Mixtures of two self- and mutually-associating liquids: Phase behavior, second virial coefficients, and entropy-enthalpy compensation in the free energy of mixing

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The theoretical description of the phase behavior of polymers dissolved in binary mixtures of water and other miscible solvents is greatly complicated by the self- and mutual-association of the solvent molecules. As a first step in treating these complex and widely encountered solutions, we have developed an extension of Flory-Huggins theory to describe mixtures of two self- and mutually-associating fluids comprised of small molecules. Analytic expressions are derived here for basic thermodynamic properties of these fluid mixtures, including the spinodal phase boundaries, the second osmotic virial coefficients, and the enthalpy and entropy of mixing these associating solvents. Mixtures of this kind are found to exhibit characteristic closed loop phase boundaries and entropy-enthalpy compensation for the free energy of mixing in the low temperature regime where the liquid components are miscible. As discussed by Widom *et al.* [Phys. Chem. Chem. Phys. **5**, 3085 (2003)], these basic miscibility trends, quite distinct from those observed in non-associating solvents, are defining phenomenological characteristics of the “hydrophobic effect.” We find that our theory of mixtures of associating fluids captures at least some of the thermodynamic features of real aqueous mixtures. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4996921>]

I. INTRODUCTION

Solutions of water soluble polymers in binary mixtures of water and other hydrogen bonding solvents find many applications in manufacturing and medicine. Most biomacromolecules are water soluble, and various “osmolyte” cosolvent molecules (alcohols, sugars, amino acids, urea and methylamines, salts)^{1,2} and “crowding agents,” such as other biomacromolecules and self-assembled molecular complexes within cells, exert a large role in regulating cellular homeostatic equilibrium¹ and other essential biological activities of living systems.^{3–5} To address the thermodynamic properties of this broad class of material systems, we first focused on developing a theoretical framework for describing the solubility of polymers in mixed solvents whose molecules competitively bind to the polymer.^{6–9} However, the theoretical treatment of polymers in real mixed solvents is often further complicated by the presence of self- and mutual-association between the solvent molecules themselves, an effect neglected in our previous modeling of the phase behavior of polymers in fluid mixtures.^{6–8} Although there is ample experimental^{10–15} evidence and evidence from simulations^{16–20} for these molecular association processes, their thermodynamic consequences are largely unknown.

Hirschfelder *et al.*²¹ first emphasized the influence of association processes on the phase behavior of fluid mixtures, and Barker and Fock²² implemented the first statistical mechanical description of the phase behavior of fluid mixtures exhibiting both associative and van der Waals interactions. However, all previous approaches to the thermodynamics of associating liquid mixtures that are based on lattice models are limited in scope due to their neglect of the *coupling* between self- and mutual-association of the solvent molecules and the resultant formation of large scale molecular assemblies of solvent molecules that greatly influence the thermodynamic and dynamic properties of such solutions. For example, Corrales and Wheeler²³ studied phase equilibria by using a lattice model of a fluid mixture in which two monomers of species A and C reversibly associate at equilibrium to form dimers AC, while Talanquer²⁴ generalized this work²³ to ternary mixtures undergoing an additional association reaction of the type, $X + Y \rightarrow Z$. Jackson²⁵ correspondingly pioneered off-lattice simulations of the phase behavior of fluids undergoing mutual- and self-association separately, but they likewise did not consider mixtures having *both* of these interactions simultaneously. These interesting off-lattice simulations²⁵ indicate the existence of phase behavior with many features in common with the lattice model calculations of Corrales and Wheeler²³ and later calculations by Dudowicz *et al.*^{26–28} for solutions of mutually-associating and self-associating molecules in a non-associating solvent, respectively. Since both self- and mutual-linear chain association processes have been observed

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in both experiments^{13,16} and simulations²⁹ to be prevalent in mixtures of water and other hydrogen-bonding fluids, the current paper addresses the influence of the presence of *both* self- and mutual-association processes on the phase behavior of mixtures of associating liquids in the absence of any polymer additive to avoid further complications to our analysis. Because experimental studies have further established the formation of large scale supramolecular assemblies of polymeric clusters in many aqueous associating fluids,^{30–33} we also incorporate polymeric self-assembly of solvent molecules in our model of mixtures of associating fluids. In particular, our theory of these associating fluid mixtures is based on an extension of Flory-Huggins theory to fluid mixtures interacting through *both* associative and van der Waals interactions and builds on our previous studies of fluid mixtures in which only one of the fluid components is either self- or mutually-associating.^{26–28,34–36}

Any serious investigation of the solubility of molecules in water inevitably leads to a consideration of the “hydrophobic effect,” which is defined by observational trends in the solubility of alkanes, proteins, and other biomolecules in water.³⁷ There have been numerous attempts at modeling the hydrophobic effect, leading to a huge scientific literature, along with diverse mathematical models aimed in particular at understanding the solubilities of macromolecules in water.³⁷ Since competitive self- and mutual-solvent associations are basic aspects of mixtures of water and other hydrogen bonding molecules, we investigate whether any essential features of the hydrophobic effect can be captured by our minimal model of associating solvent mixtures. As noted above, our coarse-grained model of associating solvent mixtures emphasizes both competitive molecular binding and the large-scale supramolecular assembly of the solvent molecules into diffuse polymeric type clusters rather than the formation of hypothetical “flicking ice clusters” encapsulating molecular additives;^{38–41} a qualitative physical picture that is often invoked to rationalize the hydrophobic effect.³⁷ Of course, our model does not address the dipolar and polarizable nature of water and does not include quantum effects, all of which are important for understanding the quantitative nature of the hydrogen bonding interaction in water and other associating liquids. On the other hand, recent modeling of water based on the Jagla intermolecular potential,^{42–46} characterized by an isotropic pair potential having two interaction length scales, has been found to reproduce essential trends in the “anomalous” thermodynamic and dynamical properties of real water without any consideration of dipolar interactions, polarizabilities, and quantum effects. This type of coarse-grained model of water has also been extended to methanol-water mixtures⁴⁷ and has been found to describe general trends (discussed below) in the thermodynamic properties rather well. Based on these encouraging results, we anticipate that our coarse-grained model of aqueous mixtures, emphasizing competitive associative and van der Waals interactions, should be sufficient to capture qualitative trends in the thermodynamics of the hydrophobic effect.

While there is no consensus about the physical origin of the hydrophobic effect, there are observational patterns that characterize and quantify this phenomenon from an

experimental standpoint. In particular, Widom *et al.*³⁷ have summarized experimental trends that define the hydrophobic effect, and we take their analysis of this phenomenon as a framework for determining which properties of associating fluid mixtures should be emphasized in relation to understanding the thermodynamics of aqueous solutions. First, closed loop phase behavior is a common characteristic of solutions of water and other associating solvents.^{48–53} For example, this phase behavior has been found by us before for mixtures of associating liquids with non-associating liquids²⁸ and in polymers dissolved in solvents and solvents mixtures that have specific binding interactions with the polymer, as well as van der Waals interactions that promote phase separation.^{7,54} Widom *et al.*³⁷ explain that the existence of this type of closed loop phase behavior leads to non-monotonic changes in the solubility of additives in water with increasing temperature. They have also emphasized³⁷ that the solvation of molecules in water normally exhibits “entropy-enthalpy compensation”^{55–58} in the low temperature regime where the fluids are miscible, i.e., below the lower critical solution temperature. Specifically, the enthalpy of mixing Δh_{mix} and the entropy of mixing Δs_{mix} are observed to be nearly proportional to each other. To gain insight into these singular miscibility trends, we determine the phase behavior (the spinodal curves), along with the excess enthalpy and excess entropy of solvent mixtures, and with the second osmotic virial coefficients $\mathcal{B}_2^{(A)}$ and $\mathcal{B}_2^{(C)}$, since the latter quantities are useful predictors of fluid miscibility in non-associated fluids. As expected, our analysis of mixtures of two associating solvents reveals the same miscibility patterns emphasized by Widom *et al.*³⁷ as being characteristic of the hydrophobic effect.

The development of a generalized FH type theory for binary mixtures of two self- and mutually linearly associating liquids is summarized in Sec. II, and the final expressions for the basic thermodynamic functions, the spinodal condition, and the second osmotic virial coefficients are discussed. Calculations of the phase boundaries, second osmotic virial coefficients, and enthalpy and entropy of mixing are described in Secs. III–V, respectively.

II. THEORY

A. Lattice model of two mutually associating and self-associating small molecule liquids

A binary mixture of two mutually associating and self-associating small molecule liquids is formed by mixing n_A^o and n_C^o molecules of species A and C, respectively. The standard lattice model of this type of mixtures describes each molecule of both components as entity occupying a single lattice site on a three-dimensional lattice with N_l lattice sites, coordination number $z = 6$, and with no vacant sites present. Either of the two volume fractions $\phi_A^o \equiv n_A^o/N_l$ and $\phi_C^o \equiv n_C^o/N_l = 1 - \phi_A^o$ determines the initial composition of the mixture, i.e., its composition before association.

The association of species A and C is assumed to proceed in two stages. The first step involves the reversible formation of linear complexes $A_p C_q$,

which can further self-assemble reversibly into larger clusters. The latter process can be expressed by the more general reaction,

(This model of association has been invoked before to describe the phase behavior of mixtures of lipids and cholesterol.⁵⁹)

Figures 1 and 2 depict schematic models of a single complex $A_p C_q$ and of a typical cluster $(A_p C_q)_{k=3}$ composed of three complexes $A_2 C_3$ and having the structure of a linear polymer chain. Inspection of Figs. 1 and 2 reveals that the synthesis of a complex $A_p C_q$, the basic “monomeric” unit of the higher order clusters $\{(A_p C_q)_k\}$, occurs through the formation of $(p-1)$ self-associative interactions A-A, $(q-1)$ self-associative

interactions C-C, and a single intra-associative interaction A-C that generally differs from the inter-associative interaction A-C. The equilibrium mixture contains polydisperse clusters $\{(A_p C_q)_k, k = 1, 2, 3, \dots, \infty\}$, as well as free (unassociated) molecules of solvents A and C. The equilibrium constants,

$$K_{pq} = \exp\{-[\Delta h_{pq} - T\Delta s_{pq}]/k_B T\} \quad (3)$$

and

$$K_{pol} = \exp\{-[\Delta h_{pol} - T\Delta s_{pol}]/k_B T\} \quad (4)$$

for the reactions of Eqs. (1) and (2), respectively, are expressed in terms of the free energy parameters; the dimensionless enthalpies⁶⁰ $\Delta h_{pq}/k_B T$ and $\Delta h_{pol}/k_B T$ are defined as

$$\Delta h_{pq}/k_B T \equiv [\Delta h_{AC}^{(intra)} + (p-1)\Delta h_{AA} + (q-1)\Delta h_{CC}]/k_B T \quad \text{and} \quad \Delta h_{pol}/k_B T \equiv \Delta h_{AC}^{(inter)}/k_B T, \quad (5)$$

and the dimensionless entropies $\Delta s_{pq}/k_B$ and $\Delta s_{pol}/k_B$ are given by

$$\Delta s_{pq}/k_B \equiv [\Delta s_{AC}^{(intra)} + (p-1)\Delta s_{AA} + (q-1)\Delta s_{CC}]/k_B \quad \text{and} \quad \Delta s_{pol}/k_B \equiv \Delta s_{AC}^{(inter)}/k_B, \quad (6)$$

with k_B being Boltzmann’s constant and T denoting the absolute temperature. The subscripts AA, CC, and AC on $\Delta h_{\alpha\beta}$ and $\Delta s_{\alpha\beta}$ in Eqs. (5) and (6) specify the type of associative interaction, while the superscripts (intra) and (inter) on Δh_{AC} and Δs_{AC} indicate the position of the A-C physical bond in the polymeric clusters $\{(A_p C_q)_k\}$, namely, inside individual “monomeric” complexes $A_p C_q$ and between them as a linking “bond,” respectively. The equilibrium constant K_{pol} is assumed to be independent of the cluster size (i.e., of the index k) and is, thus, taken as common for all successive reactions of Eq. (2).

In addition to the above mentioned strong self- and mutual-association processes, van der Waals interactions are also present in the system. More specifically, all mutually non-bonded nearest neighbor segment pairs $\alpha\gamma$ belonging to the associated complexes $\{(A_p C_q)_k\}$, as well as to unassociated molecules of species A and C, interact between themselves through attractive weak van der Waals forces with the interaction energy $\epsilon_{\alpha\gamma}$. In order to maintain the minimal number of adjustable parameters of the theory, each $\epsilon_{\alpha\gamma}$ is taken to depend only on the type of the nearest neighbor segments α and γ , regardless of the individual chemical species to which these two segments pertain.

FIG. 1. Schematic model of a single $A_4 C_3$ complex. Physical associative bonds between the molecules of solvent A (magenta circles) and solvent C (blue circles) are denoted by magenta and blue lines, respectively. Physical associative bonds A-C are distinguished by a cyan line.

Notice that Eqs. (1) and (2) describe a combination of self- and mutual-association processes for all pairs of the stoichiometric indices p and q , except $p = q = 1$. The latter case corresponds exclusively to mutual association. Other models for the simultaneous self- and mutual-associations that postulate the formation of clusters $\{A_i\}$ and $\{C_j\}$ of single species, in addition to mixed clusters $\{(AC)_k\}$, are much less realistic since the free energy parameters for the physical “bonds” A-A, C-C, and A-C generally have similar orders of magnitude. The inadequacy of these models to describe the thermodynamic properties of real mixtures of both self- and mutually associating liquids has been confirmed by calculations of phase boundaries for these model systems that reveal qualitative disagreement with the experimentally observed closed loop phase diagrams.

B. The Helmholtz free energy

The dimensionless Helmholtz free energy density $f = F/(N_l k_B T)$ for the liquid mixture composed of clusters $\{(A_p C_q)_k\} \equiv \{X_k\}$ ($k = 1, 2, 3, \dots, \infty$) and unassociated molecules of species A and C is the sum of the free energy density f_{assoc} arising from the presence of strong associations and the free energy density f_ϵ stemming from van der Waals interactions,

$$\frac{F}{N_l k_B T} = f = f_{assoc} + f_\epsilon, \quad (7)$$

FIG. 2. Schematic model of a cluster $(A_2 C_3)_3$ composed of three complexes $A_2 C_3$. Physical bonds A-C between and within individual complexes $A_2 C_3$ are denoted as orange and cyan lines, respectively.

where the total number of lattice sites,

$$N_l = n_A^o + n_C^o = n_A + n_C + \sum_{k=1}^{\infty} k(p+q) n_{X_k}, \quad (8)$$

is kept constant, as indicated by Eq. (8). These two portions of the free energy density f emerge from the extension of classic Flory-Huggins (FH) theory to an equilibrium multicomponent associating fluid as

$$f_{assoc} = \phi_A \ln \phi_A + \phi_C \ln \phi_C + \sum_{k=1}^{\infty} \frac{\phi_{X_k}}{k(p+q)} \ln \phi_{X_k} + \sum_{k=1}^{\infty} \phi_{X_k} f_{X_k} \quad (9)$$

and

$$f_{\epsilon} = -\frac{z}{2} \left[\frac{\epsilon_{AA}}{k_B T} \left\{ \phi_A^2 + 2\phi_A \sum_{k=1}^{\infty} \phi_{X_k} \frac{p}{p+q} + \left(\sum_{k=1}^{\infty} \phi_{X_k} \frac{p}{p+q} \right)^2 \right\} + \frac{\epsilon_{CC}}{k_B T} \left\{ \phi_C^2 + 2\phi_C \sum_{k=1}^{\infty} \phi_{X_k} \frac{q}{p+q} + \left(\sum_{k=1}^{\infty} \phi_{X_k} \frac{q}{p+q} \right)^2 \right\} + 2 \frac{\epsilon_{AC}}{k_B T} \left\{ \phi_A \phi_C + \phi_A \sum_{k=1}^{\infty} \phi_{X_k} \frac{q}{p+q} + \phi_C \sum_{k=1}^{\infty} \phi_{X_k} \frac{p}{p+q} + \left(\sum_{k=1}^{\infty} \phi_{X_k} \right)^2 \frac{pq}{(p+q)^2} \right\} \right], \quad (10)$$

where the notation $\phi_A \equiv \phi_{A_1}$ and $\phi_C \equiv \phi_{C_1}$ is employed and f_{X_k} is defined to be the free energy density of a single cluster X_k .⁶¹ The free energy density f_{X_k} depends of the structure of the clusters. For convenience, the clusters are taken as having linear structure (see Figs. 1 and 2). Then f_{X_k} has the form

$$f_{X_k} = \frac{1}{k(p+q)} \ln \frac{2\alpha^2}{z k(p+q)} + \frac{k(p+q)-1}{k(p+q)} - \ln \alpha + \frac{k}{k(p+q)} \frac{(\Delta h_{pq} - T \Delta s_{pq})}{k_B T} + \frac{k-1}{k(p+q)} \times \frac{\Delta h_{pol} - T \Delta s_{pol}}{k_B T}, \quad k \geq 1, \quad (11)$$

produced by the addition of the free energy Δf_{X_k} for the formation of a given cluster X_k (from single molecules of species A and C) to the free energy terms linear in the volume fraction ϕ_{X_k} that emerge from standard FH theory. The chain stiffness parameter α of Eq. (11) equals unity for completely stiff polymeric clusters and $(z-1)$ for completely flexible polymeric clusters, while the free energy parameters $(\Delta h_{pq}, \Delta s_{pq})$ and $(\Delta h_{pol}, \Delta s_{pol})$ for the reactions in Eqs. (1) and (2), respectively, are specified by Eqs. (5) and (6). The free energies f_{A_1} and f_{C_1} of single molecules of species A and C are taken as vanishing to establish the zero of the free energy.

C. The distribution of clusters $\{X_k\}$

The condition of chemical equilibrium for the system described by the reactions of Eqs. (1) and (2) implies that the chemical potentials $\mu_A \equiv \mu_{A_1}$, $\mu_C \equiv \mu_{C_1}$, and μ_{X_k} of species A_1 , C_1 , and X_k , respectively, satisfy the relation,

$$\mu_{X_k} = p k \mu_A + q k \mu_C. \quad (12)$$

Calculating the chemical potentials $\{\mu_{\gamma}\}$ ($\gamma \equiv A, C, X_k$) that are defined as the derivatives of the Helmholtz free energy F of Eq. (7),

$$\frac{\mu_{\gamma}}{k_B T} = \frac{1}{k_B T} \frac{\partial F}{\partial n_{\gamma}} \Big|_{T, \{n_{\beta \neq \gamma}\}} = f \frac{\partial N_l}{\partial n_{\gamma}} + N_l \frac{\partial f}{\partial n_{\gamma}} \Big|_{T, \{n_{\beta \neq \gamma}\}}, \quad (13)$$

and substituting the resulting expressions for $\{\mu_{\gamma}\}$, along with the expression for f_{X_k} from Eq. (11), into Eq. (12) lead to the desired equation for the distribution of clusters $\{X_k\}$,

$$\phi_{X_k} = k C_{pq} \mathcal{A}^k, \quad k \geq 1, \quad (14)$$

where

$$C_{pq} = \frac{z(p+q)}{2 \alpha^2 K_{pol}} \equiv (p+q) \mathcal{C}, \quad \mathcal{C} \equiv \frac{z}{2 \alpha^2 K_{pol}} \quad (15)$$

and

$$\mathcal{A} = \phi_A^p \phi_C^q K_{pq} K_{pol} \alpha^{p+q}, \quad 0 < \mathcal{A} < 1. \quad (16)$$

Equation (14) specifies the equilibrium concentrations $\{\phi_{X_k}\}$ of clusters $\{X_k\}$ in terms of the equilibrium volume fractions ϕ_A and ϕ_C of the unassociated molecules of the components A and C, respectively. The latter are determined, in turn, by numerically solving a set of two mass conservation constraints for the components A and C,

$$\phi_A^o = \phi_A + \frac{p}{p+q} \sum_{k=1}^{\infty} \phi_{X_k} = \phi_A + p \frac{\mathcal{C} \mathcal{A}}{(1-\mathcal{A})^2} \quad (17)$$

and

$$\phi_C^o = \phi_C + \frac{q}{p+q} \sum_{k=1}^{\infty} \phi_{X_k} = \phi_C + q \frac{\mathcal{C} \mathcal{A}}{(1-\mathcal{A})^2}. \quad (18)$$

The solutions of Eqs. (17) and (18), i.e., the equilibrium concentrations ϕ_A and ϕ_C , are functions of temperature T and the initial composition $\phi_A^o = 1 - \phi_C^o$ of the mixture and have been calculated for representative sets of the stoichiometric indices p and q , and the free energy parameters Δh_{AA} , Δs_{AA} , Δh_{CC} , Δs_{CC} , $\Delta h_{AC}^{(intra)}$, $\Delta s_{AC}^{(intra)}$, and $\Delta h_{AC}^{(inter)}$, $\Delta s_{AC}^{(inter)}$.

The insensitivity of the cluster distribution in Eq. (14) to the van der Waals interaction energies $\{\epsilon_{\beta\gamma}\}$ arises from our simplifying assumption (see subsection A) that there are only three different van der Waals interaction energies ϵ_{AA} , ϵ_{CC} , and ϵ_{AC} in the system. In other words, the nearest neighbor van der Waals interaction energies $\{\epsilon_{\beta\gamma}\}$ are taken as independent of the individual chemical species to which the neighboring pairs β and γ pertain.

D. The final expression for the Helmholtz free energy

The next step in developing our theory for the thermodynamics of mixtures of two self- and mutually associating molecules of species A and C consists in substituting the expressions for the cluster distribution from Eq. (14) and for the Helmholtz free energy densities f_{X_k} (of single polymeric clusters) from Eq. (11) into a multicomponent generalization of the FH free energy in Eqs. (7)–(11). Performing the summations over all possible cluster sizes produces then the final expression for f ,

$$\frac{F}{N_l k_B T} \equiv f = \phi_A^o \ln \phi_A + \phi_C^o \ln \phi_C + \phi_A^o - \phi_A + \phi_C^o - \phi_C - \frac{\mathcal{C} \mathcal{A}}{1-\mathcal{A}} + f_{\epsilon}, \quad (19)$$

where the dimensionless van der Waals free energy density f_ϵ coincides with that corresponding to a binary mixture before association, denoted by f_ϵ^o ,

$$f_\epsilon^o = -(z/2) [\epsilon_{AA}(\phi_A^o)^2 + \epsilon_{CC}(\phi_C^o)^2 + 2\epsilon_{AC}\phi_A^o\phi_C^o] / k_B T. \quad (20)$$

The rather compact equation (19) is the main result of our theory, which is further employed below to determine basic thermodynamic properties of the associating fluid mixtures, such as the internal energy, entropy, second osmotic virial coefficient, and phase boundaries (see below).

E. Internal energy and entropy

The internal energy U is related to the Helmholtz free energy F by the standard derivative,

$$U = \frac{\partial (F/k_B T)}{\partial (1/k_B T)}|_{N_i}. \quad (21)$$

Differentiating $F/k_B T$ from Eq. (19) yields the internal energy density u ,⁶²

$$u \equiv \frac{U}{N_l k_B T} = \frac{C\mathcal{A}}{(1-\mathcal{A})^2} \left[\frac{\Delta h_{pq}}{k_B T} + \mathcal{A} \frac{\Delta h_{pol}}{k_B T} \right] + \phi_A^o \phi_C^o \chi_{AC}, \quad (22)$$

where the enthalpies Δh_{pq} and Δh_{pol} are defined by Eq. (5) and the interaction parameter χ_{AC} is a linear combination of the three nearest neighbor van der Waals interaction energies,

$$\chi_{AC} = (z/2) [\epsilon_{AA} + \epsilon_{CC} - 2\epsilon_{AC}] / k_B T. \quad (23)$$

Notice that the terms proportional to the derivatives $\partial \phi_A / \partial (1/k_B T)|_{N_i}$ and $\partial \phi_C / \partial (1/k_B T)|_{N_i}$ vanish identically in Eq. (22) due to the mass conservation relations from Eqs. (17) and (18).

The dimensionless entropy density $s \equiv S/(k_B N_l)$ follows simply from the definition of the Helmholtz free energy density f ,

$$f = u - s, \quad (24)$$

where f and u are given by Eqs. (19) and (22), respectively.

The Helmholtz free energy of mixing ΔF_{mix} is evaluated from the Helmholtz free energy of a binary mixture by subtracting the contributions of the pure components,

$$\Delta F_{mix} = F - \phi_A^o F_A - \phi_C^o F_C = \Delta U_{mix} - T \Delta S_{mix}, \quad (25)$$

where F_γ is the Helmholtz free energy of the pure component γ ($\gamma \equiv A, C$) and ΔU_{mix} and ΔS_{mix} are the internal energy of mixing and the entropy of mixing, respectively.

The dimensionless specific⁶³ free energy of mixing, $\Delta f_{mix} = \Delta F_{mix}/(N_l k_B T)$, is a linear combination of the dimensionless specific internal energy of mixing, $\Delta u_{mix} \equiv \Delta U_{mix}/(N_l k_B T)$, and the specific entropy of mixing, $\Delta s_{mix} \equiv \Delta S_{mix}/(k_B N_l)$. For a binary mixture of two self- and mutually associating species, these three thermodynamic functions have the following forms:

$$\begin{aligned} \Delta f_{mix} = & \phi_A^o \ln \phi_A + \phi_C^o \ln \phi_C + \phi_A^o - \phi_A + \phi_C^o - \phi_C - \frac{C\mathcal{A}}{1-\mathcal{A}} \\ & + \phi_A^o \phi_C^o \chi_{AC} - \phi_A^o \left[\frac{C_A (A_A^*)^2}{(1-A_A^*)^2} + \ln \frac{A_A^*}{K_A} \right] \\ & - \phi_C^o \left[\frac{C_C (A_C^*)^2}{(1-A_C^*)^2} + \ln \frac{A_C^*}{K_C} \right], \end{aligned} \quad (26)$$

$$\begin{aligned} \Delta u_{mix} = & \frac{1}{k_B T} \frac{\partial \Delta f_{mix}}{\partial (1/k_B T)} = \frac{C\mathcal{A}}{(1-\mathcal{A})^2} \left[\frac{\Delta h_{pq}}{k_B T} + \mathcal{A} \frac{\Delta h_{pol}}{k_B T} \right] \\ & + \phi_A^o \phi_C^o \chi_{AC} - \phi_A^o \left[\frac{C_A (A_A^*)^2}{(1-A_A^*)^2} \frac{\Delta h_{AA}}{k_B T} \right] \\ & - \phi_C^o \left[\frac{C_C (A_C^*)^2}{(1-A_C^*)^2} \frac{\Delta h_{CC}}{k_B T} \right] \end{aligned} \quad (27)$$

and

$$\Delta s_{mix} = \Delta u_{mix} - \Delta f_{mix}, \quad (28)$$

where

$$C_A = \frac{z}{2\alpha K_A} \quad \text{and} \quad C_C = \frac{z}{2\alpha K_C}, \quad (29)$$

$$A_A^* \equiv A_A(\phi_A^o = 1), \quad A_A = \phi_A^* K_A \quad \text{and} \quad A_C^* \equiv A_C(\phi_C^o = 1), \quad A_C = \phi_C^* K_C, \quad (30)$$

and the superscript $*$ refers to a pure component. Self-association in the pure component liquids has been assumed to proceed democratically (i.e., as in the free association model). The association constants K_A and K_C correspond to the reactions,⁶⁴

and

respectively, and are defined in terms of the respective free energy parameters; the enthalpies $\Delta h_{\gamma\gamma}$ and the entropies $\Delta s_{\gamma\gamma}$

($\gamma \equiv A, C$),

$$K_A = \exp\{-[\Delta h_{AA} - T \Delta s_{AA}]/k_B T\}, \quad (33)$$

and

$$K_C = \exp\{-[\Delta h_{CC} - T \Delta s_{CC}]/k_B T\}. \quad (34)$$

F. Second osmotic virial coefficients

Because each component of a binary mixture can be in the minority or in the majority, two different osmotic pressures (π_A and π_C) and, correspondingly, two different second osmotic

virial coefficients $\mathcal{B}_2^{(A)}$ and $\mathcal{B}_2^{(C)}$ exist for a mixture of two self- and mutually associated liquids A and C . The osmotic pressures π_A and π_C are defined in terms of the chemical potentials μ_A and μ_C of the respective monomeric species,

$$\frac{\pi_A v_{cell}}{k_B T} = \frac{\mu_A^o}{k_B T} - \frac{\mu_A}{k_B T} \quad (35)$$

and

$$\frac{\pi_C v_{cell}}{k_B T} = \frac{\mu_C^o}{k_B T} - \frac{\mu_C}{k_B T}, \quad (36)$$

where v_{cell} designates the volume associated with a single lattice site and the subscripts A and C on π , μ , and on the function g (defined below) label the majority species. The superscript o on μ_γ ($\gamma \equiv A, C$) refers to the liquid of the pure component γ that is maintained in osmotic equilibrium with the main system.

Evaluating the chemical potentials μ_A , μ_C , μ_A^o , and μ_C^o by using their definitions from Eq. (13) and the free energy density f expression from Eqs. (19) and (20) converts Eqs. (35) and (36) into the forms

$$\frac{\pi_A v_{cell}}{k_B T} = -\ln \phi_A - \phi_A^o - \phi_C^o + \phi_A + \phi_C + \frac{\mathcal{C} \mathcal{A}}{1 - \mathcal{A}} - \chi_{AC} (\phi_C^o)^2 = g_A - 1 - \chi_{AC} (\phi_C^o)^2 \quad (37)$$

and

$$\frac{\pi_C v_{cell}}{k_B T} = -\ln \phi_C - \phi_A^o - \phi_C^o + \phi_A + \phi_C + \frac{\mathcal{C} \mathcal{A}}{1 - \mathcal{A}} - \chi_{AC} (\phi_A^o)^2 = g_C - 1 - \chi_{AC} (\phi_A^o)^2. \quad (38)$$

The standard method for calculations of the second osmotic virial coefficients $\mathcal{B}_2^{(\gamma)}$ ($\gamma \equiv A, C$) consists in expanding the function $g_\gamma = -\ln \phi_{\beta \neq \gamma} + \phi_A + \phi_C + \mathcal{C} \mathcal{A} / (1 - \mathcal{A})$ in the power series of ϕ_β^o around $\phi_\beta^o = 0$,

$$g_\gamma(\phi_\beta^o) = g_\gamma(\phi_\beta^o = 0) + \frac{\partial g_\gamma}{\partial \phi_\beta^o} \bigg|_{\phi_\beta^o=0} \phi_\beta^o + \frac{1}{2} \frac{\partial^2 g_\gamma}{\partial \phi_\beta^{o2}} \bigg|_{\phi_\beta^o=0} (\phi_\beta^o)^2 + \dots, \quad \gamma \equiv A, C, \beta \neq \gamma, \quad (39)$$

and in collecting all the terms, including the van der Waals term $\chi_{AC} (\phi_\beta^o)^2$, that are quadratic in ϕ_β^o . This procedure leads to the following expressions:

$$\mathcal{B}_2^{(C)} = \frac{1}{2} \left[-3 \mathcal{C} \sigma^2 \left(\frac{\partial \phi_A}{\partial \phi_A^o} \bigg|_{\phi_A^o=0} \right)^2 + \left(\frac{\partial \phi_C}{\partial \phi_A^o} \bigg|_{\phi_A^o=0} \right)^2 - 2 \chi_{AC} \right], \quad p = 1, q \text{ arbitrary}, \quad (40)$$

and

$$\mathcal{B}_2^{(A)} = \frac{1}{2} \left[-3 \mathcal{C} \sigma^2 \left(\frac{\partial \phi_C}{\partial \phi_C^o} \bigg|_{\phi_C^o=0} \right)^2 + \left(\frac{\partial \phi_A}{\partial \phi_C^o} \bigg|_{\phi_C^o=0} \right)^2 - 2 \chi_{AC} \right], \quad q = 1, p \text{ arbitrary}, \quad (41)$$

where the superscripts A and C on $\mathcal{B}_2$ indicate the majority component and $\sigma \equiv K_{pq} K_{pol} \alpha^{p+q}$. The derivatives $\partial \phi_A / \partial \phi_A^o|_{N_i, T}$ and $\partial \phi_C / \partial \phi_A^o|_{N_i, T}$ (or $\partial \phi_A / \partial \phi_C^o|_{N_i, T}$ and $\partial \phi_C / \partial \phi_C^o|_{N_i, T}$) are evaluated by differentiating the mass conservation constraints in Eqs. (17) and (18) with respect to the initial volume fractions ϕ_A^o (or ϕ_C^o) and by solving the resulting sets of two linear equations for the two unknowns.

G. Defining limits of phase stability: Spinodal curves

An assembly of various clusters $\{A_p C_q\}_k$ and unassociated molecules of components A and C can formally be treated as a binary mixture of species A and C . Its phase boundary $T = T(\phi_A^o)$ at constant volume V (i.e., $N_i = \text{const.}$) is then determined by the vanishing of the second derivative of the free energy density f with respect to the initial composition ϕ_A^o of the mixture,

$$\frac{\partial^2 f}{\partial \phi_A^{o2}} \bigg|_{T, N_i} = 0. \quad (42)$$

When the Helmholtz free energy density f is specified by Eqs. (19) and (20), the spinodal condition of Eq. (42) becomes

$$\frac{1}{\phi_A} \frac{\partial \phi_A}{\partial \phi_A^o} \bigg|_{T, N_i} - \frac{1}{\phi_C} \frac{\partial \phi_C}{\partial \phi_A^o} \bigg|_{T, N_i} - 2 \chi_{AC} = 0, \quad (43)$$

where the interaction parameter χ_{AC} is defined by Eq. (23) and the derivatives $\partial \phi_A / \partial \phi_A^o|_{T, N_i}$ and $\partial \phi_C / \partial \phi_A^o|_{T, N_i}$ simply follow, as explained above, from differentiating and solving the resulting mass conservation equations.

Notice that Eq. (43) transforms into the well known spinodal condition for a binary mixture of two single bead nonassociating liquids A and C ,

$$1/\phi_A^o + 1/\phi_C^o - 2\chi_{AC} = 0, \quad (44)$$

upon setting $\phi_A = \phi_A^o$ and $\phi_C = \phi_C^o$, which, in turn, implies that $\partial \phi_A / \partial \phi_A^o = 1$ and $\partial \phi_C / \partial \phi_A^o = -1$.

III. CALCULATIONS OF PHASE BOUNDARIES

The strength of the hydrogen bond interaction is intermediate between that of a typical van der Waals interaction energy of 1 kJ/mol and the energy of a molecular bond, on the order of 400 kJ/mol.⁶⁵ Hydrogen bonds at room temperature are thus inherently transient associations whose interaction energy is on the order of thermal energy, $k_B T$. Dielectric relaxation measurements provide a good source of information about the free energy parameters for hydrogen bonding of “typical” associating liquids and their mixtures that are used in our illustrative calculations below. For example, Dannhauser and Bahe^{14,15} estimated the enthalpy Δh and entropy Δs of

the formation of a hydrogen bond to be, respectively, in the ranges (−27 to −33) kJ/mol and (−35 to −126) J/(mol K) for a number of low molar mass alcohols. Dielectric determinations of these associative parameters for water are consistent with those found for alcohols, although they lie to the low end of the ranges reported for alcohols, i.e., $\Delta h = -23.3$ kJ/mol and $\Delta s = -37.1$ J/(mol K).⁶⁶ Of course, the experimental estimate of these parameters depends on the type of experimental technique employed and the definition of “hydrogen bond.”⁶⁷ Corresponding estimates of these parameters from molecular dynamics simulations are uncertain because they are sensitive to the choice of intermolecular pair potential, inclusion of polarizability, and other additional assumptions introduced into the simulations.⁶⁸ Despite these uncertainties, we view dielectric relaxation measurements to be a reliable source of rough estimates of Δh and Δs for real hydrogen bonded fluids.

In our previous series of papers devoted to molecular association in liquids,^{26,34–36,54,69,70} we chose representative values of the free energy parameters for self- and mutual-association, $\Delta h = -35$ kJ/mol and $\Delta s = -105$ J/(mol K) that just happen to coincide with the ranges just indicated for simple hydrogen bonded liquids. These “representative” free energies of association were originally determined from experimental investigation of the living polymerization of poly (α -methylstyrene) in methylcyclohexane.^{71–73} This choice of free energy parameters ensures that the molecular clustering transition occurs near room temperature, which is apparently a basic feature also of many hydrogen bonding fluids. In the present paper, we then take the association free energies to be equal to the representative values, $\Delta h = -35$ kJ/mol and $\Delta s = -105$ J/(mol K), unless otherwise indicated.

Our illustrative calculations also require the choice of representative values of the van der Waals interaction energy, χ , appropriate for describing mixtures of hydrogen bonding fluids. Phase boundaries (spinodal curves) are determined by solving Eq. (43). The FH interaction parameter χ_{AC} of Eq. (23) fixed as $\chi_{AC} = 1000/T$ in these calculations ensures that the calculated upper critical solution temperatures $T_c^{(up)}$ for the closed loop portion of the phase diagram lie in the general range observed⁵¹ for mixtures of water and polar organic liquids (i.e., in the range from 400 K to 500 K). Clearly, χ_{AC} is significantly larger than normally found for synthetic non-polar polymer blends and synthetic polymers dissolved in organic solvents solutions, but binary mixtures of two self- and mutually-associating (often polar) liquids clearly have a different molecular structure and chemistry than mixtures of synthetic non-polar homopolymers [e.g., poly (α -olefins)]. All calculated spinodal curves described below refer to systems in which all association processes are promoted upon cooling, in accord with experimental observation for waters containing mixtures. An enhancement of the formation of associating clusters in low temperatures translates generally into negative values of both enthalpy and entropy of the chemical reactions of Eqs. (1) and (2) [i.e., ($\Delta h_{AA} < 0$, $\Delta s_{AA} < 0$), ($\Delta h_{CC} < 0$, $\Delta s_{CC} < 0$), ($\Delta h_{AC}^{(intra)} < 0$, $\Delta s_{AC}^{(intra)} < 0$), and ($\Delta h_{AC}^{(inter)} < 0$, $\Delta s_{AC}^{(inter)} < 0$)]. The analysis of the miscibility of liquids A and C begins from

considering a simple mixture of liquids A and C that form only a dimer AC, a system studied theoretically by Corrales and Wheeler.²³

A. Mixtures of monomeric liquids A and C that form dimers AC

When the stoichiometric indices p and q of the chemical reaction from Eq. (1) are both equal to unity ($p = q = 1$), and the second chemical process leading to the appearance of the higher order complexes $(AC)_k$ is absent, the equilibrium mixture is composed of dimers AC and unreacted monomers A_1 and C_1 . Because the formation of dimers AC is assumed to be promoted upon cooling ($\Delta h_{pq} = \Delta h_{AC}^{(intra)} < 0$, $\Delta s_{pq} = \Delta s_{AC}^{(intra)} < 0$), a binary mixture becomes completely miscible at low temperatures. Consequently, an upper critical solution temperature (UCST) phase diagram [reflecting the immiscibility of a mixture of two single bead *non-associating* molecules of species A and C over wide ranges of temperature and system’s composition (ϕ_A^o)] transforms into a closed loop phase diagram. Its UCST $T_c^{(up)}$ lies somewhat below the critical temperature T_c^o of our reference system of unassociating species A and C, while the lower critical solution temperature (LCST) $T_c^{(low)}$ (quantifying the improvement in miscibility due to the formation of a new species AC) very often lies not far $T_c^{(up)}$. Figure 3 illustrates this simple mechanism for the appearance of a reentrant type of phase diagram, denoted by the solid red curve and contrasted with the UCST phase boundary of a reference mixture (see the green curve). The symmetry of the phase diagrams in Fig. 3 follows from the specified identity of the molecular sizes for species A and C. The dotted red curve in Fig. 3 indicates further that the ability of dimers AC to form longer chain clusters leads only to a marginal improvement of miscibility when the free energy parameters for the chemical reactions of Eqs. (1) and (2) are taken for simplicity to be

FIG. 3. Spinodal curves calculated for a mixture of mutually associating liquids A and C (red curves) and for a mixture of nonassociating liquids A and C (green curve). The interaction parameter χ_{AC} of Eq. (23) is taken as $\chi_{AC} = 1000/T$ in all calculations in Figs. 3–15. The solid red curve corresponds to a mixture in which only dimers AC can form, while the dotted and dashed red curves refer to mixtures with polydisperse clusters $\{(AC)_k, k = 1, 2, \dots, \infty\}$. The free energy parameters governing the process of Eq. (1) are chosen as $\Delta h_{AC}^{(intra)} = -35$ kJ/mol and $\Delta s_{AC}^{(intra)} = -105$ J/mol K, whereas those driving the reaction of Eq. (2) are selected as $\Delta h_{AC}^{(inter)} = \Delta h_{AC}^{(intra)}$ and $\Delta s_{AC}^{(inter)} = \Delta s_{AC}^{(intra)}$ (dotted curve), and $\Delta h_{AC}^{(inter)} = -45$ kJ/mol and $\Delta s_{AC}^{(inter)} = \Delta s_{AC}^{(intra)}$ (dashed curve). The composition variable is chosen as the initial volume fraction ϕ_A^o of species A.

equal (i.e., when $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)}$ and $\Delta s_{AC}^{(intra)} = \Delta s_{AC}^{(inter)}$). However, if $|\Delta h_{AC}^{(inter)}| > |\Delta h_{AC}^{(intra)}|$ or $|\Delta s_{AC}^{(inter)}| < |\Delta s_{AC}^{(intra)}|$, an enhancement in miscibility, due to the switching on the second process, is noticeable (see, for instance, the red dashed curve in Fig. 3). Measurements indicate that the strength of the associative interactions between water and other polar solvents is often somewhat stronger than the hydrogen-bonding water-water interaction.^{74–77} Preferred binding between distinct molecular species is signaled by strong (temperature dependent) peaks in the concentration dependence of many properties of mutually associating fluid mixtures (e.g., dielectric constant and shear viscosity) near the stoichiometric concentrations where the bonding capacity of both types of molecules is optimally satisfied.³⁶

The three closed loop phase boundaries in Fig. 3 have been obtained by setting $\Delta h_{AC}^{(intra)} = -35$ kJ/mol and $\Delta s_{AC}^{(intra)} = -105$ J/mol K. An increase of $|\Delta h_{AC}^{(intra)}|$ or/and decrease of $|\Delta s_{AC}^{(intra)}|$ implies a higher equilibrium constant K for the reaction in Eq. (1), a higher concentration ϕ_{AC} of dimers AC , the shrinkage of a closed loop, and finally its vanishing, i.e., complete miscibility. Similar conclusions have been formulated by Corrales and Wheeler in their pioneering treatment of the phase transitions driven by a chemical reaction.

The size of a closed loop phase diagram is commonly expressed in terms of the difference ΔT_c between the upper (T_c^{upp}) and lower (T_c^{low}) critical temperatures. For an equilibrium mixture of the monomers A and C and the dimers AC , the difference ΔT_c satisfies the well-known empirical relation,

$$\Delta T_c / T_c^{doub} = \text{const} |\lambda - \lambda^*|^{1/2}, \quad (45)$$

where T_c^{doub} is the temperature corresponding to a “double critical point” in which the upper and lower critical temperatures coincide with each other, λ is the ratio of the enthalpy to the entropy of dimerization, $\Delta h_{AC}^{(intra)} / \Delta s_{AC}^{(intra)}$, and λ^* is the “critical” value of λ for which the critical temperatures T_c^{upp} and T_c^{low} become identical to the closed loop “double critical point” temperature T_c^{doub} .⁷⁸ Figure 4 presents the reduced temperature $\Delta T_c / T_c^{doub}$ as a function of $|\lambda - \lambda^*|^{1/2}$ for systems in which the absolute value of the enthalpy $\Delta h_{AC}^{(intra)} \equiv \Delta h$ is increased, while keeping the entropy $\Delta s_{AC}^{(intra)}$ constant and for the opposite where the absolute value of the entropy $\Delta s_{AC}^{(intra)} \equiv \Delta s$

FIG. 4. Graphical test of the validity of Eq. (45). The axis labels are explained in the text. Symbols are the results of calculations, and the lines are the least square fits to these results.

is decreased when $\Delta h_{AC}^{(intra)}$ is fixed. Figure 4 thus demonstrates the validity of the relation of Eq. (45). The symbols in Fig. 4 are the calculational data, and the lines indicate the least square fits. Blue and red symbols and lines correspond to different values of the interaction parameter, $\chi = 600/T$ and $\chi = 1000/T$, respectively. The validity of Eq. (45) extends further beyond the mixtures of two self- and mutually associating small molecule liquids that are examined in the current paper. In particular, our earlier studies reveal that Eq. (45) also applies to other mixtures exhibiting a closed loop phase behavior, such as solutions of a single self-associating species in a polymeric solvent or solutions of polymers solvated by a small molecule solvent.

B. Mixtures of monomeric liquids A and C that form complexes $\{(A_p C_q)_k, k = 1, 2, \dots, \infty\}$

1. The case of equal stoichiometric indices $p = q \neq 1$

When both p and q depart from unity, strong self associative interactions AA and CC are appended to the list of important variables governing the phase behavior of the system. Figure 5 presents the computed spinodal curves for binary mixtures of species A and C , with $p = q = 1, 2, 3$, and 4, when all strong interactions are taken as identical, i.e., $\Delta h_{AA} = \Delta h_{CC} = \Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = -35$ kJ/mol and $\Delta s_{AA} = \Delta s_{CC} = \Delta s_{AC}^{(intra)} = \Delta s_{AC}^{(inter)} = -105$ J/mol K. Unsurprisingly, increasing the chain length of an $A_p C_q$ “monomeric” unit (see Fig. 1) leads to the worsening of miscibility. In particular, the closed loop phase boundary becomes larger with an increase of p and q , and its shape resembles more a bell rather than a circle. More surprising, at first glance, is the appearance of two UCST branches in the regions of low temperatures and small initial concentrations ϕ_A^o and ϕ_C^o . A larger UCST branch corresponds to a larger $p = q$, which is understandable. The origin of each UCST immiscibility window lies in the influence of the self-association upon cooling on the phase behavior. More specifically, a UCST phase diagram is a typical phase behavior for a binary mixture of two self-associating components A and C or for solutions (in a non-associating solvent) of a single species that polymerizes upon cooling.²⁶ The miscibility

FIG. 5. Spinodal curves computed for mixtures of self- and mutually associating liquids A and C where polydisperse clusters $\{(A_p C_q)_k\}$ form. Different curves correspond to different stoichiometric indices p and q . The free energy parameters are chosen as common for all pairs p and q , and equal $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = \Delta h_{AA} = \Delta h_{CC} = -35$ kJ/mol and $\Delta s_{AC}^{(intra)} = \Delta s_{AC}^{(inter)} = \Delta s_{AA} = \Delta s_{CC} = -105$ J/mol K.

FIG. 6. Spinodal curves computed for mixtures of self- and mutually associating liquids A and C where polydisperse clusters $\{(A_5C_5)_k\}$ form. The free energy parameters are the same as those used in Fig. 5. Spinodal curves corresponding to mixtures of polydisperse clusters with $p = q = 1$ and $p = q = 2$ are included for comparison.

window in the region of low temperatures and not very different initial concentrations for the two components (see Fig. 5) arises from the facilitated formation of $(A_pC_q)_k$ clusters in this regime. Figure 6 demonstrates that further increasing of $p = q$ magnifies immiscibility through the merging of a closed loop portion of the phase diagram with its two low temperature UCST branches. A miscibility window is maintained for similar volume fractions ϕ_A^o and ϕ_C^o .

While Figs. 5 and 6 illustrate general miscibility trends induced by the variation of $p = q$ for fixed $\overline{\Delta h} \equiv \Delta h_{AA} = \Delta h_{CC} = \Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = -35$ kJ/mol and $\overline{\Delta s} \equiv \Delta s_{AA} = \Delta s_{CC} = \Delta s_{AC}^{(intra)} = \Delta s_{AC}^{(inter)} = -105$ J/mol K, Fig. 7 presents the spinodals computed for fixed $p = q = 2$ but variable $\overline{\Delta h}$ ranging from -35 kJ/mol to -45 kJ/mol. A higher $\overline{\Delta h}$ similarly implies a higher Δh for mixtures with $p = q = 1$, a smaller closed loop portion of the phase diagram (i.e., an improvement of miscibility at high temperatures), and a larger UCST branch (i.e., a reduction of miscibility at low temperatures due to the formation of long chains that typically prefer not to mix). Figure 7 also includes the spinodal curve (dashed blue curve) for a special limiting case where $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)}$

FIG. 7. Spinodal curves for mixtures of self- and mutually associating liquids A and C where polydisperse clusters $\{(A_2C_2)_k\}$ form, as computed for different sets of the free energy parameters of the reaction of Eqs. (1) and (2). The red, green, and blue solid curves correspond to $\overline{\Delta h} \equiv \Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = \Delta h_{AA} = \Delta h_{CC}$ equal -45 kJ/mol, -40 kJ/mol, and -35 kJ/mol, respectively. The dashed blue curves refer to $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = -35$ kJ/mol and vanishing Δh_{AA} and Δh_{CC} (i.e., $\Delta h_{AA} = \Delta h_{CC} = 0$). The entropy parameters of the reactions of Eqs. (1) and (2) are the same as those used in Figs. 5 and 6.

FIG. 8. Spinodal curves for mixtures of self- and mutually associating liquids A and C where polydisperse clusters $\{(A_pC_q)_k\}$ form. Different curves refer to different stoichiometric indices p and q . The free energy parameters are the same as those used in Figs. 5 and 6.

$= -35$ kJ/mol, but both Δh_{AA} and Δh_{CC} are set to zero. The comparison between the spinodal corresponding to $\overline{\Delta h} = -35$ kJ/mol (see the solid blue curve in Fig. 7) and the spinodal referring to $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = -35$ kJ/mol and $\Delta h_{AA} = \Delta h_{CC} = 0$ (see the dashed blue curve in Fig. 7) indicates that even very weak self-associating energetic interactions AA and CC do not eliminate immiscibility at low temperatures. In fact, the UCST for the latter case (dashed blue curve) exceeds that for the former case (solid blue curve).

2. The case of unequal stoichiometric indices $p \neq q$

Different stoichiometric indices p and q and different Δh_{AA} from Δh_{CC} (or Δs_{AA} from Δs_{CC}) arise from the different molecular structure and size of the mixture components. Figure 8 displays a few examples of spinodal curves for mixtures specified by the same $\overline{\Delta h} = -35$ kJ/mol and the same $\overline{\Delta s} = -105$ J/mol K but different pairs of p and q . The phase boundaries in Fig. 8 are amalgamations of a closed loop and a single UCST phase diagram. If p exceeds q , the UCST diagram located in the composition range corresponding to the minority of component A combines with the closed loop, while the

FIG. 9. Spinodal curves for mixtures of self- and mutually associating liquids A and C where polydisperse clusters $\{(A_3C_2)_k\}$ form, as computed for different sets of the free energy parameters of the reactions of Eqs. (1) and (2). The green and red curves correspond to the free energy parameter sets $\overline{\Delta h} = -48$ kJ/mol and -45 kJ/mol, respectively, while the blue curve refers to $\Delta h_{AC}^{(intra)} = \Delta h_{AC}^{(inter)} = -35$ kJ/mol and $\Delta h_{AA} = \Delta h_{CC} = -48$ kJ/mol. The entropy parameters are common for all curves and equal to those used in Figs. 5 and 6.

other one vanishes (see Figs. 7 and 8), and vice versa if $p < q$. Different stoichiometric indices p and q can also lead to a closed loop that is separated from a UCST branch of the phase diagram. Examples of such behavior are presented in Fig. 9 which exhibit the spinodals for fixed $p = 3$ and $q = 2$ and two various values of Δh (see red and green curves in the figure). The asymmetry of each of these two portions of the phase diagram increases when the mutual- and self-interactions are different (see blue curves in Fig. 9 and the figure caption) and, of course, when the self-interaction free energy parameters Δh_{AA} and Δs_{AA} vary, respectively, from Δh_{CC} and Δs_{CC} .

IV. CALCULATIONS OF SECOND OSMOTIC VIRIAL COEFFICIENTS $B_2^{(A)}$ AND $B_2^{(C)}$

Many polymer systems exhibiting a closed loop phase diagram, such as solutions of a self-associating species in a polymer matrix and solvated polymers in single or mixed small molecule solvents, exhibit a strong correlation between miscibility and the second osmotic virial coefficient B_2 . In particular, miscibility and immiscibility occur, respectively, at temperatures for which B_2 is positive and negative, and the theta temperatures (i.e., the temperatures where B_2 vanishes) are the limits approached by the corresponding critical temperatures when the polymerization index N of the polymer becomes very large ($N \rightarrow \infty$). This behavior does not appear for mixtures of two self- and mutually associated (A and C), in spite of the fact that long chain polymer clusters often form. Figure 10 demonstrates, for instance, that B_2 for these mixtures ($p = q = 1$) is a monotonic function of the absolute temperature T , including the temperature regime where the spinodal curves have a closed loop shape (see Fig. 3 or 5). Moreover, when q exceeds 2, two additional theta temperatures arise and these theta temperatures lack counterparts in the critical temperatures (see Fig. 9 where the spinodal curves exhibit only a single critical temperature).⁷⁹ In order to understand this initially unexpected behavior, we refer to our earlier calculations for solutions of a single self-associating species in a

FIG. 10. The second osmotic virial coefficient $B_2^{(C)}$ for the infinitely dilute self-associating liquid A in the self-associating liquid C (that also associates with the component A) as a function the absolute temperature T . Different curves refer to different numbers q of the molecules of liquid C in the basic cluster $A_{p=1}C_q$, as indicated in the figure. The stoichiometric index p for the number of molecules A in this cluster is always equal to one. The black curve corresponds to mixtures of nonassociating liquids A and C . The free energy parameters are the same as those used in Fig. 5.

FIG. 11. The second osmotic virial coefficient $B_2^{(C)}$ for the infinitely dilute self-associating liquid A in a self-associating liquid C (that also associates with the component A) as a function the absolute temperature T . Solid and dashed curves refer, respectively, to the two-step association model [see Eqs. (1) and (2) and Fig. 10] and to the single step association model where AC dimers do not polymerize further between themselves.

one-bead (monomeric) solvent. The calculations indicate that indeed the critical solution temperature T_c for these systems approaches the theta temperature T_θ^o for the bare mixture (i.e., devoid of associative interaction) when association becomes very strong, i.e., $|\Delta h|$ is very large (or $|\Delta s|$ is very small), and consequently long chain polymeric clusters are dominant. On the other hand, strong association, however, implies the vanishing of the closed loop immiscibility region, i.e., thus promoting complete miscibility.

The presence of the further polymerization of $A_{p=1}C_q$ clusters seems to be necessary to ensure that the second osmotic virial coefficients $B_2^{(C)}$ become negative at low temperatures for arbitrary q . Figure 11 demonstrates, for instance, that the absence of mutual associative interactions between $A_{p=1}C_q$ clusters leads to rather unphysical behavior where $B_2^{(C)}$ becomes positive at the low temperature regime.

V. ENTROPY-ENTHALPY COMPENSATION

Equations (26) and (28) enable the evaluation of the specific internal energy of mixing, Δu_{mix} , and the specific entropy of mixing, Δs_{mix} , for a binary mixture of self- and mutually-associating liquids, A and C . These two quantities represent the enthalpy and the entropy of dissolution of one liquid in another. Illustrative calculations of Δu_{mix} and Δs_{mix} have been performed for a mixture of the species A and C which can form clusters $\{(A_pC_q)_k, k = 1, 2, \dots, \infty; p = q = 1\}$ upon cooling, and these mixture often exhibit a closed loop type of phase boundary (see the dotted red curve in Fig. 3). Figures 12 and 13 depict Δu_{mix} plotted against Δs_{mix} at fixed temperatures T in the low and high temperature regimes, respectively. Each curve in Figs. 12 and 13 covers the whole composition range from $\phi_A^o = 0.01$ to $\phi_A^o = 0.99$. The analysis of Figs. 12 and 13 reveals that a linear variation of Δu_{mix} with Δs_{mix} appears only in the low temperature regimes, where the mutual association of both species dramatically improves their miscibility. The linearity of these plots is a clear manifestation of the entropy-enthalpy compensation phenomenon.⁵⁵ Notice that this compensation effect is predicted to vanish above the lower critical temperature, $T_c^{(low)} = 354$ K, where the mixture becomes immiscible (in a

FIG. 12. The dimensionless specific internal energy of mixing, $\Delta u_{mix} = \Delta U_{mix}/(N_I k_B T)$, plotted vs. the dimensionless specific entropy of mixing, $\Delta s_{mix} = \Delta S_{mix}/(N_I k_B)$, as computed for a binary mixture of two mutually associating liquids at constant temperature (the low temperature regime $250 \text{ K} \geq T \geq 350 \text{ K}$). The free energy parameters for the reactions of Eqs. (1) and (2) are identical to those corresponding to the dotted spinodal curve in Fig. 3, and are also kept, as the stoichiometric indices $p = 1$ and $q = 1$, the same in all Figs. 12–15. The composition of the mixture along each line changes from $\phi_A^o = 0.01$ to $\phi_A^o = 0.99$.

certain concentration range around $\phi_A^o = 0.5$) and also above the upper critical temperature T_c^{up} where the mixture is again miscible.

A more complete investigation of the entropy-enthalpy phenomenon illustrated in Figs. 12 and 13 also requires plotting Δu_{mix} versus Δs_{mix} for mixtures at constant compositions ϕ_A^o . These plots in Figs. 14 and 15 refer to roughly symmetric and nonsymmetric mixture compositions, respectively. The figures demonstrate unequivocally that the best linearity of the plots of Δu_{mix} versus Δs_{mix} exists for the symmetric composition $\phi_A^o = 0.5$ of the system. When the composition departs more from this symmetric value, the range of Δs_{mix} for which the plots are linear shrinks (see Fig. 14). On the other hand, mixtures with a significant asymmetry between the volume fractions of the two components exhibit nonlinear variations of Δu_{mix} with Δs_{mix} (see Fig. 15). The plots in Figs. 14 and 15 remain in full agreement with those in Figs. 12 and 13, thereby confirming that the entropy-enthalpy compensation is due to the presence of mutual association.

FIG. 13. The dimensionless specific internal energy of mixing, Δu_{mix} , plotted vs. the dimensionless specific entropy of mixing, Δs_{mix} , as computed for a binary mixture of two mutually associating liquids at constant temperature (in the high temperature regime $375 \text{ K} \geq T \geq 500 \text{ K}$). The mixture composition along each curve changes from $\phi_A^o = 0.01$ to $\phi_A^o = 0.99$.

FIG. 14. The dimensionless specific internal energy of mixing, Δu_{mix} , plotted vs. the dimensionless specific entropy of mixing, Δs_{mix} , as computed for a binary mixture of two mutually associating liquids at constant composition near the symmetrical composition $\phi_A^o = 0.5$.

FIG. 15. The dimensionless specific internal energy of mixing, Δu_{mix} , plotted vs. the dimensionless specific entropy of mixing, Δs_{mix} , as computed for a binary mixture of two mutually associating liquids at constant composition varying significantly from the symmetrical composition $\phi_A^o = 0.5$.

Additional calculations indicate that allowing the stoichiometric indices p and q to depart from unity and to be distinct does not introduce new qualitative features to those illustrated in Figs. 11–15 except that the best linearity of plots of Δu_{mix} versus Δs_{mix} no longer appears for the composition $\phi_A^o = 0.5$, and plots for constant $\phi_A^o = 0.5 - a$ and $\phi_A^o = 0.5 + a$ (see Fig. 14) are not identical.

VI. DISCUSSION

Our theory for binary mixtures of self- and mutually-associating small molecule liquids is derived in the spirit of the FH mean field approximation, which implies the neglect of all non-random mixing effects stemming from the coupling between strong and weak interactions and from correlations between these interactions and the molecular structure of the associative clusters. Deficiencies in this theory are minimized by treating the free energy parameters of the association reactions as adjustable parameters. The insensitivity of the equilibrium distribution of the clusters arising from associative interactions to the van der Waals interaction energies is another theoretical simplification and stems from our assumption that each van der Waals interaction energy $\epsilon_{\beta\gamma}$ depends only on the types of the nearest-neighbor segments β and γ ,

regardless of the individual chemical species to which these two segments belong. Despite these simplifying approximations, the theory is able to predict a rich phase behavior for these binary mixtures and general trends in their thermodynamic properties that are at least qualitatively validated by experiments.

The self-association and mutual-association of molecules in real mixtures of liquids *A* and *C* are characterized by rather greatly different stoichiometric indices *p* and *q* in the “monomeric” cluster $A_p C_q$, unsymmetric self-association free energy parameters for the components of the mixture, $\Delta h_{AA} \neq \Delta h_{CC}$ and $\Delta s_{AA} \neq \Delta s_{CC}$, as well as by different free energy parameters for the mutual association inside individual complexes $A_p C_q$ and between them, $\Delta h_{AC}^{(inter)} \neq \Delta h_{AC}^{(intra)}$ and $\Delta s_{AC}^{(inter)} \neq \Delta s_{AC}^{(intra)}$. In addition, both $\Delta h_{AC}^{(intra)}$ and $\Delta h_{AC}^{(inter)}$ generally depart from the parameters used to specify the self-associations, i.e., from Δh_{AA} and Δh_{CC} , and likewise both $\Delta s_{AC}^{(intra)}$ and $\Delta s_{AC}^{(inter)}$ depart from Δs_{AA} and Δs_{CC} . Our theory for these binary mixtures predicts a closed loop phase diagram in the high temperature regime and a single UCST branch in the low temperature regime. This UCST branch typically appears in the region of unsymmetrical compositions of the mixture, similar to a UCST phase diagram for solutions of a single self-associating species in a nonassociating solvent. Experiments for aqueous mixtures over a large range of temperatures are limited because of crystallization and vaporization of water at low and high temperatures, which can make either the closed loop or the UCST branch inaccessible to measurement. Adding salt and polymers, however, can be expected to make these complex phase boundaries more detectable.⁸⁰ For example, we suggest that the lack of an appearance of a UCST branch in the experimental studies of phase separation in mixtures of water and other hydrogen-bonding liquids by Sengers and co-workers⁵¹ is due to the limited temperature range investigated. Anderson and Wheeler have also predicted the UCST phase boundary below the closed loop phase boundary in an Ising model of phase separation in mixed associating solvents.⁵⁰

Although experimental evidence exists that hydrogen bonding fluids form dynamic polymer chains of molecules, there is no reason to expect linear chain association to be a *universal mode* of molecular assembly in mixtures of real hydrogen bonding fluids. The assignment of the topological form of clusters is normally difficult based on experimental data, and the assignment of the particular type of clustering is correspondingly often controversial.⁸¹ For example, many studies suggest that water tends to form a branched dynamic polymer network rather than chains having a linear chain topology.⁸² Yet, even though this fluid has been exhaustively studied, some authors argue for a prevalent linear chain association in view of x-ray scattering measurements.⁸³ Fortunately, past computational studies indicate that the phase behavior and the molecular clustering transitions of both linear and branched chain associating fluids display similar patterns of thermodynamic phase behavior when the associating molecules having both van der Waals and directional associative interactions.⁸⁴ We thus expect similar general thermodynamical trends for fluids exhibiting linear or branched self-assembly.

We also examine the thermodynamics of mixtures of two associating solvents with an emphasis on gaining insights into the “hydrophobic effects.” The general tendency of mixtures of water with other associating liquids to exhibit closed loop phase boundaries, as discussed by Widom *et al.*,³⁷ naturally explains the observation of non-monotonic changes in the miscibility of aqueous mixtures displaying the hydrophobic effect. Our FH type theory for associating mixtures often predicts this kind of phase boundaries as a consequence of the competition between association of the components of the mixture and the weaker van der Waals interactions of solvent molecules. This aspect of the phenomenology of the “hydrophobic effect” is also exhibited rather universally by ions dissolved in water⁸⁵ and is captured by our theory of mixed associating fluids.

We also consider other intrinsic features of the thermodynamics of mixing associating fluids with water. In particular, entropy-enthalpy compensation is often observed in a low temperature regime where the fluids are miscible, while at the same time they exhibit appreciable self- and mutual-association, yielding “micro-segregated” fluid structures that are relatively large in scale in comparison to the size of the solvent molecules. Competitive self- and mutual-association and fluid heterogeneity are naturally consequences of these interactions and appear to be essential features of the thermodynamics of aqueous solutions. This large scale heterogeneity is quite apparent in neutron, x-ray, and static scattering measurements for small molecule associating fluid mixtures where the existence of these dynamic clusters leads to critical scattering properties similar to those observed in polymer blends.^{30–33,86}

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- ⁶²The expression for u in Eq. (22) also contains terms $-(1/2)z\phi_A^o\epsilon_{AA}/k_B T$ and $-(1/2)z\phi_C^o\epsilon_{CC}/k_B T$ which can be omitted by setting $\epsilon_{AA} = \epsilon_{CC} = 0$ and expressing the magnitude of energy ϵ_{AC} relative to this reference state.
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- ⁶⁴The reactions for the free association model can be written in a more general way to permit chain growth to proceed by the addition of a single monomer or by the linkage of two chains. Similarly, chains may break in the middle, or segments may dissociate from the chain ends (see Ref. 26).
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