How glycosidases operate: combining crystallography and quantum mechanics to uncover new mechanisms

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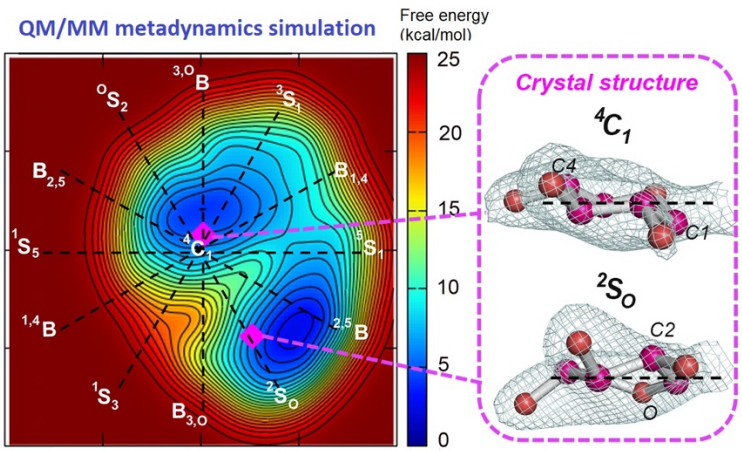
Glycosidases (GHs) are amongst the most proficient of enzymes, showing typical rate enhancements of up to 10^{17}-fold. Large efforts have been devoted since many decades to uncover their catalytic mechanisms. Most GHs follow the Koshland classical mechanisms for retaining and inverting glycosidases, in which two essential carboxylic acid residues catalyze the cleavage of the glycosidic bond. It is also recognized that GHs favor certain distorted sugar shapes or conformations upon binding to the enzyme [1,2]. However, there are notorious exceptions such as GHs following neighboring group participation and GHs with uncommon (e.g. Tyr, Cys) or yet uncharacterized nucleophiles, for which the molecular mechanisms remain elusive. Recently, we have uncovered the molecular mechanisms of GHs that either follow non-Koshland mechanisms or challenge the common view of the enzyme recognizing high energy substrate conformations. In this dual oral communication, we will bring our new discoveries which were based on both state-of-art experiments (discussion led by Mariana Morais) and theoretical calculations (discussion led by Carme Rovira).We will report the detailed molecular mechanism of two GHs with uncommon active site nucleophile residues [3,4], as well as exo-acting GHs that, unlike their endo-counterparts, do not require substrate distortion for catalysis [5,6]. We will also highlight how the enzymatic microenvironment can influence the substrate distortion [7], including new findings of GH families with distinct active-site topologies.



Conformations adopted by the xylopyranosyl ring at the −1 subsite of GH43 exo-oligoxylanase as showed by simulations and X-ray crystallography [8]

Bibliographic references:

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