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Computational study on 3D structure of L-aspartic acid and L-glutamic acid: molecular descriptors and properties

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Abstract. The aim of this work is to provide a comprehensive and complex analysis of molecular descriptors and properties of two similar amino acids, L-Aspartic acid and L-Glutamic acid, using a software tool for calculations and properties predictions. As amino acids are model compounds for predicting the physical-chemical properties and behavior of biological, larger molecules as peptides or proteins, researches were focused on providing accurate mechanical calculations using: molecular/mechanical methods. Our study aims to initiate a linear scaling approach, by dividing a large system into small subsystems and performing the calculations for each, individually, then, embedding and correcting the information globally. The calculations were performed on the 3D structure of the studied amino acids that were first generated, as CPK model, and optimized by energy minimization. A comparative assay on their topological, molecular descriptors and properties was conducted, in vacuum and in water, using the Hartree-Fock model and second-order Møller–Plesset perturbation theory MP2 for predicting structure, energy and property calculations with Spartan'14 software. Values of molecular properties such as area, volume, polar surface area, polarizability, ovality, logP, dipole moment, HOMO-LUMO gap, distances and angles between atoms, were obtained. The results have been interpreted in terms of electronic effects of side chain groups, molecular deformability, steric factors and reactivity. This approach can be extended to other amino acids in order to predict protein-ligand interactions, important aspects in drug design studies and protein engineering.

Keywords: amino acids, computational molecular descriptors

1. Introduction

Amino acids are the key constitutive units of larger systems such as peptide and proteins, thus their experimental properties and computational modeling of their behavior in physiological media or in diluted electrolytes solutions that mimics physiological media, represent a starting point for creating and developing reliable models for describing the conformational changes of proteins chains and to assess their global properties and their thermodynamic behavior [1, 2].

Researchers have focused their studies for the development of new approximate methods, such as semiempirical approaches, reduced-scaling methods, and fragmentation methods [3, 4]. Because of the difficulties of scaling approach derived from the large size of the molecular systems as biomolecules, new linear-scaling quantum mechanical methods were initiated, by macromolecule fragmentation and computational study of individual fragments [4].

Continuing our studies on amino acids experimental and calculated physico-chemical properties in water and in water - electrolyte solutions [5, 6], in this paper we present some computed parameters on two amino acids, L-Aspartic acid and L-Glutamic acid, in vacuum and in water. Our goal is to initiate a fragmentation approach, by dividing a large system such as amyloid peptides, formed by 40 and 42 amino acids units, into small subsystems and performing the calculations for each of them, individually, then, embedding and correlating the information globally. Some researchers have already report computed data on molecular structure, harmonic and anharmonic vibrational frequencies, molecular properties of L-aspartic acid [7] or ionization equilibria of L-Glutamic acid and L-aspartic acid [8]. This paper aims to supplement data using the Hartree-Fock model with two basis sets and second-order Møller–Plesset perturbation theory MP2, to improve the characterization of molecular ground state.

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2. Computational details

First, using Spartan 14 software Wavefunction, Inc. Irvine CA USA on Intel(R) Core i5 at 3. 2 Ghz CPU PC, the 3D CPK models (ball-and-spoke) of the L-Aspartic acid and L-Glutamic acid were generated. Second step was the optimization of their geometry by energy minimization. Conformational analysis was performed to find the more stable conformer (presenting the energy minima) of each compound. On its structure, a series of calculations of molecular properties, properties valuable for quantitative structure–activity relationships (QSAR) and measurements of distances and angles between the atoms were performed, using the software algorithms: Hartree-Fock model [9, 10] 3-21G and 6-31+G* basis sets [11] for vacuum and water solvation, and Møller Plesset MP2, 6-31* set, for equilibrium geometry at ground state [12].

3. Results and Discussions

In drug design modeling, physical properties depending on the molecular weight and the number of hydrogen bond donors (HBDs) and a bioavailability scoring model based on polar surface area (PSA) are important contributions that interfere with the possibility of a protein to interact with a small molecule (the ligand) [13]. In Table 1, the main characteristics for L-Aspartic acid and L-Glutamic acid are presented. Properties that are particularly valuable in QSAR type analyses have been calculated and listed: area, volume, PSA (Table 2) and ovality (Table 1), obtained from a space–filling model, and other structure dependent indicators: the octanol-water partition coefficient (logP), the number of HBD and acceptor sites (HBA) (Table 1), polarizability (Table 2). The studied amino acids which differ in their chain only by the presence of a $–CH_2$ group, present the same number of HBA and HBD. On the same reason, as expected, due to the presence of an extra CH_2- group in L-Glutamic acid structure, its area and volume are slightly larger (Table 2). LogP, that is a component of "Lipinski' rule of 5" [14], useful to predict drug-likeness of various compounds, provides information on the liophilicity or hydrophobicity, becoming an important parameter to predict the distribution of a compound in a biological system. LogP represent the ratio of concentration of a compound in aqueous phase to the concentration in an immiscible solvent, as the neutral molecule. The values found for logP, much lower than 5 (see Table 1) predict good absorption and permeation, important to rationalize interactions with other molecules. Negative values for logP (*e.g.*-1) means 1:10 Organic:Aqueous, thus showing a hydrophilic nature. The ovality index is a measure of the deviation of a molecule from the spherical shape, considering the minimum surface for the spherical shape. Thus, this parameter is related to the molecular surface area and the minimum surface area corresponding to the Van der Waals volume of the molecule [15]. The ovality index is unitary for spherical molecules and increases with increasing linearity of the molecule. The computed data shows that similar structure of acids gives them a similar physico-chemical behavior. The data reported may be useful for future quantitative structure–activity relationships (QSAR) and quantitative structure properties relationships (QSPR) studies.

Table 1. L-Aspartic acid and L-Glutamic acid characteristics

Formula	**$C_4H_7NO_4$**	**$C_5H_9NO_4$**
Molecular weight (g/mol)	133.103	147.130
Tautomers	3	3
Conformers	81	243
HBD Count*	2	2
HBA Count*	3	3
logP	-1.67	-1.39
Ovality	1.25	1.29/1.30

*H-Bond donors (HBD) and –acceptors (HBA)

Table 2. Computed properties for CPK Model computations for L-Aspartic in vacuum and in water using Spartan'14 V1.1.4 software.

Property	**Method**	**Vacuum**	**Water**
Area ($Å^2$)	(1)	144.15	144.85
	(2)	144.31	145.59
	(3)	144.71	-
Volume ($Å^3$)	(1)	117.07	117.35
	(2)	116.71	117.07
	(3)	117.57	-
PSA ($Å^2$)	(1)	86.860	87.897
	(2)	87.606	89.174
	(3)	87.672	-
Polarizability (10^{-30} m^3)	(1)	47.26	47.24
	(2)	47.70	47.71
	(3)	47.24	-
Dipole moment (debye)	(1)	5.07	5.73
	(2)	4.42	5.67
	(3)	4.50	-
E HOMO (eV)	(1)	-11.14	-11.06
	(2)	-11.76	-11.56
	(3)	-11.64	-
E LUMO (eV)	(1)	4.28	4.57
	(2)	1.61	1.92
	(3)	4.08	-

(1): Hartree-Fock model, 3-21G basic set, Energy conformer: -506.632451 a.u (vacuum); -506.648659 a.u. (water)
(2): Hartree-Fock model, 6-31+G*set, Energy conformer: -509.496664 a.u (vacuum); -509.517622 a.u. (water)
(3): Møller Plesset model, MP2, 6-31* set, Energy conformer: -510.861421 a.u. (vacuum)

From Tables 2-3, it can be observed the values of increasing polarizability, correlated with the dipole moment, for L-Glutamic acid *vs* L-Aspartic acid. Also, the polar surface area, slightly larger for L-Glutamic acid.

Table 3. Computed properties for CPK Model computations for L-Glutamic acid in vacuum and in water using Spartan'14 V1.1.4 software

Property	Method	Vacuum	Water
Area ($Å^2$)	(1)	164.30	164.64
	(2)	164.85	166.55
	(3)	165.71	-
Volume ($Å^3$)	(1)	135.95	136.06
	(2)	135.44	135.72
	(3)	136.35	-
PSA ($Å^2$)	(1)	88.665	89.097
	(2)	88.852	89.461
	(3)	88.698	-
Polarizability (10^{-30} m^3)	(1)	48.75	48.78
	(2)	49.31	49.32
	(3)	48.78	-
Dipole moment (debye)	(1)	8.78	10.49
	(2)	8.55	9.02
	(3)	5.10	-
E HOMO (eV)	(1)	-11.40	-11.01
	(2)	-11.86	-11.26
	(3)	-11.81	-
E LUMO (eV)	(1)	4.38	4.50
	(2)	1.15	1.80
	(3)	3.82	-

(1): Hartree-Fock model, 3-21G basic set, Energy conformer: -545.432677 a.u (vacuum); -545.452857 a.u. (water)
(2): Hartree-Fock model, 6-31+G*set, Energy conformer: -548.514029 (vacuum); -548.546549 a.u. (water)
(3): Møller Plesset model, MP2, 6-31* set, Energy conformer: -550.011339 a.u. (vacuum)

The polarizability is useful to predict and asses the interactions between non-polar atoms or groups and other electrically charged species, such as ions and polar molecules having a strong dipole moment. Due to the zwitterionic structure of the organic molecules studied, in order to obtain reliable values for dipole moment by software predictions, a cluster of 14-21 molecules, including all surrounding molecules (amino acids and/or water molecules) that are closer that 3-5 Å distance threshold to any atom of the central molecule, must be taken into account [16] and many iterations must be conducted to obtain prediction results compared to experimental data provided by multipole refinement of X-ray diffraction. Multiple geometric positions from different models lead to variation in the dipole moment prediction. The intermolecular interactions dictated by the polarizability and the dipole moment, plus the hydrophilicity, are important factors that affect drug-receptor interactions. The calculated values for the highest-occupied (HOMO) and lowest –unoccupied (LUMO) orbitals are clearly indicated in Table 4 for L-Aspartic acid and in Table 5 for L-Glutamic acid, among the calculated HOMO–LUMO gap (ΔE). In Figure 1, the energy level for representative frontier molecular orbitals, HOMO (a) and LUMO (b), respectively, in mesh representation, for vacuum conditions, for L-Aspartic acid, are presented. Similarly, the same representation in an energy level diagram for frontier molecular orbitals HOMO (a) and LUMO (b) are presented in Figure 2 for L-Glutamic acid, in water. The discussed compounds have similar molecular orbital energy profiles, presenting close values for the interfrontier energy gap (ΔE).

Table 4. HOMO and LUMO orbitals energy values (eV) for L-Aspartic acid in vacuum and in water, calculated with Spartan'14 V1.1.4 software, Hartree-Fock model, 3-21G basic set

	Orbitals	Vacuum	Water
L-Aspartic acid	HOMO	-11.1	-11.0
	HOMO{-1}	-12.1	-12.1
	HOMO{-2}	-12.3	-12.4
	HOMO{-3}	-12.9	-12.7
	HOMO{-4}	-13.4	-13.2
	HOMO{-5}	-14.6	-14.5
	HOMO{-6}	-14.8	-14.6
	HOMO{-7}	-15.4	-15.1
	HOMO{-8}	-15.8	-15.5
	HOMO{-9}	-16.6	-16.6
	HOMO{-10}		-16.7
	LUMO	4.3	4.6
	LUMO{+1}	5.0	4.9
	ΔE^*	15.4	15.7

Table 5. HOMO and LUMO orbitals energy values (eV) for L-Glutamic acid in vacuum and in water, calculated with Spartan'14 V1.1.4 software, Hartree-Fock model, 3-21G basic set

	Orbitals	Vacuum	Water
L-Glutamic acid	HOMO	-11.3	-10.9
	HOMO{-1}	-12.1	-12.1
	HOMO{-2}	-12.5	-12.4
	HOMO{-3}	-12.7	-12.5
	HOMO{-4}	-12.7	-12.7
	HOMO{-5}	-14.4	-13.9
	HOMO{-6}	-14.6	-14.2
	HOMO{-7}	-15.0	-14.7
	HOMO{-8}	-15.3	-14.8
	HOMO{-9}	-15.9	-15.6
	HOMO{-10}	-	-
	LUMO	4.3	4.5
	LUMO{+1}	5.0	5.1
	ΔE^*	15.6	15.4

* ΔE = HOMO-LUMO gap

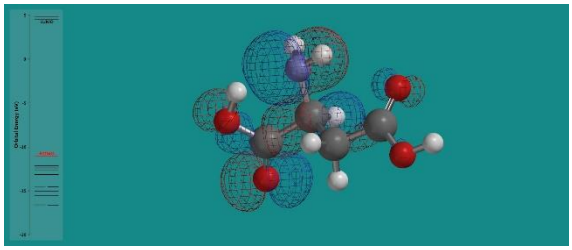

Figure 1 (a) Energy level diagram for L-Aspartic acid in water: HOMO orbital (-10.9 eV), Hartree-Fock model, 3-21G basic set

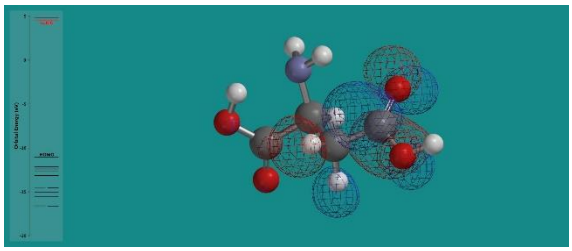

Figure 1 (b) Energy level diagram for L-Aspartic acid in water: LUMO orbital (4.6 eV), Hartree-Fock model, 3-21G basic set

This approach can be applied to predict protein - ligand interactions, relevant aspects in drug design studies and protein engineering. A particular example is the possibility to assess and predict the oligomerization process of amyloid peptides, important to understand the occurrence of neurotoxic species and the dynamicity of the aggregation process, in order to establish future strategies in Alzheimer disease treatment.

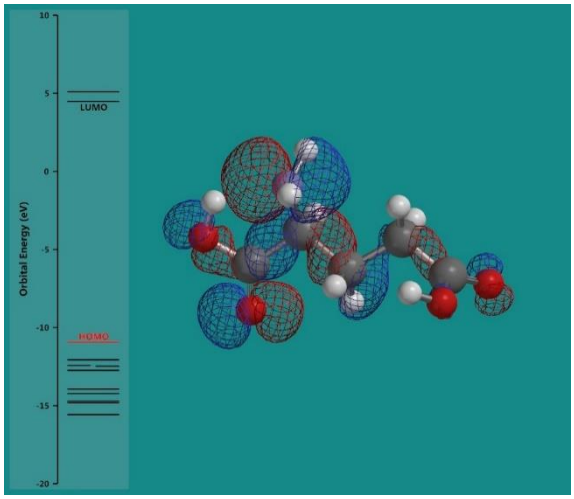

Figure 2 (a) Energy level diagram for L-Glutamic acid in water: HOMO orbital (-10. 9 eV), Hartree-Fock model, 3-21G basic set

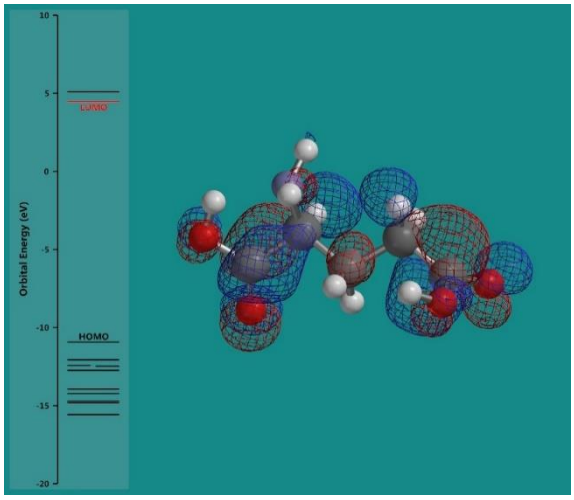

Figure 2 (b) Energy level diagram for L-Glutamic acid in water: LUMO orbital (4.5 eV), Hartree-Fock model, 3-21G basic set

4. Conclusions

The work presents some computational physico-chemical parameters of L-Aspartic acid and L-Glutamic acid, obtained using Spartan 14 package program, with different algorithms and sets calculations. The calculations were made on the most stable conformer, after geometry optimizations. Values of important properties used in QSAR and QSPR studies are presented and compared, taking into accound the molecular descriptors and the molecular frontier energy values. The specifies calculation of QSAR descriptors are based on the electron density surface, the electrostatic potential map and the local ionization potential map.

The computed data represent important information for physical-chemical behavior of the studied amino acids, which is quite similar. The results could have many applications in rational drug design studies and protein engineering.

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