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Density Functional Theory (DFT) and Thermodynamics Calculations of Amino Acids with Polar Uncharged Side Chains †

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Abstract: The goal of the present work was to evaluate the chemical reactivity of amino acids with polar uncharged side chains (serine, threonine, asparagine and glutamine) using density functional theory (DFT) and thermodynamics modeling by calculating a series of molecular descriptors and properties of their optimized geometries. The predictive calculations were achieved with Spartan software from Wavefunction, Inc. Irvine, CA, USA, hybrid algorithm B3LYP (Becke's three-term functional; Lee, Yang, Parr exchange hybrid) and polarization basis set 6-31G(d,p) for equilibrium geometry at ground state in vacuum and in water, after energy minimization and geometry optimization. Thermodynamic properties (zero-point energy, enthalpy, constant volume heat capacity, entropy and Gibbs energy) for these derivatives were calculated and related to electrochemical ligand behavior. Reduction and oxidation potentials were correlated to their calculated energy levels for molecular orbitals.

Keywords: density functional theory; amino acids; thermodynamics

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1. Introduction

One of the most useful manners by which to classify the standard amino acids is based on the polarity of the side chain. The group of amino acids with polar uncharged side chains is composed of serine, threonine, asparagine and glutamine. The side chains in this group possess a spectrum of functional groups. However, most have at least one atom (nitrogen, oxygen or sulfur) with electron pairs available for hydrogen bonding to water and other molecules.

The main aim of this study was to investigate all possible intermolecular interactions of these amino acids using density functional theory. The ground state geometries of the molecules in gas phase were optimized using density functional theory (DFT) [1]. To improve the description of the van der Waals interactions, we employed the empirical van der Waals correction proposed by Grimme, as implemented in the B3LYP functional in conjunction with 6-31G(d,p) basis set [2].

2. Computational Procedure

The calculations were carried out using Spartan 14 software Wavefunction, Inc., Irvine, CA, USA [3] on an Intel(R) Core i5 3.2 GHz CPU PC, with the software algorithm

hybrid B3LYP model (Becke's three-parameter hybrid exchange functional with the Lee–Yang–Parr correlation functional) [4] and polarization basis set 6-31G* [3,5] in vacuum, for equilibrium geometry at ground state.

3. Results and Discussion

The characteristics of amino acids with polar uncharged side chains given by the Spartan 14 software are shown in Table 1. The characteristics were obtained on the optimized geometries of these amino acids by energy minimization in order to obtain the most stable conformer.

Table 1. The characteristics of amino acids with polar uncharged side chains.

Chemical Formula	$C_3H_7NO_3$	$C_4H_9NO_3$	$C_4H_8N_2O_3$	$C_5H_{10}N_2O_3$
Molecular weight (g·mol^{-1})	105.09	119.12	132.12	146.14
Tautomers	1	1	3	3
Conformers	81	81	81	243
HBD Count	2	2	2	2
HBA Count	3	3	4	4
Log P	−1.75	−1.43	−2.33	−2.05
Ovality	1.21	1.26	1.26	1.32

Hydrogen bond donors (HBDs) have the same values for all amino acids of the study, containing the same donors (nitrogen), and the hydrogen bond acceptors (HBAs) are slightly increased for asparagine and glutamine due to the presence of an amide group occurring on the side chain.

The octanol–water partition coefficient (log *p*) was also evaluated and is listed in Table 1. Log *p* values are negative, showing their good affinity for lipophilic phases, and decrease in the order: threonine > serine > glutamine > asparagine.

The ovality increased with the molecular weight; this parameter suggests the deviation of molecules from the spherical shape, considering the minimum surface for the spherical shape. The ovality index is related to molecular surface area and van der Waals volume and increases with the linearity of the structures in the same order.

Table 2 shows the results of chemical calculations in water and in vacuum, which provide information on quantitative structure–property relationships for the investigated amino acids with polar uncharged side chains.

Table 2. The characteristics of amino acids with polar uncharged side chains.

Parameter	Vacuum	Water	Vacuum	Water	Vacuum	Water	Vacuum	Water
	L-Serine		L-Threonine		L-Asparagine		L-Glutamine	
E_{HOMO} (eV)	−7.08	−6.92	−6.78	−6.69	−6.2	−6.46	−6.78	−6.91
E_{LUMO} (eV)	0.13	0.1	0.01	−0.04	0.34	0.19	0.29	0.21
$\Delta E(E_{HOMO}\text{-}E_{LUMO})$ (eV)	−7.21	−7.02	−6.79	−6.65	−6.54	−6.65	−7.07	−7.12
$I = -E_{HOMO}$ (eV)	7.08	6.92	6.78	6.69	6.2	6.46	6.78	6.91
$A = -E_{LUMO}$ (eV)	−0.13	−0.1	−0.01	0.04	−0.34	−0.19	−0.29	−0.21
$\chi = (I + A)/2$ (eV)	3.475	3.41	3.385	3.365	2.93	3.135	3.245	3.35
$\eta = (I - A)/2)$ (eV)	3.605	3.51	3.395	3.325	3.27	3.325	3.535	3.56
$\sigma = I/\eta$	1.96	1.97	2.00	2.01	1.90	1.94	1.92	1.94
$\mu = (E_{HOMO} + E_{LUMO})/2$	−3.475	−3.41	−3.385	−3.365	−2.93	−3.135	−3.245	−3.35
$\omega = \mu^2/2\eta$	21.77	20.41	19.45	18.82	14.04	16.34	18.61	19.98

From results of Table 2 it can be observed that area and volume for investigated compounds increase in the order: serine < threonine < asparagine < glutamine, as expected, correlated with the molecular weight and the chemical structure. The same behavior can

also be observed for polar surface area (PSA) values and polarizability, showing increased induction (polarization) interactions, resulting from an ion or a dipole inducing a temporary dipole in an adjacent molecule.

The parameters from Table 3 are important quantum global chemical reactivity descriptors of the studied molecules in terms of their reactivity and site selectivity. Serine has the highest ionization potential and electron affinity, which reflects the superior capability to interact with heavy metal cations and to accept one electron from a donor. In terms of chemical hardness, large ΔE signifies hard molecules, and small ΔE refers to soft molecules. In this context, serine presents the hardest structure. The values obtained for the electrophilicity index (ω) are not in the same order. This indicates the unexpected global electrophilic nature of these molecules as a measure of energy lowering due to maximal electron flow between donor and acceptor [6].

Table 3. Calculated global reactivity parameters according to Koopmans' theorem [7].

Parameter	Vacuum	Water	Vacuum	Water	Vacuum	Water	Vacuum	Water
	L-Serine		L-Threonine		L-Asparagine		L-Glutamine	
E_{HOMO} (eV)	−7.08	−6.92	−6.78	−6.69	−6.2	−6.46	−6.78	−6.91
E_{LUMO} (eV)	0.13	0.1	0.01	−0.04	0.34	0.19	0.29	0.21
$\Delta E(E_{HOMO}-E_{LUMO})$ (eV)	−7.21	−7.02	−6.79	−6.65	−6.54	−6.65	−7.07	−7.12
$I = -E_{HOMO}$ (eV)	7.08	6.92	6.78	6.69	6.2	6.46	6.78	6.91
$A = -E_{LUMO}$ (eV)	−0.13	−0.1	−0.01	0.04	−0.34	−0.19	−0.29	−0.21
$\chi = (I + A)/2$ (eV)	3.475	3.41	3.385	3.365	2.93	3.135	3.245	3.35
$\eta = (I - A)/2)$ (eV)	3.605	3.51	3.395	3.325	3.27	3.325	3.535	3.56
$\sigma = I/\eta$	1.96	1.97	2.00	2.01	1.90	1.94	1.92	1.94
$\mu = (E_{HOMO} + E_{LUMO})/2$	−3.475	−3.41	−3.385	−3.365	−2.93	−3.135	−3.245	−3.35
$\omega = \mu^2/2\eta$	21.77	20.41	19.45	18.82	14.04	16.34	18.61	19.98

Thermodynamic properties such as zero-point vibrational energy, enthalpy, constant volume heat capacity, entropy and Gibbs energy were calculated with the DFT method for equilibrium geometry at ground state for Z and E conformers, over a temperature range between 273.15 and 373.15 K. Except for the zero-point energy (ZPE), all depend on temperature. Their calculated values are listed in Table 4 for 298.15 K. The values of enthalpy, constant volume heat capacity (Cv), entropy (S) and free Gibbs energy (G), increase with temperature, in agreement with the enhancement of the molecular vibrational intensities as the temperature rises [8]. Obtained thermodynamic functions listed in Table 4 can be used to estimate directions of further chemical reactions by computing them to other thermodynamic functions and relationships.

Table 4. Predicted thermodynamic properties at 298.15 K for serine, threonine, asparagine and glutamine in ground state.

Parameter	L-Serine	L-Threonine	L-Asparagine	L-Glutamine
ZPE(/kJ·mol^{-1})	300.9	300.90	300.90	300.90
ΔH (a.u.)	−398.82796	−398.82796	−398.82796	−398.82796
Cv (J·mol^{-1})	86.96	104.31	111.29	123.23
S (J·mol$^{-1)}$	336.36	336.36	336.36	336.36
G (a.u.)	−398.87	−438.11	−492.29	−531.57

4. Conclusions

The work presents some computational physicochemical parameters of amino acids serine, threonine, asparagine and glutamine, obtained using the Spartan 14 package program. The calculations were made on the most stable conformer, after geometry optimizations.

The computed data represent important information for physicochemical behavior of the studied amino acids; the presence of a second, additional hydroxyl group on the amino acid skeleton, at serine, strongly affects the electron charge distribution, and consequently the polar surface area (PSA) and the dipole moment are greatest for serine. The value of the water-partition coefficient (log *p*) suggests a more hydrophilic behavior. Serine has higher hydrogen bonding ability, thus it can bind to the protein surface by its side-chain hydroxyl oxygen to form a hydrogen bond with the protein backbone or with a variety of polar substrates. Serine actively influences the active site of many hydrolases (e.g., proteases, lipases). The chemical binding within peptides and proteins dictate the conformation kinetic stability. Serine is a part of a catalytic triad (along with histidine and aspartic acid), acting as a base catalyst. Thus, the polarized hydroxyl group of serine is easily protonated. Removal of an electron leads to an alkoxide ion, a powerful nucleophile. Electronic movements along amino acid and peptide skeletons can be explained and predicted by computed electronic properties and partial charges of their constitutive units.

Such studies could be helpful in protein engineering or evaluation of intramolecular interactions in protein–ligand complexes from biological environments.

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