

“Short term mobility” program - year 2009

Title - Models for the interactions between Cu^I and Cu^{II} ions and amyloid peptides implied in the Alzheimer's pathology

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Summary of the activities during the visit of Giovanni La Penna to Faller's Lcc laboratory during the period 22/04/2009 - 12/05/2009.

Prof. Peter Faller and coworkers performed several types of measurements on the interactions between Cu ions, in both I and II oxidation states, and the A β (1-16) peptide. This latter is a convenient *in vitro* model of the A β (1-42) peptide (the major component of amyloid fibrils in the Alzheimer's disease) that is sufficiently stable in a monomeric form for performing spectroscopical studies and that contains the region of interaction with metal ions with largest binding affinity [1].

Several studies in the literature, based on X-ray, XAS and EPR measurements, proposed a stable linear coordination for Cu⁺ by the N δ 1 atoms of His 13 and His 14 [2,3]. The ¹H- ¹³C-NMR measurements performed in the Lcc laboratory, together with XAS studies and electrochemical measurements, are more consistent with the involvement of all the His (6, 13 and 14) sidechains in the Cu⁺ coordination and with a non trivial reorganization of ligands around Cu upon oxidation. The visit to Lcc of dr. Giovanni La Penna opened the possibility of clarifying by using computational models the coordination of Cu⁺ in the 1-16 region of

amyloid- β peptide. This is a first step for understanding the extent of ligand reorganization around Cu upon its redox activity.

The Cu^+ ion is d^{10} configuration, isoelectronic with Zn^{+2} , and thus is expected to adopt coordination geometries dominated by the steric hindrance of ligand groups. On the other hand, due to the larger accessibility of empty p orbitals and to the smaller charge density, the Cu^+ ions can adopt different types of coordinations, compared to Zn^{+2} , including a linear coordination 2. This latter type of coordination is indeed observed for Cu^+ complexes in the crystal phase with imidazole ligands [2] and in the glassy phase for the $A\beta$ peptide ligand [3]. The His sidechains of the peptide are the favourite ligand groups for copper in many biological macromolecules and therefore they are investigated in the published studies, as well as by Faller's group in Lcc.

Dr. Giovanni La Penna built several models with different number of potential ligand atoms close enough to Cu to form a chemical bond. This model structures have been built by using biased self-avoiding random walks with an atomistic empirical force-field describing the $A\beta(1-16)$ peptide together with Cu and Zn ions. The water solvent was neglected. This kind of approach allowed a reasonable estimate of initial structures for detailed calculations in similar systems [4,5]. The bias was modulated in order to progressively build coordinations 2 and 3 of Cu^+ by different sets of His sidechains and by different ligand atoms in these sidechains, namely $\text{N}\delta 1$ and $\text{N}\epsilon 2$. Summarizing, exploiting only His sidechains as possible ligands, there are 12 possible types of coordination 2 for Cu and 8 possible types of coordination 3. Initial configurations for all of these possibilities were built, including several possibilities for the structure of the entire $A\beta(1-16)$ ligand for each of these coordination types. The interplay between the coordination of Cu and the intramolecular stress of the ligand has been investigated. Solvation effects will be computed on the basis of the structures built with non-solvated models.

First-principle molecular dynamics simulations of some of these models were performed during the visit. The first model, with the segment Ace-His-His-NMet (representing the His13-His14 moiety) bonded with both $\text{N}\delta 1$ atoms to Cu, showed the stability of the linear N-Cu-N coordination, with significant perturbations due both to thermal fluctuations, that become significant at the temperature of 200 K, and to interactions between Cu and the carbonyl oxygen of His 13 backbone, that is forced to point out from Cu by the binding of the two $\text{N}\delta 1$ atoms. These dynamical effects could be investigated only by first-principle simulations (in the Car-Parrinello scheme in this case), because the standard procedure of comparing energies of optimized structures would not allow the evaluation of thermal induction of the significant distortions observed here.

In the second model, His 6 was included as the Ace-His-NMet model approaching Cu with $\text{N}\delta 1$ atom. This structure was built according to the entire 1-16 peptide. On the basis of the calculations performed so far, the possibility for

Cu⁺ to coordinate two His sidechains at a time, with His 6 favoured in entering the coordination sphere and replacing His 13, was supported. No evidence is provided for a 3-coordinated Cu⁺ ion stable up to $T = 300$ K: when three His are initially coordinated to Cu, one of them (His 13) tends to move outside the Cu coordination sphere, mainly because of the mechanical stress in the His 13-His 14 moiety. This propensity will be checked also for the other coordination types, because the involvement of N ϵ 2/N δ 1 pairs can, in theory, provide stabilization to trigonal and, possibly, tetrahedral coordinations, with the fourth coordination site occupied by a ligand oxygen (of carboxylate or carbonyl groups).

This work will be continued completing the statistics of all the coordination types enumerated above. The oxidation of some of these complexes will be exploited in the second stage of the project.

An application to access the Idris high performance computing infrastructure in Paris was completed during the first week of may, in order to acquire computational resources to complete the project. A similar project was submitted for the John von Neumann HPC infrastructure in Juelich (DE).

Proponent and beneficiary



24/05/2009

Dr. Giovanni La Penna

References

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- [5] S. Furlan, G. La Penna, "Modeling the Zn⁺² binding in the 1-16 region of the amyloid-beta peptide involved in Alzheimer's disease", *Phys. Chem. Chem. Phys.*, DOI:10.1039/B822771C (2009).