COMP: Division of Computers in Chemistry

393 - Solvation and primary structure effects on the deamidation of asparaginyl residues in peptides

View Session Detail

Jeroen Van der Mynsbrugge[2] *, jeroen.vandermynsbrugge@ugent.be, Samuel L.C. Moors*[32] *, Veronique Van Speybroeck*[2] *, Saron Catak*[12]
[1] Chemistry Department, Bogazici University, Istanbul, Turkey; [2] Center for Molecular Modeling, Ghent University, Zwijnaarde, Belgium; [3] Eenheid Algemene Chemie, Vrije Universiteit Brussel, Brussels, Belgium

Abstract: Deamidation of peptides and proteins is the conversion of an amide group on the sidechain of an amino acid to a carboxylate. Deamidation of Asn and Gln residues occurs spontaneously under physiological conditions, significantly altering the structure and properties of proteins.[1] The instability of these residues has been suggested to be their primary function, allowing them to serve as a timer for biological events.[2] In an experimental study on pentapeptides, Robinson et al. have shown that Asn deamidation rates depend on nearby variations in the primary structure, primarily of the n+1 residue on the carboxyl side (Yyy).[3]

In the current study, we investigate the effect of different n+1 residues (Yyy=Gly, Ile, Tyr, Lys, Glu) on the mechanism and kinetics of succinimide-mediated deamidation.[4] The dynamics of the five pentapeptides in a water box are studied using Replica-Exchange Molecular Dynamics (REMD) simulations performed with GROMACS 4. Next, the influence of both variations in the n+1 residue and the presence of solvent molecules on the deamidation of the Asn side-chain are assessed using implicit-solvent DFT calculations and QM/MM calculations with explicit water molecules performed with Gaussian 09.

[1] Robinson, NE, Robinson, AB Proc. Natl. Acad. Sci. USA 2001 , 98, 944.
[2] Robinson, NE, Robinson, AB 'Molecular Clocks: Deamidation of Asparaginyl and Glutaminyl Residues in Peptides and Proteins', Althouse Press: Cave Junction, OR, 2004.
[3] Robinson, NE J. Peptide Res. 2004 , 63, 426.
[4] Catak, S., Monard, G., Aviyente, V., Ruiz- López, MF J. Phys. Chem. A 2009 , 113, 1111.