Theoretical study on keto-enol tautomerization of glutarimide for exploration of the isomerization reaction pathway of glutamic acid in proteins using density functional theory

Shuichi Fukuyoshi[a], Tomoki Nakayoshi[a], Ohgi Takahashi[b], Akifumi Oda[a, c]

[a]Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa, Ishikawa 920-1192, Japan
[b]Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan
[c]Institute for Protein Research, Osaka University, 3-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Abstract

The majority of proteins are built from L-amino acids. However the proteins containing the D-amino acid residues were recently discovered. The D-amino acid residues were detected from crystalline for lens and amyloid-beta in the brain. So it is pointed out that D-amino acid and age-related diseases may be related. Because the D-amino acid in protein will change the conformation of the protein, the activity of proteins might be strongly influenced. The D-amino acid residues in the proteins that have been chiefly founded were D-aspartic acid. L-Aspartic acid residues in peptides are known to undergo spontaneous non-enzymatic reactions to form D-aspartic acid residues via cyclic succinimide intermediate. Takahashi et al. studied a series of reaction pathway of aspartic acid using a density functional theory[1,2,3,4]. In that study a barrier of the water assisted racemization pathway ware estimated at less than 30 kcal/mol. This result is consistent with the experimental fact. Although glutamic acid is similar in structure to aspartic acid, little has been reported on racemization of glutamic acid residues in a protein. In order to elucidate the reason why glutamic acid residues have lesser racemization reactivity than asparaginic acid, we investigated the racemization energy barrier of piperidinedione, which is the presumed intermediate of the isomerization reaction of L-Glu to D-Glu, by density functional theory calculations. In two-water-molecule-assisted racemization, the activation barrier for keto-enol isomerization was 28.1 kcal/mol. The result showed that the activation barrier for the racemization of glutamic acid residues was not different from that for the racemization of aspartic acid residues. Thus, glutamic acid residues can possibly cause the racemization reaction if the cyclic intermediate stably exists.

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