Lattice Thermodynamics for Aqueous Salt–Polymer Two-Phase Systems

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ABSTRACT: A lattice model is presented to compute salt-induced liquid–liquid phase separation in aqueous polymer solutions. The Gibbs energy of mixing contains an electrostatic contribution given by Pitzer's extension of the Debye–Hückel function, and the extended Flory–Huggins theory that uses empirical functions of temperature and composition as binary interaction parameters. Our Flory–Huggins theory assumes complete dissociation of salt into ions, but it does not distinguish between cation and anion; our theory represents the water–salt–polymer mixture as an incompressible ternary system consisting of water, ion, and polymer. In the extended Flory–Huggins theory, the binary interaction parameter between water and ion, and that between water and polymer, are obtained by correlating the observed activity of water in each of the two relevant binary systems. The electrostatic contribution does not contain adjustable parameters. We show that the electrostatic contribution to the Gibbs energy of mixing is responsible for inducing salt–polymer aqueous two-phase systems. Calculated phase diagrams are compared with experiment for aqueous solutions containing polyethylene glycol and a single salt at room temperature. The efficiency of a salt to form salt–polymer aqueous two-phase systems is discussed in terms of ion valence and the interaction parameter between ion and polymer. © 1998 John Wiley & Sons, Inc. J Appl Polym Sci 68: 2007–2017, 1998

Key words: aqueous two-phase systems; electrolyte solutions; liquid–liquid equilibria; polymer solutions; salting out

INTRODUCTION

In aqueous polymer solutions, inorganic salt[1,2] or alcohol[3] are often used to precipitate polymers by inducing phase separation. The precipitated phase is usually a dense liquid phase,[1,3] but it can also be a solid phase for crystallizable polymers, including globular proteins.[4,5] In this work, we are concerned with liquid–liquid phase separation of aqueous polymer solutions induced by an inorganic salt. Salt-induced precipitation of polymers has useful applications in biotechnology. Salt–polymer aqueous two-phase systems have potential use as separation media for liquid–liquid extraction of biological molecules.[6,7] Salt-induced (or polymer-induced) precipitation is also used to recover globular proteins from aqueous solutions.[8]

Although salt-induced precipitation of polymers has been extensively studied, there is little

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understanding of how intermolecular forces cause phase separation in aqueous polymer solutions by salt. It is often argued that the primary role of salt is to modify the effective interaction between solvent and polymer by changing the structure of water.[9] For solutions containing polyelectrolytes, such as globular proteins, the effect of salt is also to screen the repulsive electrostatic repulsion between charged macromolecules.[2]

Recent theoretical work by Kenkare et al.,[10–12] however, shows that Coulombic interactions among salt ions lead to phase separation in aqueous mixtures of salts and in aqueous mixtures of charged hard spheres and neutral hard spheres that mimic aqueous mixtures of salt and large neutral molecule. In these systems, phase separation follows from the competition between entropy of mixing that favors mutual solubility and ion pairing that enthalpically favors phase separation.[10–12] Therefore, to increase understanding, Coulombic interactions among salt ions need careful consideration in modeling salt-induced precipitations of polymers in aqueous solutions. Regrettably, these interactions are usually neglected by thermodynamic models that represent salt-induced precipitation of globular proteins.

In this work, we present a simple, application-oriented molecular–thermodynamic model that elucidates the effect of Coulombic interactions among salt ions for salt-induced precipitation of polymers in aqueous solutions. Our objective is to develop a semiempirical lattice model that represents the observed phase behavior of salt–polymer aqueous two-phase systems. We are particularly interested to understand better how ion valence affects the phase boundary. Although several molecular–thermodynamic models have been proposed for salt–polymer aqueous two-phase systems,[12,13] most published work concerns fitting of ternary phase diagrams using several adjustable parameters.[13] A major exception is the recent model by Kenkare and Hall[12] that predicts, in part, the observed phase behavior of aqueous two-phase systems containing polyethylene glycol (PEG) and salt.[1]

We use the lattice theory[14] because of its computational simplicity for calculating the spinodal curve and the critical point for ternary systems. In this work, the Gibbs energy of mixing contains an electrostatic contribution given by Pitzer's extension of the Debye–Hückel function,[15,16] and the extended Flory–Huggins theory. The extended Flory–Huggins theory combines the well-known Flory entropy of mixing with an enthalpy of mixing that uses empirical functions of temperature and composition as binary interaction parameters.[17,18] We use the semiempirical extended Flory–Huggins theory because it is flexible for correlating thermodynamic properties of mixtures.

Our extended Flory–Huggins theory assumes complete dissociation of the salt into ions, but it does not distinguish salt cation and salt anion. The water–salt–polymer mixture is modeled as an incompressible ternary system consisting of water, ion, and polymer. Binary interaction parameters between water and ion, and between water and polymer, are obtained by correlating the observed activity of water in the relevant binary system. The electrostatic contribution to the Gibbs energy of mixing does not contain adjustable parameters.

Consistent with the recent theoretical work by Kenkare and Hall,[12] we found that the electrostatic contribution is responsible for inducing salt–polymer aqueous two-phase systems. The efficiency of a salt to form two-phase systems is first discussed in terms of ion valence by neglecting the interaction parameter between water and ion and that between ion and polymer in the Flory–Huggins theory. Theory is then compared with experiment using the interaction parameters between water and ion that are regressed from the measured activity of water in binary water–salt systems. Predicted phase behavior of salt–polymer aqueous two-phase systems is compared with experiment for solutions containing PEG and a single salt at room temperature.[1] The importance of the interaction parameter between ion and PEG is also discussed.

THEORETICAL FRAMEWORK: LATTICE THEORY

In the lattice theory, we first define the molar Gibbs energy of mixing ΔG by

$$\frac{\Delta G}{RT} \equiv \frac{G_{\text{mixture}}}{RT} - \sum_{i=1}^{l} \phi_i \frac{G_i^0}{RT} \tag{1}$$

where G_{mixture} is the molar Gibbs energy of the mixture, G_i^0 is the molar Gibbs energy of component i in the standard state, l is the number of components, ϕ_i is the segment fraction of component i, R is the gas constant, and T is the absolute temperature. Some comments on the standard

state are given later. In eq. (1) and the following equations, the molar Gibbs energy is the Gibbs energy per mole of lattice sites.

We assume that the molar Gibbs energy of mixing contains an electrostatic contribution given by a Debye–Hückel-type function and a contribution from extended Flory–Huggins theory, as follows:

$$\frac{\Delta G}{RT} = \frac{\Delta G^{DH}}{RT} + \frac{\Delta G^{FH}}{RT} \tag{2}$$

where superscripts *DH* and *FH* denote Debye–Hückel and Flory–Huggins contributions, respectively. Although the extended Flory–Huggins theory uses interaction parameters that are empirical functions of composition and temperature,[17,18] thermodynamic properties of mixtures containing salt (or weakly charged polyelectrolyte) cannot be represented by the extended Flory–Huggins theory alone. Models for these mixtures require a theoretical term that accounts for the electrostatic contribution to the Gibbs energy of mixing. Equation (2) is a general expression applicable to both binary and ternary systems.

The Gibbs energy of mixing given by eq. (2) requires some clarification. First, it is not rigorous to combine the Debye–Hückel theory with the Flory–Huggins theory by eq. (2) because the former is based on a set of independent variables different from those used by the latter.[19] However, for systems containing weakly charged polyelectrolyte and salt,[20–23] eq. (2) has been successfully used to provide semiquantitative understanding of the effect of electrostatic contribution to the Gibbs energy of mixing. As shown in this work, our theory based on eq. (2) can represent observed phase behavior of salt–polymer aqueous two-phase systems.

Second, the standard state for ion in the Debye–Hückel theory uses an unsymmetric convention in which the activity coefficient of ion approaches unity as the molality of ion approaches zero. In that event, the standard state for ion is the ideal solution of ion at unit concentration. For water, the Debye–Hückel theory uses a symmetric convention in which the standard state of water is the pure liquid. On the other hand, the Flory–Huggins theory uses a symmetric convention for both components. The molar Gibbs energy of mixing that uses a symmetric convention for ion can be converted to that based on an unsymmetric convention for ion by subtracting a term that is linear on the segment fraction of ion. This linear term does not affect phase-equilibrium calculations if coexistence curves are computed by satisfying, for each component, the equality of chemical potential in the coexisting phases. Therefore, we need not be concerned by the difference between the standard state for ion in the Debye–Hückel theory and that in the Flory–Huggins theory.

We first present the lattice theory for binary water–salt and binary water–polymer systems; we then extend the theory to ternary water–salt–polymer systems. Only neutral polymers are considered in this work. We confine attention to systems at room temperature. All systems are assumed to be incompressible.

BINARY WATER–SALT SYSTEMS

We consider a binary water–salt system containing a salt of type, as follows:

$$(M^{z_M})\nu_M(X^{z_X})\nu_X \tag{3}$$

where M and X are the cation and anion, respectively; ν_M and ν_X are the stoichiometric numbers for the salt; and z_M and z_X are the valences of M and X ions, respectively.

Theoretically based models for water–salt systems use the ionic strength of solution I as the composition variable. For binary water–salt systems containing the salt type given by eq. (3), the ionic strength is defined by

$$I = \tfrac{1}{2}m\nu|z_M z_X|, \quad \nu = \nu_M + \nu_X \tag{4}$$

where m (mol/kg water) is the molality of salt, and ν is the number of ions per salt. To obtain eq. (4), we use the condition for electroneutrality $|\nu_M z_M| = |\nu_X z_X|$.

In lattice theory, however, thermodynamic properties are expressed in terms of segment fraction. To express the electrostatic contribution using segment fraction, we first model a binary water–salt system at solute molality m as a binary mixture containing νm moles of ion and 1 kg water. Here, ion represents a hypothetical representative ion that comes from complete ionization of the salt. We then express the solute molality and ionic strength in terms of the segment fraction of that representative ion.

To illustrate, consider a mixture containing m

moles of salt given by eq. (3) and 1 kg of water. We assume that water has one segment and ion has one segment. The segment fraction of water ϕ_1 and that of ion ϕ_2 are given by

$$\phi_1 = \frac{1000/W}{1000/W + \nu m},$$

$$\phi_2 = 1 - \phi_1 = \frac{\nu m}{1000/W + \nu m} \quad (5)$$

where W is the molecular weight of water in g/mol (that is, $W = 18.0$ g/mol). In terms of ϕ_1 or ϕ_2, the molality of salt is given by

$$m = \frac{\phi_2(1000/W)}{\nu\phi_1} = \frac{\phi_2(1000/W)}{\nu(1 - \phi_2)} \quad (6)$$

The ionic strength of solution is also expressed in terms of ϕ_1 or ϕ_2 by substituting eq. (6) into eq. (4), as follows:

$$I = \frac{1}{2}\left[\frac{\phi_2(1000/W)}{\phi_1}\right]|z_M z_X| = \frac{1}{2}\left[\frac{\phi_2(1000/W)}{1 - \phi_2}\right]|z_M z_X| \quad (7)$$

We use Pitzer's form of the Debye–Hückel-type function[15,16] as the electrostatic contribution to the molar Gibbs energy of mixing. In the lattice notation, our electrostatic contribution to the molar Gibbs energy of mixing is given by

$$\frac{\Delta G^{DH}}{RT} = \phi_1\left(\frac{W}{1000}\right)\left[-A_\varphi\left(\frac{4I}{b}\right)\ln(1 + bI^{1/2})\right] \quad (8)$$

where I is given by eq. (7), $A_\varphi = 0.392$, and $b = 1.2$. The values for A_φ and b are those at 25°C. The electrostatic contribution does not contain adjustable parameters.

The Flory–Huggins contribution to the molar Gibbs energy of mixing is given by the following[14,17,18]:

$$\frac{\Delta G^{FH}}{RT} = \phi_1 \ln \phi_1 + \phi_2 \ln \phi_2 + g_{12}(\phi_2)\phi_1\phi_2 \quad (9)$$

where the first two terms and the last term on the right-hand side of eq. (9) represent, respectively, the configurational entropy of mixing and the residual free-energy, mostly enthalpic, interaction between water and salt ion. Interaction parameter g_{12} is defined later. In this version of Flory–Huggins theory, we do not distinguish salt cation and salt anion; g_{12} refers to the interaction between water and ion.

For a binary water–salt system, eqs. (8) and (9) are combined to give the molar Gibbs energy of mixing given by

$$\frac{\Delta G}{RT} = \phi_1\left(\frac{W}{1000}\right)\left[-A_\varphi\left(\frac{4I}{b}\right)\ln(1 + bI^{1/2})\right] + \phi_1 \ln \phi_1 + \phi_2 \ln \phi_2 + g_{12}(\phi_2)\phi_1\phi_2 \quad (10)$$

For salts having the same set of ν and $|z_M z_X|$, the electrostatic contribution and configurational entropy of mixing are independent of the type of salt. In that event, binary interaction parameter g_{12} in the Flory–Huggins contribution differentiates one particular salt from other salts.

We determine g_{12} by correlating the observed activity of water in a water–salt system at 25°C. In this work, g_{12} is an empirical function of mixture composition ϕ_2 given by

$$g_{12}(\phi_2) = \sum_{k=1}^{n} c_k \phi_2^{k-1} \quad (11)$$

where c_k is a coefficient at 25°C. Calculated phase diagrams of ternary systems are sensitive to the interaction parameters. Because we are concerned with the prediction of ternary phase diagrams over a narrow range of salt concentration, we obtain g_{12} by accurately correlating the observed activity of water in several water–salt systems. For 1 : 1 salts, we use $n = 5$. However, as the valence of salt ion rises, $n = 5$ is not sufficient. Therefore, we use $n = 8$ for salts consisting of multivalent ions.

In the literature, thermodynamic properties of water–salt systems are usually tabulated in terms of the molal osmotic coefficient φ defined by

$$\varphi = \frac{-1000}{\nu m W} \ln a_1 \quad (12)$$

where a_1 is the activity of water. This activity is related to $\Delta\mu_1$, the difference between the chemical potential of water in the solution and that of pure water, by

$$\ln a_1 = \frac{\Delta\mu_1}{RT} = \frac{1}{RT}\left[\frac{\partial(N_1 + N_2)\Delta G}{\partial N_1}\right]_{T,N_2} \quad (13)$$

where N_1 is the number of moles of water, and N_2 is the number of moles of ion. From eqs. (10) and (13), $\Delta\mu_1$ is given by

$$\frac{\Delta\mu_1}{RT} = \frac{2A_\varphi I^{3/2}}{1 + bI^{1/2}}\left(\frac{W}{1000}\right) + \ln\phi_1 + (\phi_2^2 g_{12} - \phi_1\phi_2^2 g'_{12}) \quad (14)$$

where I is given by eq. (7) and

$$g'_{12} = \left(\frac{\partial g_{12}}{\partial \phi_2}\right)_T \quad (15)$$

On the right-hand side of eq. (14), the second term is the ideal contribution to $\Delta\mu_1$ that favors mixing. The remaining terms may be identified as the nonideal contribution to $\Delta\mu_1$.

In the extended Flory–Huggins theory for binary systems, the Flory interaction parameter χ_{12} is often used to discuss the nonideal contribution to $\Delta\mu_1$. Parameter χ_{12} is defined by

$$\chi_{12} \equiv \frac{\Delta\mu_1}{RT\phi_2^2} - \frac{\ln\phi_1}{\phi_2^2} \quad (16)$$

In the present model, χ_{12} consists of the electrostatic contribution χ_{12}^{DH}, and the Flory–Huggins contribution χ_{12}^{FH}; χ_{12} is given by

$$\chi_{12} = \chi_{12}^{DH} + \chi_{12}^{FH} \quad (17)$$

where

$$\chi_{12}^{DH} = \frac{2A_\varphi I^{3/2}}{(1 + bI^{1/2})\phi_2^2}\left(\frac{W}{1000}\right) \quad (18)$$

$$\chi_{12}^{FH} = g_{12} - \phi_1 g'_{12} \quad (19)$$

BINARY WATER–POLYMER SYSTEMS

For binary aqueous solutions containing neutral polymers, the molar Gibbs energy of mixing has only the contribution from the Flory–Huggins theory given by the following[14,17,18]:

$$\frac{\Delta G}{RT} = \phi_1\ln\phi_1 + \frac{\phi_3}{r_3}\ln\phi_3 + \chi_{13}\phi_1\phi_3 \quad (20)$$

where ϕ_1 and ϕ_3 are the segment fractions of water and polymer, respectively; r_3 is the number of segments per polymer; and χ_{13} is the segmental interaction parameter between water and polymer at 25°C. In this work, we assume that χ_{13} is independent of composition. However, if desired, a composition dependence can be introduced into χ_{13} to achieve better correlation of experimental data.[17,18] Equation (20) is subject to the condition $\phi_3 = 1 - \phi_1$.

TERNARY WATER–SALT–POLYMER SYSTEMS

Finally, we consider ternary water–salt–polymer systems in which components 1, 2, and 3 represent water, ion, and polymer, respectively. The segment fractions of components 1, 2, and 3 are given by ϕ_1, ϕ_2, and ϕ_3, respectively, and $\phi_1 + \phi_2 + \phi_3 = 1$. For the ternary, we use eq. (2).

To extend eq. (8) to ternary systems, we need a definition of ionic strength I in an aqueous system that, in addition to salt, also contains polymer. We assume that the ionic strength is given by

$$I = \frac{1}{2}\left[\frac{\phi_2(1000/W)}{1 - \phi_2}\right]|z_M z_X| \quad (21)$$

Equations (8), (9), (11), (20), and (21) are substituted in eq. (2). For a ternary water–salt–polymer system, the molar Gibbs energy of mixing is given by

$$\frac{\Delta G}{RT} = \phi_1\left(\frac{W}{1000}\right)\left[-A_\varphi\left(\frac{4I}{b}\right)\ln(1 + bI^{1/2})\right] + \phi_1\ln\phi_1 + \phi_2\ln\phi_2 + \frac{\phi_3}{r_3}\ln\phi_3 + g_{12}(\phi_2)\phi_1\phi_2 + \chi_{13}\phi_1\phi_3 + \chi_{23}\phi_2\phi_3 \quad (22)$$

where χ_{23} is the interaction parameter between ion and polymer at 25°C. χ_{23} is assumed to be independent of composition. We also assume that parameters A_φ and b are equal to their respective values in binary water–salt systems. The right-hand side of eq. (22), excluding the leading term, is the molar Gibbs energy of mixing for ternary systems given by the extended Flory–Huggins theory.[17,18] In a ternary system, we assume that g_{12} is a function of ϕ_2 only.

Table I Coefficients c_k for g_{12} Regressed from the Osmotic-Coefficient Data

	NaCl	NaOH	Na formate	$(NH_4)_2SO_4$	Na_2SO_4
c_1	−0.60132 *e* + 0	−0.82292 *e* + 0	−0.11596 *e* + 1	0.29548 *e* + 0	−0.24039 *e* + 0
c_2	0.46993 *e* + 1	0.55931 *e* + 1	0.49293 *e* + 1	0.54921 *e* + 1	0.81471 *e* + 1
c_3	−0.21886 *e* + 2	−0.30229 *e* + 2	−0.38926 *e* + 2	−0.47999 *e* + 2	−0.12195 *e* + 3
c_4	0.14555 *e* + 3	0.19431 *e* + 3	0.28007 *e* + 3	0.36914 *e* + 3	0.11586 *e* + 4
c_5	−0.24657 *e* + 3	−0.30463 *e* + 3	−0.74974 *e* + 3	−0.11504 *e* + 4	−0.47005 *e* + 4
c_6	0	0	0	−0.40683 *e* + 3	−0.21487 *e* + 4
c_7	0	0	0	0.11459 *e* + 5	0.78847 *e* + 5
c_8	0	0	0	−0.19796 *e* + 5	−0.17610 *e* + 6
% rms[a]	0.3	0.2	0.1	0.3	0.7
m[b]	0.1–6	0.1–6	0.1–3.5	0.1–5.5	0.1–4

	Li_2SO_4	$ZnSO_4$	Na_3PO_4
c_1	−0.24193 *e* + 1	−0.49923 *e* + 1	−0.12635 *e* + 2
c_2	0.10996 *e* + 2	0.42492 *e* + 2	0.27591 *e* + 2
c_3	−0.18131 *e* + 3	−0.15630 *e* + 4	−0.17662 *e* + 4
c_4	0.20063 *e* + 4	0.41077 *e* + 5	0.51156 *e* + 5
c_5	−0.96790 *e* + 4	−0.66564 *e* + 6	−0.69316 *e* + 6
c_6	−0.64362 *e* + 4	0.63868 *e* + 7	−0.16287 *e* + 7
c_7	0.24055 *e* + 6	−0.32948 *e* + 8	0.15145 *e* + 9
c_8	−0.64248 *e* + 6	0.70238 *e* + 8	−0.11880 *e* + 10
% rms[a]	0.7	1.1	0.1
m[b]	0.1–3	0.1–3.5	0.1–0.7

[a] Percent room-mean-square relative deviations.
[b] Range of salt molality used in the fit.

COMPUTATION PROCEDURES

Regression of Binary Parameters

Interaction parameters g_{12} between water and ion were determined from experimental osmotic coefficients of binary water–salt systems. Osmotic coefficients are compiled in Hamer and Wu,[23] Goldberg,[24] and Robinson and Stokes.[25] In this work, we use data given by Robinson and Stokes.[25] For 1 : 1 salts, we set n to 5 in eq. (11). For 1 : 2, 1 : 3, and 2 : 3 salts, we regress g_{12} using $n = 8$. Osmotic coefficients are fitted to eq. (12) using eq. (14) for $\Delta\mu_1$. Table I gives coefficients c_k for g_{12} and a measure of how well the data are fitted.

For water–salt systems, an interesting question is the sign and relative magnitude of electrostatic contributions and Flory–Huggins contributions, as indicated by the Flory interaction parameter χ_{12} defined by eq. (16). Equation (18) indicates that the electrostatic contribution to χ_{12} is always positive. To illustrate, Figure 1 shows χ_{12} for ammonium sulfate at 25°C. For this salt, the Flory–Huggins contribution indicated by χ_{12} is negative. Crudely, negative and positive contributions to χ_{12} favor, respectively, phase separation and mutual solubility of water and ion. The positive electrostatic contribution favors phase separation.

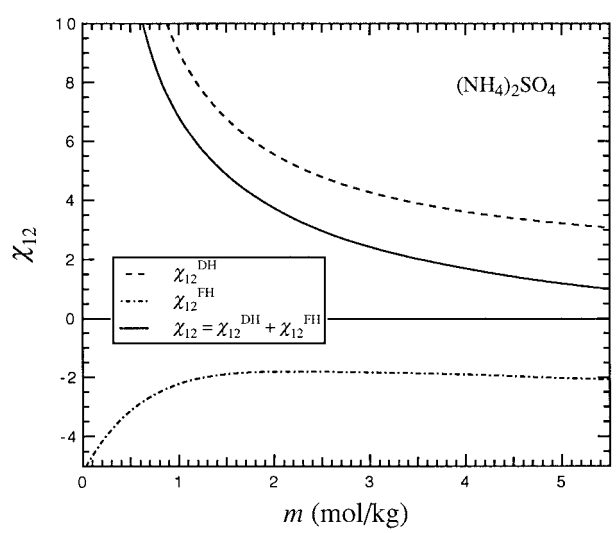

Figure 1 χ_{12} for aqueous ammonium sulfate at 25°C.

We compare theory with experiment for aqueous solutions containing PEG and salt. The segmental interaction parameters between water and PEG (χ_{13}) were taken from Cheluget et al.[13] for PEG molecular weights of 3350 and 8000 g/mol; these polymers are denoted as PEG3350 and PEG8000, respectively. Cheluget et al.[13] determined χ_{13} from vapor–liquid equilibrium (VLE) measurements for aqueous solutions containing 5–40 wt % PEG at 25°C reported by Haynes et al.[26] Using composition-independent χ_{13}, Cheluget et al.[13] report good (but not optimum) representation of VLE data measured by Haynes et al.[26] χ_{13} given by Cheluget et al.[13] are 0.426 and 0.464 for PEG3350 (r_3 = 155) and PEG8000 (r_3 = 370), respectively. Here, r_3 is determined by the molar volume of PEG relative to that of water at 25°C.

Phase-Equilibrium Calculations for Ternary Systems

Coexistence curves are computed by satisfying three equations of phase equilibrium. For each component, the chemical potential must be the same in the two coexisting phases. The difference between the chemical potential of component i in the mixture and that in the standard state is defined by

$$\frac{\Delta\mu_i}{RT} \equiv \frac{1}{RT}\left[\frac{\partial(N_1 + N_2 + N_3)\Delta G}{\partial N_i}\right]_{T,N_{j\neq i}} \quad (i, j = 1, 2, 3) \quad (23)$$

where N_i is the number of moles of component i. Components 1, 2, and 3 represent water, ion, and polymer, respectively. ΔG is given by eq. (22).

To solve eq. (23), we need good initial guesses for the compositions of the two coexisting phases. The compositions of the coexisting phases are estimated from the location of the spinodal curve and the critical point. Lattice theory provides computational simplicity for calculating the spinodal curve and the critical point for a ternary system. For multicomponent systems, systematic expressions for spinodals and critical points are given in Koningsveld and Staverman.[27]

RESULTS AND DISCUSSION

Calculated Phase Diagrams for Ternary Water–Salt–Polymer Systems with $g_{12} = 0$ and $\chi_{23} = 0$

In modeling the phase behavior of water–salt–polymer systems, an important question is to determine if the electrostatic contribution to the Gibbs energy of mixing is responsible for inducing phase separation. A recent theoretical study by Kenkare et al.[10–12] shows that Coulombic interactions among ions lead to phase separation in aqueous mixtures of charged hard spheres and neutral hard spheres that represent aqueous mixtures of salt and neutral molecules. The model by Kenkare et al. is based on integral-equation theory.[10–12] Here, we examine if our model, based on much simpler lattice theory, also predicts phase separation due to Coulombic interactions among salt ions.

To isolate the effect of the electrostatic contribution to the Gibbs energy of mixing, we first compute phase diagrams using $g_{12} = \chi_{23} = 0$. That is, we neglect the enthalpic interaction between water and ion and that between ion and polymer. Parameters that represent a binary water–polymer system are those for aqueous solutions containing PEG3350 at 25°C (r_3 = 155 and χ_{13} = 0.426). Using these parameters, the extended Flory–Huggins theory does not predict phase separation in the ternary water–salt–PEG3350 system.

However, our model predicts phase separation in the ternary water–salt–PEG3350 system when the electrostatic contribution and the extended Flory–Huggins theory with $g_{12} = \chi_{23} = 0$ are combined to give the Gibbs energy of mixing. Figure 2 shows calculated coexistence curves for three water–salt–PEG3350 systems containing 1 : 1, 1 : 2, and 2 : 2 salts with $g_{12} = \chi_{23} = 0$. Although not shown in this figure, the calculated coexistence curve containing 1 : 3 salt is close to that containing 2 : 2 salt. Our coexistence curves are plotted in terms of the segment fraction that is close to the weight fraction. In each system, the mixture separates into two coexisting phases when the overall composition of the mixture lies above the coexistence curve. Also shown in Figure 2 are the tie lines that connect compositions of coexisting phases whose compositions are denoted by solid circles. The solid square is the critical point at which the compositions of two coexisting phases become identical.

Although calculated coexistence curves were computed by neglecting the interaction between water and ion and that between ion and polymer, the model calculations presented in Figure 2 reveal some interesting characteristics of phase behavior of salt–polymer aqueous two-phase systems. First, phase separation in these systems can be induced by the electrostatic contribution to the

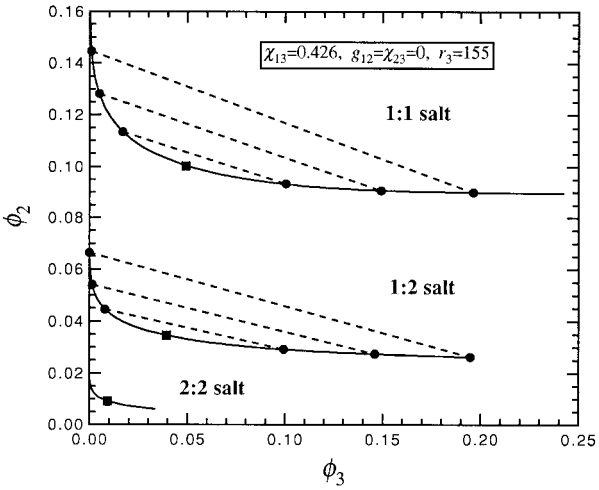

Figure 2 Theoretical coexistence curves in segment fraction for three water–salt–PEG3350 systems containing 1 : 1, 1 : 2, and 2 : 2 salts with $g_{12} = \chi_{23} = 0$ at 25°C. In each system, the mixture separates into two coexisting phases when the overall composition of the mixture lies above the coexistence curve. Also shown are tie lines that connect compositions of coexisting phases denoted by solid circles. The solid square is the calculated critical point. Although not shown in this figure, the theoretical coexistence curve containing a 1 : 3 salt is close to that containing a 2 : 2 salt.

Gibbs energy of mixing, even though the extended Flory–Huggins theory (without the enthalpic interaction between ion and water and that between ion and polymer) does not predict phase separation. Consistent with the recent theoretical study by Kenkare and Hall,[10–12] the electrostatic contribution to the Gibbs energy of mixing plays an essential role in forming salt–polymer aqueous two-phase systems.

Second, our model predicts that, as the ion valence rises, a smaller amount of salt (in segment fraction that is close to weight fraction) is required to induce salt–polymer aqueous two-phase systems. This prediction is, in general, consistent with the observed phase behavior of ternary water–salt–PEG systems. In addition, the amount of salt required to form two-phase systems predicted by the model is comparable to that observed by experiment for several salt–PEG aqueous two-phase systems.[1,28–30] To make a detailed comparison of theory with experiment, however, it is necessary to consider parameters g_{12} and χ_{23}. Using g_{12} regressed from the activity of water in binary salt–water systems, comparison of theory with experiment is given later for ternary water–salt–PEG systems.

Consistent with experiment, theory also predicts that salt partitions preferentially to the polymer-poor phase.[28–30] In addition, theory correctly predicts that the concentration of polymer in that phase approaches zero as the concentration of salt rises. This behavior is not due to unfavorable interaction between ion and PEG. In Figure 2, the Flory–Huggins theory neglects the interaction between ion and polymer ($\chi_{23} = 0$).

Finally, we consider the effect of PEG molecular weight on the phase diagram of the system water–salt–PEG at 25°C. For aqueous solutions containing a 1 : 2 salt, Figure 3 shows the theoretical coexistence curve for PEG3350 and that for PEG8000 at 25°C with $g_{12} = \chi_{23} = 0$. Parameters that represent the binary water–PEG8000 system are $r_3 = 370$ and $\chi_{13} = 0.464$. As the molecular weight of PEG rises, theory predicts that the two-phase region in the ternary phase diagram expands over the entire composition range. When the composition of salt in segment fraction is plotted against that of polymer, the slope of the tie line slightly decreases as the molecular weight of PEG rises. The calculated effect of PEG molecular weight on a ternary diagram is consistent with experiment reported by Zaslavsky et al.[29] for aqueous solutions containing PEG and ammonium sulfate.

Calculated Phase Diagrams for Ternary Water–Salt–PEG Systems with $\chi_{23} = 0$ and g_{12} Regressed from the Observed Activity of Water in Binary Water–Salt Systems

To make a detailed comparison of theory with experiment, it is first necessary to include parame-

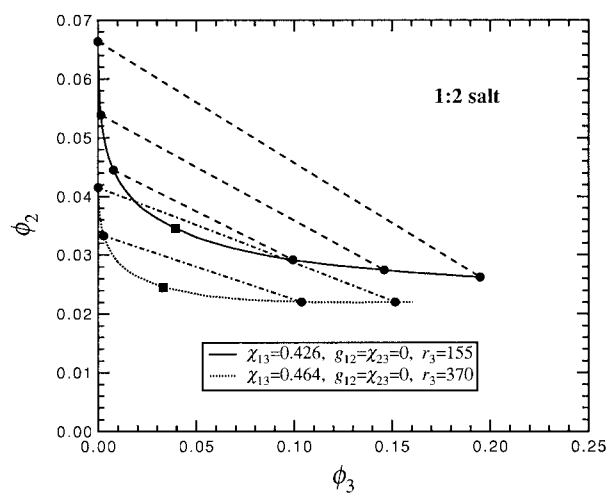

Figure 3 Theoretical coexistence curves at 25°C with $g_{12} = \chi_{23} = 0$ for aqueous solutions containing 1 : 2 salt and PEG: (——) PEG3350; (· · · · ·) PEG8000.

ter g_{12} that represents the interaction between water and ion in the extended Flory–Huggins theory. For ions that interact strongly with a polymer, theory may also require the interaction parameter between ion and polymer (χ_{23}). There are, however, no available binary data for regressing χ_{23}. Therefore, we compare measured phase diagrams for water–salt–PEG3350 systems with theoretical coexistence curves computed with $\chi_{23} = 0$ and g_{12} regressed from the binary osmotic-coefficient data.

Binary water–PEG systems show a closed-loop-type temperature–composition diagram with partial miscibility between an upper critical solution temperature (UCST) and a lower critical solution temperature (LCST) that lies below UCST. For the water–PEG3350 system, LCST is about 155°C.[31] As small amounts of salt are added to the solution, LCST starts to decrease.[32] At a given salt concentration, the salt that depresses LCST the most is the one that requires the least amount of salt to form salt–polymer aqueous two-phase systems at a constant temperature.[1] Because phase separation in water–salt–PEG systems corresponds to LCST behavior, the two-phase region of the ternary diagram expands as temperature rises.

Figure 4(a) shows predicted coexistence curves for water–salt–PEG3350 systems at 25°C with $\chi_{23} = 0$. For each salt shown in Figure 4, Table I gives coefficients c_k for g_{12}. The salt concentration in Figure 4(a) is calculated by assuming that the density of solution (including both salt and polymer) is 1 g/cm^3. In each system, the mixture separates into two phases when the overall composition of the mixture lies above the coexistence curve. Figure 4(b) shows data from Ananthapadmanabhan and Goddard[1] for water–salt–PEG3350 systems. (Regrettably, Ananthapadmanabhan and Goddard did not mention how the salt concentration was calculated.) Ho-Gutierrez et al.,[28] Zaslavsky et al.,[29] and Snyder et al.[30] also give measured phase diagrams at room temperature of salt–PEG aqueous two-phase systems that are consistent with those from Ananthapadmanabhan and Goddard.

For solutions containing PEG3350 and Na salt, theory predicts that salt becomes more effective (and lesser amounts of salt are required to form two-phase systems with PEG3350) as the valence of the anion rises. This prediction is consistent with experimental results from Ananthapadmanabhan and Goddard.[1] For the solution containing Na formate and for that containing Na_2SO_4, theoretical phase boundaries agree roughly with experiment.[1] In addition, consistent with experiment, theory with $\chi_{23} = 0$ predicts that NaCl does not form two-phase systems with PEG3350 at 25°C.[1,28] When $\chi_{23} = 0$, however, theory underestimates the salt concentration on the phase boundary for solutions containing Na_3PO_4.[1]

Ananthapadmanabhan and Goddard report that NaOH also forms two-phase systems with PEG3350 at 25°C.[1] Our model with $\chi_{23} = 0$, however, does not predict phase separation for that

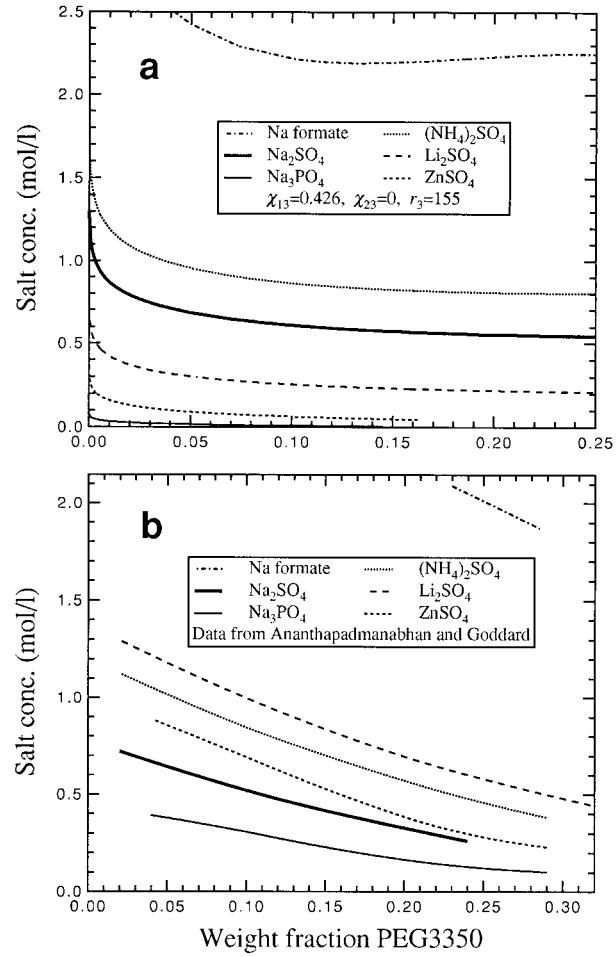

Figure 4 (a) Predicted coexistence curves for water–salt–PEG3350 systems at 25°C[1] with $\chi_{23} = 0$ and g_{12} regressed from the observed activity of water in water–salt systems. For salts shown in Figure 4, Table I gives coefficients c_k for g_{12}. Salt concentration is calculated by assuming that the density of solution (including both salt and polymer) is 1 g/cm^3. In each system, the mixture separates into two phases when the overall composition of the mixture lies above the coexistence curve. (b) Measured phase diagrams for water–salt–PEG3350 systems from Ananthapadmanabhan and Goddard,[1] who, regrettably, do not mention how the salt concentration was calculated.

case. Theory with $\chi_{23} = 0$ predicts that most 1 : 1 salts, including KOH, do not form two-phase systems with PEG3350 at 25°C. To predict phase separation for solutions containing NaOH, theory requires a positive χ_{23} that represents unfavorable interaction between salt ion and PEG. Experiment shows that KOH also forms two-phase systems with PEG at room temperature.[1]

For aqueous solutions containing PEG3350 and sulfates, theory with $\chi_{23} = 0$ shows only partial agreement with experimental results from Ananthapadmanabhan and Goddard.[1] In Figure 4, theoretical phase boundaries with $\chi_{23} = 0$ agree with experiment for the solution containing $(NH_4)_2SO_4$ and for that containing Na_2SO_4.[1] Among five sulfates shown in Figure 4, however, theory with $\chi_{23} = 0$ does not predict correctly the order of salt that represents the effectiveness in forming two-phase systems with PEG3350 at 25°C. Theory with $\chi_{23} = 0$ predicts that salt becomes less effective (and greater amounts of salt are required to induce phase separation) in the order of Na_3PO_4, $ZnSO_4$, Li_2SO_4, Na_2SO_4, and $(NH_4)_2SO_4$. Experiment, however, shows that salt becomes less effective in the order of Na_3PO_4, Na_2SO_4, $ZnSO_4$, $(NH_4)_2SO_4$, and Li_2SO_4.[1]

In forming two-phase systems with PEG, $ZnSO_4$ and Li_2SO_4 are not as effective as predicted by theory with $\chi_{23} = 0$. To explain such behavior by the present model, theory requires a χ_{23} that represents favorable interactions between salt ion and polymer. For solutions containing salt and PEG, there may be favorable interactions between the ether oxygens of PEG and salt cations. It is often argued that multivalent cations interact strongly with the ether oxygens of PEG.[1] (Salts with divalent cations are also not effective in precipitating globular proteins.[4])

CONCLUSIONS

A molecular–thermodynamic model based on the lattice theory is presented to predict phase diagrams of salt–polymer aqueous two-phase systems at 25°C. Assuming complete dissociation of salt, our theory represents a mixture of water, salt, and polymer as an incompressible ternary system consisting of water, ion, and polymer. To obtain the molar Gibbs energy of mixing, we combine the electrostatic contribution given by Pitzer's Debye–Hückel-type function with the extended Flory–Huggins theory. In our theory, the Flory–Huggins theory does not distinguish between salt cation and salt anion. The interaction parameter between water and ion is regressed from the observed activity of water in a binary water–salt system. The electrostatic contribution to the Gibbs energy of mixing does not contain adjustable parameters.

Consistent with the recent theoretical work by Kenkare et al.,[10–12] our model shows that the electrostatic contribution to the Gibbs energy of mixing plays a major role in forming salt–polymer aqueous two-phase systems. When a Debye–Hückel-type function is combined with our Flory–Huggins theory, the combined theory predicts phase separation even when the Flory–Huggins theory alone does not predict phase separation.

It is not possible to determine independently the interaction parameter between ion and polymer (χ_{23}) because no suitable binary data are available for obtaining χ_{23}. Theoretical ternary phase diagrams calculated by neglecting the interaction parameter between ion and polymer ($\chi_{23} = 0$) predict phase diagrams in semiquantitative agreement with experiment for salt-PEG aqueous two-phase systems. As the valence of salt ion rises, theory correctly predicts that salt becomes more effective and lesser amounts of salt are required to form two-phase systems with PEG. Consistent with experiment, theory also predicts that salt preferentially partitions into the polymer-poor phase and the concentration of polymer in that phase approaches zero as the concentration of salt rises.

For systems containing NaOH, $ZnSO_4$, and Li_2SO_4, theoretical phase boundaries with $\chi_{23} = 0$ do not agree with experiment. For those systems, to correlate phase diagrams, it is necessary to include parameter χ_{23}.

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REFERENCES

1. K. P. Ananthapadmanabhan and E. D. Goddard, *Langmuir,* **3,** 25 (1987).

2. W. Melander and C. Horvath, *Arch. Biochem. Biophys.,* **183,** 200 (1977).
3. H. G. Schild, M. Muthukumar, and D. A. Tirrell, *Macromolecules,* **24,** 948 (1991).
4. M. L. Broide, T. M. Tominc, and M. D. Saxowsky, *Phys. Rev. E.,* **53,** 6325 (1996).
5. W. C. K. Poon, *Phys. Rev. E.,* **55,** 3762 (1997).
6. P. A. Albertsson, *Partition of Cell Particles and Macromolecules,* 3rd ed., Wiley-Interscience, New York, 1986.
7. D. Fisher and I. A. Sutherland, Eds., *Separations Using Aqueous Phase Systems,* Plenum Press, New York, 1989.
8. R. K. Scopes, *Protein Purification: Principles and Practice,* 3rd ed., Springer-Verlag, New York, 1994.
9. K. D. Collins and M. W. Washabaugh, *Q. Rev. Biophs.,* **18,** 323 (1985).
10. P. U. Kenkare, C. K. Hall, and C. Caccamo, *J. Chem. Phys.,* **103,** 8098 (1995).
11. P. U. Kenkare, C. K. Hall, and C. Caccamo, *J. Chem. Phys.,* **103,** 8111 (1995).
12. P. U. Kenkare and C. K. Hall, *AIChE J.,* **42,** 3508 (1996).
13. E. L. Cheluget, S. Marx, M. E. Weber, and J. H. Vera, *J. Sol. Chem.,* **23,** 275 (1994).
14. P. J. Flory, *Principles of Polymer Chemistry,* Cornell University Press, Ithaca, NY, 1953.
15. K. S. Pitzer, *J. Phys. Chem.,* **77,** 268 (1973).
16. K. S. Pitzer and G. Mayorga, *J. Phys. Chem.,* **77,** 2300 (1973).
17. L. Yilmaz and A. J. McHugh, *J. Appl. Polym. Sci.,* **31,** 997 (1986).
18. D. J. Geveke and R. P. Danner, *J. Appl. Polym. Sci.,* **47,** 565 (1993).
19. H. Hartounian, S. I. Sandler, and E. W. Kaler, *Ind. Eng. Chem. Res.,* **33,** 2288 (1994).
20. V. Y. Borue and I. Y. Erukhimovich, *Macromolecules,* **23,** 3625 (1990).
21. M. Benmouna, S. Aziz, and T. A. Vilgis, *J. Polym. Sci., Polym. Phys. Ed.,* **31,** 587 (1993).
22. P. G. Higgs and J. F. Joanny, *J. Chem. Phys.,* **94,** 1543 (1991).
23. W. J. Hamer and Y. C. Wu, *J. Phys. Chem. Ref. Data,* **1,** 1047 (1972).
24. R. N. Goldberg, *J. Phys. Chem. Ref. Data,* **10,** 671 (1981).
25. R. A. Robinson and R. H. Stokes, *Electrolyte Solutions,* 3rd ed., Butterworths Scientific Publications, London, 1970.
26. C. A. Haynes, R. A. Beynon, R. S. King, H. W. Blanch, and J. M. Prausnitz, *J. Phys. Chem.,* **93,** 5612 (1989).
27. R. Koningsveld and A. J. Staverman, *J. Polym. Sci. A-2,* **6,** 325 (1968).
28. I. V. Ho-Gutierrez, E. L. Cheluget, J. H. Vera, and M. E. Weber, *J. Chem. Eng. Data,* **39,** 245 (1994).
29. B. Y. Zaslavsky, N. D. Gulaeva, S. Djafarov, E. A. Masimov, and L. M. Miheeva, *J. Colloid Interface Sci.,* **137,** 147 (1990).
30. S. M. Snyder, K. D. Cole, and D. C. Szlag, *J. Chem. Eng. Data,* **37,** 268 (1992).
31. Y. C. Bae, S. M. Lambert, D. S. Soane, and J. M. Prausnitz, *Macromolecules,* **24,** 4403 (1991).
32. S. Saeki, N. Kuwahara, M. Nakata, and M. Kaneko, *Polymer,* **18,** 1027 (1977).