding. In this paper we review the main computational strategies used to deal with the Cu^{2+}-Aβ coordination and build plausible Cu^{2+}-Aβ models that will afterwards allow determining physicochemical properties of interest, such as their redox potential. [http://dx.doi.org/10.1063/1.4921072]

I. INTRODUCTION

Alzheimer Disease (AD) is the most common form of neurodegenerative dementia. Among several neurological hallmarks, it is characterized by the presence of extracellular fibrillar deposits and by an excessive production of reactive oxygen species (ROS) in the cerebral medium.[1,2] Extracellular deposits are formed by the aggregation of the amyloid-β peptide (Aβ),[3,4] a small peptide from 40 to 42 amino acids long, obtained from the cleavage of amyloid precursor protein (APP) by γ and β-secretases. Analysis of post-mortem brain tissues from AD patients have revealed high concentrations of essential metal cations such as $Cu^{+/2+}$, $Fe^{2+/3+}$ and Zn^{2+} in these plaques[5] and the presence of redox active metals has been associated with the increased oxidative stress observed in the brain of these patients.[6,7] Several *in vitro* studies have related the formation of the deposits and the observed toxicity to the interaction of Aβ with these metal cations.[8–14] In this sense, copper has been the most intensively studied[15–22] because of its abundance in the cerebral medium and its high redox activity. In particular, several studies have focused in the determination of the copper coordination center at different pH values by means of continuous wave electron paramagnetic resonance (CW-EPR) and hyperfine sublevel correlation (HYSCORE) spectroscopy.[20,22] These studies have revealed the existence of two main species in the physiological pH range (see Scheme 1): i) one referred to component I at lower pH (6.3-6.9)[23,24] and ii) a second one named component II at higher pH (8-9), for which two metal coordination environments have been proposed.[25,26]

Elucidation of the copper coordination of Cu^{2+} to Aβ is essential to understand the role of this metal on the peptide aggregation and for the design of new strategies against AD. However,

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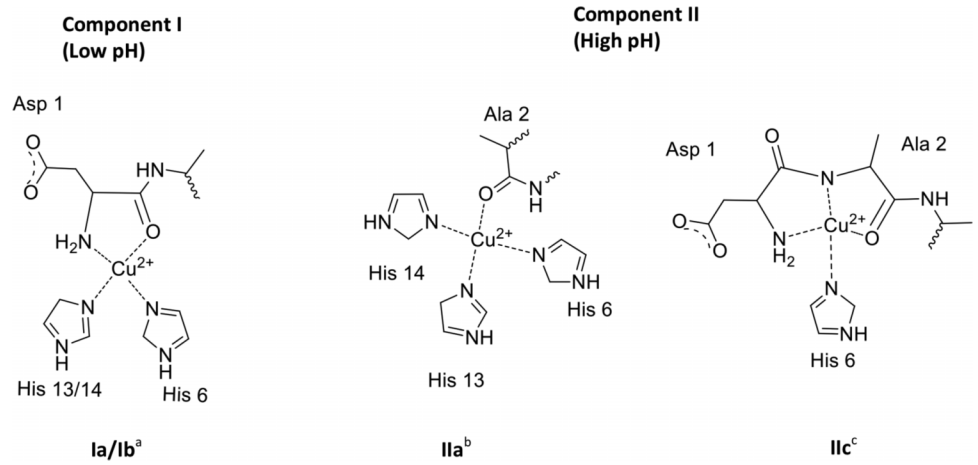

SCHEME 1. Coordination spheres proposed experimentally for the different Cu^{2+}-Aβ(1-16) complexes from CW- EPR spectroscopy. [a]From Refs. 23 and 24 [b]From Ref. 26 [c]From Ref. 25.

as important as characterizing the first metal coordination sphere, is the determination of the whole structure of Cu-Aβ, since the conformation adopted by the peptide upon copper attachment may also determine the physicochemical properties of the formed complexes. For instance, this information could be useful as starting point for understanding the role of metal cation interactions in the initial stages of nucleation and plaque formation as well as to explain the high redox activity observed by mediation of these metal complexes. In this context, computational modeling can provide considerable insights into the structure of the Cu-Aβ complexes as well as on the possible damaging mechanisms.

The computational modelling of Cu-Aβ complexes requires addressing two fundamental aspects: the metal coordination sphere and the conformation adopted by the peptide upon copper binding. The first element requires the use of electronic structure methods, which become computationally too costly even for relative low weight peptides like the Aβ(1–42) of the natural system. The second requires computational approaches able to explore vast conformational spaces of order of magnitudes wider than those accessible by quantum mechanical (QM) based approaches. This implies using simplified energetic functions (like force fields) associated with stochastic search algorithms. To date, methods able to model under a unique process the binding of the metal and the induced organization of the peptide are not yet achievable.

Early studies[27–32] used QM methods to compute model systems that include only the first coordination sphere of the metal. In particular, Rauk *et al*. have used B3LYP[33–35] functional to evaluate the complex stabilities, ligand preferences and reaction pathways for a series of model systems of $Cu^{+/2+}$-Aβ complexes.[28–31,36] These model systems have been very useful to study different coordination spheres as well as to determine some molecular properties such as standard reduction potentials (SRP) or stability constants, the computed values being in reasonable agreement with experimental results.[27] Model systems have also been used to study the possible reaction pathways allowing the generation of H_2O_2 catalyzed by Cu-Aβ complexes.[36] While they provided very valuable information, the main limitation of these model systems is that the effect of the rest of the peptide on the copper coordination preferences is neglected.

More recently, the increase in the computational performance has enabled the full QM treatment of intermediate systems such as Cu^{2+}-Aβ(1-7) or Cu^{2+}-Aβ(1-16).[37–41] The latter complexes include the first 16 amino acids, which constitute the hydrophilic part of the peptide, known to interact with the metal cation, and have allowed studying the importance of the peptidic moiety in the metal coordination sphere and determining the global stability of the complex.[40,41] It is worth mentioning that many experiments have also been done using the truncated Aβ (1-16) peptide, since it is more soluble than Aβ(1-42) and experimental evidences have shown that it can be very useful to understand its redox behavior, metal cation affinities, metal coordination and other physicochemical properties.[20,22,42–45] Other truncated models such as Cu^{2+}-Aβ(1-7) have been considered

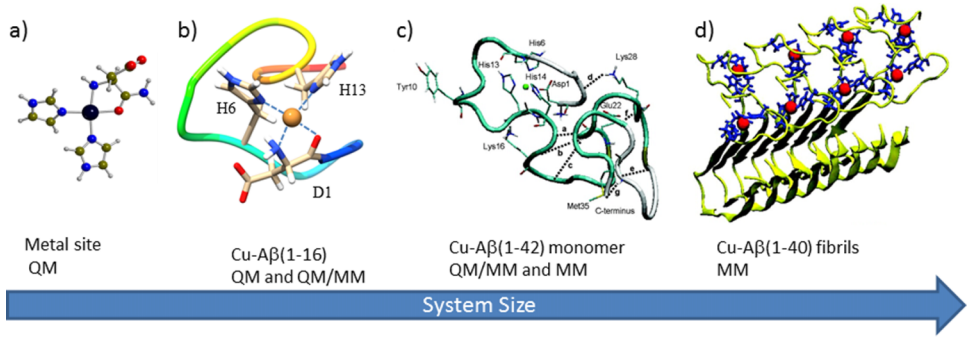

FIG. 1. Models used to study the interaction of copper with Aβ peptide and the computational methods suitable for treating each system. c) and d) are adapted from Refs. 46 and 48, respectively.

to study the mechanism of Cu^{2+} reduction using quantum chemical methods,[37] but the interaction of Cu^{2+} with larger systems including the whole Aβ(1–42) peptide have only been considered by means of classical molecular dynamic simulations.[46] The consideration of the full peptide Aβ(1-42) at the quantum mechanics level is computationally too expensive and thus, metal ion complexes are studied by using computational approaches that combine a quantum mechanical treatment for the copper coordination center and a molecular mechanics (MM) approach for the peptide moiety.[47] The interaction of metal cations with the mature fibrils has been considered only by using MM approaches.[48] Figure 1 illustrates the different methodologies applied to the study of the Cu-Aβ system, depending on the size of the considered model.

Building 3D structures for Cu-Aβ is the starting point for the calculation of molecular properties such as the standard reduction potentials or the affinity constants, among others. In this paper we address the main aspects related to the computational treatment of Cu-Aβ and the calculation of some of these properties. The main drawbacks are also discussed as well as the challenges in this research area.

II. BUILDING Cu^{2+}-Aβ 3D STRUCTURES

Building plausible models for Cu^{2+}-Aβ complexes requires the use of methods that provide a proper description of both the metal site and the peptide configuration. We will first address the electronic structure methods used to study the first coordination sphere of the metal cation. Secondly, we will discuss conformational sampling strategies to define the peptide configuration in increasingly complex systems. Finally, we will present an integrative computational approach to build and evaluate Cu^{2+}-Aβ complexes.

A. Electronic Structure Methods

Cu^{2+} is a $3d^9$ metal cation that can lead to a significant variety of coordination complexes, whose proper description requires the use of electronic structure methods. In most cases, the electronic structure methods used are based on density functional theory (DFT) since they provide a good relationship between computational cost and chemical accuracy. However, due to its open-shell nature, its electronic description is delicate. Indeed, previous studies for Cu^{2+}-L systems have shown that GGA functionals (e.g. BLYP[33,49]) or hybrid functionals with a low percentage of exact exchange (e.g. B3LYP) tend to overstabilize lower coordinated structures. In particular, for Cu^{2+}-$(H_2O)_n$ clusters, it was found[50] that the relative energies of different coordinating systems were, in general, better described with functionals that involve a larger amount of exact exchange such as BHLYP,[33,51] MPWB1K[52] or M06-2X.[53] Results in Table I show that BLYP or B3LYP functionals tend to overstabilize four coordinated systems as compared to five or six coordinated complexes, whereas with CCSD(T) four and five coordination spheres are almost degenerate. Noticeably, with BLYP the energy difference is as large as 7 kcal mol^{-1}, the fourth coordinated system

TABLE I. Relative energies (in kcal mol^{-1}) for the different Cu^{2+}-$(H_2O)_6$ complexes with different DFT functionals[a] and with the CCSD(T) method. CN: copper coordination number as shown in Figure 2.

System	State	CN	BLYP	B3LYP	BHLYP	MPWB1K	M06-2X	CCSD(T)
Cu42	$^2B_3$	4	0.0	0.0	0.0	0.0	0.0	0.0
Cu51	^2A	5	7.3	5.2	2.4	1.8	-0.5	0.7
Cu60	^2A	6	16.6	12.3	6.2	4.9	0.0	3.2

[a]For Cu the basis set is the Wachter's (15s11p6d1f)/[10s7p4d1f] all electron basis.[56–58] For O and H the basis set is 6-31++G(d,p).

being largely favored (Table I). This behavior has been related to a too large spin density delocalization in systems with low coordination numbers (Figure 2), a situation that is overstabilized as a result of a bad cancellation of the self-interaction part by the exchange-correlation functional.[54] Similar trends[50] are observed when including scalar relativistic effects for Cu through the use of the LANLDZ pseudopotential. Moreover, a good description of the second ionization energy of Cu is an important issue for an accurate determination of the Cu^{2+}-Aβ/Cu^{+}-Aβ redox potentials. Results in Table II show that the GGA BLYP functional provides a too large second ionization energy, whereas the hybrid MPWB1K and M06-2X lead to values in good agreement with CCSD(T) and the experimental value (20.3 eV).[55]

Last but not least, the functional chosen should provide a good description of hydrogen bonding and dispersion forces to properly account for the peptide configuration and stability if the entire bioinorganic moiety is considered at the DFT level. Among a series of functionals tested, M06-2X has been shown to provide the lowest mean average errors for a set of biological relevant molecules presenting noncovalent interactions.[53] Overall, M06-2X seems to be a reasonable functional for the description of the metal coordination properties, the redox potential and stabilities of Cu^{2+}-Aβ complexes.

B. Conformational Sampling

When considering longer fragments of the Aβ peptide in computational simulations one of the main issues to take into account is the exploration of the conformational space of the system, especially in high flexible peptides like Aβ. The fragments not coordinated to copper can be considered as loops, i.e., flexible segments of contiguous polypeptide chains that connect two secondary structures, in such a way that the conformational sampling can be assumed to be a loop structure modeling problem and treated with template-based or template-free methods. The first method uses database information to predict the most plausible conformation adopted by the peptide and the

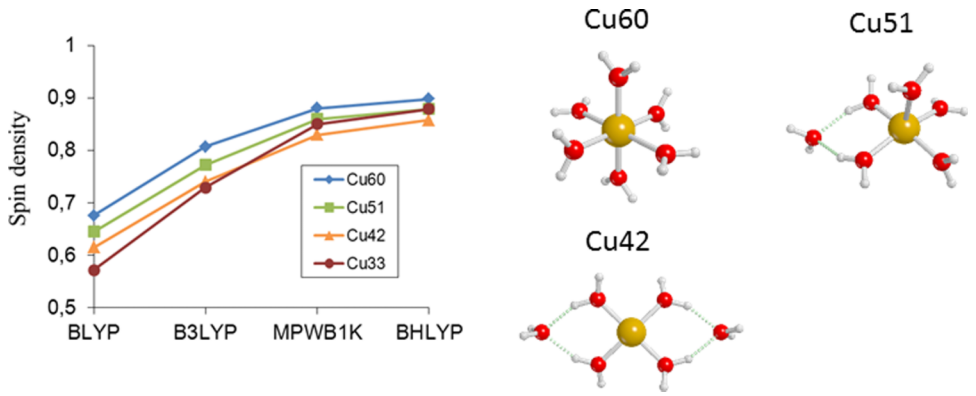

FIG. 2. Copper spin density in different $Cu^{2+}(H_2O)_6$ clusters. Adapted from Ref. 50. Copyright 2010 American Chemical Society.

TABLE II. Second ionization energy of Cu[a] (in eV). Experimental value is 20.3 eV.[55]

BLYP	B3LYP	BH&HLYP	MPWB1K	M06-2X	CCSD(T)
21.2	20.8	19.9	20.1	20.2	20.2

[a]Basis set for Cu is the Wachter's (15s11p6d1f)/[10s7p4d1f] all electron basis.[56–58]

second one uses an energy function to predict the most stable conformations by optimizing this function. Template-based methods are highly dependent on the available structures on the database (e.g. the number and quality of structures reported on the PDB) and its use is limited to short loops, since the number of possible conformations grows exponentially with the loop length.[59] On the other hand, template-free methods are dependent on the computational power available to deal with the energy function used for the loop modeling. This energy function is obviously more complex as the system size increases. Due to the fact that the copper coordination modifies substantially the secondary structure of the Aβ, a combination of template-based methods to build up the structure and a template-free approach to refine the loops seems to be an appropriate strategy to model the loops formed upon copper binding.

One strategy to build up and evaluate models for Cu-Aβ systems is the combination of quantum mechanics calculations with homology modeling (HM) simulations.[40,41] These HM techniques are widely used in biochemistry and pharmacology to generate three dimensional models of proteins based on crystallographic structures of homologues and are based on the theorem of Chothia's *et al*.[60] which states that the highest the sequence similarity between two proteins, the highest their structural similarity. Based on this idea, computational techniques have been developed to generate three dimensional models of a protein of unknown structure (usually referred as the *target)* from analogues whose structures have been experimentally resolved (commonly referred as the *template(s)*). Three dimensional models of the target are generated by first constructing its backbone and then performing conformational searches of the entire bunch of its side chains. The best structural models are selected according to energetic and structural criteria. Like most force fields techniques, homology modeling approaches are not optimized for dealing with metal ions, even less for transition metal cations with subtle electronic features like copper. The impact of metal ions on the target structure can be included externally from quantum chemical calculations, as additional constraints in the homology modeling process. In this line, a new protocol that combines homology modeling techniques with quantum mechanical calculations has been designed to explore Cu^{2+} complexation with Aβ. The template used for these calculations was the metal bound amyloid Zn^{2+}-Aβ(1-16) (PDB code 1ZE9),[61] obtained in similar conditions to those in which copper should bind the amyloid with a three nitrogen containing coordination sphere.

The computational protocol used to build 3D structures for Cu^{2+}-Aβ is summarized in Figure 3. The protocol starts by studying restricted models, with the metal site coordinations determined experimentally (see Scheme 1), with QM techniques. The geometry of each metal configuration is optimized with DFT and subsequently, an initial model of the entire metal-Aβ complex is generated using HM techniques. To this end, we considered that His coordination to the metal center could occur either through the ε or δ N of the imidazole group. In this part of the protocol the geometrical variables related to the first coordination sphere of the metal are included in the calculation as additional special constraints. Many candidates are generated in the HM runs for each metal configuration and a series of structural filters are used to select those that are the most probable ones. The models are finally refined with quantum chemical calculations and including solvent effects by means of the SMD[62] polarized continuum model. Thermodynamic corrections were obtained assuming unscaled harmonic vibrational frequencies, and the rigid rotor approximation by standard statistical methods. Moreover, quantum chemical calculations of both the metal site and the peptide allow us to analyze the influence of each moiety in the overall stability. Overall, this integrative computational methodology provides the tools to address a phenomenon that requires both a conformational exploration and the modeling of fine electronic effects, which allows determining plausible models for Cu^{2+}-Aβ complexes with different coordination spheres.

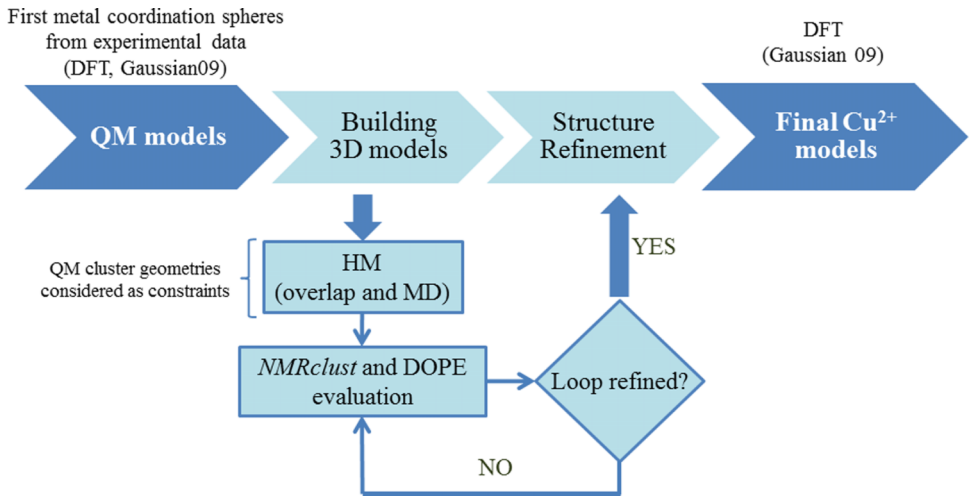

FIG. 3. Computational protocol for the construction and evaluation of Cu^{2+}-Aβ(1-16) models.

As an illustrative case, Figure 4 shows the 3D structures obtained for the four different configurations of component Ia, derived from different imidazole (δ or ε) coordinations, and Table III their relative stabilities. This table also includes the relative stability of the metallic (ΔE_{MC}) and peptidic (ΔE_{pept}) moieties, as well as the number of hydrogen bond contacts observed in the peptidic moiety. Refined structures show a distorted square planar coordination environment for the metal site and a spin density of 0.7-0.8 at Cu^{2+}, in accordance with the $3d^9$ electronic structure of Cu^{2+}. Comparison between the energy of the metal site at the geometry of the whole Cu^{2+}-Aβ system with that of the fully relaxed model system, enclosing only the first coordination sphere, indicates that the peptide destabilizes the metal center by about 7-13 kcal mol^{-1}. On the other hand, it can be observed in Table III that relative ΔE values are mainly driven by the peptidic moiety and not by the metal site, variations observed for the metal site being less than 7 kcal mol^{-1}, whereas those observed for the peptidic moiety being as large as 27 kcal mol^{-1}, in terms of potential energies. These large variations are related to the number of hydrogen bond contacts, particularly to salt bridge interactions, found in the peptide configuration, which for component Ia drives Ia_δδ to be the most stable species. As expected, thermal corrections lead to smaller relative free energies due to enthalpy-entropy compensation effects. Considering the small Gibbs energy differences found between complexes in some cases it is not possible to identify one particular structure as a unique answer. Indeed, dynamical effects will have entropic contributions that could moderate the relative stabilities between the most stable complexes.

III. STANDARD REDUCTION POTENTIAL CALCULATIONS

Standard reduction potential is an essential property to understand how copper complexes participate in the generation of H_2O_2 and thus, in the final production of ROS. For Cu-Aβ complexes, SRP versus the standard hydrogen electrode can be estimated by considering the following semi reactions:

$$\text{`}Cu^{2+}\text{'}_{(aq)} + e^- \rightarrow \text{`}Cu^{+}\text{'}_{(aq)} \qquad \Delta G^{Cu}$$
$$H^+ + e^- \rightarrow {}^1/_2H_2 \qquad \Delta G^{SHE}$$

where "Cu^{2+}" and "Cu^{+}" represent the oxidized and reduced species of the $Cu^{+/2+}$-Aβ couple in aqueous solution, respectively, and ΔG^{Cu} y ΔG^{SHE} (SHE: standard hydrogen electrode) are the free energy changes for the semi reactions, ignoring the electron. The SRP is calculated using the following equation:

$$E^\circ\ (\text{`}Cu^{2+}\text{'}/\text{`}Cu^{+}\text{'}) = -(\Delta G^0{}_{Cu} - \Delta G^0{}_{SHE})/F$$

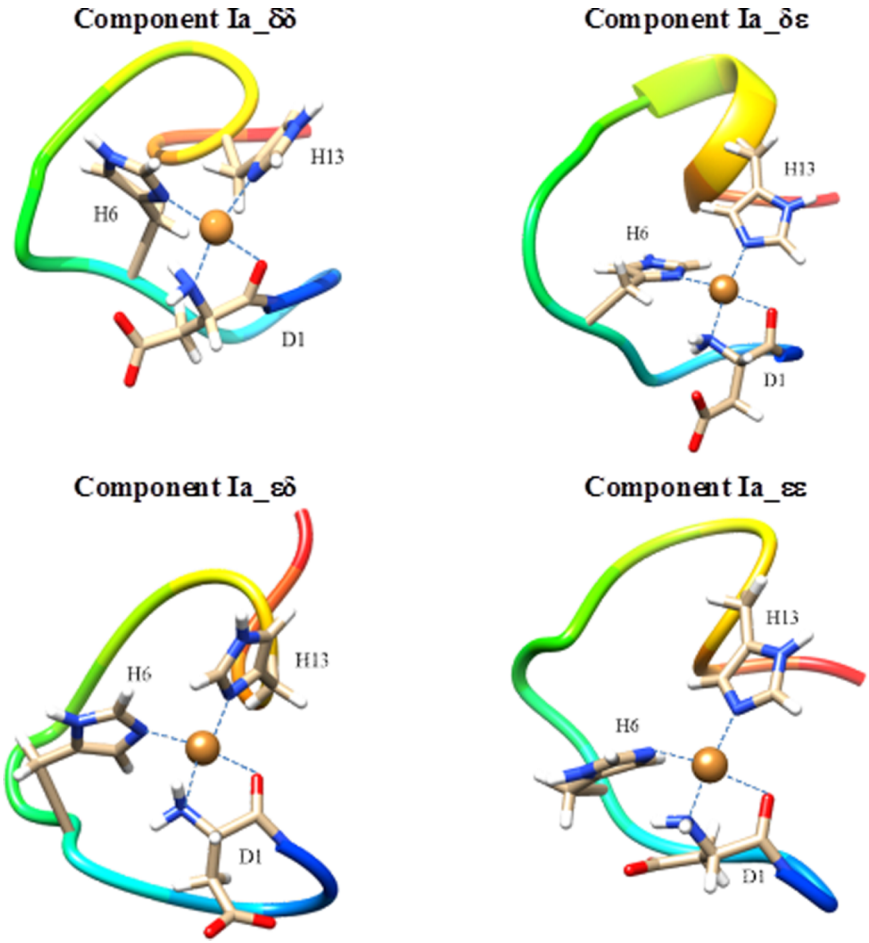

FIG. 4. Built models for Component Ia, according to protocol shown in Figure 3. Adapted from Ref. 40.

where F is the Faraday constant (23.061 kcal V^{-1} mol^{-1}). For the reduction of the proton in aqueous solution the experimental value can be used, $\Delta G^{SHE} = -99.9$ kcal mol^{-1}.[63] Note that ~2.3 kcal mol^{-1} would account for 0.1 V and thus, accurate values for SRP require determining ΔG^{Cu} values with errors not larger than 2-3 kcal mol^{-1}. Considering the nature of the system, which involves a metal cation for which different DFT methods may provide ionization energies that differ up to 0.5 eV (11.8 kcal mol^{-1}), as well as the difficulties in computing entropy changes in systems with a significant flexible character and the limitations of taking into account solvent effects with an implicit model, the determination of SRP may exhibit large differences when compared to experimental data.

TABLE III. Relative energies for Component Ia [CO^{D1}, N_{ter}, N^{H6}, N^{H13}] complexes. ΔE_{MC} and ΔE_{pept} are the relative energies of the metal center and the peptide moiety, respectively. N_{HBC} is the total number of hydrogen bond contacts (hydrogen bond cutoff distance ≤ 2.1Å) observed in the peptidic moiety, and N_{SB} the number of salt bridges. All the energies are in kcal $\cdot$ mol^{-1}.

Models	ΔE	ΔE_{MC}	ΔE_{pept}	ΔG	N_{HB}	N_{SB}
Ia_δδ	0.0	0.0	0.0	0.0	10	2 (E3-K16/R5-D7)
Ia_δε	19.1	−4.1	21.8	4.6	5	1 (R5-D7)
Ia_εδ	23.8	0.2	26.7	13.9	6	1 (K16-CO2-ter)
Ia_εε	18.4	−6.6	22.5	10.4	7	1 (D1-R5)

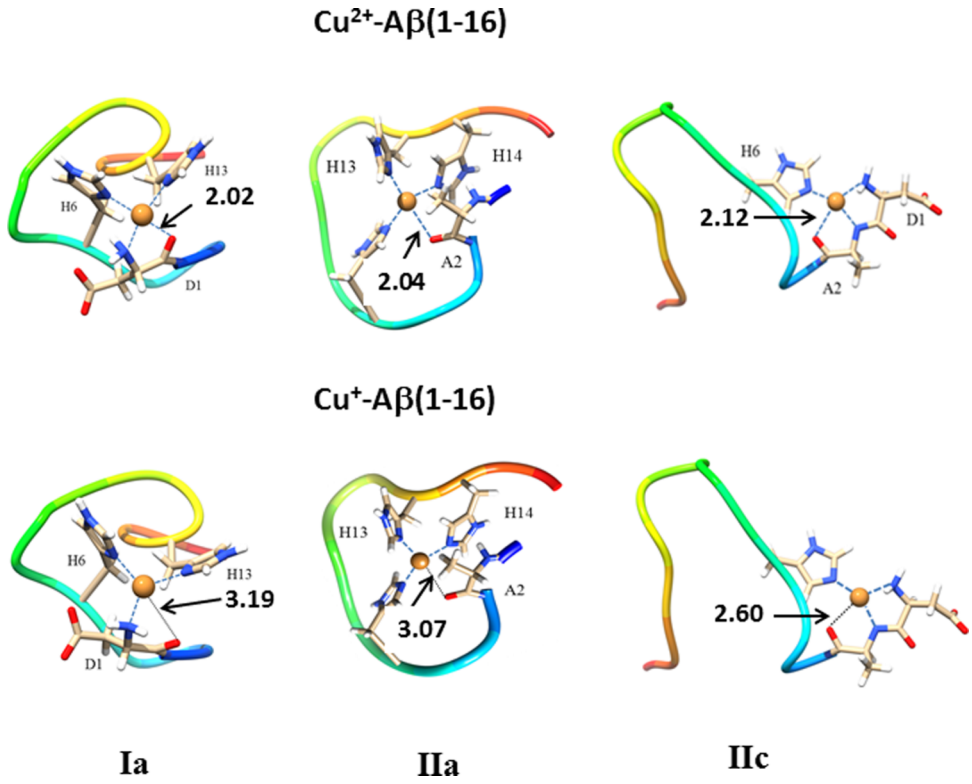

FIG. 5. Structures of the oxidized and reduced species of the most stable models for components Ia, IIa, and IIc of Cu^{2+}-Aβ (1−16) complexes. Cu···O distances are in Å. Adapted from Ref. 40.

Limitations on the level of theory used can partially be overcome by adding the difference obtained between the calculated and experimental second ionization energy of atomic copper to the calculated ΔH.[31] Alternatively, an empirical correction, defined as the difference between the calculated and experimental SRP for the free metal ion in aqueous solution can be added to the values calculated for the $Cu^{+/2+}$-Aβ couple.[40,64] This latter approximation has been considered to evaluate the SRP of Cu^{2+}-Aβ complexes involving different coordination spheres.[40]

Figure 5 shows the most stable models obtained for Cu^{2+}-Aβ enclosing the different experimentally proposed coordination spheres, as well as the Cu^{+}-Aβ structures obtained upon reduction. Reaction energies and Standard Reduction Potentials are given in Table IV. It can be observed that SRP computed for component Ia and IIa (0.28 and 0.21 V, respectively) are similar and both are significantly larger than the one of component IIc (−0.81 V). This was to be expected considering that metal coordination in IIc involves a negatively charged ligand, which hinders reduction as compared to the other components. Indeed, previous studies using *ab initio* molecular dynamic simulation have shown that for efficient reduction the interacting deprotonated amide nitrogen has to be protonated.[37] On the other hand, structural relaxation after reduction mainly occurs at the

TABLE IV. Reaction energies for the reduction of the most stable Cu^{2+}-Aβ complexes (in kcal mol^{-1}) and SRP *vs.* standard hydrogen electrode (in V). E^{o}_{corr} is the value obtained after considering the empirical correction (see text).

System	ΔE	ΔH	$T\Delta S_{298}$	ΔG_{298}	E^{o}_{corr}
$[Cu^{+/2+}(H_2O)_4]^{+/2+}$	−95.7	−98.1	3.1	−101.2	0.16
Component Ia_δδ	−99.1	−100.4	3.7	−104.0	0.28
Component IIa_εδε	−96.0	−98.3	4.0	−102.3	0.21
Component IIc_ε	−85.5	−84.7	−5.8	−78.8	−0.81

metal site, changes on the peptidic moiety being minor. In particular, reduction decreases the metal coordination number, from tetracoordinated in the oxidized species to tricoordinated in the reduced ones.[37,40]

Major geometrical changes are associated to the Cu^{2+}-$CO_{backbone}$ distance, which in general increases from ~2.0 Å to ~ 3.0 Å. For IIc_ε the Cu^{2+}-O distance only increases up to 2.6 Å, due to the formation of a hydrogen bond interaction with the backbone. In many cases reduced species show T-shaped structures that could further evolve to linear dicoordinated species.[37,40] These latter species are expected to be particularly stable when both, His13 and His14, coordinate to the metal through the δ nitrogen of imidazole.[65] Computed SRP value for Ia is in very good agreement with the most recent experimental values determined for Cu^{2+}-Aβ (1−16) complex (between 0.28 and 0.34V),[45,66,67] in accordance with the fact that this is the dominant species at pH ~7.

IV. CONCLUDING REMARKS

In the last years, the modeling of Cu-Aβ systems has experienced a significant advance. The first studies, mainly carried out by Rauk et al.,[27–32] considered the first coordination sphere of the metal cation at a quantum mechanical level. Other studies have partially incorporated the effect of the rest of the peptide using truncated models such as Aβ (1-7)[37] or Cu-Aβ (1-16) complexes.[38–41] Although this latter systems can nowadays be studied by means of quantum mechanical methods, larger systems such as Cu^{2+}-Aβ (1-42) or oligomers are still computationally too demanding to be considered fully at the QM level.

Cu-Aβ (1-16) is a common model used also in experiments to mimic the real Aβ (1-42) system and a proper modeling requires the accurate treatment of both, the metal coordination sphere and the configuration adopted by the peptide upon copper binding. These points are addressed in the integrative computational approach used previously by us to generate physically 3D models of Cu^{2+}-Aβ complexes, enclosing metal coordination environments proposed from EPR experiments at different pH. This protocol, which combines homology modeling techniques with quantum based approaches and includes solvent effects with polarized continuum models, has provided us with the exploration of the conformational space and the modelling of the fine electronic effects necessary to generate plausible models. Moreover, it has allowed us to determine that the overall stability of the complex is, in general, driven by the peptidic moiety. However, considering the small Gibbs energy differences found in many complexes, it has not been possible to identify one particular structure as a unique answer. Dynamical effects could have entropic contributions that could moderate the relative stabilities between the most stable complexes. Generated models can then be used to evaluate the redox properties of complexes that exhibit different coordination environments. Results highlight the importance of the nature of the ligands on the standard reduction potential, the computed values for component IIc that encloses negatively charged ligands in the coordination sphere being significantly smaller than those of component Ia and IIa involving neutral ligands. Moreover, results obtained indicate that major structural changes upon reduction occur at the metal site, which decreases its coordination number due to the decoordination of the interacting CO.

Overall, the present protocol has allowed us to obtain atomistic information on the complexes derived from the coordination of Cu^{2+} to the hydrophilic part of Aβ peptide and obtain trends on the redox properties as a function of the coordination environment. However, the determination of the affinity constant of Cu^{2+} to amyloid peptide from computational approaches, which is an important and controversial issue, is much more challenging. Quantum chemical calculations can provide accurate information on intrinsic metal-ligand interaction energies that can be very useful to estimate which the preferred ligands around Cu^{2+} would be. These preferences, however, can largely be modulated in solution, particularly when dealing with charged ligands or ligands that need to deprotonate for binding. Despite many advances done in the determination of accurate solvation energies by means of polarized continuum models, a well-balanced description of all processes taking place upon Aβ binding to the metal cation, particularly entropy changes, is very challenging and computed affinity constants may significantly vary depending on the reactions considered in the calculation and the models used. While this can partially be overcome by referring the affinity constant of the unknown system to a known reference system that holds the same charge

and involves the same number of species, the development of new computational strategies in this direction will be highly desirable. Also challenging is the determination of the mechanism of the peptide folding in the presence of metal cations since several metal coordinated intermediates are possible, whose accurate conformational sampling is likely to be unachievable. In this context, the combination of molecular dynamics simulations at different resolutions (atomistic force field and coarse grained) may provide complementary information.

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