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165 - Elucidation of the acetamide hydrolysis mechanism using QM metadynamics simulations as a model for amide hydrolysis in proteins

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The reaction mechanism for the hydrolysis of amide bonds is a much debated topic in literature. This is not surprising when considering the variety of biologically significant domains in which this reaction is of interest. For instance, asparagine (Asn) and glutamine (Gln) residues are known to undergo spontaneous nonenzymatic deamidation in water, forming aspartic acid and glutamic acid residues. Deamidation could be the result of a hydrolysis reaction, either via a concerted or a stepwise mechanism.

In this work, we perform quantum mechanical dynamics and metadynamics simulations of the hydrolysis of acetamide as a model compound for Asn or Gln. The methodological aspects related to a careful selection of collective variables and an interpretation of the multidimensional free energy surface will be discussed, leading to the identification of the most competitive pathway for peptide sidechain deamidation. These results give a clearer insight in deamidation processes on proteins and polypeptides.

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