Computational Analysis on Deamidation Mechanisms of Asparagine Residues Catalyzed by Acetic Acid

Tomoki Nakayoshi[1,2], Kota Wanita[1], Koichi Kato[1,3], Eiji Kurimoto[1], Akifumi Oda[1,2,4]

[1]Graduate School of Pharmacy, Meijo University, Nagoya, Aichi, Japan

[2]Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan

[3]Department of Pharmacy, Kinjo Gakuin University, Nagoya, Aichi, Japan

[4]Institute for Protein Research, Osaka University, Suita, Osaka, Japan

Asparagine (Asn) residues in peptides and proteins are prone to nonenzymatic deamidation with the release of ammonia molecule. At pH higher than 5, Asn-residue deamidation proceed via five-membered ring succinimide (Suc) intermediate, subsequently the Suc-intermediate hydrolysis forms Asp of isoAsp residues. That is, the Asn-residue deamidation alters the charge state of the protein. Therefore, Asn-deamidation is considered to cause the aberrant conformational changes of the protein and to trigger some age-related diseases, such as cataract [Prog. Biophys. Mol. Biol., 115, 21–31, 2014] and Parkinson's disease [Protein Sci., 18, 1766–1773, 2009]. Asn-residue deamidation has been observed not only in biological proteins but also in antibody drugs, and may affect the efficacy of antibody drugs. Recently, Connolly et al. experimentally showed that the various carboxylic acid can catalyzed Asn-residue deamidation [Mol. Pharmaceutics, 11, 1345–1358, 2014]. However, the deamidation mechanisms of Asn residues has not been fully elucidated so far. In this study, we calculated the reaction pathways from the Asn residue to the formation of the Suc intermediate using a model in which an acetic acid (AcOH) was placed around Asn residue. In addition, we also investigated the reaction pathway which AcOH–water complex (with one or two explicit water molecules placed around AcOH) catalyzes Asn-residue deamidation.