chemistry proceedings

Proceedings

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

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† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

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 [1], hybrid algorithm B3LYP (the Becke's 3-term functional; Lee, Yang, Parr exchange Hybrid) [2] and polarization basis set 6-31G (d, p) for equilibrium geometry at ground state in vacuum and in water, after minimization energy and geometry optimization. Thermodynamic properties (zero-point energy, enthalpy, constant volume heat capacity, entropy and Gibbs energy) for these derivatives have been calculated and related to ligands electrochemical behavior. Reduction and oxidation potentials have been correlated to their calculated energy levels for LUMO and HOMO 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 are 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 is 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) [3]. To improve the description of the van der Waals interactions, we employed the empirical van der Waals correction proposed by Grimme, as implemented in B3LYP functional in conjunction with 6-31G (d, p) basis set [4].

2. Computational Procedure

The calculations were carried out using Spartan 14 software Wavefunction, Inc. Irvine CA USA [5] on Intel(R) Core i5 at 3. 2 Ghz CPU PC, software algorithm hybrid B3LYP model (the Becke's three parameter hybrid exchange functional with the Lee-Yang-Parr correlation functional) [6] and polarization basis set 6-31G* [5,7] 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 is shown in the Table 1. The characteristics have been 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 ($g{\cdot}mol^{-1}$)	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 donor (HBD) have the same values for all amino acids of the study, containing the same donors (nitrogen) and the hydrogen bond acceptor (HBA) have a little bit increased for asparagine and glutamine due to the presence of amide group occurring on its side chain.

The octanol-water partition coefficient (log *p*) is also evaluated and 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 has 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.

In Table 2 are given 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.

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

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

Property	Vacuum	Water	Vacuum	Water	Vacuum	Water	Vacuum	Water
	L-Serine		L-Threonine		L-Asparagine		L-Glutamine	
Area (Å^2)	123.73	124.05	145.06	145.74	149.65	150.8	172.41	172
Volume (Å^3)	97.33	97.48	116.39	116.6	121.29	121.59	139.99	139.64
PSA (Å^2)	74.802	74.872	77.885	78.51	94.453	95.671	94.796	94.368
Polarizability	47.6	47.62	49.21	49.26	49.67	49.67	51.06	51.02
Dipole moment (debye)	4.82	5.51	2.21	2.95	2.1	3.2	6.63	11.86

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. It indicates an unexpected global electrophilic nature of these molecules, as measure of energy lowering due to maximal electron flow between donor and acceptor [8].

Table 3. Calculated global reactivity parameters according Koopmans' theorem [9].

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
$\Delta E(E_{\mathrm{HOMO}}\text{-}E_{\mathrm{LUMO}})$ (eV)	−7.21	−7.02	−6.79	−6.65	−6.54	−6.65	−7.07	−7.12
$I = -E_{\mathrm{HOMO}}$ (eV)	7.08	6.92	6.78	6.69	6.2	6.46	6.78	6.91
$A = -E_{\mathrm{LUMO}}$ (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
$\mu = (E_{\mathrm{HOMO}} + E_{\mathrm{LUMO}})/2$	−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 have been calculated with 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 Tables 6 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 [10]. Obtained thermodynamic functions listed in Table 4 are useful to estimate directions of further chemical reactions, by computing those 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 physico-chemical parameters of amino acids serine, threonine, asparagine and glutamine, obtained using Spartan 14 package program. The calculations were made on the most stable conformer, after geometry optimizations.

The computed data represent important information for physical-chemical behavior of the studied amino acids; the presence of a second, additional hydroxyl group on the amino acid skeleton, at Serine, affects strongly the electron charge distribution and consequently, the polar surface area (PSA) and the dipole moment are greatest for Serine. Also, the value of the water-partition—coefficient (log *p*) suggests a more hydrophilic behavior. Serine as higher ability to hydrogen bonding, thus it can bind on the proteins surface by its side-chain hydroxyl oxygen, to form a hydrogen bond with the protein backbone or with a variety of polar substrates. Serine influences actively the active site of many hydrolases (e.g., proteases, lipases). The chemical binding within peptide and proteins dictate the conformation kinetic stability. Serine is a part of catalytic triad (along with Histidine and Aspartic acid), acting as a base catalyst. Thus, the polarized hydroxyl group of Serine will be easily protonated. Removal of an electron leads to 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 intra-molecular interactions in proteins-ligands complexes from biological environments.

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