Computational and Theoretical Chemistry 1038 (2014) 17–25

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

A comparison of L- and D-Asp and Asn α-radicals a case study for atropisomerism

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ARTICLE INFO

Article history:
Received 21 January 2014
Received in revised form 25 February 2014
Accepted 1 March 2014
Available online 19 April 2014

Keywords:
Kinetic and thermodynamic stability of Asp radical
Asp radical Ramachandran surface
Axis chirality
Ab initio quantum chemistry

ABSTRACT

Asp radical has enantiomeric D and L form, due to axis chirality. This pair of degenerate minima is occurring on a single 4D-Ramachandran Potential Energy Hyper Surface (PEHS). The $^{\cdot}\beta_D$ and $^{\cdot}\beta_L$ radicals are interconverted on a pair of enantiotopic paths of the 4D-PEHS each of which has a lower and a higher transition state. These barriers are always higher for the Asp in comparison to those of the Asn radical.

1. Introduction

According to recent findings, proteins in human tissue not only contain L-amino acid residues, but their enantiomeric D-configurations are also present as well. These D-configurations were mostly found in elderly tissue, particularly in aorta [1], in teeth [2], in eye lens [3] and also in brain tissues [1,4]. It was observed, that the older the examined tissue was, the more D-amino acid it contained. These results indicated that the ratio of D- to L-residue increases during the process of aging [4–6].

The radical reactions of proteins, caused by oxidative stress are important inasmuch as several diseases including Alzheimer's and Parkinson's disease, vascular dementia, type II diabetes [7–9] are associated with these processes. Reactive oxygen species ($OH^{\cdot}$, H_2O_2, $O_2^{-\cdot}$) may cause hydrogen abstraction from amino acid residues, and therefore change the structure of the protein [10,11].

Asparagine (Asn) is a non-essential amino acid that usually deamidates spontaneously into aspartic acid (Asp) [12]. As Asn plays an important role in many biochemical reactions [13–16] its deamidation is a common protein degradation pathway [17–19].

Previously, molecular computations have been carried out for Gly and Ala radicals, which are planar and they have either no side-chain or small side-chains and are achiral [11]. More recently, it has been pointed out that amino acids with a longer side-chain that is able to interact with the backbone do behave differently [20]. Calculations on Asn diamide have shown that L- to D-configurational changes are possible due to axis chirality [20]. The purpose of the current paper is to compare this process, with its acid analogue: Asp. Asp is stated to be the most frequently enantiomerised (L → D) amino acid, it is used in forensic science to estimate the age of an unknown human victim from its percentage of D-Asp in his teeth [19,21].

Since L- to D-epimerization of both asparagine and aspartic acid residues play important roles in molecular aging, the comparison of the two Cα-centered radicals of Asn and Asp represents a key question. The present paper aims to compare the two radical species generated from Asn and Asp. Scheme 1 shows the mechanism of Asp involving α-free radical intermediate.

2. Methods

In the previous study made on Asn radical, preliminary geometry optimization was completed at B3LYP/6-31G(d) level of theory, reoptimized at B3LYP/6-311++G(d,p) level of theory. Gibbs free energies were determined at MP2/cc-pVTZ and CCSD(T)/cc-pVTZ levels of theory by using B3LYP/6-311++G(d,p) geometries. Since the results have shown that higher level of calculation than B3LYP/6-31G(d) do not make any major improvement, therefore the geometry optimizations for the present comparison for Asp and Asn radicals were carried out using at B3LYP/6-31G(d) level

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http://dx.doi.org/10.1016/j.comptc.2014.03.040
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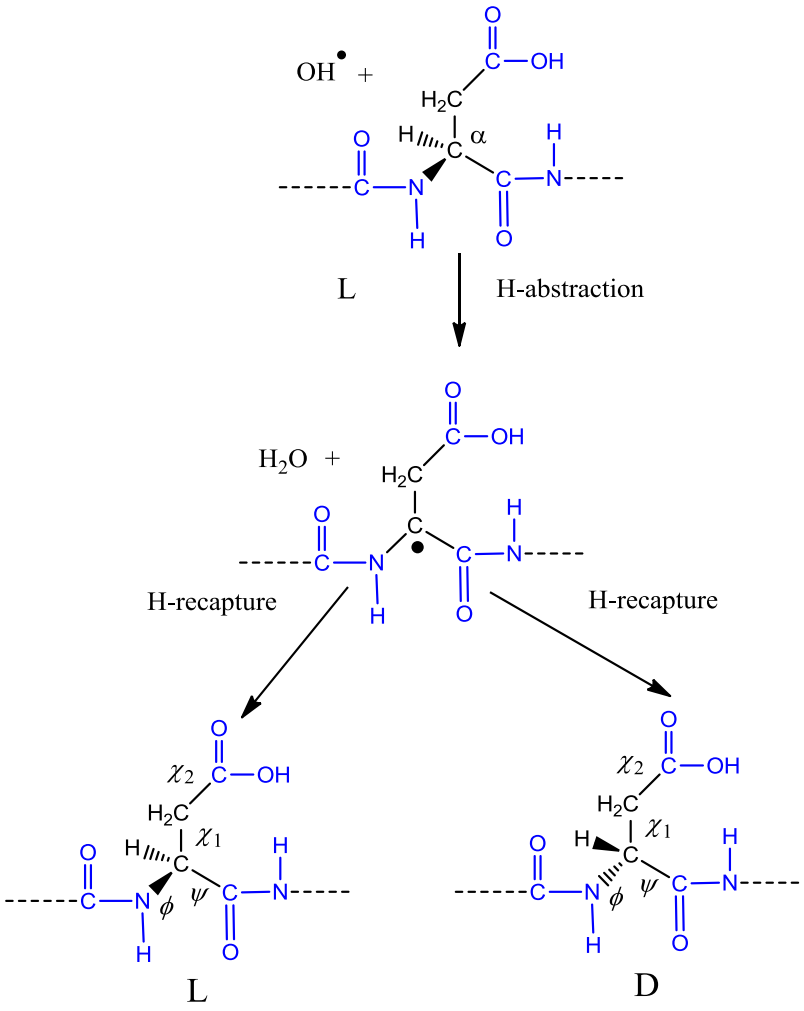
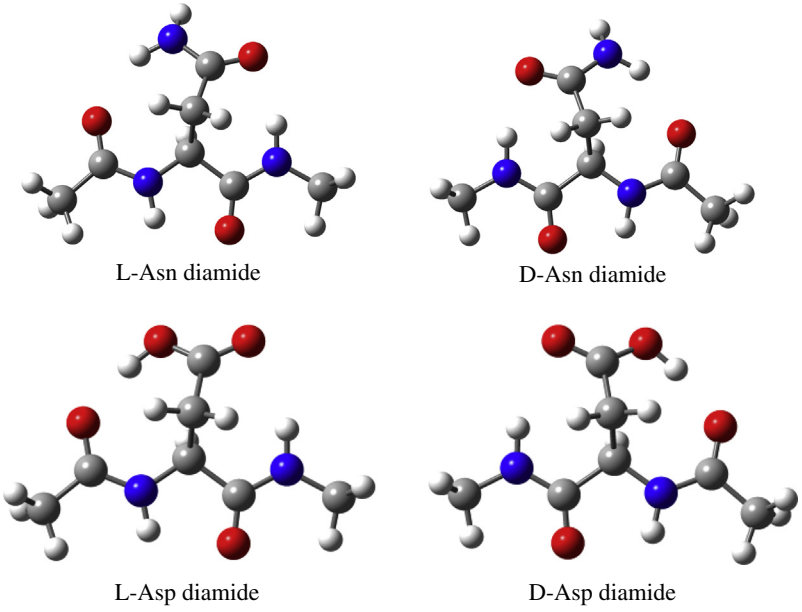


Scheme 1. L to D enantiomerization of Asp *via* α-free radical formation.



Scheme 2. Structures of the enantiomeric L-and D-Asn and Asp diamides in their extended backbone conformers; namely β_L and β_D.