Quantum mechanical characterization of proteins with hybrid functionals: the case of the small protein crambin

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Molecular simulations of proteins have been usually accomplished through empirical or semi-empirical potentials, due to the large size and inherent complexity of these biological systems. On the other hand, a theoretical description of proteins based on quantum-mechanical methods would provide an unbiased description of their electronic properties, possibly offering a precious link between these and the final biological activity. Yet, such approaches have been historically hindered by the large amount of requested computational power and limited, in practice, to mixed QM/MM simulations. More recently, however, the availability of new and improved High Performance Computing (HPC) architectures has made the fully ab-initio treatment of proteins within the reach of quantum-mechanical computational software. Particularly, here we demonstrate the application of the periodic Density Functional Theory CRYSTAL14 code,[1] in its efficient massively parallel version,[2] to the description of the small plant's seed protein crambin (46 aminoacids), a common test case. We have employed the accurate hybrid B3LYP functional, coupled to an empirical description of London interactions (D*) to optimize the crambin crystal geometry, starting from an high resolution neutron diffraction structure (PDB: 4FC1),[3] with an increasing amount of water molecules in the cell (up to 166 waters per cell, close to the actual crambin crystal). A good agreement with the experiment has been achieved for both protein geometry (backbone RMSD = 0.432 Å) and protein-water interactions. Inclusion of water proved to be essential for a correct description of the system. The energetics has been computed, obtaining accurate crystal formation energies, protein-water, protein-protein and water-water interaction energies. The unique information obtained from a fully ab-initio treatment of the system allowed to study the electronic properties of the protein, such as its electrostatic potential and the charge transfer involved in its interaction with water. Finally, the full infra-red spectrum of crambin has been modeled. These results proved that accurate quantum-mechanical simulations of small proteins are now possible in a reasonable amount of time, thanks to efficiently parallelized computational codes, coupled to modern HPC architectures.

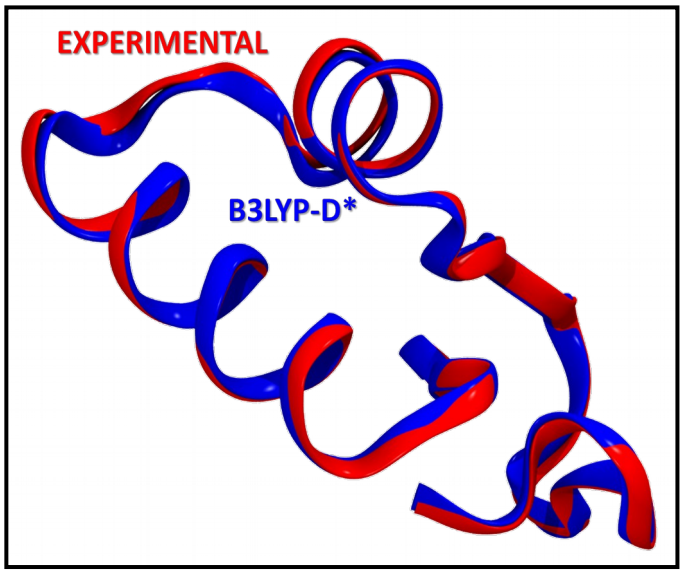

Figure 1. *B3LYP-D* optimized structure of crambin (in blue; only the backbone is shown) superimposed to the experimentally determined structure (in red, PDB ID: 4FC13).*

(1) Dovesi, R. et al. *Int. J. Quantum Chem.* **2014**, *114*, 1287–1317.
(2) Orlando, R. et al. *J. Comput. Chem.* **2012**, *33*, 2276–2284.
(3) Chen, J. C.-H. et al. *Proc. Natl. Acad. Sci.* **2012**, *109*, 15301–15306.