Modelling Reaction-Competent Carboxypeptidase A-Peptide-Complexes

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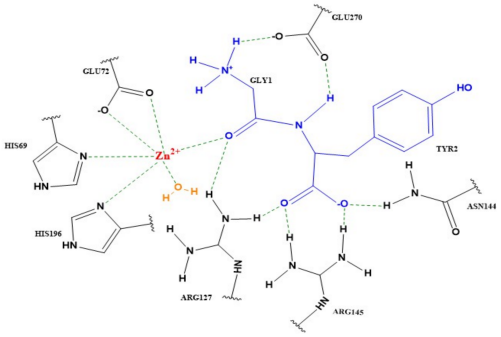

Carboxypeptidase A is a zinc-dependent protease that hydrolyses peptides at the C-terminal end and is specific to residues with hydrophobic side chains. According to the proposed mechanisms in the literature, catalysis requires a water molecule to be close to the zinc center.

In our study, we designed two complexes: one with Ala-Gly-Tyr and another with Ala-Ala-Gly-Tyr. These complexes are analogous to the known Gly-Tyr complex[1]. We performed molecular dynamics simulations with AMBER using the 12-6-4-LJ[2] and EZAFF[3] (Extended Zinc AMBER Force Field) models and compared their properties.

Our modeling approaches resulted in stable simulations with the ligand bound to the active site of the complex. This approach allows us to observe the interactions between the ligand and the complex and to compare the 12-6-4 and EZAFF models. The EZAFF model aims for a natural 5-fold geometry (without bound water) or a 6-fold geometry (with bound water) at the zinc center, whereas the 12-6-4 model produces unnatural 6- to 7-fold coordinating geometries. The behavior of water, which is essential for the expected mechanism, differs significantly as well. Moreover, our modelling results give hints about the reactivity of the ligand. The smaller Ala-Gly-Tyr ligand enables mechanistically important coordination of water to the zinc center; however, this is spatially blocked by the larger Ala-Ala-Gly-Tyr ligand.

[1] Jorge Antonio Amador Balderas, Frank Beierlein, Anselm H. C. Horn, Senta Volkenandt, Leon Völcker, Nikoo Mokhtari, Jules Cesar Epee Ndongue, and Petra Imhof. Mode of metal ligation governs inhibition of carboxypeptidase a. International journal of molecular sciences, 25(24), 2024. doi: 10.3390/ijms252413725

[2] Pengfei Li and Kenneth M. Merz. Taking into account the ion-induced dipole interaction in the nonbonded model of ions. Journal of chemical theory and computation, 10(1):289#297, 2014. doi: 10.1021/ct400751u.

[3] Zhuoqin Yu, Pengfei Li, and Kenneth M. Merz. Extended zinc amber forcefield (ezaff). Journal of chemical theory and computation, 14(1):242#254, 2018. doi: 10.1021/acs.jctc.7b00773.