AMINO ACIDS IN NaCl AQUEOUS SOLUTIONS AT 298.15 K: VOLUMETRIC ANALYSIS AND COMPUTED MOLECULAR DESCRIPTORS

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This work aims to provide a comprehensive analysis of calculated molecular properties and experimental volumetric data for a homologous series of amino acids (Glycine, L-Alanine, DL-Serine, DL-Glutamic, DL-Histidine) in aqueous NaCl solutions at 298.15K. Using Spartan 14 software, a study of molecular properties of amino acids has been conducted on their 3D optimized structure. Topological descriptors, conformational characteristics and quantitative structure–activity relationship (QSAR) properties have been predicted. Group contribution method was used to evaluate the volumetric behavior of amino acids in water and aqueous NaCl solutions. The contributions of zwitterionic group and lateral chain of different amino acids at transfer volume at 298.15K were investigated and the influence of the interactions on the volumetric properties was assessed.

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Keywords: amino acids, transfer volumes, molecular descriptors

1. Introduction

The amino acids, as key units of more complex macro structures as polypeptides, proteins or enzymes, could represent the starting point for calculations and predictions of properties for such substances in various aqueous media. Several authors have reported volumetric and viscometric properties of amino acids in aqueous solutions containing electrolytes [1-6], thus a more extended approach must be taken into account, aiming to provide useful information on interactions, stability and conformational changes occurring in these systems.

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The present work is a continuation of our researches on thermodynamic properties of amino acids in aqueous NaCl systems [7-9]. Based on our experimental volumetric data, we have calculated the constituents group contributions at the transfer volumes values for L-Alanine, L-Glutamic acid and DL-Histidine from water to aqueous NaCl solutions, at 298.15K, varying the salt concentration.

In addition, a study of their main molecular descriptors, computed using Spartan 14 software, on the 3D amino acids conformation, after energy minimization and geometry optimization, was achieved, as useful tools in understanding the nature of molecular and ionic interactions that determine the volumetric behavior of amino acids in such systems. The calculations were performed on a wider series of amino acids: Glycine, L-Alanine, DL-Serine, DL-Glutamic acid, DL-Histidine, representing a novelty in the field.

2. Experimental

L-Alanine, L-Histidine (both from Merck, purity >99 %), L-Glutamic acid (Sigma-Aldrich, purity >99%), and NaCl (Merck, purity >99.8%), were dried in a vacuum desiccator over $CaCl_2$ for 24 hours, at room temperature, without further purification. Details for solutions preparation, density measurements and methodology were previously described [7-9].

3. Computational procedure

The computed data were obtained using Spartan 14 software (Wavefunction, Inc. Irvine CA USA) using an Intel Core i5 3.2 GHz processor. First, the space-filling calotte models (CPK models, ball-and-spoke) of amino acids 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 descriptors (surface area, volume, polar surface area, polarizability, ovality, log P, dipole moment), were performed using the software algorithm with Hartree-Fock method [10, 11] and split-valence 3-21G* basis set [12], both in vacuum and in water for equilibrium geometry at ground state.

4. Results and Discussions

From our experimental volumetric data [7-9] and other values found in literature [1] for transfer volumes of amino acids from water to aqueous NaCl solutions, a comparative investigation of their volumetric behavior, at 298.15K

and various salt concentrations, was made in this work by taking into account their different constituent groups contributions.

The equation used for calculation of transfer volumes of amino acid from water to aqueous salt solution was [1, 3]:

$$\Delta_{tr}V_{\Phi}^{0} = V_{\Phi}^{0}\ (II) - V_{\Phi}^{0}\ (I) \quad (1)$$

where V_{Φ}^{0} *(II)* is the standard aparent molar volume of amino acid dissolved in aqueous NaCl solutions and V_{Φ}^{0} *(I)* is the standard apparent molar volume of amino acid in its solution (without salt). V_{Φ}^{0} parameter is, generally, the standard partial molar volume or the infinite dilution apparent molar volume.

For these calculations, regarding V_{Φ}^{0} values, we used own data for L-Alanine [7], L-Glutamic acid [8] and L-Histidine [7, 9] dissolved in water and in aqueous NaCl solutions having 0.5, 1 and 1.5 salt molality, at 298.15 K.

For all studied amino acids dissolved in aqueous NaCl systems, V_{Φ}^{0} and $\Delta_{tr}V_{\Phi}^{0}$ present positive values. The increase in salt concentration induces an increase of the transfer volumes values for all amino acids. To their dissolution in water the amino acids appear as amphions, exhibiting a zwitterionic structure which is hydrated. In aqueous NaCl media, the occurring electrostatic interactions between salt ions and zwitterionic groups of amino acids lead to reducing electrostriction of water molecules near to amino acid and to the superposition of their hydration spheres, resulting apparent molar volumes that increase their values with the added salt; therefore, positive transfer volumes values are expected to be obtained.

In ternary systems containing water, amino acid and electrolytes, several types of interactions can occur: ion - ion, ion - hydrophilic group, ion – non-polar group, non-polar group – non-polar groups.

From observed positive and increasing values of the standard partial molar volume of amino acid in aqueous NaCl solutions V_{Φ}^{0}, and from the transfer volumes, ΔV_{Φ}^{0}, also positive, it can be concluded that the ion-ion interactions (between zwitterionic groups and either the anion or the cation of the salt) are predominantly.

The transfer volume value expresses all contributions from different groups within the structure of the amino acid. Assuming that there is no interaction between groups of amino acids, their contribution to the value of ΔV_{Φ}^{0} is additive, so it can be calculated as the difference between the transfer volumes

of two amino acids, whose structure differs by a group, such as - CH_2, - OH, etc. Thus, the contribution of methyl group can be calculated as the difference:

$$\Delta V_{\Phi}^{0}(Ala) - \Delta V_{\Phi}^{0}(Gly) = \Delta V_{\Phi}^{0}(CH_3) \tag{2}$$

Also, from experimental data, a linear correlation between transfer volumes and the number of carbon atoms of the side chain of an amino acid in aqueous solution was established. Thus, for calculating the contributions of the side chain of an amino acid and the zwitterionic groups, it can use the following relations [13, 14]:

$$\Delta V_{\Phi}^{0} = \Delta V_{\Phi}^{0}(NH_3^+, COO^-) + n\Delta V_{\Phi}^{0}(CH_2) \tag{3}$$

$$\Delta V_{\Phi}^{0}(CH_3) = 1.5\Delta V_{\Phi}^{0}(CH_2) \tag{4}$$

$$\Delta V_{\Phi}^{0}(CH) = 0.5\Delta V_{\Phi}^{0}(CH_2) \tag{5}$$

where *n* is the number of carbon atoms in the lateral side chain of the amino acid.

In Table 1, the calculated contributions (eqs. 2-5) to the transfer volume from water to water+NaCl solutions, for lateral side chain and zwitterionic groups of studied amino acids are listed for different salt concentrations (0.5, 1 and 1.5 mol kg^{-1} NaCl) at 298.15K. The values resulted from own experimental data are in good agreement with the literature. As Table 1 shows, the resulted values for zwitterionic groups are close to those obtained by other authors [15] for similar salt concentrations: 1.11, 1.90, and 2.45, respectively.

Table 1

Contribution of amino acids constituents groups at transfer volume values at 298.15K

m_{NaCl} (mol·kg^{-1})	$10^6\Delta V_{\Phi}^{0}$, (m^3·mol^{-1})			
	0.5	**1**	**1.5**	
(NH_3^+, COO^-)	1.583	2.506	2.966	
	1.11[15]	1.90[15]	2.45 [15]	
(CH_3)	0.7	1.61	1.16	Ala – Gly
(CH_2 – OH)	0.26	0.53	-0.02	Ser – Gly
($CH_2C_3N_2H_3$)	0.35	-0.26	-0.11	His – Gly
($C_3N_2H_3$)	-0.11	0.81	0.88	His – Gly – CH_2
($C_3H_4NO_2$)	1.45	1.09	0.95	Glu – Gly

Also, from Table 1 it can be observed that the contribution of zwitterionic groups at the total transfer volume is greater than any other contribution of the

lateral chain for the studied amino acids. This can be explained that, regardless of the nature of the lateral side chain (hydrophilic or hydrophobic), its contribution is smaller than of the zwitterionic groups of the amino acid at the transfer volume of amino acid in water + salt solutions.

The contribution of L-Histidine lateral side chain at transfer volume is negative for salt concentrations 1 and 1.5 $mol \cdot kg^{-1}$; if, from this contribution is subtracted the value of - CH_2, the result is a contribution generally positive of imidazole ring, respectively values of 0.81 for 1 $mol \cdot kg^{-1}$ NaCl and 0.88 to 1.5 $mol \cdot kg^{-1}$ NaCl were obtained. This means that, at increasing NaCl concentration, the interactions between imidazole and solvent medium (NaCl + water) became important in the system and they overcome the hydrophobic effect.

The obtained contributions of the various groups of amino acids show that the ionic interactions are more important in amino acid + water + salt solutions, rather than side-chain interactions with the ions. For better understanding the interactions of studied amino acids in water and in electrolyte solutions, another approach was conducted for a homologous series of amino acids (Glycine, L-Alanine, DL-Serine, DL-Glutamic, DL-Histidine) as pure substances. The most stable conformer of each amino acid with its 3D optimized structure was used to calculate a series of molecular descriptors, using Spartan 14 V1.1.4 software. The geometrical parameters that are the most significant descriptors are: molecular surface area, polar surface area (PSA), and ovality. The other calculated descriptors are: a structure dependent indicator which is the octanol-water partition coefficient (log P), indicators for interractions as polarizability and dipole moment, as well as the hydrogen-bonding capability expressed as H-Bond acceptor/donor counts (HBD and HBA). Their calculated values are listed in Tables 2 and 3, for both in vacuum and in water, respectively. It can be observed that their values vary slightly, except dipole moment value which is very different.

Table 2

Computed molecular descriptors of amino acids in vacuum using Spartan'14 V1.1.4 software, Hartree-Fock method

Amino acid	**Gly**	**L-Ala**	**DL-Ser**	**DL-Glu**	**DL-His**
Formula	$C_2H_5NO_2$	$C_3H_7NO_2$	$C_3H_7NO_3$	$C_5H_9NO_4$	$C_6H_9N_3O_2$
Molecular weight (g/mol)	75.067	89.094	105.093	147.130	155.157
Area ($Å^2$)	95.98	115.32	121.20	164.53	177.52
PSA ($Å^2$)	56.061	55.547	71.064	88.949	78.203
Volume ($Å^3$)	71.53	89.77	96.26	135.69	148.63
Ovality	1.15	1.19	1.19	1.29	1.31
Log P	-1.39	-0.90	-1.75	-1.39	-2.08
Polarizability ($10^{-30} \cdot m^3$)	43.40	44.92	45.50	48.67	50.23
Dipole moment (debye)	6.34	6.06	5.69	5.40	4.46
HBD Count	1	1	2	2	1
HBA Count	2	2	3	3	3

Table 3

Computed molecular descriptors of amino acids in water using Spartan'14 V1.1.4 software, Hartree-Fock method

Amino acid	Gly	L-Ala	DL-Ser	DL-Glu	DL-His
Area ($Å^2$)	95.81	115.13	122.37	164.86	177.48
PSA ($Å^2$)	55.926	55.427	72.688	89.276	78.611
Volume ($Å^3$)	71.49	89.72	96.50	135.81	148.70
Ovality	1.15	1.19	1.20	1.29	1.31
Log P	-1.39	-0.90	-1.75	-1.39	-2.08
Polarizability ($10^{-30} \cdot m^3$)	43.44	44.97	45.57	48.72	50.22
Dipole moment (debye)	7.38	7.12	6.40	6.48	5.67

As expected, due to their increasing molecular weight in the series: Gly > Ala > Ser > Glu > His, the area, the polar surface area, and the volume increase slightly in a similar way, showing the following contributions of the lateral side chain to these parameters: ($-CH_3$) for Ala, ($-CH_2$) and an additional hydroxyl group for Serine, two ($-CH_2$) groups and a carboxyl group for Glutamic acid, and (CH_2-) and imidazole ring for Histidine.

The octanol-water partition coefficient (log P) is a structure dependent indicator providing information on the liophilicity or hydrophobicity. The obtained log P values are much lower than 5, and therefore, correlated with the "Lipinski rule of 5" [16, 17], they predict good absorption and permeation, important to rationalize interactions with other molecules. Interestingly, Glycine and DL-Glutamic acid present the same value for log P (-1.39) in vacuum.

The ovality parameter in computational chemistry is a measure of the deviation of a molecule from the spherical shape, considering the minimum surface for the spherical shape. Thus, this descriptor is related to the molecular surface area and the minimum surface area corresponding to the van der Waals volume of a molecule [18]. The ovality index is unitary for spherical molecules and increases with increasing linearity (elongated shape) of the molecule. In the studied series, it increases in the order: Gly <Ala < Ser < Glu < His in both vacuum and water media.

The polarizability is useful to evaluate 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 amino acids an accurate prediction of dipole moment values using software applications requires, taking into account the surrounding molecules for each compound, a cluster formed by 14-21 molecules that are closer that 3-5 Å distance threshold to any atom of the central molecule [19]. Various possible geometric positions of the neighborhood molecules lead to variation in the dipole moment prediction.

The predicted values for dipole moment and polarizability suggest a similar behavior of amino acid in electrolyte solutions as can be observed from

investigation of volumetric behavior. The polarizability, dipole moment and hydrophobicity of studied structures are important factors that determine intermolecular interactions: ion-ion interactions, ion-hydrophilic group interaction and ion - non polar group interactions.

5. Conclusions

For a comparative investigation, a set of homologous amino acids that differ in structure by the nature of their side chain was chosen to highlight the influence of different groups of amino acids on the volumetric behavior. The contribution of zwitterionic groups overcomes in their value any other contribution of the lateral chain for the studied amino acids. The ionic interactions are prevalent in these systems, compared to side-chain interactions with the ions in the solution.

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