Chemical Physics 457 (2015) 180–187

Contents lists available at ScienceDirect

Chemical Physics

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

Importance of asparagine on the conformational stability and chemical reactivity of selected anti-inflammatory peptides

Catalina Soriano-Correa [a,*], Carolina Barrientos-Salcedo [b], Linda Campos-Fernández [a], Andres Alvarado-Salazar [a], Rodolfo O. Esquivel [c]

[a] Química Computacional, Facultad de Estudios Superiores (FES)-Zaragoza, Universidad Nacional Autónoma de México (UNAM), Iztapalapa, C.P. 09230 México, D.F., Mexico
[b] Laboratorio de Química Médica y Quimiogenómica, Facultad de Bioanálisis Campus Veracruz-Boca del Río, Universidad Veracruzana, C.P. 91700 Veracruz, Mexico
[c] Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa (UAM-Iztapalapa), C.P. 09340 México, D.F., Mexico

ARTICLE INFO

Article history:
Received 24 February 2015
In final form 12 June 2015
Available online 27 June 2015

Keywords:
Anti-inflammatory peptides
Asparagine amino acid
Chemical reactivity
Conformational stability
M06-2X study

ABSTRACT

Inflammatory response events are initiated by a complex series of molecular reactions that generate chemical intermediaries. The structure and properties of peptides and proteins are determined by the charge distribution of their side chains, which play an essential role in its electronic structure and physicochemical properties, hence on its biological functionality. The aim of this study was to analyze the effect of changing one central amino acid, such as substituting asparagine for aspartic acid, from Cys–Asn–Ser in aqueous solution, by assessing the conformational stability, physicochemical properties, chemical reactivity and their relationship with anti-inflammatory activity; employing quantum-chemical descriptors at the M06-2X/6-311+G(d,p) level. Our results suggest that asparagine plays a more critical role than aspartic acid in the structural stability, physicochemical features, and chemical reactivity of these tripeptides. Substituent groups in the side chain cause significant changes on the conformational stability and chemical reactivity, and consequently on their anti-inflammatory activity.

1. Introduction

It is known that inflammatory response events are initiated by a complex series of molecular interactions generated by several chemical intermediaries; to date, these interactions continue to be partially understood [1–4]. Some molecules, such as free radicals and proteins, derive from the invading organism at the site of the damaged tissues, while others are the products of cells participating in the inflammatory response [2–5]. Several studies have shown that electron delocalization along the amino acid side chains of peptides and proteins could be caused by a substituent group along the peptide backbone; this substitution is significantly important for modifying the behavior of the physicochemical features and the chemical reactivity of peptides and proteins [6–12]. Also, peptide conformation and protein folding are controlled by several factors, including the following: electronic properties; hydrophobicity; inductive effect; pKa; conformational changes, and steric effects, which in turn might affect the chemical reactivity of molecules with pharmacological activity [7,13–18]. Moreover, the conformations adopted by a peptide or protein depend on its internal interactions (amino acids) and their ability to form hydrogen bonding with other side chain residues or backbone atoms that also contribute to stabilize the structure [13,19–22]. On the other hand, hydrogen bonding interactions becomes very specific when additive effects (often cooperative) occur [23–25]; thus, hydrogen bonds between the functional groups of peptides and proteins play a significant role in their physicochemical properties (Acid–Base) and chemical reactivity [8,10,13]. Therefore, quantum chemistry calculations are important to account for substituent effects that may provide insight into these electronic and physicochemical properties [6–8,11–14,26]. According to the latter, in earlier works our investigation group has studied the relationship between the physicochemical and structural properties of a small family of anti-inflammatory peptides [27–29]. Thus, the importance of the substituent effect of amino acid side chains on the physicochemical and chemical reactivity of these molecules was observed. Furthermore, we studied the competition between intra- and intermolecular hydrogen bonds and its influence on the structural stability of the Cys–Asn–Ser tripeptide in gas phase and in aqueous solution [22]. Hence, in this work, we focused in analyzing the effect produced by the exchange of one central amino acid (Asn) for (Asp) on the conformational stability, physicochemical properties and chemical reactivity in their

* Corresponding author. Tel.: +52 (55) 5773 6333.
E-mail address: csorico@comunidad.unam.mx (C. Soriano-Correa).

http://dx.doi.org/10.1016/j.chemphys.2015.06.005
0301-0104/

anti-inflammatory activity of the Cys–Asn–Ser (CNS) and Cys–Asp–Ser (CDS) tripeptides, through several quantum-chemical descriptors at the density functional theory (DFT)-M06-2X level of theory.

2. Computational details

The generic chemical structures of CNS, CDS, and their conformers studied in this work are depicted in Fig. 1. Electronic structure calculations were performed with the Gaussian 09 suite of programs [30]. All neutral, anionic, and cationic structures were optimized at the density functional theory (DFT) level of theory, utilizing a hybrid meta-exchange–correlation functional (M06-2X), which is known to describe non-covalent interactions adequately [31–33]. Calculations were carried out with a 6-311+G(d,p) basis set [34]. Energies were corrected for zero-point vibrational energy (ZPVE) at the M06-2X/6-311+G(d,p) level. Single-point calculations were performed on optimized structures (neutral, anionic, and cationic) at the M06-2X level in a 6-311++G(2d,2p) basis set. All calculations were undertaken in an aqueous environment (with a dielectric constant of water of $\varepsilon = 78.3553$). Solvent effects were described through the polarizable continuum model [35–38]. In order to determine the relative acidity of the Serine (Ser) amino acid, deprotonation energy (ΔE_{ac}) was calculated by deprotonation of the H2 hydrogen atom (see Fig. 1), according to the following reaction:

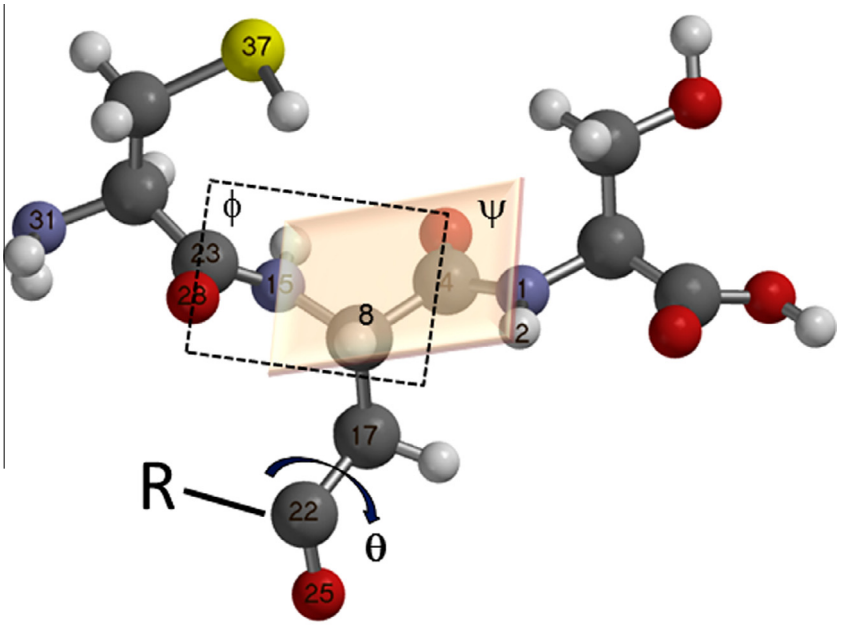
$$MN1H2 \rightarrow MN1^{-} + H2^{+}$$

Thus, small (ΔE_{ac}) values imply a more acidic amide (CON1H2) group [6,39,40]. In addition, proton affinity energies (ΔE_{PA}) provide a good method for analyzing the basicity of the amino group of the cysteine amino acid, in which a larger value is indicative of a more basic molecule. Therefore, (ΔE_{PA}) were calculated utilizing the isodesmic type of reactions, from which good results may be obtained in a relatively inexpensive manner [6,41]. ΔE_{PA} are given by the following reaction:

$$XH^{+} + CH_3 - NH_2 \rightarrow X + CH_3 - NH_3^{+}$$

were XH^{+} and X correspond to the protonated and neutral forms of the peptides. Total energy values at the M06-2X level for the pair $CH_3 - NH_2/CH_3 - NH_3^{+}$ are −95.77527/−96.11273 a.u., respectively. Moreover, we calculate atomic and group charges, fitted to the electrostatic potential (ESP), using standard model (CHELPG) [42] in order to examine some active sites of atoms and groups of CNS and CDS conformers, respectively.

To explore a more reliable characterization of the electronic structure, we employed some global reactivity descriptors, such as hardness (η) and electrophilicity index (ω). To calculate the electrophilicity index, we were required to compute electronic chemical potential and chemical hardness. For an N-electron system with external potential $v(r)$ and total energy E, the electronic chemical potential μ, that is, the negative of electronegativity χ, is defined as the partial derivative of the energy with respect to the number of electrons at constant external potential [43–45].



Where:

$[Cys - Asn - Ser\ (CNS), R = -NH_2]$

$[Cys - Asp - Ser\ (CDS), R = -OH\ ]$

$\theta = O_{25} - C_{22} - C_{17} - C_8$

$\phi = C_{23} - N_{15} - C_8 - C_4$

$\psi = N_{15} - C_8 - C_4 - N_1$

Fig. 1. Generic structure and convention used in numbering the atoms for Cys–Asn–Ser (CNS) and Cys–Asp–Ser (CDS) tripeptides; where the color scheme for each atom is the following: white (Hydrogen); gray (Carbon); blue (Nitrogen); red (Oxygen) and yellow (Sulfur). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)