ALUMINUM,
A WALK ON PART IN THE WAR OR A LEAD ROLE IN A CAGE ?

Gabriele Dalla Torre[1,2], Jon I. Mujika[1], Xabier Lopez[1], Maria João Ramos[2]

[1] *Kimika Fakultatea, Euskal Herriko Unibertsitatea UPV/EHU, and Donostia International Physics Center (DIPC), P.K. 1072, 2080 Donostia, Euskadi, Spain*

[2] *REQUIMTE, Departamento de Química e Bioquímica da Faculdade de Ciências da Universidade do Porto, Portugal*

Within the framework of aluminum chelation therapy[1], one of the main goals is the thorough characterization of the structural and *physico*-chemical properties of Al(III)-chelator complexes.
Here, we propose a QM/MM-based approach for the investigation of some hexadentate Al(III) chelating agents that have been experimentally shown to exert high affinity toward aluminum, such as TRENCAMS[2], O-TRENSOX[2], the commercial drug Desferrioxamine (Desferal®)[3], and a novel class of peptide-based Al(III) chelators (**Fig.1**).
Since reliable Force-Field parameters for aluminum are not available, the metal is treated *quantum* mechanically at the semiempirical level of theory. Accordingly, the first step is the identification of the most reliable semiempirical method able to properly describe Al(III)-ligand interactions through a rigorous validation against available experimental data.
Then, QM/MM Molecular Dynamics simulations are carried out using the Replica Exchange technique (REMD) in order to enhance the sampling of the potential energy surface related to the metal-chelator complexes.
Besides, binding energies and enthalpies will be calculated at the B3LYP-D3(BJ)/6-311++G(3df,2p)//B3LYP-D3(BJ)/6-31++G(d,p) level of theory. Moreover, Al(III)-ligand binding features are also thoroughly characterized by means of the Bader's Quantum Theory of Atoms In Molecules (QTAIM), the Natural Bond Orbital (NBO) theory and the Energy Decomposition Analysis (EDA) scheme by Ziegler and Rauk.
Overall, our approach would shed some light in the rather controversial field of aluminum biochemistry, as well as to propose a suitable theoretical protocol that can be applied in the investigation of pharmaceutically interesting Al(III)-chelator complexes.

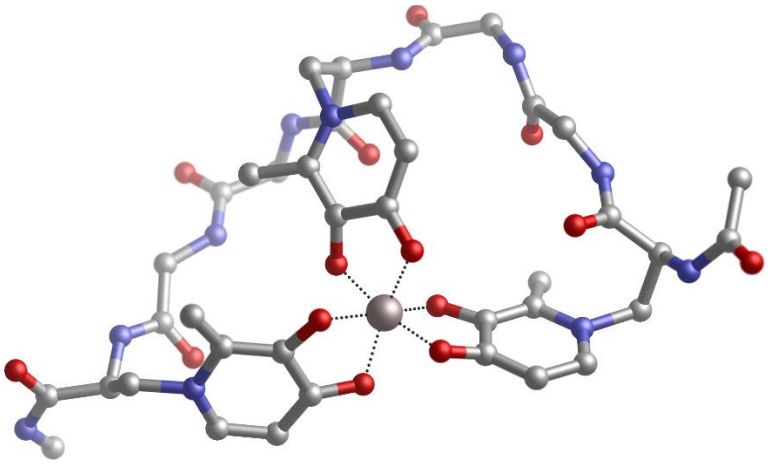

Fig.1. Peptide-based aluminum chelating agent. The three chelation units are composed of a Mimosine amino acid tuned with a methyl (electron donating group) in order to enhance the chelation affinity toward Al(III).

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[3] T. Kiss et al., *J. Inc. Phenom. and Mol. Rec. in Chem.*, **1998**, *32*, 385-403.