

Short communication

Study of Thermodynamic Properties of Solution of Ampicillin Sodium in Methanol at $T = 298.15\text{ K}$

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Abstract

Osmotic coefficients of the solution of Ampicillin sodium in methanol at $T = 298.15\text{ K}$ were measured using the isopiestic technique and head space-gas chromatography. The experimental osmotic coefficients have been correlated using the ion interaction model of Pitzer, e-NRTL model of Chen, NRF and a fourth-order polynomial in terms of molality. In this work, reference solution is NaI-CH₃OH. The vapor pressures of the solutions and the solvent activities have been calculated from the osmotic coefficients. Reliability of the models in expression of the osmotic coefficients were compared on the basis of standard deviation of the fittings. The best fit of experimental osmotic coefficients data have been obtained by the Pitzer based ion interaction model.

Keywords: Antibiotic; Osmotic coefficient; Vapor pressure; Thermodynamic models

1. Introduction

The process industry is concerned with the modeling and simulation of varieties of chemical products and processes that involve electrolyte systems in aqueous or mixed solvent solutions. Rigorous and accurate representation of the thermodynamic properties of these electrolyte systems is essential for successful modeling and simulation of such chemical products and processes.¹ It is estimated that half of all drug molecules used in medical therapies are administered as salts. Process modeling has not been practiced extensively in the pharmaceutical industry aside from emission reduction and solvent recovery studies, whereas process modeling and molecular thermodynamics could bring significant benefits to the pharmaceutical industry. The industry screens and develops hundreds of new drug candidates each year. Process chemists and engineers are tasked to develop process recipes that involve multiple reaction steps and separation steps such as crystallization or extraction. Formulation chemists are interested in understanding and enhancing drug solubility in therapeutically formulations. They are also interested in the effect of drug solubility of pharmacokinetics. When the molecular parameters are identified for solvent and solute molecules,

the model offers a predictive tool for chemists and engineers to qualitatively estimate the activity coefficients and compute the solubility in pharmaceutical process design.²

In this work, we measured the osmotic coefficients of the solution of Ampicillin sodium (C₁₆H₁₈N₃NaO₄S; a 1–1 electrolyte solution) in methanol by isopiestic method and head space-gas chromatography (HS-GC) at 298.15 K. In the isopiestic measurements for solution of Ampicillin sodium in methanol, sodium Iodide was used as isopiestic reference. The measured osmotic coefficient data have been represented by the ion interaction model of Pitzer,³ the local composition (LC) models including e-NRTL of Chen⁴ and the NRF model of Haghtalab and Vera.⁵ The data have been also correlated with a fourth-order polynomial equation in terms of molality. Fitted model parameters have been used to predict the osmotic coefficients and vapor pressure of the solutions.

2. Experimental

2.1. Materials

Methanol and NaI used in this work were purchased from Merck. They were all suprapure reagents (absolute methanol, GR, minimum 99.8% by mass; NaI, GR, mini-

imum 99.5% by mass). Methanol was dried following the method described by Vogel⁶ and stored on the molecular sieves with 4 Å mesh. NaI was dried under a vacuum using an electrical oven at the temperatures 330.15–340.15 K prior to use. Ampicillin sodium was obtained from Sigma-Aldrich. The sources of the materials used in work are given in the table 1.

Table 1: provenance of the materials.

Materials	purity	provenance
Ampicillin sodium	minimum 99% by mass	Sigma-Aldrich
Sodium Iodide	minimum 99.5% by mass	Merck
Methanol	minimum 99.8 % by mass	Merck

2. 2. Methods and Apparatus

The isopiestic apparatus employed is essentially the same as the one used previously.^{7–13} This apparatus consisted of a five-leg manifold attached to round-bottom flasks. The five flasks were typically used as follows. Two flasks contained the standard NaI solution, two flasks contained investigated solutions, and the central flask was used as methanol reservoir. The apparatus was held in a constant-temperature bath at least 120h for equilibration at $T = 298.15$ K. The temperature was adjusted at $T = 298.15 \pm 0.005$ K. After equilibrium had been reached, the manifold assembly was removed from the bath and each flask was weighted with a high precision (10^{-7} kg) analytical balance. It was assumed that the equilibrium condition was reached when the differences between the molalities of each duplicate was less than 1%. The equilibrium was reached in a time interval of 5 to 7 days depending on the concentration of the solutions. The interval in which the weight of the samples reached a constant value, were determined primarily by continues weighting of a concentrated ($m \approx 7$ mol.kg⁻¹) and a dilute sample ($m \approx 0.09$ mol.kg⁻¹). In all cases, the mean of the duplicates are reported as final isopiestic molalities.

Head space-gas chromatography has been used to determine activity coefficients in various mixtures^{14,15} including non-aqueous electrolyte solutions.¹⁶ Following the standard relations, the vapor pressure of the solvent over the studied solutions (p) is evaluated with the help of the equation:

$$\frac{p}{p^*} = \frac{D}{D^*} \quad (1)$$

in which p and D , are vapor pressure and response of detector, respectively; superscript * refers to the pure solvent. Since for the studied solutions $1 < p/p^* < 1.2$, the detector response will be linear and consequently we can use equation (1). A Shimadzu model GC-16A gas chromatograph equipped with FID detector was used.

Solution of Ampicillin sodium in methanol was prepared gravimetrically and thermostatted (298.15 ± 0.005 K) with a Heto temperature controller. Samples (0.3 ml) of the headspace above the solution were taken using a 1 ml gas-tight syringe and injected into the gas chromatograph and the value of peak area as detector response (D) was measured. Then the same volume of the vapor above the pure solvent was injected and the value of peak area as detector response (D^*) was also measured. Usually samples at time intervals of 2 h of interval time were injected. All measurements were repeated four to six times and the standard deviation of activity was calculated and found to be in the range of 0.0002–0.001, which assured us of the reproducibility of the measurements.

3. Results and Discussion

3. 1. Experimental Results

The results of the experiments including the isopiestic equilibrium molalities, the osmotic coefficients, activities, activity coefficients, and vapor pressures of the solutions have been collected in tables 2.

The osmotic coefficients of the considered solutions were obtained from the equilibrium molalities via the following relation:

$$\Phi = \frac{m_r}{m} \Phi_r \quad (2)$$

where Φ_r is the osmotic coefficient of the reference NaI solution at the molality m_r which is in equilibrium with the antibiotic solutions in the molality m . In this work, reference solution is NaI-CH₃OH. Φ_r was calculated by the Pitzer equation with the help of the parameters reported by M.T. Zafarani- Moattar for methanol solutions. The Pitzer parameters for reference solution in the case of methanol are $\beta^{(0)} = 0.40830$, $\beta^{(1)} = 1.04430$, $\beta^{(2)} = -0.875$, $C^{(\Phi)} = -0.02224$. In the Pitzer model, the optimum values of α_1 , α_2 and b parameters for solution of Ampicillin sodium in methanol are respectively 2, 1.4 and 3.2. The vapor pressure of the solutions could be easily obtained from the osmotic coefficients using the following set of equations:

$$\ln(a_1) = -vmM_1\Phi \quad (3)$$

$$\ln(a_1) = \ln\left(\frac{p}{p^*}\right) + \frac{B - V^*}{RT}(p - p^*) \quad (4)$$

In these equations M_1 , B , p^* and V^* are the molar mass, the second virial coefficient, the vapor pressure, and the molar volume of the pure solvent at $T = 298.15$ K, respectively; a_1 and p are activity of the solvent in the solu-

Table 2. Isopiestic equilibrium molalities, osmotic coefficient, activity, activity coefficient and vapor pressure solution of Ampicillin sodium in methanol at 298.15 K.^a In this work, reference solution is NaI-CH₃OH.

m_r (mol · kg ⁻¹)	D/D*	m (mol · kg ⁻¹)	Φ_A	$\ln a_1$	$\ln \gamma_1$	p (kPa)
0.0000	–	0.0000	1.000	0.0000	0.0000	16.958
–	0.9808	0.3412	0.874	–0.0191	0.0025	16.632
–	0.9741	0.5042	0.801	–0.0259	0.0059	16.518
0.5398	–	0.5362	0.897	–0.0308	0.0030	16.436
–	0.9687	0.6874	0.712	–0.0314	0.0117	16.427
–	0.9636	0.8751	0.651	–0.0365	0.0181	16.341
0.7166	–	1.0834	0.616	–0.0428	0.0244	16.238
0.6856	–	1.2082	0.525	–0.0406	0.0339	16.273
–	0.9409	1.8197	0.515	–0.0601	0.0502	15.956
–	0.9253	2.1685	0.551	–0.0766	0.0536	15.691
–	0.9055	3.0687	0.498	–0.0979	0.0816	15.355
–	0.8866	3.9004	0.475	–0.1187	0.1044	15.035
–	0.8455	5.0246	0.514	–0.1655	0.1136	14.339
2.4213	–	5.4485	0.620	–0.2165	0.0830	13.618
–	0.7743	6.0254	0.654	–0.2525	0.0740	13.130
–	0.7316	6.4200	0.750	–0.3086	0.0360	12.407
3.603	–	6.8707	0.891	–0.3923	–0.0275	11.401
3.7892	–	7.1802	0.920	–0.4233	–0.0448	11.049
3.5686	–	7.3411	0.822	–0.3867	–0.0011	11.465

^a m_r : molality of isopiestic reference; D: response of detector of solvent; D*: response of detector of the pure solvent; m : molality of studied solution; Φ_A : osmotic coefficient; $\ln \gamma_1$: Logarithm of activity coefficient of solvent; $\ln a_1$: Logarithm activity of solvent; p : vapor pressure; Uncertainty for molality $\delta(m) = \pm 0.0001$ mol · kg⁻¹, Uncertainty for osmotic coefficient $\delta(\Phi) = \pm 0.025$, Uncertainty for vapor pressure $\delta(p) = \pm 0.001$ kPa.

tion and vapor pressure of the solution respectively. R and T are also the universal gas constant and the absolute temperature and ν in equation (3) is the total number of ions in one molecule of the solute.

3. 2. Correlation of Data

3. 2. 1. Pitzer Model

The Pitzer's equation for a binary solution of a 1:1 electrolyte in a solvent has the following form: in which

$$\Phi = 1 + f^\Phi + mB^\Phi + m^2C^\Phi \quad (5)$$

in which

$$f^\Phi = \frac{-A_\Phi \sqrt{I}}{1 + b\sqrt{I}} \quad (6)$$

and

$$B^\Phi = \beta^{(0)} + \beta^{(1)} \exp(-\alpha_1 \sqrt{I}) + \beta^{(2)} \exp(-\alpha_2 \sqrt{I}) \quad (7)$$

In the above equations A_Φ and I are Debye–Hückel constants for the osmotic coefficients and ionic strength

on a molal basis ($I = (1/2) \sum_{i=ions} m_i z_i^2$); b , α_1 and α_2 are constant parameters of the model; $\beta^{(0)}$, $\beta^{(1)}$, $\beta^{(2)}$ and C^Φ

are adjustable parameters fitted to the experimental osmotic coefficient data.

3. 2. 2. LC Models

In the LC models, the excess Gibbs free energy of electrolyte solutions (g^{ex}) and consequently solvent activity coefficient (γ_1) has been composed of two long-range (LR) and short-range (SR) contribution:

$$g^{ex} = g_{LR}^{ex} + g_{SR}^{ex} \quad (8)$$

and

$$\ln \gamma_1 = \ln \gamma_1^{LR} + \ln \gamma_1^{SR} \quad (9)$$

3. 2. 3. Long-range Contribution

Various equations have been used as LR term for the excess Gibbs free energy of an electrolyte solution, such as the Pitzer–Debye–Hückel (PDH) equation that proposed by Pitzer¹⁸ and used by Chen⁴ or a simplified MSA term of Kunz et al.¹⁹ that used by Sardroodi et al. In this work, we used the PDH equation for the LR contribution. This equation has the following form:

$$\frac{g^{ex}}{RT} = -4 \sqrt{\frac{1}{M_1} \frac{A_\Phi I_x}{\rho}} \ln(1 + \rho \sqrt{I_x}) \quad (10)$$

In which I_x is the ionic strength in a mole fraction basis and ρ is the closest distance parameter whose value.

3. 2. 4. The e-NRTL Model

The SR contribution for the excess Gibbs free energy provided by the e-NRTL model is

$$\frac{g_{LC}^{ex}}{RT} = -2X_c^2 \left[\frac{2G_{ca,1}^2 \tau_{ca,1}}{2X_c G_{ca,1} + X_1} + \frac{\tau_{1,ca}}{X_c + X_1 G_{1,ca}} \right] \quad (11)$$

where X_c , X_1 , $\tau_{ca,1}$ and $\tau_{1,ca}$ are effective mole fractions of cation and the solvent, salt–solvent and solvent–salt interaction parameters respectively. The effective mole fraction of species i is defined as $X_i = Z_i x_i$, in which Z_i is the charge number for ionic species and unity for molecular species and x_i is the bulk mole fraction of i . The quantity of G_i is defined as

$$G_i = \exp(-\alpha \tau_i) \quad (12)$$

where α is the non-randomness factor set to 0.2.⁴

3. 2. 5. The NRF Model

The SR contribution for the excess Gibbs free energy provided by the NRF model has the following form

$$\ln \gamma_{i,NRF} = X_c \left\{ \left[\frac{2X_c \lambda_E}{Z_c} \right] \left[1 + \frac{\exp(-\frac{\lambda_E}{Z})}{(X_c \exp(-\frac{\lambda_E}{Z}) + X_1)^2} \right] - \frac{X_1 \lambda_s \left(\frac{2}{Z_c} \right) - 2 \exp(-\frac{\lambda_s}{Z})}{2X_c \exp(-\frac{\lambda_s}{Z}) + X_1} \times \right. \quad (13)$$

$$\left. \left[2 - X_1 \left(1 + \frac{1}{2X_c \exp(-\frac{\lambda_s}{Z}) + X_1} \right) \right] \right\}$$

$$\lambda_E = \frac{g_E - g_{E1}}{RT} \quad (14)$$

$$\lambda_s = \frac{g_{E1} - g_{11}}{RT} \quad (15)$$

where Z is the coordination number and set to 8;²⁰ λ_E and λ_s are the adjustable parameters of the model.

The appropriate equations for the correlation of osmotic coefficient data by data, according to the considered LC models have been obtained using the following well-known thermodynamic relation and the definition of the osmotic coefficient, equation (3).

$$\ln \gamma_i = \left(\frac{\partial G^{ex} / RT}{\partial n_i} \right)_{T,P,n_{j \neq i}} \quad (16)$$

The polynomial equation used for correlation the osmotic coefficient data has the following form:

$$\Phi = 1 + a_0 m^{0.5} + a_1 m + a_2 m^{1.5} + a_3 m^2 \quad (17)$$

Tables 3 to 6 contain the model parameters and corresponding standard deviation in osmotic coefficient $\sigma(\Phi)$, activity $\sigma(a1)$, activity coefficient $\sigma(\ln \gamma_i)$ and vapor pressure $\sigma(p)$,

$$\sigma(\Phi) = \sqrt{\frac{\sum_i (\Phi_{exp} - \Phi_{cal})_i^2}{N}} \quad (18)$$

for Pitzer, e-NRTL, NRF models and polynomial equation, respectively. The results verify that the average $\sigma(\Phi)$ for the Pitzer model and polynomial equation with four adjustable parameters give better fit for osmotic coefficients than the e-NRTL and NRF models with only two adjustable parameters.

The parameters of the studied models can be used for qualitative molecular interpretation of the experimental results. The ion pair was form due to the high valence of ions or low dielectric constant of the solvent. We studied the methanol solutions of the Ampicillin salt and due to the low dielectric constant of methanol and consequently the high probability of the formation of ion-pairs, $\beta^{(2)}$ parameter was used. The standard ion interaction model does not use $\beta^{(2)}$ term for 2–1 and 1–1 electrolytes, although its inclusion makes it possible to fit aqueous solu-

Table 3. Pitzer model parameters for the studied solution and reference solution

Solution	m_r (mol · kg ⁻¹)	$\beta^{(0)}$	$\beta^{(1)}$	$\beta^{(2)}$	C_Φ	$\sigma(\Phi)$	$\sigma(a1)$	$\sigma(\ln \gamma_i)$	$\sigma(p)$
Ampicillin sodium+ Methanol	0.0–7.3411	0.047513	6.172359	-3.717943	0.005942	0.051	0.01	0.0138	0.1709
Solution	m_r (mol · kg ⁻¹)	$\beta^{(0)}$	$\beta^{(1)}$	$\beta^{(2)}$	C_Φ	$\sigma(\Phi)$	A_Φ	$\alpha 1$	$\alpha 2$
NaI+Methanol	0.02–4.33	0.40830	1.04430	-0.875	-0.02224	0.006	1.294	2	1.4

m_r : Concentration range of application; $A_\Phi, \alpha 1, \alpha 2, \beta^{(0)}, \beta^{(1)}, \beta^{(2)}$ and C_Φ : Adjustable parameters of the Pitzer model; $\sigma(\Phi)$: Standard deviation in osmotic coefficient; $\sigma(a1)$ Standard deviation in activity of solvent; $\sigma(\ln \gamma_i)$ Standard deviation in Logarithm of activity coefficient of solvent; $\sigma(p)$ Standard deviation in vapor pressure.

tion properties to very high concentrations. According to Pitzer theory, this parameter was introduced to account the association effect in low concentrated solutions of 2–2 electrolytes, and by using $\alpha_1 = 1.4$ and $\alpha_2 = 12$. In more recent studies^{21–24} the authors show that introducing the $\beta^{(2)}$ parameter into a model for binary systems of 2–1, 3–1 and 3–2 electrolytes and vary the values of α_1 and α_2 can significantly improve fit of the data, and fully to account ion association in a whole solution concentration range.

The e-NRTL model parameters could be interpreted physically; they are related to the differences between free energies of the interactions (g_{ij}) between particles i and j as the following equations:

$$\tau_{ca,1} = \frac{g_{c1} - g_{11}}{RT} = \frac{g_{a1} - g_{11}}{RT} \quad (19)$$

and

$$\tau_{1,ca} = \frac{g_{1c} - g_{ac}}{RT} = \frac{g_{1a} - g_{ca}}{RT} \quad (20)$$

In other words the $\tau_{ca,1}$ parameter can be related to the extent of the solvation phenomenon and the $\tau_{1,ca}$ parameter can be related to the extent of ion-pair formation. Hence, the numerical values of the e-NRTL model parameters are useful in qualitative deductions about solvation and ion-pair formation in the electrolyte solutions. Generally, these results are consistent with the trends of osmotic coefficients as a function the composition of the solution.

Equation (19) states that if $\tau_{ca,1}$ parameter tends to the negative, it corresponds more to either the lower ion-solvent interaction (g_{c1} or g_{a1}) or higher solvent-solvent interaction (g_{11}); in other words the solvation is negligible. Moreover, equation (20) means that when $\tau_{1,ca}$ parameter is great, then the solvent-ion interaction (g_{1c} or g_{1a}) is great or ion-ion interaction in the solution (g_{ca} or g_{ac}) is small; in other words the ion-pairing is negligible. The vapor pressure of a solution is a result of competition between the extent of the solvation phenomena and ion-pairing equilibrium. If the solvation in a solution occurs to a valuable extent, its vapor pressure decrease severely; and if the ion pairing extensively occurs, vapor pressure depression will be negligible.

It is observed that the general relation between e-NRTL parameters ($\tau_{1,ca} \approx -2\tau_{ca,1}$) is valid for the studied salts. This relation is a very interesting aspect of this model can be useful in the correlation of other thermodynamic properties such as excess volume. It is also observed from table 4 that for studied salts the salt-solvent interaction parameter, $\tau_{ca,1}$, that is proportional to the difference between anion-cation and solvent-solvent interaction, is negative. This is expectable since ion-ion interaction is stronger than the solvent-solvent interaction.

The parameters of the NRF model have collected in table 5. These results show that the model parameters are consistent.

The electrolyte parameter of this model is negative for all salts. This means that the attraction between two oppositely charged ions in solution is stronger than attrac-

Table 4. e-NRTL model parameters for the studied solution.

Solution	$\tau_{ca,1}$	$\tau_{1,ca}$	$\sigma(\Phi)$	$\sigma(a1)$	$\sigma(\ln g_1)$	$\sigma(p)$
Ampicillin sodium	-3.95939	8.92607	0.099	0.022	0.0299	0.3761

$\tau_{ca,1}$, $\tau_{1,ca}$: Adjustable parameters of e-NRTL model; $\sigma(\Phi)$: Standard deviation in osmotic coefficient; $\sigma(a1)$ Standard deviation in activity of solvent; $\sigma(\ln g_1)$ Standard deviation in Logarithm of activity coefficient of solvent; $\sigma(p)$ Standard deviation in vapor pressure.

Table 5. NRF model parameters for the studied solution.

Solution	λ_E	λ_S	$\sigma(\Phi)$	$\sigma(a1)$	$\sigma(\ln g_1)$	$\sigma(p)$
Ampicillin sodium	-10.32669	8.5817	0.078	0.022	0.0214	0.271

λ_E and λ_S : Adjustable parameters of NRF model; $\sigma(\Phi)$: Standard deviation in osmotic coefficient; (a1) Standard deviation in activity of solvent; ($\ln g_1$) Standard deviation in Logarithm of activity coefficient of solvent; (p) Standard deviation in vapor pressure.

Table 6. Parameters of the polynomial equation for the studied solution.

Solution	a_0	a_1	a_2	a_3	$\sigma(\Phi)$	$\sigma(a1)$	$\sigma(\ln g_1)$	$\sigma(p)$
Ampicillin sodium	0.125	-0.8452	0.4304	-0.052	0.0495	0.0097	0.0136	0.101

a_0 , a_1 , a_2 , and a_3 Parameters for polynomial equation; $\sigma(\Phi)$: Standard deviation in osmotic coefficient; $\sigma(a1)$ Standard deviation in activity of solvent; $\sigma(\ln g_1)$ Standard deviation in Logarithm of activity coefficient of solvent; $\sigma(p)$ Standard deviation in vapor pressure.

tion between an ion with a solvent molecule. The solvent parameter is also positive, that is the oppositely charged ions interact in the solution more powerful than two solvent molecules. In addition, the parameters of the polynomial equation have collected in table 6.

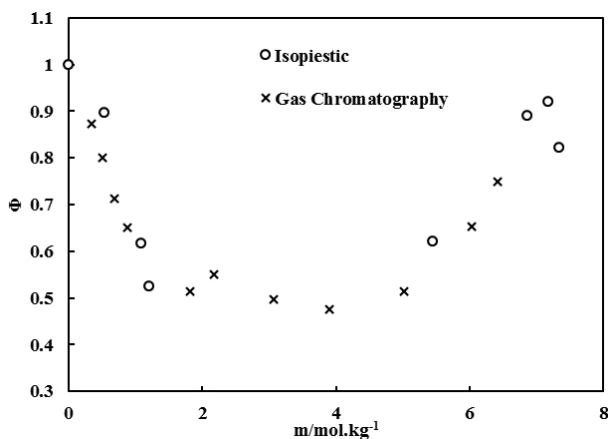


Figure 1. Osmotic coefficients of the studied solutions against the molality at $T = 298.15$ K.

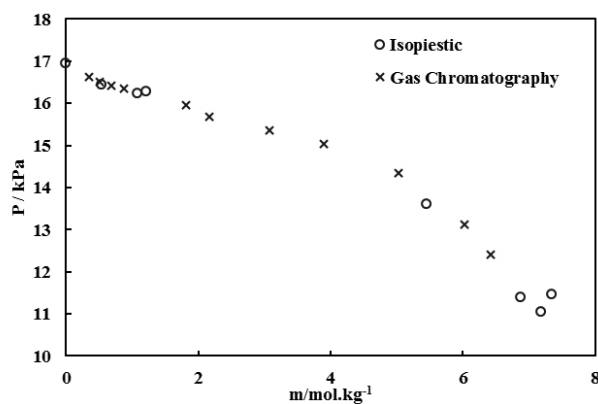


Figure 2. Vapor pressures of the studied solutions against molality at $T = 298.15$ K.

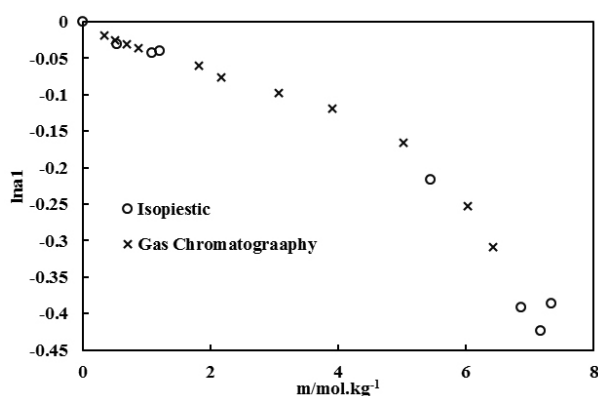


Figure 3. Logarithm activity of solvent against molality at $T = 298.15$ K.

The variations of the experimental osmotic coefficients, vapor pressure of the solvent, and activity of solvent as a function of molality are presented in figures 1–3 respectively. A close examination of these figures show that the larger molar mass of the solution the lower vapor pressure of the solvent and activity of solvent.

Figures 4 include the experimental osmotic coefficients and those calculated from the considered models for Ampicillin sodium.

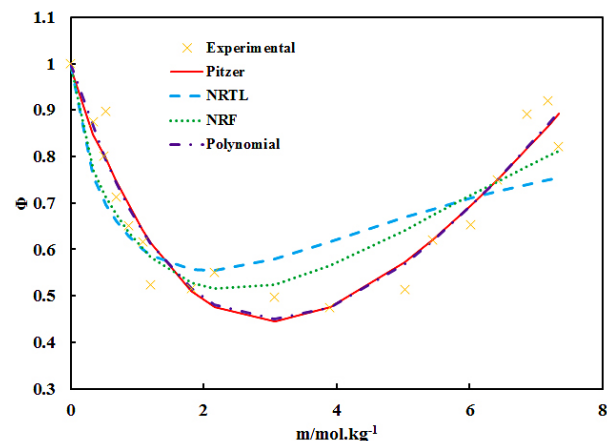


Figure 4. Experimental and predicted osmotic coefficients of Ampicillin Sodium in methanol at $T = 298.15$ K.

These figures show that the Pitzer model and the polynomial equation excellently describe osmotic coefficients in the entire concentration range. However, calculated osmotic coefficients produced by e-NRTL and NRF models have considerable experimental values.

4. Conclusions

The osmotic coefficients of the solutions of Ampicillin sodium in methanol at 298.15K have been measured by the isopiestic method and head space-gas chromatography and correlated by the ion interaction model of Pitzer, e-NRTL model, the NRF model and a polynomial equation. The results show that the considered models give reliable fittings; however, the best fit of experimental osmotic coefficients data have been obtained by the Pitzer based ion interaction model. However, the e-NRTL and the NRF models with two fitting parameters give relatively acceptable results.

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Povzetek

Z izopiestično metodo in plinsko kromatografijosmo določili osmozne koeficiente raztopin natrijevega ampicilina v metanolu pri $T = 298.15$. Eksperimentalne vrednosti smo analizirali z Pitzerjevem, e-NRTL Chenovim in NRF modelom ter ponazorili s polinomom četrte stopnje glede na molalnost. S pomočjo določenih osmoznih koeficientov smo izračunali parni tlak raztopin ter aktivnost topila. Zanesljivosti modelov in uporabljenih zvez smo primerjali na osnovi standardnih deviacij.