DFT-based Elucidation of Asparagine Deamidation in Peptides

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Asparagine (Asn) residues spontaneously – yet non-enzymatically – deamidate to form aspartate under physiological conditions, causing time-dependent changes in the conformation of proteins, limiting their lifetime [1]. Deamidation has been associated with aging, development and protein turnover. 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 feasibility of the tautomerization route was further explored with QM metadynamics calculations. The current study also introduces a new 'competing' route for deamidation of asparagine residues. The aim is to comparatively analyze the feasibility of this new mechanism against the traditional succinimide route. These results will help identify the lowest energy pathway for asparagine deamidation and will serve as a stepping stone for calculations on deamidation in proteins.

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