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Computational study of the electronic structure characterization of a novel anti-inflammatory tripeptide derived from monocyte locomotion inhibitory factor (MLIF)-pentapeptide

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ABSTRACT

The structure and properties of molecules are determined by their charge-density distribution. Several works have shown that electron delocalization along the peptide backbone and side-chain modulates the physical and chemical features of peptides and protein properties. Research on *Entamoeba histolytica*-soluble factors led to the identification of the pentapeptide Met-Gln-Cys-Asn-Ser, with anti-inflammatory *in vivo* and *in vitro* effects. A synthetic pentapeptide, Met-Pro-Cys-Asn-Ser, maintained the same anti-inflammatory actions in experimental assays. A previous theoretical study allowed proposing the Cys-Asn-Ser tripeptide (CNS tripeptide) as the pharmacophore group of both molecules. This theoretical hypothesis was recently confirmed experimentally. The aim of this study was to characterize the electronic structure and physico-chemical properties of the CNS tripeptide through a theoretical study at the second-order Møller–Plesset perturbation theory (MP2) and density functional theory (DFT) theoretical levels. Our results in deprotonation energies show that the hydrogen atom (H2) of the serine-amide group possesses acidic characteristics. This result was confirmed by means of a study of bond order. Atomic charges, dipole moment, frontier molecular orbitals (Highest occupied molecular orbital [HOMO − 1] and Lowest unoccupied molecular orbital [LUMO + 1]), and electrostatic potential isosurface and its geometric parameters permitted to characterize its electronic structure and physico-chemical features and to identify some reactive sites that could be associated with this tripeptide's anti-inflammatory activity.

1. Introduction

Tissue damage caused by a wound or invasion by a pathogenic microorganism induces a complex sequence of events collectively known as the inflammatory response. Inflammatory-response events are initiated by a complex series of interactions involving several chemical mediators; these interactions continue to be at present only partially understood. Some of these interactions derive from the invading organism, some are released by the damaged tissue, several are generated by various plasma enzyme systems, and others are the products of several white blood cells participating in the inflammatory response [1,2]. Recently, works have shown that electron delocalization along the main chain bond of amino-acid side-chain peptides can be considered as a substituent group along the peptide backbone; both situations are important in modulating peptide chemical and physical features and therefore, the protein properties [3–6]. Amino-acid side-chain electronic properties, such as inductive and field effects, have not yet been characterized in any detail. Quantum mechanical calculation and fundamental equations that account for substituent effects may provide insight into these important properties [3,4]. Also, hydrophobicity and steric effects comprise two major factors that govern protein folding [3,7]. In addition, the weakness of the individual bond is such that it is frequently not sufficient for providing the strength and specificity necessary for biological processes. If hydrogen-bond donors or acceptors are arranged in particular geometries, hydrogen-bonding interactions become very specific, with additive—and often cooperative—strengths. Thus, hydrogen bonding between functional

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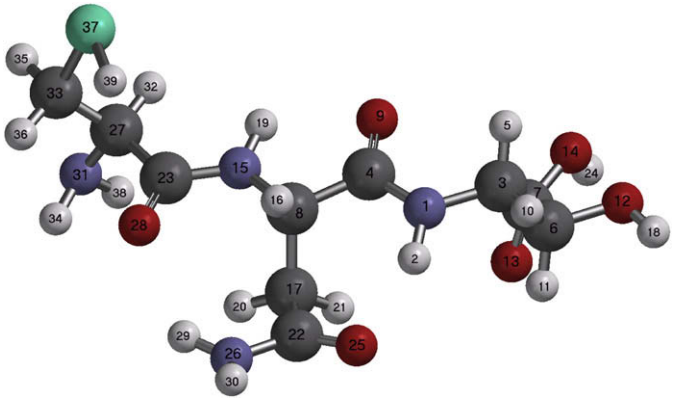

Fig. 1. Convention used in numbering atoms for analysis of atomic charges for the Cys-Asn-Ser (CNS) tripeptide.

groups occurring in biological molecules plays an important role in the electronic density of these bonds, as well as in their physico-chemical and structural features [3–7]. From a theoretical point of view, we are interested in the electronic, physico-chemical, and structural properties of small peptides with anti-inflammatory activity. Thus, Kretschmer and co-workers [8] investigated anti-inflammatory factor production by means of the parasite *Entamoeba histolytica* [9], which produces a thermostable pentapeptide (Met-Gln-Cys-Asn-Ser) that *in vitro* inhibits mononuclear phagocyte locomotion; the original name assigned is human monocyte locomotion inhibitory factor (MLIF). These authors established that the same synthetic sequence possesses similar anti-inflammatory properties to those of native MLIF [10], while another analogous pentapeptide, i.e., the proline amino acid, was substituted with glutamine in the second position (Met-Pro-Cys-Asn-Ser, pMLIF), presented anti-inflammatory activity; nevertheless, another pentapeptide with the same amino acids but a different arrangement (Gln-Cys-Met-Ser-Asn, sMLIF) did not present anti-inflammatory activity. These findings allowed studying the relationship between physico-chemical and structural properties with the anti-inflammatory activity of the three pentapeptides (MLIF, pMLIF, and sMLIF) by Soriano-Correa et al. [11,12]. These investigators carried out a theoretical study that related the importance of structural, physico-chemical, and electronic features with MLIF, pMLIF, and sMLIF anti-inflammatory activity. They found that MLIF and pMLIF pentapeptides maintained a great structural similarity [11,12], particularly among the last three amino acids (Cys-Asn-Ser, CNS) (Fig. 1). Later, Rico et al. carried out experimental studies in *in vivo* and *in vitro* models on the novel CNS tripeptide's anti-inflammatory activity with >95% purity and synthesized by the American Peptide Company [13]; they found that the Cys-Asn-Ser (CNS) tripeptide's carboxyl-terminal end group maintained 100% of its biological and anti-inflammatory properties, similar to the MLIF, thus experimentally verifying the pharmacophore group's anti-inflammatory activity proposed in the MLIF molecule predicted theoretically [11,12].

Therefore, the focus of this work was to perform calculations employing second-order Møller–Plesset perturbation theory (MP2) and density functional theory (DFT) theoretical levels to characterize electronic structure, physico-chemical properties, and geometric parameters utilizing standard and complementary density descriptors, with the purpose of better understanding the inflammatory processes and in this manner, design new small peptides with specific anti-inflammatory features.

2. Computational details

The electronic structure calculations were carried out employing the Gaussian 03 software program suite [14]. Also, with the purpose to gauge the effects of electron correlation, the structures were analyzed at the second-order Møller–Plesset perturbation theory (MP2) and density functional theory (DFT) theoretical levels. Because, we considered that the results of both methods are complementary between themselves, i.e., MP2 results of frequency calculations are more reliable, such that the optimized geometries are characterized by harmonic vibrational frequencies, which confirmed that the structures obtained are minima on the potential-energy surface [15]. In addition, the DFT-B3LYP theoretical level presents good descriptions of chemical reactivity. Also, in order to check the usefulness of DFT results, frequently important for large molecules for which more sophisticated methods require a long CPU time [16]. All neutral structures were optimized at MP2 and DFT-B3LYP levels utilizing Becke's three-parameter hybrid functional and the Lee–Yang–Parr correlation [17–20], while deprotonated (anionic) structures were optimized at unrestricted UMP2 and DFT-UB3LYP levels, all these with a 6–311 + G(d,p) basis set [21,22]. Optimized geometries are characterized by harmonic vibrational frequencies, which confirmed that the structures obtained are minima on the potential-energy surface. Energies were corrected to include zero-point vibrational energy (ZPVE) at B3LYP/6–311 + G(d,p) levels [14,21,22]. It is important to mention that the RMP2 and DFT-RB3LYP to UMP2, and DFT-UB3LYP SCF solution stability were tested for anionic molecules. Single-point calculations were performed on optimized structures (neutral and anionic) at MP2 and DFT (B3LYP) levels with a 6–311++G(2d,2p) basis set. To determine serine (Ser)- and cysteine (Cys)-amino acid relative acidity, deprotonation energy (ΔE) was calculated by deprotonating H2 and H39 hydrogen atoms, respectively (Fig. 1), according to the following reaction:

$$MXH \rightarrow MX^- + H^+ \quad (1)$$

where X = N1 or S37, and H = H2 or H39, respectively. Then, small ΔE values imply more acidic amide [23–25] (COHNH2) and thiol (SH39) groups. In addition, atomic and group charges fitted to the electrostatic potential (ESP) [26] were obtained to examine amide- and thiol-group acidic character and CNS-tripeptide active sites. Additionally, a bond-order analysis employing Natural bond orbital (NBO) scheme [27–29] was performed to provide an alternative insight into amide- and thiol-group relative acidity with the purpose of analyzing reactive sites. Also, dipole-moment analysis (μ) was undertaken at the same theoretical level to assess the charge's electronic distribution. Furthermore, we determined frontier molecular orbitals (Highest occupied molecular orbital [HOMO − 1] and Lowest unoccupied molecular orbital [LUMO + 1])

Table 1
Deprotonation energies, ΔE, for the CNS tripeptide at MP2 and B3LYP/6–311++G(2d,2p)//B3LYP/6–311 + G(d,p) levels.

Method	$-E$ (a.u.) MXH	$-E^-$ (a.u.)MN1$^-$	ΔE (kcal/mol)	$-E^-$ (a.u.) MS37$^-$	ΔE (kcal/mol)
MP2	1457.78570	1457.24429	330.52	1457.23907	336.30
B3LYP	1460.90395	1460.35790	333.40	1460.35401	338.37

Where X = N1 or S37 and H = H2 or H39. CNS tripeptide, Cys-Asn-Ser tripeptide.

Table 2
Bond order for the CNS tripeptide at MP2 and B3LYP/6-311++G(2d,2p)//B3LYP/6–311 + G(d,p) levels.

Method	N1–H2	N15–H19	C22–O25	C23–O28	N26–H29	N31–H34	S37–H39
MP2	0.654	0.677	1.256	1.225	0.705	0.717	0.756
B3LYP	0.645	0.664	1.272	1.251	0.724	0.740	0.757

CNS tripeptide, Cys-Asn-Ser tripeptide.

and electrostatic potential isosurface. From the geometric parameters, we selected certain dihedral angles [30] that were analyzed for characterizing amide-group deviation in the asparagine amino-acid side-chain, which forms an interesting hydrogen bond with the amide group between asparagine and serine amino acids and that might contribute to this tripeptide's geometric stability.

3. Results and discussion

Deprotonation energy values (ΔE) for the CNS tripeptide studied are presented in Table 1, and the molecular structure is presented in Fig. 1. We selected H2 and H39 hydrogen atoms to study the CNS-tripeptide's relative acidity because we suppose that these two hydrogen atoms are involved in this peptide's chemical reactivity and geometric stability. Studies carried out previously in other biological molecules that possess aminoacyl groups have shown that a smaller ΔE value is evidence of a more acidic group [23,24]. It may be observed from Table 1 that bond (N1–H2) possesses the smallest ΔE with respect to bond (S37–H39), this result suggesting that the amide group's hydrogen atom (H2) is more acidic than the thiol group (H39), i.e., H2 possesses more acidic characteristics than H39, this in agreement with pK_a experimental values Cys (HNH) p$K_a = 10.8$ and Ser (HNH) p$K_a = 9.15$ [31]. It is noteworthy that this trend persists at both calculation levels.

In Table 2, we present the values of some selected bond orders including the following: N1–H2; N15–H19; C22–O25; C23–O28; N26–H29; N31–H34, and S37–H39. We may further comment on the relative acidity of the amide and thiol groups by analyzing mainly the tripeptide's Cys (N31–H34), (S37–H39), Asn (N15–H19), and Ser (N1–H2) bond orders, respectively, because a smaller bond order should be indicative of a more acidic group [6,23–25]. We are able to observe that bond order (N1–H2) for Ser possesses the smallest value with respect to Asn (N15–H19), Cys (N31–H34), and (S37–H39) amino acids, respectively. Note that values are closer between Ser and Asn; nonetheless, the larger bond-order values of (N31–H34) and (S37–H39) imply small relative acidity and therefore, a larger amide-group proton affinity on the cysteine amino acid, which is in agreement with pK_a experimental values [31]. Considering now the two main bond orders, we observe that Ser (N1–H2) bond order is less than the Cys (S37–H39), i.e., the relative acidity of Ser's amide group is larger than the thiol group, this is in agreement with deprotonation energy (Table 1). It is important to note that (N1–H2) amide-group bond order is the smallest when compared with other amide groups such as N15–H19 and N26–H29 (see Table 2).

Table 3 presents the values of the atomic charges (fitted to the ESP) for N1, H2, N15, O25, N26, O28, N31, S37, and H39 atoms; we also analyzed the atomic charges by group, such as those of the HNH group of the asparagine side-chain and HNH cysteine amino acids, in addition to side-chain groups denominated R(Cys), R(Asn), and R(Ser), as well as the full atomic charges of Cys, Asn, and Ser amino acids, respectively. We explored whether the atomic, group, and full amino-acid charges are related with the studied tripeptide's anti-inflammatory activity. First, we investigated the effect of charges on N1, N15, N26, N31, O25, O28, and S39 to analyze the nucleophilic nature of these sites (Fig. 1). Thus, we observe in Table 3 that N1, N15, N26, N31, O25, and O28 possess negative charges, suggesting that these atoms are more exposed to electrophilic attacks on these atoms; hence, these sites might be the tripeptide's target. In contrast, we observed in Table 3 that H2 and H39 hydrogen atoms have positive values and a more positive charge on the H2 atom; thus, nucleophilic attacks can also occur at this site. These results are in agreement with the relative acidity of H2 calculated by means of deprotonation energy and bond orders (see Tables 1 and 2) for N1–H2 of the amide group, i.e., a more positive charge implies a lesser bond order and small deprotonation energy, and consequently stronger acidity with respect to the S37–H39 thiol group. Second, with regard to side-chain groups, one can observe small atomic-charge values in the three amino acids; in addition, it is observed that the R(Ser's) side-chain has larger negative charge than R(Cys) and R(Asn) amino acids. On the other hand, regarding cysteine and asparagine amine groups, our results illustrated that the cysteine's amine group Cys (HNH) possesses a larger negative charge than that of the Asn (HNH) asparagines group; therefore, the Cys (HNH) cysteine group contains more basicity characteristics than Ser (HNH) serine group; this result is in agreement with experimental evidence in which Cys (HNH) p$K_a = 10.8$ and Ser (HNH) p$K_a = 9.15$ [31]. Analysis of the full atomic charge of each full amino acid demonstrates that Cys possesses a positive charge in contrast with Ser and Asn. Finally, the position of the hydrogen atom (H2) suggests the formation of a hydrogen bond between CONH2···O25C, as can be observed in R(H2···O25), a distance whose value is 2.01 Å (see Fig. 2). Analyzing this intramolecular interaction, it can be observed that its distance value is shorter than the van der Waals radii [32–35]. It is noteworthy that this finding is reinforced by the H2 atom's larger positive charge and O25's larger negative charge, i.e., the density localized on the O25 atom, bond order, and the (H2) hydrogen atom's relatively acidity (Tables 1–3) (Fig. 2b). These findings illustrated the presence of a hydrogen bond, which might contribute to increase CNS-tripeptide structural stability. These trends are maintained at two calculation levels (DFT and MP2).

In order to explore the CNS-tripeptide's electronic charge, a dipole-moment (μ) analysis was performed. In Table 4, we tabulated total dipole-moment values in addition to its CNS-tripeptide components. From the results for dipole-moment analysis, we

Table 3
Atomic and groups charges for the CNS tripeptide at MP2 and B3LYP/6–311++G(2d,2p)//B3LYP/6–311 + G(d,p) levels.[a]

Method	N1	H2	N15	O25	N26	O28	N31	S37	H39	Cys HNH	Asn HNH	Cys R	Asn R	Ser R	Cys	Asn	Ser
MP2	−0.890	0.311	−0.794	−0.580	−0.870	−0.582	−0.983	−0.301	0.188	−0.263	−0.090	−0.054	−0.018	−0.076	0.136	0.022	−0.157
B3LYP	−0.887	0.309	−0.827	−0.603	−0.850	−0.593	−0.956	−0.298	0.180	−0.242	−0.084	−0.067	−0.026	−0.083	0.155	−0.009	−0.146

[a] Atomic and group charges values are given in (a.u.). CNS tripeptide, Cys-Asn-Ser tripeptide.

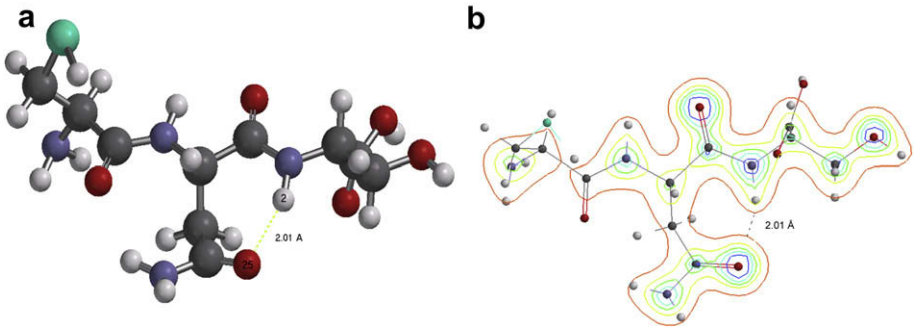

Fig. 2. (a) Optimized structure for the Cys-Asn-Ser (CNS) tripeptide carboxyl-terminal end group illustrates the possibility of forming an intramolecular hydrogen bond; (b) density contour showing electronic density on the oxygen atom (O25) and the hydrogen atom (H2).

Table 4
Total dipole-moment values and its components for the CNS tripeptide at MP2 and B3LYP/6–311++G(2d,2p)//B3LYP/6–311 + G(d,p) levels.[a]

Method	μ (x)	μ (y)	μ (z)	μ (total)
MP2	0.37	2.09	0.01	2.12
B3LYP	0.50	2.42	0.02	2.47

[a] Total dipole-moment values and its components are given in Debyes. CNS tripeptide, Cys-Asn-Ser tripeptide.

found that the tripeptide's components exhibit the largest positive value on the *y*-axis, indicating that the positive charge is oriented toward the cysteine amino acid's side-chain. This observation may be associated with atomic charges in the cysteine amino acid; therefore, this may contain an important reactive site. Also, it can be observed that *x*- and *z*-axis electronic distributions are small; these values comprise evidence that these amino acids may possess small atomic charges, and this behavior is in agreement with the atomic charge analysis (Table 3). Another significant observation is that dipole-moment values continue to present similar trends in the two methods. In Fig. 3, the frontier molecular orbitals (HOMO − 1 and LUMO + 1) are shown. This result illustrates that HOMO − 1 molecular orbitals are located in the cysteine amino acid, while LUMO + 1 molecular orbitals are located in the amino-acyl side-chain and the serine amino acids (Fig. 3). In addition, we analyzed electrostatic potential isosurfaces for the CNS tripeptide; we can observe a larger electronic-density distribution on the carboxyl-terminal group, as shown in Fig. 4.

Table 5 presents CNS-tripeptide-optimized geometric-parameter values. Optimized geometric parameter values obtained for the tripeptide with the two methods are in good agreement with available X-ray experimental data [36–38]. In general, calculated geometric parameters for B3LYP and MP2 methods are practically the same, with deviations among these on the order of $<0.02^{\circ}$ Å for bond lengths and <2.00 for bond angles. It is important to mention that N1–H2 bond lengths are shorter than those of S37–H39; this result is in agreement with bond order and deprotonated energy, i.e., small values are observed for bond order and ΔE of N1–H2 with respect to S37–H39. Finally, we analyzed some selected dihedral angles to study the tripeptide's planarity, mainly the dihedral angles of asparagine and serine amino-acid amide groups. H2–N1–C4–C8 and O28–C23–N15–C8 dihedral-angle values are closer to 180° in the two methods (Table 5). These observations demonstrate that amide-group H2 and O28 atoms are co-planar to backbone of asparagine and serine amino acids, respectively. Additionally, it is noteworthy that experimental studies of the CNS tripeptide have been carried out at the same time [13]. These have shown that the CNS tripeptide's carboxyl-terminal end group of MLIF maintained 100% of the MLIF pentapeptide's biological and anti-inflammatory properties, which could be observed as a potential therapeutic agent and as a possible inflammatory-response modulator, at least in the experimental models utilized [10,13].

This and prior computational analyses had led to verifiable hypotheses that, to date, have been confirmed by *in vivo* and *in vitro* experiments. Nevertheless, caution must be maintained while projecting this *in vacuo* analysis to real-life complexity. It is known for biologically relevant molecules, for example, that receptor-bound conformations in co-crystal structures can differ dramatically from energy-minimum conformations *in vacuo*. Also the MLIF biological environment in amebiasis could range from intestinal lumen to necrotic abscess, also far different from eventual pharmacologic environments (blood, dermis, cavities, etc.). The influence remains to be established of particular micro-environmental conditions in the final conformation and in CNS or MLIF electronic

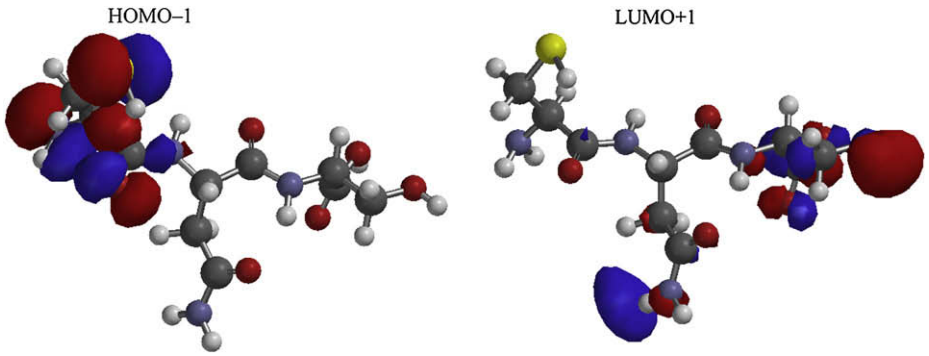

Fig. 3. Frontier molecular orbitals (HOMO − 1 and LUMO + 1) determined for the Cys-Asn-Ser (CNS) tripeptide carboxyl-terminal end group.

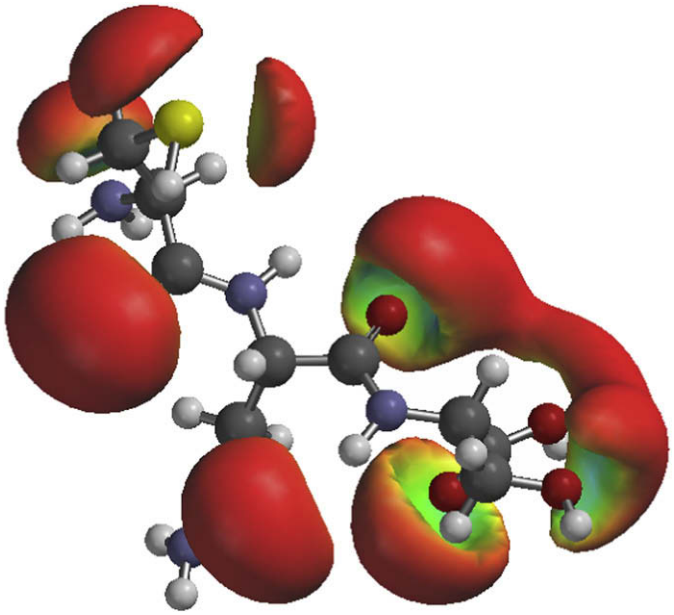

Fig. 4. Electrostatic potential isosurfaces showing electronic density for the Cys-Asn-Ser (CNS) tripeptide carboxyl-terminal end group.

Table 5
Geometric parameters for the CNS tripeptide at MP2 and B3LYP/6–311 + G(d,p) levels.[d]

Parameter	MP2	B3LYP	X-ray [36–38]
N1–H2	1.02	1.01	0.94[a]
C3–N1	1.44	1.45	1.485[a]
C8–N15	1.44	1.43	1.479[b]
C22–O25	1.23	1.22	1.259[b]
C33–S37	1.82	1.83	1.811[c]
C27–N31	1.46	1.45	1.493[c]
S37–H39	1.34	1.35	
N1–C3–C6	107.54	107.85	109.7[a]
H2–N1–C4	117.06	118.50	117.0[a]
N1–C3–C7	109.82	110.86	110.8[a]
O13–C7–O14	124.51	123.80	125.2[a]
N26–C22–O25	123.69	123.41	125.6[b]
H2–N1–C4–C8	16.18	10.72	
O28–C23–C8–N15	−5.71	−4.99	
O25–C22–C17–C8	−85.14	−81.08	

[a] Ref. [36].
[b] Ref. [37].
[c] Ref. [38]. CNS tripeptide, Cys-Asn-Ser tripeptide.
[d] Bond lengths are given in Amstrong (Å); bond angles and dihedral angles are given in degrees (°).

parameters in the theoretical aspect, and in *in vitro* and *in vivo* real-life conditions in terms of biological activities.

4. Conclusions

We performed *ab initio* and DFT theoretical levels of a novel tripeptide with anti-inflammatory activity; we characterize the most relevant electronic and geometrical parameters, as well as their physico-chemical features, which could be linked with its anti-inflammatory activity. Our results show that N1–H2 bond possesses smallest deprotonation energy values with respect to S37–H39 bond. Bond order demonstrated that (N1–H2) bond order is slightly weaker than S37–H39, corroborating that the amide group is the more acidic group. Also, a trend is observed in two B3LYP and MP2 theory levels. Atomic and group charges illustrate that the CNS tripeptide possesses important interaction sites, particularly on H2 and H39 atoms, suggesting that these atoms could be exposed to nucleophilic attacks. Additionally, results revealed that the CNS tripeptide could form hydrogen bonds between CONH2···O25C, suggesting that the presence of the hydrogen bond might contribute to an increase in the CNS tripeptide's structural stability. The tripeptide's dipole-moment components show that the larger positive value on the *y*-axis is oriented toward the cysteine amino-acid side-chain. The CNS tripeptide's electrostatic potential isosurfaces exhibited a larger electronic-density distribution on the carboxyl-terminal end group. Dihedral-angle analysis suggests that asparagines- and serine-amino-acid amide-group co-planarity plays an important role in structural stability, and perhaps in the tripeptide's activity. Studies of small anti-inflammatory peptides from a theoretical viewpoint are relevant because inflammation is a process involved in several diseases, such as bacterial infections, acute coronary syndrome, urologic diseases, chronic liver disease in hepatic inflammation, and cancer, among others. Finally, we wish to emphasize that detailed knowledge of the electronic structure of peptides may help to understand the mechanism of biological action, as well as the design of new peptides with specific features.

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