

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, ranging from peptide bonds to protein side chain degradation. For instance, asparagine (Asn) and glutamine (Gln) residues are known to undergo spontaneous nonenzymatic deamidation in water to form aspartic acid and glutamic acid residues under physiological conditions. Deamidation could be the result of a hydrolysis reaction, either via a concerted or a stepwise mechanism.[1] Gas phase calculations have shown that explicit water molecules can play an important role in this reaction, but to date, no simulations of hydrolysis pathways using an extensive, periodic water model have been performed.

In this work, we perform quantum mechanical dynamics and metadynamics simulations on the hydrolysis of acetamide as a model compound for Asn or Gln. The periodic simulation cell consists of one acetamide molecule and 90 water molecules in a cubic 15 Å box. 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 and show that an adequate description of the natural surroundings of the active species is necessary for obtaining a realistic image of biological processes.

Keywords: hydrolysis, deamidation, metadynamics

[1] S. Catak, G. Monard, V. Aviyente and M.F. Ruiz-López, *J. Phys. Chem.*, **113**, 1111-1120 (2009)