QM/MM Meta-Dynamics Study of Asparagine Deamidation in Proteins

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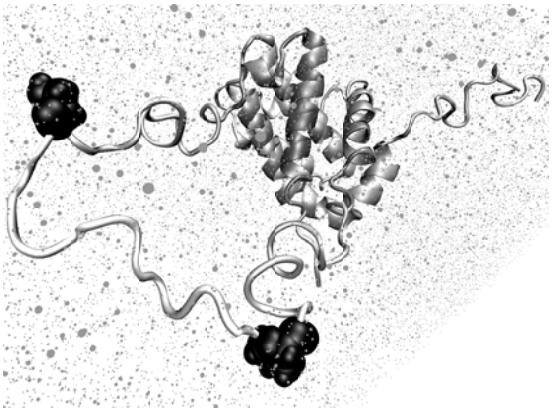
Asparagine (Asn) residues in peptides and proteins are subject to spontaneous non-enzymatic deamidation to form aspartate or iso-aspartate at a rate determined by protein structure and environment [1]. Deamidation causes time-dependent changes in charge and conformation and limits the lifetime of peptides and proteins. This has led to the '*molecular clocks'* hypothesis [2], which suggests deamidation is a biological molecular timing mechanism that could be set to any desired time interval by genetic control of the primary, secondary, and tertiary structure surrounding the amide. A notable example is Bcl-x_L, an anti-apopotic protein that regulates cell death and undergoes a 'complete loss' of function upon deamidation; suppression of deamidation in Bcl-x_L plays a pivotal role in the survival of tumor cells [1].

Deamidation occurs over a wide range of biologically relevant time intervals; this suggests that different mechanisms may be operative. While a succinimide-mediated deamidation pathway was originally suggested [3-5], two new 'competing' routes for deamidation of asparagine residues will be presented. In order to compare relative energetics and feasibilities of plausible routes, QM/MM molecular dynamics simulations, in a periodic water box, were performed on a model peptide. Free energies of competing pathways were calculated *via* meta-dynamics calculations utilizing the CP2K code [6], where the catalytic effect of water molecules was explicitly analyzed. These calculations have served as a stepping stone for QM/MM metadynamics calculations on deamidation of Bcl-x_L.



Keywords: Deamidation, asparagine, Bcl-x_L, meta-dynamics, QM/MM, CP2K

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