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Activity Coefficient and Solubility of Amino Acids in Water by the Modified Wilson Model

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The modified Wilson model for the phase behavior of polymer aqueous solutions has been applied to calculate activity coefficients and the solubility of amino acids and small peptides in aqueous solutions. The interaction parameters estimated from the activity coefficients and the solubility data are used to evaluate the solubility of amino acids. The model can accurately represent the activity coefficients of amino acids with only two adjustable parameters per system. It is also used to describe the solubility of several amino acids with satisfactory results. After introduction of the influence of temperature on the energy parameters, it is possible to obtain better predictions of the solubility at higher temperatures than those from UNIFAC and UNIQUAC. The results achieved for the solubility of a mixture of two amino acids are in good agreement with the literature data.

Introduction

The physical properties of amino acids such as solubility and activity coefficients in water are indispensable to the design and scale-up of chemical processes for separation, concentration, and purification of valuable biochemicals. Therefore, model development for activity coefficients has drawn much attention during the past decades.

The conventional thermodynamic models including empirical local composition and group contribution methods, such as Wilson,¹ electrolyte NRTL,² UNIQUAC,³ and UNIFAC^{4–7} equations, to represent the activity coefficients of amino acids, have been reviewed in detail by Khoshkbarchi and Vera.^{8,9}

Recently, the achievements of the perturbation theory have also been incorporated into the amino acid systems. Khoshkbarchi and Vera⁸ first proposed to correlate the activity coefficients of amino acids based on the perturbation theory. Several extensions^{9–13} have been used to correlate and predict the thermodynamic properties for several binary and ternary aqueous amino acid systems.

In this study, an expression extended from the residual contribution of the modified Wilson model for polymer aqueous solutions¹⁴ is proposed to describe the activity coefficients and solubility of amino acids in aqueous solutions. Each binary system studied has been correlated separately, and the results obtained are very satisfactory, even considering the influence of temperature on the solubility. The solubility of a mixture of two amino acids in water is also investigated.

Thermodynamic Framework

In this work, the modified Wilson model for polymer aqueous solutions published earlier¹⁴ is extended to

describe the excess Gibbs energy for amino acid systems. The combinatorial contribution term defined to account for the size/shape contribution is negligible for the systems under consideration here because the molecules of amino acids and peptides are very small. Therefore, the excess Gibbs energy can be written as

$$\frac{G^E}{RT} = \frac{H^E}{RT} - \frac{1}{R} \int_{\infty}^T \frac{1}{T} \left(\frac{\partial H^E}{\partial T} \right)_{P,x} dT \quad (1)$$

After polymer molecules are replaced by small amino acid molecules, the activity coefficient expression can be easily obtained as

$$\ln \gamma_i = -\frac{1}{\alpha} \left[\ln \left(\sum_{k=1}^m x_k G_{ki} \right) - 1 + \frac{\sum_{k=1}^m x_k G_{ik}}{\sum_{j=1}^m x_j G_{jk}} \right] \quad (2)$$

where $G_{ij} = \exp(-\alpha_{ij}\tau_{ij})$, $G_{ji,ki} = \exp(-\alpha_{ji,ki}\tau_{ji,ki})$; τ is the energy parameter; x is the mole fraction; and α is the nonrandom factor, which is fixed at 0.1 in this study. The following expressions are used here to describe the influence of temperature on τ :¹⁵

$$\tau_{ji} = a_{ji}^{(1)}(T_0/T) + a_{ji}^{(2)}(T_0/T)^2 \quad (3)$$

$$\tau_{ij} = a_{ij}^{(1)}(T_0/T) + a_{ij}^{(2)}(T_0/T)^2 \quad (4)$$

$a^{(1)}$ and $a^{(2)}$ are adjustable model parameters, both temperature- and composition-independent; $a^{(2)}$ is set equal to zero in this work as previously.¹⁴

In the present work, it is assumed that all of the amino acid molecules in pure water are in zwitterionic form without any other chemical and physical interactions.¹⁶ This assumption is fully justified because more than 99% of the amino acid molecules stay in the zwitterionic form in the absence of a strong proton donor or a proton acceptor.^{16,17}

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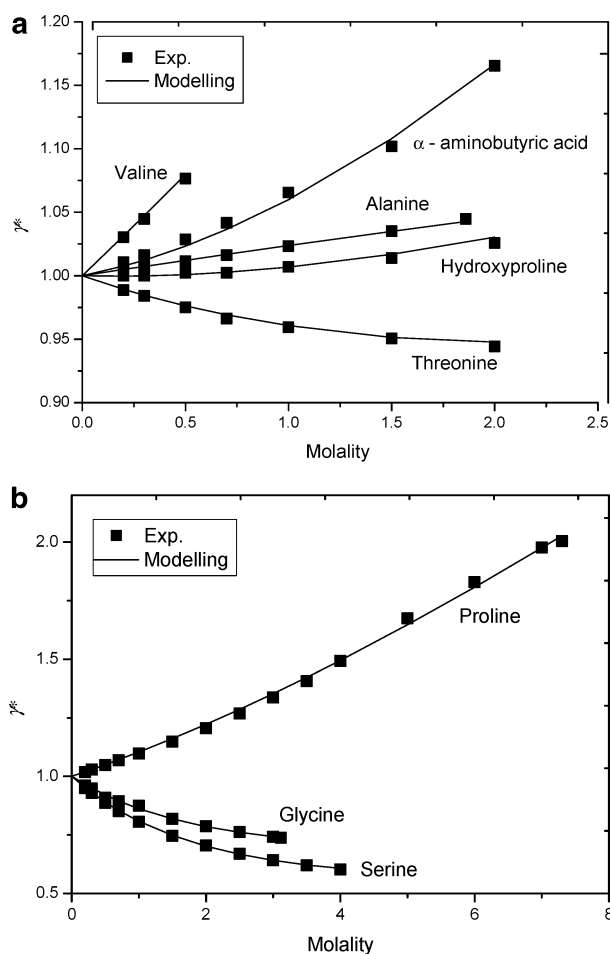
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Table 1. Regressed Parameters of Amino Acids and Peptides: Correlation Results for Activity Coefficient Data by Different Approaches^a

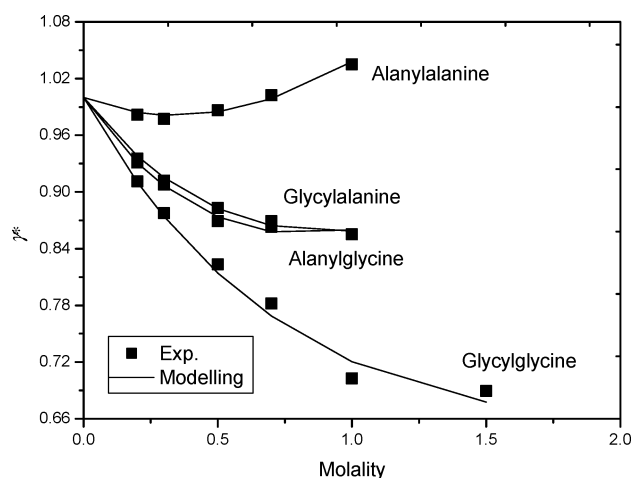
amino acids or peptides	<i>N</i>	$a_{21}^{(1)}$	$a_{12}^{(1)}$	rmsd (%) ^b	rmsd (%) ^c	rmsd (%) ^d	rmsd (%) ^e	rmsd (%) ^f	rmsd (%) ^g	rmsd (%) ^h	rmsd (%) ⁱ	rmsd (%) ^j	rmsd (%) ^k
alanine	7	-4.8220	5.2639	0.08	0.04	0.02	8.97	0.19	0.32	0.33	0.84	0.51	0.03
α-aminobutyric acid	7	-11.2612	16.3228	0.43	0.32	0.51	17.34*	17.87*	0.70	0.37	0.56	0.42	
glycine	10	-10.0016	15.3764	0.71	2.07	0.57	4.20	0.60	0.11	0.86	0.72	0.84	0.75
hydroxyproline	7	-9.3711	13.1320	0.21	0.36	0.11	0.06	0.39		0.09	0.64	0.15	
methionine	2	-17.3121	29.0341	0.31	0.86								
proline	15	-9.5801	12.7524	0.98	1.30	1.36	3.01	1.21	1.04*	4.12	0.74	7.12	1.38
serine	11	-10.1401	16.0243	0.34	2.80	0.18	3.32	0.24	0.47	1.16		1.19	0.24
threonine	7	-9.5465	13.8188	0.21	0.70	0.09	17.78*	26.12*	0.13	1.15	0.28	0.25	0.09
valine	3	-9.4511	12.0297	0.23	4.47	0.04	12.15*	16.43*		0.05		0.45	1.06
α-aminovaleric acid	5	-11.2316	15.9048	0.11		0.04		16.40*	1.81				
alanylalanine	5	-14.2025	22.3394	0.30	2.04	0.09		0.52	1.69	0.43	0.17	0.40	0.34
alanylglycine	5	-14.8505	24.3134	0.44	2.92	0.35		28.22*	3.13*	0.60	0.50	0.71	0.41
glycylalanine	5	-14.3686	23.3575	0.36	2.44	0.13		0.59	2.46*	0.57	0.28	0.52	
glycylglycine	6	-13.3805	22.1266	1.39	3.25	0.05		17.06*	1.00	1.22	1.08	2.81	0.99

^a Prediction results are indicated by asterisks. ^b This work. ^c Reference 2, NRTL. ^d Reference 3, UNIQUAC. ^e Reference 4, UNIFAC. ^f Reference 5, UNIFAC. ^g Reference 6, UNIFAC. ^h Reference 8, primitive perturbation theory. ⁱ Reference 10, a nonprimitive perturbation theory. ^j Reference 11, an improved perturbation model. ^k Reference 13, perturbation theory based on a hard-sphere reference.

**Figure 1.** (a and b) Activity coefficients of amino acids at different molalities: experimental data and modeling. Data from ref 18.

Results and Discussion

Correlation of Activity Coefficients The molality scale activity coefficient data of amino acids and small peptides reported in the literature¹⁸ with a total of 95 experimental points have been used to test the model in this work. Because the experimental data are in the unsymmetric scale, we normalize the activity coef-

**Figure 2.** Activity coefficients of four peptides at different molalities: experimental data and modeling. Data from ref 18.

ficients of the amino acids using an infinite-dilution reference state. Thus

$$\ln \gamma_i^* = \ln \gamma_i - \ln \gamma_i^{\text{ref}} \quad (i \neq 1) \quad (5)$$

where γ_i^{ref} is the activity coefficient at the infinite-dilution reference state and γ_i^* refers to the zwitterion unsymmetric activity coefficient. The conversion of the values of the activity coefficients between the mole fraction and the molality scale is given by

$$\ln \gamma_m = \ln \gamma_x - \ln[1 + (M_w/1000)\sum_i m_i] \quad (6)$$

The two adjustable energy parameters for water–amino acid (zwitterions) pairs were evaluated using the following objective function:

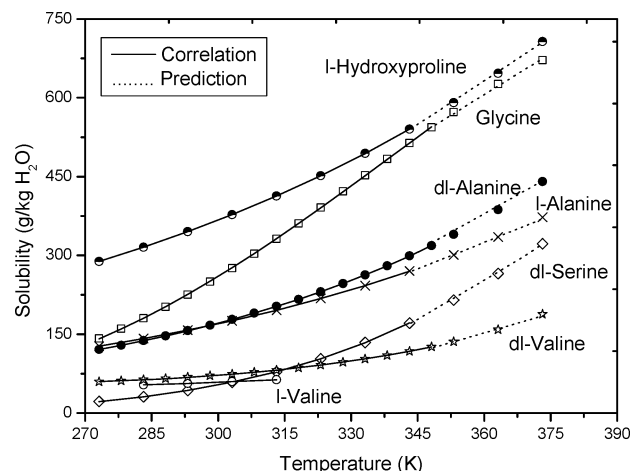
$$\text{OBJ} = \sum_i^N (\gamma_i^{*\text{cal}} - \gamma_i^{*\text{exp}}) \quad (7)$$

Figures 1 and 2 show the correlation results for the activity coefficients for several amino acids and four small peptides as a function of molality at 25 °C. The correlation results are all of high quality. The regressed parameters between amino acids and water are given

Table 2. Solubility Constants of Amino Acids in Water

amino acid	<i>a</i>	<i>b</i>	<i>c</i>	rmsd (%) ^a	rmsd (%) ^b	rmsd (%) ^c	rmsd (%) ^d	rmsd (%) ^e	rmsd (%) ^f
D-alanine	-41.6326	919.4029	6.1779	0.04		0.06	0.35		
L-alanine	-41.6730	920.6575	6.1843	0.02	0.67			0.75	4.53
DL-alanine	-49.1453	1084.3397	7.4001	0.02	0.19	0.14	0.40	0.60	4.67
glycine	81.1301	-4841.8663	-11.9366	0.25	0.14	0.29	1.62	0.48	3.29
L-hydroxyproline	-33.0188	925.0289	4.7331	0.03	0.07	0.14	0.44		2.09
L-methionine	-30.4778	186.6209	4.3404	0.12	0.11				
DL-methionine	-20.6778	-922.4044	3.1892	0.18	2.02				
L-proline	-42.8736	2274.9113	6.1541	0.08	0.14	0.27	1.68		8.38
DL-serine	48.5888	-4471.6123	-6.7490	0.53	2.85	0.64	0.39	0.85	
L-valine	-68.3623	2478.2806	9.7246	0.06	0.50	0.10	0.02	0.25	
DL-valine	-129.0020	4956.7080	18.9461	0.27		1.22	0.26	0.64	

^a This work. ^b Reference 2, NTRL. ^c Reference 3, UNIQUAC. ^d Reference 5, UNIFAC. ^e Reference 6, UNIFAC. ^f Reference 10, a nonprimitive perturbation theory.

**Figure 3.** Correlation and prediction of amino acid solubility in water. Data from refs 18 and 19.

in Table 1. The root-mean-square deviations (rmsd's) obtained in this study and with several other models are also listed in Table 1. It can be seen that the model can accurately describe the activity coefficients of amino acids and small peptides with very good results.

Effect of Temperature on the Solubility of Amino Acids. In this study, the solubility data within the temperature range 0–75 °C reported in the literature¹⁸ and the following equation are used to calculate the thermodynamic solubility constant (K_s):

$$\ln K_s = a + b/T + c \ln T \quad (8)$$

A neutral zwitterion (A^\pm) is formed during the dissolution reaction, and the chemical equilibrium relationship for the dissolution reaction is written as

$$K_s = a_{A^\pm} \quad (9)$$

The objective function is

$$\text{OBJ} = \sum_j (S_j^{\text{cal}} - S_j^{\text{exp}})^2 \quad (10)$$

where S is the solubility in grams per kilogram of water. The amino acid activity coefficients in water were computed with the model parameters presented in Table 1. The estimated results of solubility are plotted in Figure 3. Table 2 summarizes the fitted parameters and a comparison between the rmsd values of this work and of several other models. The framework proposed here

Table 3. Comparison between Literature Extrapolated Data and Predicted Solubilities (g/kg of Water) at 373.15 K

amino acid	S^{exp}	S^{cal}	error (%) ^a	error (%) ^b	error (%) ^c
D-alanine	373.0	372.2	0.22	-0.75	-2.92
DL-alanine	440.4	440.1	0.68	-0.18	-3.29
glycine	671.7	688.3	-2.47	2.98	10.99
L-hydroxyproline	706.9	710.2	-0.46	0.45	-2.15
L-proline	3355	3411	1.67	-1.02	-1.61
DL-serine	322.4	341.4	-5.83	-12.96	-12.59
DL-valine	188.1	182.0	3.23	5.74	-20.79

^a This work. ^b Reference 3, UNIQUAC. ^c Reference 5, UNIFAC.

Table 4. Estimated Binary Parameters between Two Amino Acids in Water at 298.15 K

system	a_{23}	a_{32}	rmsd of m_2 (%)	rmsd of m_3 (%)
water (1)/ DL-alanine (2)/ DL-valine	582.1631	-10.1736	0.74, ^a 0.51 ^b	0.97, ^a 0.77 ^b
water (1)/ DL-alanine (2)/ DL-serine	673.5334	-12.1562	2.98, ^a 1.71 ^b	0.66, ^a 0.46 ^b

^a This work. ^b Reference 6, UNIFAC.

seems to be very satisfactory and gives a better agreement with the literature data than other models.

The predicted solubility data of some amino acids at 373.15 K are shown in Table 3. As can be seen, our model can successfully represent the temperature influence on the solubility of amino acids, especially for DL-serine above 75 °C, with better prediction than UNIFAC and UNIQUAC models. This may be mainly due to the introduction of the temperature dependence on the energy parameter τ in eqs 3 and 4.

Solubility of Two Amino Acid Mixtures. The binary interaction parameters and the solubility constant of the amino acids listed in Tables 1 and 2 are directly used to calculate the solubility of a mixture of two amino acids in water. The binary interaction parameters between two amino acids are treated as adjustable parameters. Therefore, only two adjustable parameters are left unknown. Here, two systems are investigated: water + DL-alanine + DL-valine and water + DL-alanine + DL-serine.⁶ The estimated solubility results are plotted in Figure 4. Table 4 shows the binary interaction parameters between two amino acids and the rmsd values compared with those obtained from the UNIFAC model.⁶ It can be seen that the modified Wilson model can successfully represent the solubility of a mixture of two amino acids in aqueous solutions.

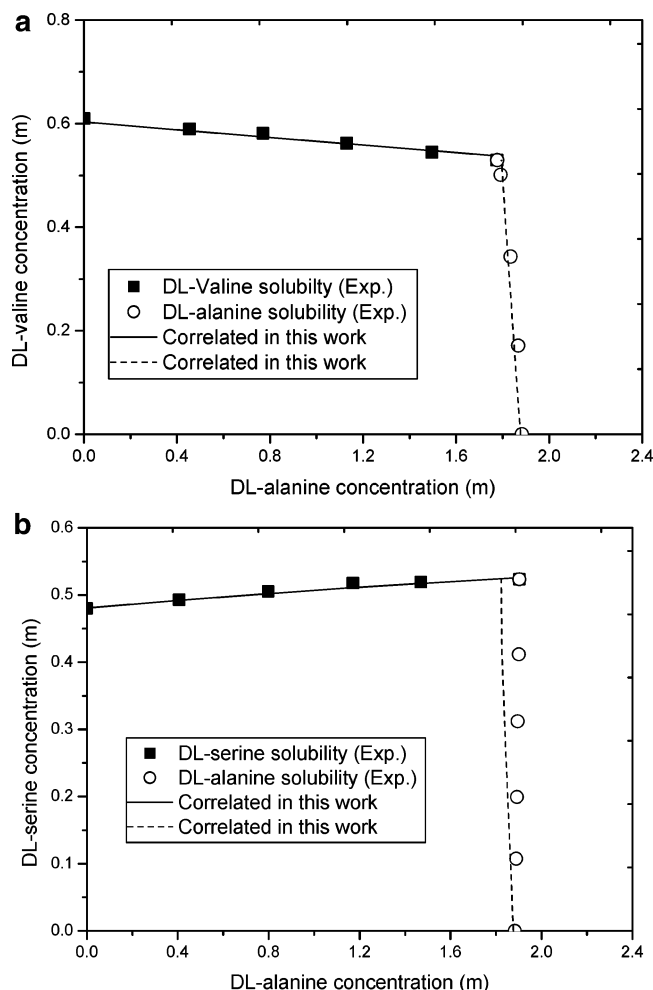


Figure 4. (a) Solubilities of DL-alanine and DL-valine in an aqueous solution at 298 K: experimental data and modeling. Data from ref 6. (b) Solubilities of DL-alanine and DL-serine in an aqueous solution at 298 K: experimental data and modeling. Data from ref 6.

Conclusions

A modified model for polymer aqueous solutions has been extended to describe the activity coefficients and solubility of amino acids. The model can represent very accurately the activity coefficients of amino acids and peptides. After introduction of a temperature dependence on the energy parameters, it was used to predict the solubility of amino acids with better results than UNIFAC and UNIQUAC models. The calculated solubility of a mixture of two amino acids is in very good agreement with the available literature experimental data.

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List of Symbols

a = interaction parameter defined in eqs 3 and 4, or activity
 A^\pm = amino acids (zwitterions)
 G = Gibbs energy
 H = enthalpy
 K_s = equilibrium constant

m = molality
 R = universal gas constant
 T = temperature
 T_0 = reference temperature, 298.15 K
 x = mole fraction

Greek Letters

α = nonrandom factor
 τ = binary energy parameter
 γ = activity coefficient
 ∂ = partial derivative
 ∞ = infinity

Subscripts

p = pressure
 x = mole fraction
 i, j, k = species

Superscripts

cal = calculated
 E = excess properties
 exp = experimental
 $*$ = unsymmetric convention

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