

## A Simplified Perturbation Model for Prediction of Mean Ionic Activity Coefficient in Aqueous Electrolyte Solution

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### Abstract

*In this work a simplified model based on perturbation theory is presented for prediction of activity coefficient of amino acids and electrolytes in aqueous electrolyte solution. In comparison with previous works, in this model a new hard sphere equation of state has been utilized as a reference term while other interactions such as charge-charge, charge-dipole, dipole-dipole and dipole-induced dipole have been considered as perturbation terms. For simplification, solvent has been considered as dielectric continuum. Finally, aqueous electrolyte solutions containing amino acids have been modeled just using two adjustable parameters. The results have been compared with similar models and it is shown that new hard spheres equation of state shows an improvement in accuracy of the model.*

**Keywords:** Activity Coefficient, Perturbation Model, Amino acid, Peptide, Hard Sphere

### 1. Introduction

Production of synthetic proteins have received more attention in recent years due to global food deficiency. In this regard separation of amino acids is helpful because of their application in production of synthetic proteins. A considerable number of experimental as well as theoretical researches have been focused on studying amino acids behavior [1-13]. Usually separation and purification of bio-molecules from dilute aqueous solutions can be as high as 90% of their total manufacturing cost. Purification

costs as well as high demands for bio-molecules, especially amino acids have encouraged researchers to find new methods for purification. Fractional precipitation and crystallization methods are applied extensively [13]. The physical properties of amino acids such as their activity coefficients are necessary in design and scale-up steps. Unfortunately complex structure of bio-molecules has caused the conventional thermodynamics models to fail in determination of amino acid physical properties. A number of attempts have been

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presented in the literature to calculate the activity coefficients of amino acid and proteins. Excess Gibbs energy models including empirical local composition and group contribution methods, such as Wilson [6], electrolyte NRTL [5], UNIQUAC [7], and UNIFAC [9-11] equations have seldom been successful in application due to the large number of adjustable parameters which were dependent on experimental data.

Khoshkbarchi and Vera [12] proposed a new model based on the perturbation theory, their work has been extended and modified to correlate and predict activity coefficients of amino acids in aqueous binary and ternary systems [14-16]. Although it has been claimed that the presented models can satisfactorily correlate the experimental data, most of them are complicated and some unnecessary complexity has been introduced in the models, making them inapplicable.

In this work, in continuation of our previous works [2,3,17], we present a primitive and simplified model based on perturbation theory for prediction of mean ionic activity coefficients of electrolytes in aqueous solution containing amino acids. In our model, a new hard sphere equation of state is used as reference state. This hard sphere equation of state was proposed by Dehghani and Modarress [17] and has shown significant ability compared to other hard sphere equation of states. In comparison with previous models, in this work the variation of dielectric constant as well as solvent effects has been considered. However, some modifications have been implemented to increase the abilities and simplicity of the perturbation model.

## 2. Theory of model

Different theories have been utilized for correlation and prediction of thermo-physical properties in aqueous electrolyte solution containing amino acids. In recent years perturbation theory has attracted more attention among different theories. Perturbation theory was initially developed by Zwanzig [18] for gases and was extended to liquids by Barker and Henderson [19]. The perturbation theory has the advantage of incorporating various types of interactions easily. However, considering all types of interactions can make them quite complex and unsuitable in engineering applications. In this work, a simplified model is presented based on perturbation theory for prediction of mean ionic activity coefficient in amino acid and peptide aqueous solution. In this theory, residual chemical potential,  $\mu_i^r$ , is defined as a summary of reference, perturbation, long range and born contributions as shown below:

$$\frac{\mu_i^r}{kT} = \left(\frac{\mu_i^r}{kT}\right)^{HS} + \left(\frac{\mu_i^r}{kT}\right)^{L-J} + \left(\frac{\mu_i^r}{kT}\right)^{D-D} + \left(\frac{\mu_i^r}{kT}\right)^{D-ID} + \left(\frac{\mu_i^r}{kT}\right)^{C-D} + \left(\frac{\mu_i^r}{kT}\right)^{ELEC} + \left(\frac{\mu_i^r}{kT}\right)^{BORN} \quad (1)$$

Where superscript *HS*, *L-J*, *D-D*, *D-ID*, *C-D*, *ELEC* and *BORN* refers to hard sphere, Lenard-Jones as dispersion term, dipole-dipole, dipole-induced dipole, charge-dipole, electrostatic and Born contributions on residual chemical potential respectively. *k* refers to Boltzmann constant ( $1.38 \times 10^{-23} \text{J.K}^{-1}$ ) and *T* is absolute temperature. The

electrostatic interactions are considered using Pitzer-Debye-Huckel model.

In perturbation based models, usually hard sphere equations are used as reference term. The accuracy of the hard sphere term is highly effective in accuracy of model. In this work we have utilized a new hard sphere equation of state which has recently been developed and has shown good performance in mean spherical approximation theory as reference term. This hard sphere equation of state was built based on new highly optimized molecular dynamics simulation data and is able to meet low density and closed packed limits of compressibility factor [17]. We refer the interested reader to the mentioned reference for more details. In this part and in the appendix just the required thermodynamic properties have been presented. According to new hard sphere EOS, the residual Helmholtz free energy  $A^r$ , and chemical potential  $\mu^r$  are defined as Eq. (2):

$$\begin{aligned} \frac{\mu_i^{r,HS}}{kT} &= \frac{A^{r,HS}}{NkT} + \rho \left( \frac{\partial(A^{r,HS}/NkT)}{\partial \rho_i} \right)_{T, Y, \rho_{j \neq i}} \\ &= \left( \frac{Y_1 + Y_2}{2} \right) C_1 - (1 + Y_1 - 2Y_2) \ln(1 - \eta_3) \\ &\quad + \left( \frac{C_4 + C_3}{2} \right) C_1 + \left( \frac{Y_1 + Y_2}{2} \right) R_{3,i} (Z_p - 1) \\ &\quad - (C_3 - 2C_4) \ln(1 - \eta_3) + \frac{(1 + Y_1 - 2Y_2) \eta_3 R_{3,i}}{1 - \eta_3} \end{aligned} \quad (2)$$

The parameters have been defined in the appendix section.

The Lenard-Jones, dipole-dipole, dipole-induced dipole, charge-dipole have been calculated based on Barker-Henderson theory

[19]. According to Tiepel-Gubbins [20] the chemical potential for these terms can be calculated through substitution of relevant intermolecular potential in equation (3):

$$\mu_i = 2\pi \frac{\partial}{\partial \rho_i} \left[ \sum_{j=1}^n \sum_{l=1}^n \rho_j \rho_l \int_{\sigma_{jl}}^{\infty} u_{jl}(r) g_{jl}^{HS}(r) r^2 dr \right] \quad (3)$$

In which  $r$ ,  $u(r)$ , and  $g^{HS}(r)$  are intermolecular distance, intermolecular potential and radial distribution function, respectively.

Lenard-Jones ( $L-J$ ), dipole-dipole ( $D-D$ ), dipole-induced dipole ( $D-ID$ ) and dipole-charged dipole ( $D-CD$ ) potentials are defined as shown below [22]:

$$u_{ij}^{L-J}(r) = 4\varepsilon \left( \frac{\sigma_{ij}^{12}}{r^{12}} - \frac{\sigma_{ij}^6}{r^6} \right) \quad (4)$$

$$u_{ij}^{D-D}(r) = -\frac{\overline{D_i} \overline{D_j}^2}{3(4\pi\varepsilon_0\varepsilon_r)^2 kTr^6} \quad (5)$$

$$u_{ij}^{D-ID}(r) = \frac{-\overline{\alpha_j} \overline{D_i}^2 - \overline{\alpha_i} \overline{D_j}^2}{(4\pi\varepsilon_0\varepsilon_r)^2 kTr^6} \quad (6)$$

$$u_{ij}^{D-CD}(r) = -\frac{z_i^2 e^2 \overline{D_j}^2}{6(4\pi\varepsilon_0\varepsilon_r)^2 kTr^4} \quad (7)$$

Where  $\varepsilon$ ,  $D$ ,  $\varepsilon_0$ ,  $\varepsilon_r$ ,  $\overline{\alpha}$ ,  $Z$  and  $e$  are depth of potential well, dipole moment, permittivity of vacuum, relative dielectric constant, polarizability, charge of ion and unit of charge, respectively.

The step function proposed by Reed and Gubbins [21] has been considered as radial

distribution function as follows:

$$g_{jl}^{HS}(r) = \begin{cases} 0 & r < \sigma_{ij} \\ 1 & r > \sigma_{ij} \end{cases} \quad (8)$$

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad (9)$$

After substitution of equations (4) to (8) in equation (3), the following equation will be derived as contribution of Lenard-Jones (*L-J*), dipole-dipole (*D-D*), dipole-induced dipole (*D-ID*) and charged- dipole (*C-D*) interactions in residual chemical potential:

$$\left(\frac{\mu_i^r}{kT}\right)^{L-J} + \left(\frac{\mu_i^r}{kT}\right)^{D-D} + \left(\frac{\mu_i^r}{kT}\right)^{D-ID} + \left(\frac{\mu_i^r}{kT}\right)^{C-D} = -\frac{4\pi}{kT} \left\{ \frac{8}{9} \rho_S \sigma_S^3 \varepsilon_S + \frac{8}{9} \rho_A \sigma_{S,A}^3 \sqrt{\varepsilon_A \varepsilon_S} + \frac{\rho_A \bar{\alpha}_S \bar{D}_A^2 kT}{3(4\pi\varepsilon_0 \varepsilon_r)^2 \sigma_{S,A}^3} + \frac{\rho_A z_S^2 e^2 \bar{D}_A^2}{6(4\pi\varepsilon_0 \varepsilon_r)^2 kT \sigma_{S,A}} \right\} \quad (10)$$

Where subscript *A* and *S* denote Amino acid and ions respectively. This equation must be expanded for ions and amino acid separately. The Born term is also used for calculating the effects of ions on solvent as continuum media. The residual chemical potential for *BORN* term is defined as [23]:

$$\frac{\mu_i^{r,BORN}}{kT} = \frac{1}{kT} \left[ \frac{Z_i^2 e^2 N_A}{8\pi\varepsilon_0 \varepsilon_r r_i} - \frac{Z_i^2 e^2 N_A}{8\pi\varepsilon_0 r_i} \right] = \frac{1}{kT} \left\{ \frac{Z_i^2 e^2 N_A}{8\pi\varepsilon_0 r_i} \left( \frac{1}{\varepsilon_r} - 1 \right) \right\} \quad (11)$$

Where *R* is born radius.

Meanwhile the mean ionic activity

coefficient of salt,  $\gamma_{\pm}$ , is defined based on Eq. (12):

$$\gamma_{\pm} = (\gamma_+^{\nu_+} \gamma_-^{\nu_-})^{(\nu_+ + \nu_-)^{-1}} \quad (12)$$

Where  $\nu$  is stoichiometric number of ions.

In all previous models, dielectric constant has been considered as a constant value, but it is clear that with changing the electrolyte and amino acid concentrations, dielectric constant will change. The concentrations of ions as well as amino acids have significant effect on dielectric constant. In this model Eq. (13) is applied for considering the variation of dielectric constant versus electrolyte molality.

$$\varepsilon_r = \varepsilon_{r_0} + A_1 I^{1/2} + A_2 \frac{I^{1/2}}{1 + I^{1/2}} \quad (13)$$

In the above equation  $\varepsilon_{r_0}$  is dielectric constant for pure water and *I* is the ionic strength of solution (Eq (14)). *A*<sub>1</sub> and *A*<sub>2</sub> are the only adjustable parameters in ternary systems.

$$I = \frac{1}{2} \sum_{i=1}^n m_i z_i^2 \quad (14)$$

Where *m* is the molality.

### 3. Model parameters

The required parameters for calculation of mean ionic activity coefficients are size parameter, amino acid's dipole moment, cation and anion's polarizability, and depth of potential well for all components such as amino acid, peptide, cations and anions. Dipole moment of amino acid and peptides

has been calculated through quantum mechanical approach using the Hyperchem molecular modeling software. Binary experimental data [26] for aqueous amino acid solution in the absence of electrolyte has been utilized for determination of amino acid

size parameters and depth of potential well. In Table 1, the obtained parameters have been presented. Ion parameters such as polarizability, crystalline size and depth of Potential well have been extracted from published papers [17,27-28].

**Table 1.** Calculated  $\sigma$ ,  $\epsilon/k$  from Correlation of Amino Acids and Peptide Experimental Activity Coefficients [26].

Amino Acid	$\epsilon/k(K)$	$\sigma \times 10^{10}(m)$	RMSD $\times 10$ 0(1)	RMSD $\times 10$ 0(2)	RMSD $\times 10$ 0(3)	RMSD $\times 10$ 0(4)	RMSD $\times 10$ 0(5)
Alanine	60.77	3.33	0.05	0.51	0.03	0.04	0.19
$\alpha$ -Amino n-butyric acid	87.06	4.8	0.4	0.42	—	0.32	17.84
Glycine	174.92	4.71	0.39	0.84	0.66	2.07	1.67
Hydroxyproline	107.57	4.24	0.07	0.15	—	0.36	0.39
Proline	62.73	4.5	1.55	7.12	1.38	1.30	1.21
Serine	196.74	5.03	0.54	1.19	0.24	2.80	0.24
Threonine	135.21	4.54	0.08	0.25	0.25	0.7	26.12
Averaged RMSD	—	—	0.44	1.50	0.51	1.08	6.81
Peptid	$\epsilon/k(K)$	$\sigma \times 10^{10}(m)$	RMSD $\times 10$ 0(1)	RMSD $\times 10$ 0(2)	RMSD $\times 10$ 0(3)	RMSD $\times 10$ 0(4)	RMSD $\times 10$ 0(5)
Alanylalanine	117.85	6.66	0.32	0.40	0.34	2.04	0.52
Alanylglycine	149.58	6.91	0.39	0.71	0.41	2.92	28.22
Glycylalanine	153.22	7.22	0.61	0.52	—	2.44	0.59
Glycylglycine	174.28	6.58	0.91	2.81	0.99	3.25	17.06
Tri-glycine	160.25	8.56	0.00	—	0.00	0.67	10.00
Averaged RMSD	—	—	0.45	1.11	0.44	2.26	11.28

(1) This Model; (2) [15]; (3) [40]; (4) [39]; (5) [10]

#### 4. Correlation

The presented model for calculation of mean ionic activity coefficients in ternary solutions needs two adjustable parameters. In our model, dielectric constant with two adjustable parameters must be determined through correlation of electrolyte activity coefficients. The parameter estimation method is effective in evaluation of the results. In order to avoid the local optimization instead of global optimization, Davidon-Fletcher-Powell (DFP) [29-31] algorithm was used. DFP is a well known procedure, which approximates the inverse Hessian matrix, to determine the global minimum. Objective function ( $OF$ ) is defined as follows:

$$OF = \sum_{i=1}^n (\ln \gamma_i^{\text{exp}} - \ln \gamma_i^{\text{cal}})^2 \quad (15)$$

Where superscript  $exp$  and  $cal$  are experimental values and calculated values, respectively. Since calculated activity coefficients are based on mole fraction and experimental data are based on molality, Eq. (16) is used to change experimental activity coefficient from molality base to mole fraction base.

$$\ln \gamma^{(x)} = \ln \gamma^{(m)} + \ln(1 + 0.001M_s \sum_i m_i) \quad (16)$$

In which  $M_s$  is molecular weight of solvent. The superscripts  $x$  and  $m$  show molality and mole fraction base activity coefficients, respectively. The deviation of our model from experimental data was calculated based on root mean square deviation ( $RMSD$ ):

$$RMSD = \sqrt{\frac{\sum_{i=1}^n (\gamma_i^{\text{exp}} - \gamma_i^{\text{cal}})^2}{n}} \quad (17)$$

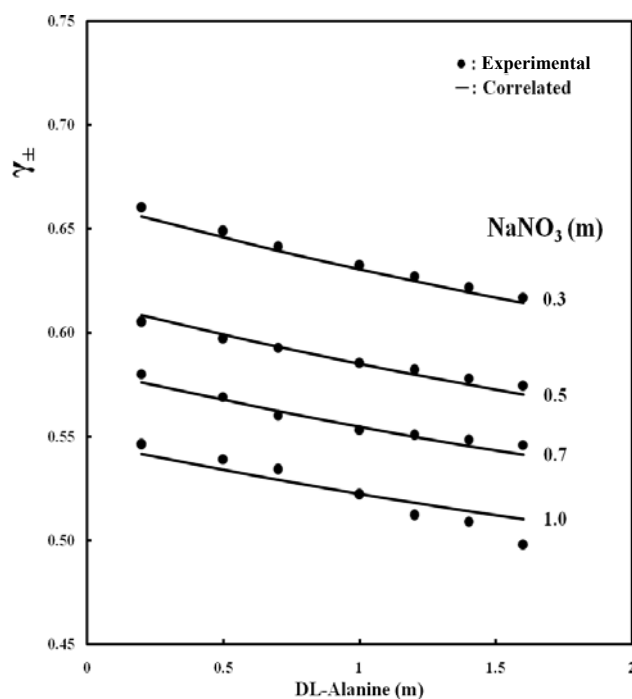
Where  $n$  is number of data.

#### 5. Results and discussion

In Table 2, calculated values for adjustable parameters ( $A_1$  and  $A_2$ ) have been presented. The experimental data at 298.15 K and at atmosphere pressure have been compared with correlated data. In Fig. 1 correlation of mean ionic activity coefficient of  $\text{NaNO}_3$  in DL-Alanine aqueous solution at different molalities of electrolyte is presented versus molality of amino acid. In the same way, Fig. 2 shows the results of modeling of mean ionic activity coefficient of  $\text{NaCl}$  in water- $\text{NaCl}$ -Glycine system. Also, results of calculated mean ionic activity coefficient of  $\text{KCl}$  in DL-Valine aqueous solution have been depicted in Fig. 3. The most important advantage of this model is its ability to model the activity coefficients in more complicated systems such as those containing peptide and electrolytes. In Fig. 4 the results of modeling of mean ionic activity coefficient of  $\text{KCl}$  in water- $\text{KCl}$ -Glycylglycine as a peptid aqueous solution has been shown. As it is presented in Table 2, the adjustable parameters and  $RMSD$  follow a good trend in a reliable range. We checked the model for other peptides and the calculations showed that this model with 1-4% error can correlate and predict the mean ionic activity coefficients of electrolyte in the system containing peptides.

**Table 2.** Adjustable parameters and RMSD of Activity Coefficients of Amino Acids and peptide in water-Electrolyte-amino acid and peptide system.

	$A_1$	$A_2$	RMSD	Ref.
DL-Alanine+NaNO <sub>3</sub>	31.2416	-75.99	0.47	[32]
Glycine+NaCl	160.00	10.00	0.46	[33]
Alanine+NaCl	110.63	80.51	0.55	[33]
Glycine+KCl	314.07	308.59	0.59	[34]
Glycylglycine+NaCl	113.78	47.86	0.32	[35]
Glycylglycine+KCl	157.98	200.00	1.64	[35]
DL-Valine+KCl	774.96	-724.44	0.37	[36]
Alanine+NaCl	694.21	-768.67	0.16	[36]
Glycine+NaCl	731.12	-728.23	0.55	[2]
Glycine+NaBr	300	-9.10	1.47	[37]
L-Valine+NaBr	-43.38	92.44	0.61	[37]
Glycine+NaCl	30.00	100.00	0.49	[38]



**Figure 1.** Mean ionic activity coefficient of NaNO<sub>3</sub> in water- NaNO<sub>3</sub>-DL-Alanine system in different molalities of electrolyte versus amino acid molalities.

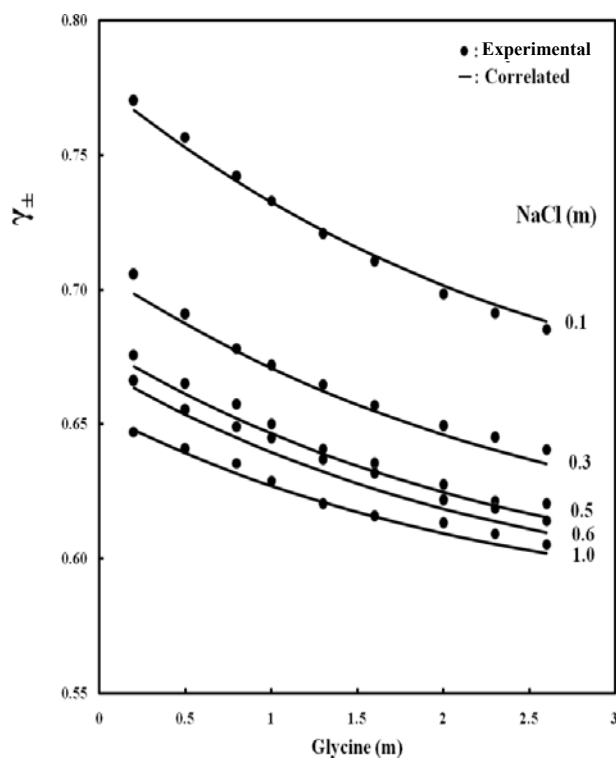


Figure 2. Mean ionic activity coefficient of NaCl in water- NaCl-Glycine system in different molalities of electrolyte versus amino acid molalities.

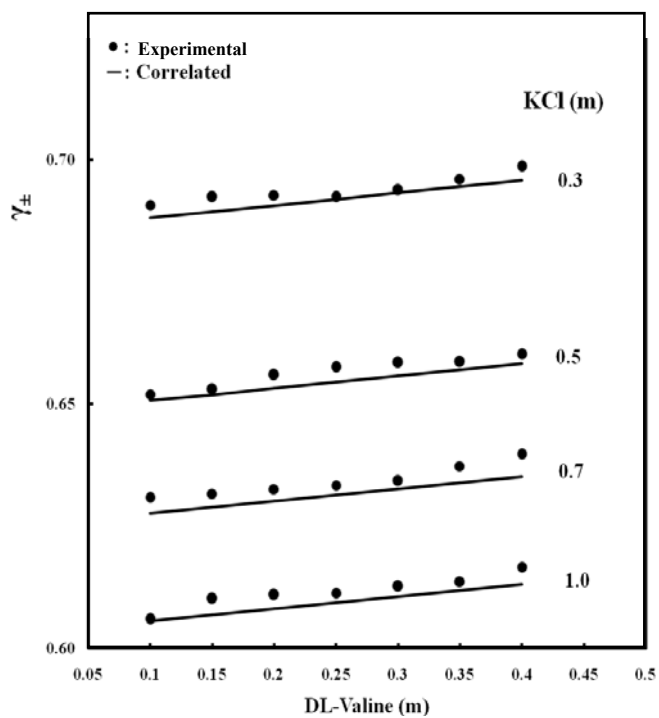
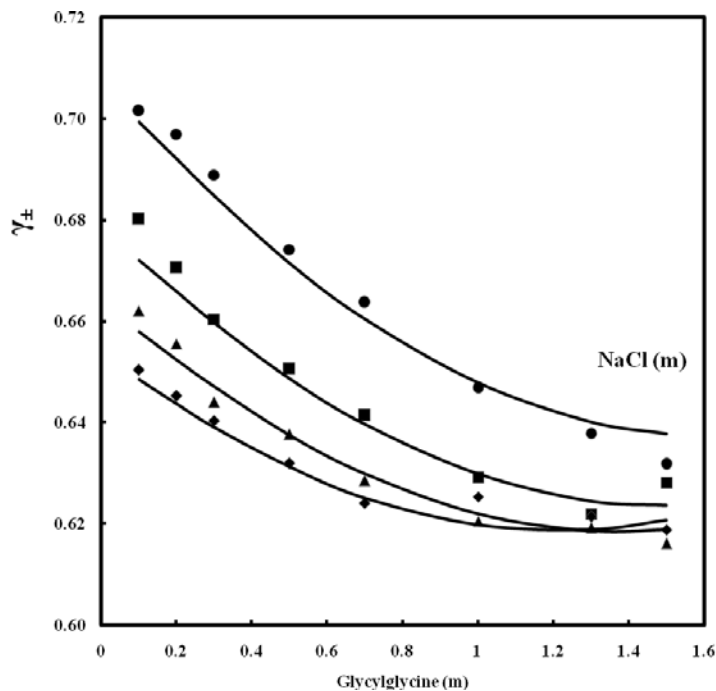


Figure 3. Mean ionic activity coefficient of KCl in water- KCl-DL-Valine system in different molalities of electrolyte versus amino acid molalities.





**Figure 4.** Mean ionic activity coefficient of KCl in water- KCl-DL-Valine system in different molalities of electrolyte versus amino acid molalities. ●:  $m_{NaCl}=0.3$ , ■:  $m_{NaCl}=0.5$ , ▲:  $m_{NaCl}=0.7$ , ◆:  $m_{NaCl}=1.0$ , — : correlated result.

The results show that adjusted values of dielectric constant are reasonable. To the best of our knowledge, there are not any experimental data on dielectric constant of electrolyte solution containing amino acid and peptides, so we cannot judge the physical meaning of the obtained dielectric constants. If we could substitute the experimental data of dielectric constants in the model, it would be possible to make a predictive model, otherwise the calculated data for dielectric constant must be considered just as an adjustable parameter. It is our opinion that the available experimental data on these systems could lead us to great achievement in modeling of amino acid-electrolyte and more complicated systems.

It is shown that the overall fitting is quite good. Obtained *RMSD* using presented model indicates that this model has very

good accuracy for correlation of experimental data. The ability of the presented model points to the application of the following items. Firstly, utilizing new hard sphere equation of state with high accuracy. Secondly, consideration of dielectric constant changes versus molality of electrolyte. In the previous works dielectric constants have been kept constant and equal to dielectric constant of pure water while it is well known that in the presence of electrolyte and amino acids this assumption is not true.

## 6. Conclusions

In this work a simplified model based on perturbation theory with two adjustable parameters was developed for correlation of activity coefficients in aqueous systems containing amino acid, peptide and electrolytes. A new hard sphere equation of

state has been utilized as a reference system. Dipole-dipole and Lennard-Jones interactions have been considered in perturbation term. The activity coefficients of more than 240 data points for aqueous amino acid- electrolyte solution have been modeled by the minimum number of adjustable parameters which had been set on dielectric constants. Results of the model denote that the effect of reference term in chemical potential of amino acids is significant. Compared to similar models, the modifications caused an improvement in the results of the perturbation model. The results of this work show that with the simplified perturbation model, the mean ionic activity coefficient of electrolyte in aqueous solution of amino acids can be calculated in a very simple way, especially for ternary systems.

## Appendix

Defined parameters in the model:

$$\eta_i = \frac{\pi}{6} \sum_j \rho_j \sigma_j^i \quad i = 0, 1, 2, 3 \quad (1)$$

Where  $\rho$  and  $\sigma$  are number densities and size parameter.

$$Y_1 = \frac{\xi_1 \xi_2}{\xi_0 \xi_3} \quad (2)$$

$$Y_2 = \frac{\xi_2^3}{\xi_0 \xi_3^2} \quad (3)$$

$\xi$  is defined as follows:

$$\xi_i = \frac{1}{\sqrt{2}} \sum_j \rho_j \sigma_j^i \quad i = 0, 1, 2, 3 \quad (4)$$

is defined as follows:

$$C_1 = -0.186\xi_3^7 - 0.866\xi_3^6 - 2.216\xi_3^5 - 4.58\xi_3^4 - 9.245\xi_3^3 - 19.845\xi_3^2 - 53.93\xi_3 - \frac{0.395}{(1-\xi_3)^3} + \frac{1.045}{(1-\xi_3)^2} - \frac{15.539}{(1-\xi_3)} - 70.46 \ln(1-\xi_3) + 14.533 \quad (5)$$

$$C_2 = -0.162\xi_3^8 - 0.742\xi_3^7 - 1.846\xi_3^6 - 3.667\xi_3^5 - 6.934\xi_3^4 - 13.23\xi_3^3 - 26.963\xi_3^2 - 70.457\xi_3 - \frac{0.395}{(1-\xi_3)^3} + \frac{1.104}{(1-\xi_3)^2} - \frac{17.63}{(1-\xi_3)} - 85.996 \ln(1-\xi_3) + 16.487 \quad (6)$$

$$C_3 = Y_1 (R_2 + R_1 - R_3 - R_0)_i \quad (7)$$

$$C_4 = Y_2 (3R_2 - R_0 - 2R_3)_i \quad (8)$$

$$R_{i,k} = \frac{\sigma_i}{\sum_j x_j \sigma_j^k} \quad (9)$$

## Nomenclature

k	Boltzmann constant ( $1.38 \times 10^{-23}$ J.K-1)
T	Absolute temperature
N	Avogadro number
r	Intermolecular distance
u(r)	Intermolecular potential
$g^{HS}(r)$	Radial distribution function
D	Dipole moment
Z	charge of ion
e	unit of charge
R	Born radius
I	ionic strength of solution
$A_1$ and $A_2$	adjustable parameters
m	molality of amino acid
d	density of solute
$d_0$	density of pure water

M	Molecular weight of amino acid
M <sub>S</sub>	molecular weight of solvent
OF	Objective function
RMSD	root mean square deviation
$\mu'_i$	Residual chemical potential
$\rho$	Number density
$\gamma$	Activity coefficient
$\nu$	stoichiometric number of ions
$\sigma$	Size parameter
$\epsilon$	Depth of potential well
$\epsilon_0$	Permittivity of vacuum
$\epsilon_r$	Relative dielectric constant
$\bar{\alpha}$	polarizability
$\epsilon_{r0}$	dielectric constant for pure water
LR	Long Range (contribution)
SR	short Range (contribution)
BORN	Born term
HS	hard sphere term
PER	Perturbation term
id	ideal solution
PDH	PDH term
L-J	Lenard-Jones (interaction)
D-D	dipole-dipole
D-ID	dipole-induced dipole
D-CD	dipole-charged dipole
exp	experimental value
cal	calculated value
x	molality base activity coefficients
m	mole fraction base activity coefficients
$\pm$	mean ionic
A	Amino acid
S	electrolyte
+	Cation
-	anion

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