Investigation of the effect of β-Cyclodextrin on Peptide Deamidation: A Molecular Dynamics Study

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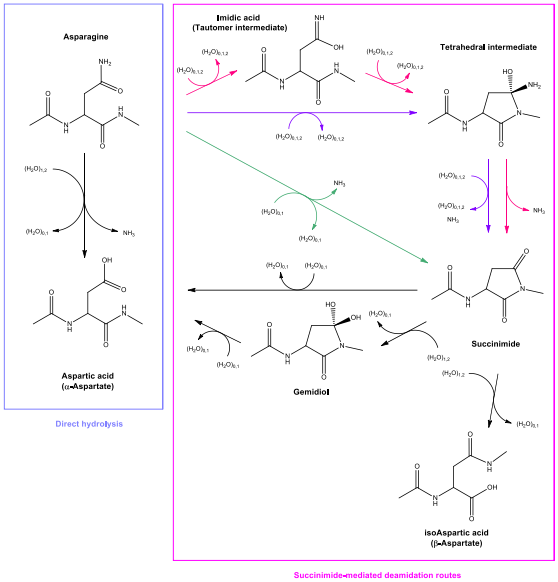

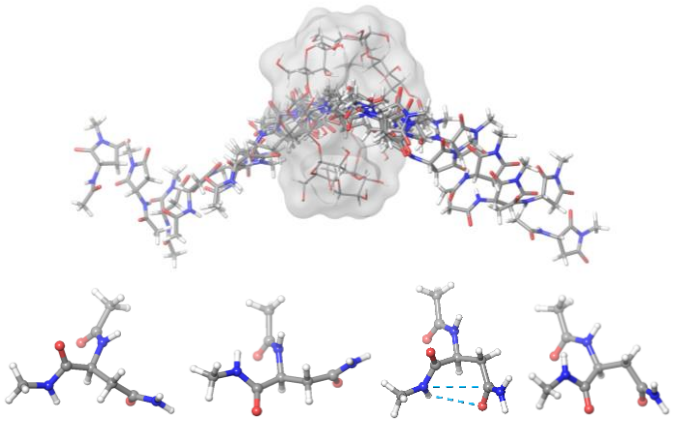

The deamidation of asparagine-containing peptides is associated with a relatively complex mechanism including tautomerization, isomerization and hydrolysis steps [1]. The resulting product distribution is known to be sensitive to the presence of a β-Cyclodextrin (β-CD) host [2]. To investigate this sensitivity, we have applied a number of classical molecular modelling based methods to peptide containing motifs in aqueous solution, namely Asparagine (Asn) and Succinimide (Succ) guests, in the presence of β-CD. We find that unbiased/standard molecular dynamics (MD) simulations are not appropriate for obtaining a converged ensemble of structures, due to the fact that the inclusion host–guest complexes dissociate in a relatively short period of time and re-association events are rare. To circumvent this issue we employed advanced sampling techniques such as umbrella sampling and replica exchange molecular dynamics (REMD), which allowed us to derive the free energy profile (Potential of Mean Force (PMF)) along the host−guest binding coordinate. The derivation of these profiles as well as their relevance to the mechanism of the deamidation reaction in the presence of β-CD will constitute the focus of the presentation.

[1] Catak S., Monard G., Aviyente V., Ruiz-López M. F., *J Phys Chem A.*, **2009**, *113(6)*, 1111–1120.

[2] Qi Y., Volmer D. A., *Eur. J. Mass Spectrom.*, **2015**, *21*, 701–705.