How does nature break and make glycosidic bonds. QM/MM metadynamics investigations

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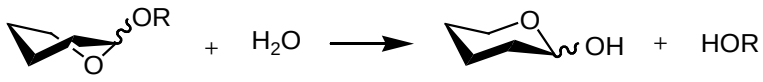
Nature has contrived a multitude of ingenious methods to cleave and form glycosidic bonds in carbohydrates. Two main groups of enzymes undertake these duties. Whereas glycoside hydrolases (or glycosidases, GHs) catalyze the cleavage of glycosidic bonds, nature's principal agents for the construction of the glycosidic bond are the glycosyltransferases (GTs). It is nowadays accepted that one of the sugar rings of the carbohydrate (the one located at the -1 enzyme subsite) distorts away from the $^4C_1$ chair conformation into a boat or skew-boat conformation, prior to cleavage of the glycosidic bond (1). We previously showed in one example that this distortion results in electronic and structural changes that are "on the path" towards the transition state (TS) of the reaction, favoring in this way the cleavage of the glycosidic linkage (2). Therefore, the distorted conformation of the substrate in the Michaelis complex gives information about the "*catalytic conformational itinerary*" (3). This is of relevant importance when designing TS-analog specific inhibitors for GHs. Here we will summarize our recent work on the prediction of catalytic conformational itineraries in different GHs, as well as catalytic mechanisms in GTs, using QM/MM metadynamics simulations (4,5).



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