The Effect of the (*N* +1) Residues on Peptide Deamidation

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Deamidation is a reaction that occurs spontaneously in peptides and proteins [1]. Many reports show that changes accompanying deamidation have a substantial effect on protein structure, which markedly affect protein function and stability. Increased amounts of deamidated proteins have been found in some aged and diseased tissues, such as human eye lens cataracts [2] and Alzheimer's plaques [3].

Deamidation occurs over a wide range of biologically relevant time intervals; this suggests that different mechanisms may be operative. A succinimide-mediated pathway is the current prevailing theory [4] and has been subject to several computational studies [5-7]. A recent experimental study on pentapeptides [8] has shown that Asn deamidation rates are directly related to the primary structure (peptide sequence) near Asn, with a more prominent effect from the carboxyl-side (Yyy) residue. However, the effect of the identity of the Yyy residue is still unclear. Herein we explore the correlation between experimental deamidation rates and primary structure for two different pentapeptides (Yyy=Gly, Ile), in order to identify the factors causing this dependence and obtain a better understanding of the effect of the immediate environment. The effect of the neighboring residue is investigated on a small model system, a pentapeptide (Gly-Gly-Asn-Yyy-Gly) in water. Replica-Exchange Molecular Dynamics (REMD) calculations were performed on these two pentapeptides with the GROMACS 4 software [9] using the GROMOS96 forcefield. Reaction barriers for the deamidation of both pentapeptides were investigated with QM/MM calculations utilizing the CP2K code.

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