FP7-PEOPLE-IEF-2008 (project no. 237651)

MetAlzComp-Understanding the role of transition metals in Alzheimer's disease on a molecular level

The morphological hallmarks of the Alzheimer's disease are intracellular neurofibrillary tangles and extracellular amyloid plaques. Latter are aggregates mainly constituted by amyloid-β peptides (Ab), containing 39-42 amino acids. The transition metal ions, which are in abnormally elevate concentration in the plaques, are an important role in the Ab aggregation process, as Cu(II) modulates the process. The other important role undertaken by Cu ion is the catalysis for the production of highly toxic reactive oxygen species (ROS), which are supposed to lead to neuronal death in Alzheimer's disease. Thus to better characterize the interaction of copper ions with Ab, will help to better understanding the role of this interaction in the development of Alzheimer's disease, which is the base of the conception of new drugs.

Thus we decided to investigate the Cu(II) and Cu(I)-Ab interaction by means of ab initio molecular dynamics, a Density Functional method. This kind of interaction is rationalizable by coordination chemistry concepts therefore the quantum treatment of the molecular system is absolutely necessary since the force field of classical simulation method are lacking in describing bonds involving transition metal ions. Nevertheless the initial structures which the ab initio simulation started from, was built by statistical methods based on classical force field in order to speed up the achievement of a reasonable conformation of peptide chain around the metal ion without claim to describe properly the ligand-ion bond.

In the case of Cu(I)-Ab(1-16), a truncated established model for Cu binding, it was proposed from experimental work that Cu(I) is bound in a linear geometry to two His residues, i.e. His-Cu(I)-His. As Ab has three His at position 6, 13 and 14, there was discussion in the literature about which His were involved and if indeed on a two His are coordinated. In order to answer these questions we built several reasonable models of coordination. The propensity of a linear His-Cu(I)-(His coordination for Cu(I) is shown by all the models investigated here. Though the His 6-Cu-His14 linear coordination is favored in truncated models, the His 13-Cu-His 14 linear coordination is favored by interactions present in the complete solvated and in vacuo models of Cu-Ab (1-16) (Fig. 1). These interactions include steric hindrance for the expulsion of His 13, hydrogen bonds between Asp and His side chains and a network of electrostatic interactions stabilizing two separated 1-10 and 11-16 peptide regions. The role of linear His 13-Cu-His 14 coordination in stabilizing Cu(I) and in increasing the Cu(II)/Cu(I) reorganization energy can be therefore modulated by boundary conditions acting on the A*b*.

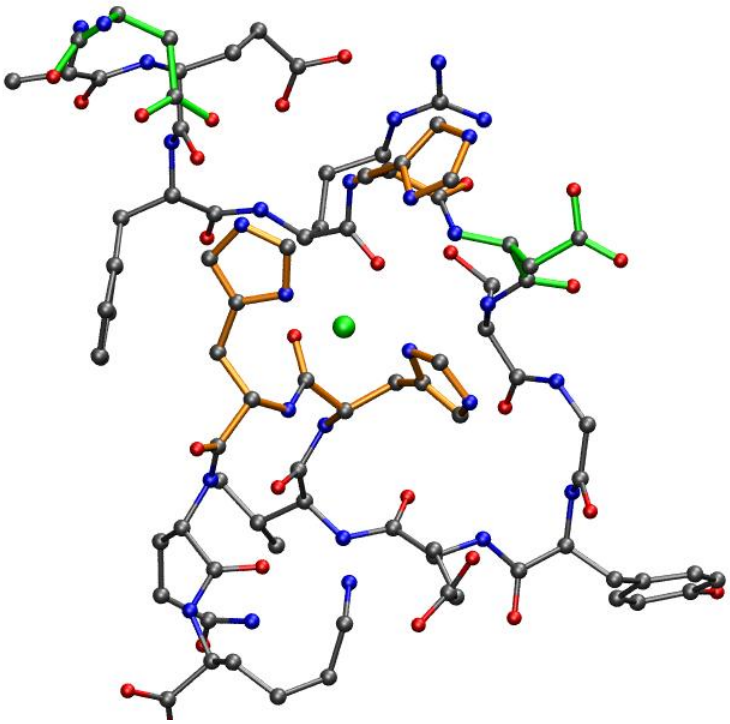
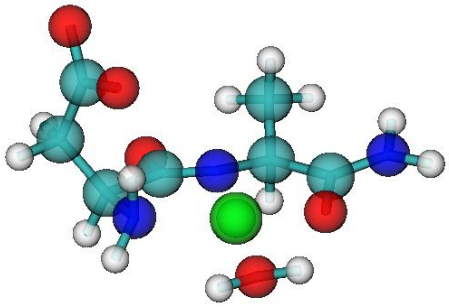


Figure 1: Calculated model of the complex of Cu(II) with Amyloid-β1-16 in water (Cu(I): gree sphere; His: orange; nitrogen; blue; oxygen red; carbon, gray)

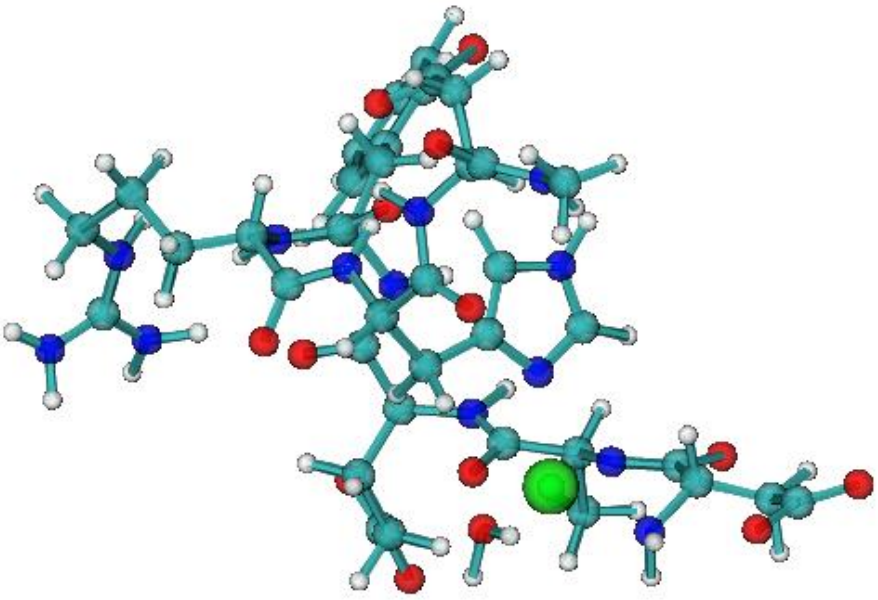
In the case of Cu(II)-binding to Ab, there are two major binding modes at physiological pH, called component I and II. Component II includes the Cu(II)-binding to the first two amino acids (Asp1 and Ala2) including the -NH_2 group at the N-terminal chain, by the N-terminus, amide (from Asp1-Ala2 bond) , and carbonyl (Ala2), as well as one His as the four equatorial ligands.



Before considering a larger sequence we performed two simulations of simplified two amino acids peptide Asp1-Ala2 coordinated around the Cu(II), in vacuo and in a box of explicit water molecules (Fig2).

Figure 1: Calculated model of the complex of Cu(II) with dipeptide Asp-Ala in water (Cu(II): green; oxygen: red; nitrogen: blue; hydrogen: white)

The behavior of the complex at room temperature in vacuo or in solvent is very different. From this preliminary results we argued that the simulations have to be done with the solvent, for this reason we used the larger Ab(1-7) peptide in a water molecules box, that is a good compromise between the computational effort and an exhaustive description of the chemical system including one histidine in position 6. We could reproduce relatively well the proposed experimental structure described above, but we observed that the His 6, initially in equatorial position is displaced in axial position by a H_2O molecule coming in equatorial position to Cu(II) (Fig. 2).



For what concerning the methodological point of view we can conclude that for describing the interaction between transition metal ion and peptide, the account of the solvent is indispensable.

Figure 3: Calculated model of the complex of Cu(II) with Amyloid-beta1-7 in water (Cu(II): green; oxygen: red; nitrogen: blue; hydrogen: white)

In conclusion, the calculation allowed as a better understanding of the binding of Cu(I) and Cu(II) to the peptide amyloid-beta, which is supposed to be linked to Alzheimer's disease.