An REMD and QM/MM study into the sequence effect on asparagine deamidation

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Asparagine residues in proteins are subject to spontaneous degradation through deamidation. Surpassing a succinimide intermediate, the asparagine is transformed into an aspartyl or isoaspartyl residue. As this destabilizes the protein by introducing a net negative charge, asparagine deamidation is key to the "Molecular Clock Hypothesis", postulating that it acts as a timer for several biological events [1]. To explore the effect of sequence on the deamidation rate, extensive experimental research has been conducted on pentapeptides. On these benchmark systems, it has been established that the amino acid downstream from asparagine heavily influences the deamidation process [2]. However, the nature of this influence and its impact on the mechanism remain unclear.

In this work in progress, we use molecular modeling to explore possible mechanisms behind the sequence effect on asparagine deamidation. Several pentapeptides of type Gly-Gly-Asn-Yyy-Gly (with Yyy: Gly, Lys, Tyr, Glu, or Ile) were selected, as these systems represent all typical side chain characters and because they display a broad variation in measured deamidation rate. Relying on Replica Exchange Molecular Dynamics (REMD) simulations [3] in a force-field description, differences in conformational population for the explicitly solvated pentapeptides are compared. The acyclic reactant species as well the cyclised succinimide intermediate are considered, the latter requiring additional force field parameterisation. Furthermore, mechanism and reaction barriers for several steps in the water-mediated deamidation are investigated using Nudged Elastic Band (NEB) simulations within a QM/MM scheme [4].

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