QM Metadynamics Study on Peptide Deamidation

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Asparagine (Asn) residues spontaneously deamidate to form aspartate under physiological conditions, causing time-dependent changes in the conformation of proteins, limiting their lifetime [1]. The '*molecular clocks*' hypothesis [2], suggests that deamidation is a biological molecular timing mechanism that could be set to any desired time interval by genetic control of the protein structure and the immediate environment of the Asn residue. The fact that deamidation occurs over a wide range of biologically relevant time intervals suggests that different mechanisms may be at play. To date deamidation is believed to occur over a succinimide-mediated pathway [3]. Concerted and stepwise pathways leading to the succinimide intermediate were previously explored with the inclusion of explicit water molecules [4]; a novel route leading to the succinimide intermediate via tautomerization of the Asn side chain amide functionality was proposed [5].

The current study introduces a new 'competing' route for the deamidation of asparagine residues. The aim is to comparatively analyze the feasibility of this new mechanism against the traditional succinimide route, taking into account the catalytic effect of the solvent environment. For this purpose, QM dynamics and meta-dynamics [6,7] calculations were performed on a model peptide placed in a periodic water box. These results will identify the lowest energy pathway for asparagine deamidation and will serve as a stepping stone for QM/MM calculations of Asn deamidation in proteins.

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