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Study of the reaction mechanism of a glutamic protease

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Proteolytic enzymes are gaining ever-growing attention due to the rise of potential industrial and therapeutic applications. Engineered proteases are regarded as potent constituents of detergents, agents against celiac disease, and cleavers of polyester-urethane. Engineering via rational design requires detailed knowledge of the enzyme's catalytic mechanism. It allows researchers to pinpoint crucial residues involved in the process of bond breaking and formation and decipher the internal logic of the catalytic site in order to enhance or transfer its action.

Among all 6 currently known protease families, glutamic proteases are the most recently discovered ones. Their catalytic mechanism has been only proposed but not yet validated https://paperpile.com/c/mAc9d8/m85X. No computational study able to model the whole dynamical process of the catalytic act was conducted to date. The goal of the presented study, therefore, was the study of the reaction mechanism of glutamic proteases utilizing molecular modeling.

We first conducted a detailed investigation of the enzyme's dynamics in the unliganded state starting from its crystal structure. Enhanced-sampling techniques allowed us to establish that catalytic Gln53 is assigned to its corresponding electron density in the erroneous conformation and thus cannot act as described in the mechanism proposed by Fujinaga et al. in 2004. We then investigated the alternative possible mechanisms and concluded that Glu69 may play an equally important role for the catalysis as Glu136 previously assigned as "catalytic". Finally, we proposed a new possible mechanism of action of glutamic proteases and validated it by full reconstruction of the reaction pathway using QM/MM modeling.

Reinvestigation of the proposed catalytic mechanism of glutamic proteases may open them to broad scientific community as potential scaffolds for engineering for industrial and therapeutic

applications. Moreover, it may facilitate further studies dedicated to the evolution and regulation of such enzymes.

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Источники и литература

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