QM Metadynamics Study on Succinimide Hydrolysis

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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. 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]. The rate determining step for the succinimide-mediated deamidation pathway has been subject to controversy. A recent study has suggested that the hydrolysis of the succinimide intermediate is the rate-determining step in the overall deamidation process [5]. Nonetheless, these calculations were limited by the use of explicit solvent molecules and failed to reproduce experimental deamidation half-times. This study has focused on the effect of the solvent environment on the hydrolysis of the succinimide intermediate, which can occur through a concerted or stepwise mechanism involving a gem-diol intermediate. For this purpose, QM dynamics and meta-dynamics [6] calculations were performed on a model peptide placed in a periodic water box. These results will help identify the lowest energy pathway for the hydrolysis of the succinimide intermediate.

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