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Solubility Limits in Lennard-Jones Mixtures: Effects of Disparate Molecule Geometries

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Abstract

In order to better understand general effects of the size and energy disparities between macromolecules and solvent molecules in solution, especially for macromolecular constructs self-assembled from smaller molecules, we use the first- and second-order exact bridge diagram extensions of the HNC integral equation theory to investigate single-component, binary, ternary, and quaternary mixtures of Lennard-Jones fluids. For pure fluids, we find that the HNCH3 bridge function integral equation (i.e., exact to third order in density) is necessary to quantitatively predict the pure gas and pure liquid sides of the coexistence region of the phase diagram of the Lennard-Jones fluid. For the mixtures, we find that the HNCH2 bridge function integral equation is sufficient to qualitatively predict solubility in the binary, ternary, and quaternary mixtures, up to the nominal solubility limit. The results, as limiting cases, should be useful to several problems, including accurate phase diagram predictions for complex mixtures, design of self-assembling nanostructures via solvent controls, and the solvent contributions to the conformational behavior of macromolecules in complex fluids.

INTRODUCTION

In molecular aggregation, especially peptide and protein aggregation in solution, one of the central, physically interesting elements entering into the fundamental mechanism is the size disparity between the polymers or aggregates and the (presumed) aqueous solvent. For this work, we use simple model mixtures for studying relative solute size and energy scaling in solution. We are concerned with the problem of crowded biomolecules in solution. The effective solute radius is central, however, to a variety of subtle chemical and physical

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Notes

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effects, e.g., polarity scales in chromophore probes of solvation dynamics.¹ We consider the problem where the mean radius of a solute is on the order of several solvent molecules. For aqueous solutions, we would be interested in solutes with a mean radius on the scale of a nanometer, or approximately 3 water molecules. This is the approximate scale at which the xRISM molecular integral equation approach becomes numerically unstable, as the number of sites in the solute begins to be large in comparison to the bulk solvent.

We calculate the chemical potentials of each species for a set of binary, ternary, and quaternary mixtures. The first result is that, while the chemical potentials of different energy species with the same size shifts in tandem as a function of total solute concentration, the relative solubilities can be changed dramatically by size disparities between solute species. This results in predicted crossover effects in solubility free energies of ternary and higher-order mixtures. This is an equilibrium effect that echoes the crossover in solvation dynamics observed by Ladanyi and co-workers for water–methanol² and benzene–acetonitrile mixtures.³

We use the HNCH2 and HNCH3 integral equations^{4,5} in this work. We compare a path-dependent excess chemical potential appropriate to theories with bridge diagrams, using the Widom charging-integral approach⁶ of Singer and Chandler.⁷ We compare with the form of Attard.⁸ We examine the numerical results for pure fluids and find that the excess chemical potential predicted for the bridge function theories quantitatively reproduces the simulation results for the model system. Furthermore, the resulting predictions for the extent of the pure gas and pure liquid sides of the phase diagram, up to the region of the coexistence boundaries, also comes within the bounds for the known results for the model.

MODEL AND THEORETICAL FOUNDATION

For this article, we work with the standard Lennard-Jones (LJ) form

$$U_{ij}(r) = 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r} \right)^{12} - \left(\frac{\sigma_{ij}}{r} \right)^6 \right] \quad (1)$$

for the potential of interaction between a molecule of species i and species j separated by distance r . The energy and radius parameters, ϵ_{ij} and σ_{ij} , for interspecies interactions are determined from the standard Lorentz–Berthelot mixing rules. In all cases examined here, the solute species parameters are scaled with respect to the solvent parameters, i.e., the basic length scale is the σ_{solvent} distance, and the energy scale is measured from $\epsilon_{\text{solvent}}$.

Initially, this work began by attempting to build on the works in the literature dealing with mixtures of molecular model systems, especially the work of Patey⁹ et al. on the effects of size and shape asymmetry^{10–12} and Wilding¹³ on Lennard-Jones mixtures. Our initial goal was to investigate the Lennard-Jones (LJ) mixtures for which the solute–solvent size ratio was representative of that for small polymer/polypeptide aqueous solutions. What we found on initial investigation was that the numerical stability of integral equation methods for Lennard-Jones mixtures was dependent on, in addition to standard numeric considerations, the relative energy of the solute molecule interactions, especially as the size ratio of solute to solvent grows large. This is recognized in standard model construction, where the n -alkane

series requires increasing Lennard-Jones energies as the chain length grows.¹⁴ In order to help understand more complicated solvation thermodynamics¹⁵ and phase behavior¹⁶ as a consequence of the solute–solvent interaction energies, we found it necessary to first examine a range of the LJ fluid two-, three-, and four-component mixtures as a function of the energy and size differences between solutes.

These studies should have some direct utility in detailed molecular studies, due to Friedman and Ramanathan,^{17,18} although the general idea they followed from Gurney¹⁹ and Frank²⁰ is connected conceptually to the Born model of solvation. The idea is that, rather than focusing exclusively on the interactions of the individual molecular types, solute to solvent, the solute molecule can be generalized to include its local solvation layer, out to a radius where the collection is effectively a spherically symmetric molecule.

METHODS

Thermodynamic Measures and Generating Equations

For this work, we use the integral equation theories previously labeled as HNCH2 and HNCH3 for radially symmetric model liquids. These equations are based upon the standard HNC integral equations, with bridge function corrections exact to ρ^2 and ρ^3 (ρ , the number density), respectively. The exact formal expression for the radial distribution functions of a mixture is given by^{21,22}

$$g_{ij}(r) = \exp(-\beta U_{ij}(r) + t_{ij}(r) + b_{ij}(r)) \quad (2)$$

where $U_{ij}(r)$ is the model potential between a single molecule of species i and one of species j , $t_{ij}(r)$ is the indirect correlation function constructed from the relation $h_{ij}(r) = g_{ij}(r) - 1 = t_{ij}(r) + c_{ij}(r)$, and the Ornstein–Zernike (OZ) equation defines the direct correlation functions

$$h_{ij}(r) = c_{ij}(r) + \sum_l \int d\mathbf{r}' c_{il}(\mathbf{r}') \rho_l h_{lj}(|\mathbf{r}' - \mathbf{r}|) \quad (3)$$

The bridge functions, the $b_{ij}(r)$ functions in eq 2, determine the level of approximation. The familiar HNC approximation sets $b_{ij}(r) = 0$. The PY approximation takes $b = 0$ and then linearizes the resulting closure equation with respect to $t_{ij}(r)$. The general form of the bridge functions is known term-by-term as a series of increasingly complex many-body integrals. The HNCH2 and HNCH3 equations are constructed using the first and second sets of bridge diagram integrals self-consistently, approximating $g_{ij}(r)$ up to order ρ^1 for the HNC approximation, order ρ^2 for the HNCH2 approximation, and order ρ^3 for the HNCH3 approximation. For single-component systems and binary mixtures, these approximations have been shown to be indistinguishable from the simulation results for single-component fluids and sufficiently close to the simulation results for mixtures that higher-order approximations (exact to ρ^4 and so on) would be prohibitively expensive in comparison to the additional accuracy gained, although recent work by Kofke and co-workers²³ shows that the computational accessibility of these higher-order approximations is increasing quickly.

For this work, we model a solvent mixture with a solute density varying from zero to the nominal, numerically stable limit for the particular level of theory. For mixtures, the thermodynamic results that we use to quantify the results are^{24,25} the excess energy

$$\frac{\beta U^{\text{ex}}}{N} = 2\pi\rho \sum_{ij} \int d\mathbf{r} \chi_i u_{ij}(r) g_{ij}(r) \chi_j \quad (4)$$

where χ_i is the mole fraction of species i , and ρ is the total number density of the system, the pressure from the virial route

$$\frac{\beta P}{\rho} = 1 - \frac{2\pi}{3} \rho \sum_{ij} \int d\mathbf{r} \chi_i r \frac{\partial u_{ij}(r)}{\partial r} g_{ij}(r) \chi_j \quad (5)$$

the Kirkwood–Buff theory G integral

$$G_{ij} = \int d\mathbf{r} h_{ij}(r) \quad (6)$$

the isothermal compressibility

$$\sum_{ij} \chi_i \tilde{c}_{ij}(k=0) \chi_j = 1 - \frac{\kappa_T^0}{\kappa_T} \quad (7)$$

and the chemical potential.

The usual form of the excess chemical potential, $\beta\mu^{\text{ex}}$, for the HNC closure has been well-known for some time, having been derived for general atomic model systems by Morita and Hiroike²⁶ and for ISM molecular systems by Singer and Chandler. For the HNC theory, the standard form is

$$\beta\mu^{\text{ex}} = \int d\mathbf{r} \left[\frac{1}{2} h^2(r) - \frac{1}{2} h(r) c(r) - c(r) \right] \quad (8)$$

We consider a form

$$\beta\mu^{\text{ex}} = \int d\mathbf{r} \left[\frac{1}{2} h^2(r) - \frac{1}{2} h(r) c(r) - c(r) + b(r) \right] \quad (9)$$

The derivation of this equation is presented in the Appendix. We compare $\beta\mu^{\text{ex}}$ from these equations with the form that includes the terms proportional to hb as found in the work of Attard and to simulation.

In either case, the general bridge function contribution to the chemical potential result was originally foreshadowed by the work of Ng.²⁷ We note that using the charging integrals directly would still be required if the bridge functions were not the exact bridge diagram series as derived from the partition function in conjunction with the OZ equation, and neither our eq 9 nor that of Attard would be directly applicable without modification appropriate to the particular theory considered.²⁸

Numerical Considerations

The basic numerical approach used here has been detailed previously. To summarize, we use standard finite grid techniques for the integral equation methods. Specifically, we employ the fast Fourier transform approach for the convolution solution to the OZ/closure equations and Gauss–Legendre quadrature for the evaluation of the bridge diagram integrals of the HNCH2/HNCH3 approximations. The numerical grids for the integral equation system solutions were systematically investigated such that a standard grid of 2048 points over a $15\sigma_{\text{solvent}}$ range ($dr = 0.007$) yielded consistent numerical convergence for all systems investigated. For the mixture systems, we use the Lorentz–Berthelot potential parameter mixing rules, and we use the notation σ_{solvent} to refer to the solvent–solvent radius and σ_{solute} to refer to the solute–solute radius and similarly for the $\epsilon_{\text{solvent}}$ and ϵ_{solute} parameters. The densities ρ_{solvent} and ρ_{solute} are usually referred to with those labels, and ρ_{solute} is usually the sum total of all solute densities in the system. Additionally, we use $\rho_1, \rho_2, \dots$, etc. to refer to the individual solute species in a given mixture.

The numerical convergence of the systems of equations couples the OZ equation and the self-consistent bridge functions. The HNCH2 and HNCH3 approximations couple 2 and 3 hierarchies of integral equations, respectively. As such, we use the standard iterative relaxation Picard method for each equation in turn

$$f(i) = (1.0 - x) f(i) + x f(i - 1) \quad (10)$$

where x is here the relaxation mixing parameter (we use 0.7 throughout), i is the iteration, and $f(i)$ is the specific pair function, with $t(r)$, $D^{(2)}(r)$, and $D^{(3)}(r)$ being iterated. We iterate each level of the hierarchy from $D^{(3)} \rightarrow D^{(2)} \rightarrow t(r)$. That is, we hold $D^{(2)}$ and $D^{(3)}$ constant while iterating $t(r)$ to convergence, then recalculate $D^{(2)}$ with the new $h(r)$, and mix $D^{(2)}$ according to eq 10. This $D^{(2)} \rightarrow t(r)$ cycle is, in turn, iterated over with $D^{(3)}$ constant until the numerical and thermodynamic measures of the various $h(r)$, $t(r)$, and $c(r)$ intermediate functions converge to acceptable tolerances, and then finally a new $D^{(3)}$ function is computed, the new $D^{(3)}$ is mixed as for eq 10, and the entire cycle is repeated.

In all cases reported, the numerical behavior of the pair functions generated was stable, although we do not attempt here to directly calculate the critical point or coexistence regions. In the theories examined here, the HNCH3 theory was the only one for which coexistence and critical behavior could be reasonably inferred. However, in that case, within the presumed coexistence region, we could not reliably generate solutions that uniformly satisfied convergence across all chosen thermodynamic measures.

Stability of the solutions, and overall convergence, was evaluated using standard measures for integral equations.^{29,30} First, the root-mean-squared difference between iterations of each function was measured directly. We found in particular that the OZ/closure cycle required $t(r)$ to single precision convergence for systematic stability across the entire phase diagram such that 10 000 iterations of each OZ/closure step in the bridge diagram iterations was necessary. This was reinforced by requiring that a solution to the cycle of equations at a particular phase point be stable as an initial value at a neighboring phase point. A standard OZ/closure cycle of 1000 iterations was found to be insufficient to continuously generate a

full set of points on the phase diagram, whereas the 10 000 OZ iterations yielded consistent stability to the neighboring (initial) value problem throughout the investigated systems.

We also used the various thermodynamic measures of the system to evaluate the relative convergence of each cycle and stability of the solutions, especially those integrals which complement the Fourier transform methods. We considered solutions to be numerically acceptable when all of the thermodynamic measures converged simultaneously. In the cases where one or more thermodynamic terms converged, but others did not, especially the isothermal compressibility and pressure (i.e., the mechanical variables), we rejected the solution.

Each of the compositional integrals chosen, chemical potential, compressibility, and Kirkwood G, can be written directly in terms of the limit as $k = 0$ of the Fourier transforms of the various functions and thus serve as direct measures of the numerical combinations of the pair functions as well as their thermodynamic limits. This provides a direct thermodynamic and numerical consistency check on the solutions at any given phase point. All results reported here are self-consistent as measured by the isothermal compressibility in combination with the other thermodynamic measures in this way. All results reported are found to be stable and smoothly convergent as measured by the other thermodynamic measures, with the exception of the HNCH3 theory in the critical and coexistence regions, as discussed below. In these regions with the HNCH3 theory, we find the various thermodynamic measures to be well-converged for any particular iteration while showing strong discontinuities between iterations. That is, the values measured for, e.g., the compressibility bounce between values for different iterations. The variations in the distribution functions between iterations are consistent with the presence of multiple solutions, as is generally considered to be present in the coexistence regions.

For the pure fluids, we use the standard reduced units, $\rho^* = \rho\sigma^3$ and $T^* = k_B T/\epsilon$, throughout.

In the mixtures, we use $\rho^* = \sum_i \rho_i \sigma_{\text{solvent}}^3$ and $T^* = k_B T/\epsilon_{\text{solvent}}$, with the solvent σ and ϵ as the reference scale throughout. Here and throughout,³¹ the total chemical potential is taken to be $\beta\mu = \beta\mu^{\text{ex}} + \ln \rho^*$, with the thermal wavelength, $\Lambda^3 = 1$. As Attard points out, the thermal wavelength sets an arbitrary zero of energy for $\beta\mu$ measurements at the same temperature. Alternatively, since the length scale σ is arbitrary, $\rho^* = \rho\Lambda^3$.

RESULTS

Pure Lennard-Jones Fluid

First, we present results for the chemical potential of the pure Lennard-Jones fluid, as a calibration. The structural, energy, and pressure results for the HNCH2 and HNCH3 approximations are known. Here, we report the $\beta\mu = \beta\mu^{\text{ex}} + \ln \rho^*$ results using the same approximations. Since the HNCH3 approximation requires a nontrivial computational investment, our ρ grids for the pure fluid here are spaced at $\sim \delta\rho = 0.1$, using the simulation results of Attard as a basis for comparison. We will refine these results in later work devoted to examining phase stability in detail.

In Figure 1, we compare the total $\beta\mu$ results of the HNC, HNCH2, and HNCH3 approximations for the pure Lennard-Jones fluid as a function of ρ^* at $T^* = 1.0$, in comparison with the simulation results of Attard at the same temperature point. (Figure 2 compares the different routes for calculating the chemical potentials of the Lennard-Jones fluid for the HNCH3 level theory and the results for simulation and HNC theory.) As with the previous thermodynamic and structural results, the improvement on including more exact bridge functions is significant. At all densities examined, the HNCH2 and HNCH3 approximations using eq 9 provide upper and lower bounds, respectively, for the simulation results.

We take advantage of this improvement to examine the approach to the gas–liquid coexistence curve of the pure LJ fluid. In Figure 3, we plot the total chemical potential for the pure LJ fluid as a function of density at the temperature points $T^* = 1.08, 1.18$, and 1.38 . If we use the Gibbs rules for the chemical potential, i.e., that a multiphase system of a pure fluid is present where the chemical potential is double-valued ($\beta\mu_{\text{gas}} = \beta\mu_{\text{liquid}}$ in this case), then we observe from the results of Figure 3 that the HNCH2 theory does not predict gas–liquid coexistence and, consequently, the approximation does not show a gas–liquid critical point, at the numerical resolutions used here. This mirrors the accepted results of the HNC and PY approximations, which are now accepted as failing to comprehensively predict gas–liquid phase transitions.

The HNCH3 approximation, however, does predict both a gas–liquid coexistence and the gas–liquid critical region, as demonstrated in Figure 4, for the $T^* = 1.25, 1.45$, and 1.85 points, as well as in Figure 5, where the isothermal compressibility, χ_T , is used as the mechanical measure of the system at $T^* = 1.25, 1.45$, and 1.85 . The compressibility (often as χ_T^{-1}) is usually used in measuring the phase behavior of integral equation theories, since it is expected to exhibit infinite compressibility (singular χ_T^{-1} behavior) at the coexistence boundaries. We point out that $\beta\mu(\rho^*)$ is double-valued around and below $T^* \simeq 1.45$, demonstrating gas–liquid coexistence via the Gibbs relation, but not above, indicating a critical temperature.

The HNCH3 χ_T and $\beta\mu$ curves for $T^* = 1.25$ are discontinuous across the known coexistence region for the Lennard-Jones fluid, where we were unable to find self-consistent, numerically stable solutions. Further work will be necessary to refine the numerical predictions in these approximations, especially devoted to elucidating the precise nature of the compressibility discontinuities in terms of phase-transition theory, but, for our present purposes, the results are sufficient to demonstrate that the HNCH3 approximation produces gas–liquid coexistence for the LJ fluid in reasonable agreement with the known behavior for the model.

Mixtures

For the mixture calculations, we will use the HNCH2 approximation. This is a compromise between the HNC and HNCH3 methods as the computational work increases geometrically with the number of species in a given mixture. As a consequence, we concentrate on broad features of the mixture phase diagrams and save consideration of finer details of mixtures

with the HNCH3 theory for later work. Given this compromise, we are able to use a finer ρ^* grid, $\delta\rho_{\text{solute}}^*=0.0004$, than was used for the pure fluid results above. As such, the plots for the mixtures use solid lines, indicating the significantly higher resolution of the density grids calculated.

Before proceeding to our systems of interest, we consider first calibration of the theory with binary mixture results. We compare against the simulation results of Kunor and Taraphder,³² which follows a series by Lamm and Hall.^{33,34} The former results give us an additional test for the theory. NPT-ensemble simulations of a binary LJ mixture were obtained across three phase points, $T^* = 1.21, 1.25$, and 1.29 and $x_{\text{large}} = 0.55, 0.60$, and 0.65 , the reduced temperatures and mole fractions of the large LJ species, respectively, at each phase point. They used Lorentz–Berthelot mixing with $\epsilon_{\text{small}}/\epsilon_{\text{large}} = 0.45$ and $\sigma_{\text{small}}/\sigma_{\text{large}} = 0.85$ ratios, respectively. Since they used the NPT-ensemble method, they report the pressure; however, we were unable to find where they reported the average densities result for their systems considered. The authors indicated they were targeting the pure liquid state of the system, between the solid and vapor coexistence regions, i.e., the phase points are meant to span the liquid state for the LJ mixture.

This presents an opportunity to test the HNCH2 theory for mixtures in two ways using the excess chemical potentials reported by Kunor and Taraphder as a reference target. First, we fix the temperatures, ϵ , σ , and mole fraction parameters to match the simulation, and then we search the total ρ^* density coordinate until the $\beta\mu^{\text{ex}}$ target value matches the simulation. The two targets we pick are, first, the reported $\beta\mu^{\text{ex}}$ value for the larger species. Second, we use the mean value at the highest temperature point as a different target, compute the $\beta\mu^{\text{ex}}$ for the larger species at that phase point, and then search total ρ^* again at the lower temperature points to find the value that keeps $\beta\mu_{\text{large}}^{\text{ex}}$ constant, in accord with the results of Kunor and Taraphder. Then, we have the $\beta\mu_{\text{small}}^{\text{ex}}$ and $\beta\mu_{\text{large}}^{\text{ex}}$ values and ρ^* values which result. For the HNC theory, in both targeting cases, we follow our pure fluid results, assume that HNCH2 has an improved phase diagram, and calculate the $\beta\mu^{\text{ex}}$ values for both species at the same total ρ^* values as were found for the HNCH2 results.

The results of these tests are plotted in Figures 6 and 7 for the $\beta\mu_{\text{large}}^{\text{ex}}$ and mean $\beta\mu^{\text{ex}}$ targets, respectively. In the first case, we found total densities of $\rho^* = 0.918, 0.891$, and 0.8645 for the $T^* = 1.21, 1.25$, and 1.29 and $x_{\text{large}} = 0.55, 0.60$, and 0.65 phase points, respectively, in targeting the $\beta\mu_{\text{large}}^{\text{ex}}$ results, and total densities of $\rho^* = 0.962, 0.935$, and 0.909 for the same phase points in targeting the mean $\beta\mu^{\text{ex}}$ result at $T^* = 1.29$ and $x_{\text{large}} = 0.65$. In both cases, the density results found are well within the Lennard-Jones liquid regime, although our results using the mean value as reference shade more toward the solid–liquid boundary than the simulations. Overall, using the HNC result as a baseline, the HNCH2 result improves the HNC result by increasing the difference between the two different species toward the result of the simulation. Using these calculations as our reference point, we then infer that the differences in chemical potential in the mixtures studied below are probably understated by using the HNCH2 theory.

Since we have previously demonstrated the quantitative results of the HNCH n theories for binary, equimolar mixtures of disparate Lennard-Jones fluids at the known liquid–liquid demixing point for the model, here we make the basic assumption that, since the models considered are a simple extension of Lennard-Jones mixtures previously considered with the same method, then to the extent that the differences in the solute are comparable, the computational method gives a reasonable prediction for the model.

For all mixture results presented, the end points of the concentration curves are the practical limits of stability of the HNCH2 solutions for the systems considered and the solutions methods used here. In each case, no acceptable solution, in the sense that all chosen thermodynamic measures of the resulting numerical solutions converged simultaneously, could be considered as being generated at higher concentrations of the respective solutes. As with the pure fluid case, we leave the precise nature of the phase behavior, if any, implied by the stability of these solutions for later work.

In Figure 8, we show the total solute chemical potentials for three different binary mixtures of Lennard-Jones fluids for which $\rho_{\text{solvent}}^* = 0.7$ and $T^* = 1.0$, the solute sizes are $\sigma_{\text{solute}} = 3\sigma_{\text{solvent}}$ for all cases, and $\epsilon_{\text{solute}} = 2\epsilon_{\text{solvent}}$, $1.5\epsilon_{\text{solvent}}$, and $1.25\epsilon_{\text{solvent}}$, respectively. The highest solute density found to be thermodynamically converged for all chosen measures is $\simeq \rho_{\text{solute}}^* = 0.014$, although there are small variations beyond this point between the different species. For this same set of binary mixtures, the solvent chemical potentials measured in each mixture are plotted in Figure 9.

Overall, we find a clear, almost linear relationship between the potential energies and the chemical potentials. The phase behavior of the system as a whole on increase of the solute densities is shown in the solvent chemical potentials, where the effect of solute species at highest densities on the solvent is small but appreciably spread over $\simeq 1k_B T$.

The mechanical forces of the systems are measured using the isothermal compressibility and are plotted in Figure 10. For this mechanical measure, in effect, there is no significant distinction between the systems due to the change in solute species, although the system with the higher energy solute does cross from a slightly higher compressibility to a slightly lower compressibility, in comparison to the other solutes.

Next, we consider ternary mixtures of Lennard-Jones fluids. As before, we hold the solvent density constant at $\rho_{\text{solvent}}^* = 0.7$ and $T^* = 1.0$ throughout. We use two different ternary mixtures and vary the total solute density while holding the relative density of the two distinct solutes constant, $\rho_{\text{solute}} = \rho_1^* + \rho_2^*$ and $\rho_1^* = \rho_2^*$, throughout, where ρ_1^* is the density of solute 1 and ρ_2^* is the density of solute 2. The two different ternary mixtures are for solutes with the same size but varying in energy and for solutes with the same energy but varying in size. For the first, the solutes are the same size as for the binary mixture, $\sigma_{\text{solute}} = 3\sigma_{\text{solvent}}$, while their energy parameters are varied, $\epsilon_1 = 1.25\epsilon_{\text{solvent}}$ and $\epsilon_2 = 1.5\epsilon_{\text{solvent}}$. For the second, the energies are held at $\epsilon_{\text{solute}} = 1.25\epsilon_{\text{solvent}}$, and the sizes are varied, $\sigma_1 = 3\sigma_{\text{solvent}}$ and $\sigma_2 = 2\sigma_{\text{solvent}}$. The results for the solute chemical potentials are shown in Figure 11. For the energy-disperse system, the maximum numerically stable ρ_1^* value found is $\rho_1^* = 0.0078$,

whereas for the size-disperse system, the maximum density is $\rho_1^*=0.012$ (note that the total solute density is $2\rho_1^*$).

The energy-disperse system results clearly reflect the binary mixture systems, i.e., the difference in energy between solutes in a ternary mixture mimics the difference between the individual solutes in their respective binary mixtures. The size disperse mixtures exhibit a subtly different overall behavior. In total comparison between both ternary systems, we see three effects. For the species in common to both ternary systems, $\sigma = 3\sigma_{\text{solvent}}$ and $\epsilon = 1.25\epsilon_{\text{solvent}}$, the chemical potential is increased substantially by including a larger second solute with weaker attractive interaction energy relative to a second solute with the same size and increased attractive energy. The second effect is that the bulk phase behavior, as measured from the chemical potentials of the relevant species, is appreciably and significantly changed due to composition, with the overall chemical potentials being more favorable for the size-disperse mixture relative to the energy-disperse mixture. Interestingly, we find that the chemical potential of the largest solute in the size-disperse system crosses over its smaller companion solute, going from least favorable solute at low densities to most favored solute at high densities.

We next examined a quaternary mixture, with the solvent fixed at $\rho_{\text{solvent}}^*=0.7$ and $T^*=1.0$ and the total solute density varied while keeping the three relative solute densities fixed, $\rho_{\text{solute}}^*=\rho_1^*+\rho_2^*+\rho_3^*$ and $\rho_1^*=\rho_2^*=\rho_3^*$. The solute radii are all equivalent at $\sigma_{\text{solute}}=3\sigma_{\text{solvent}}$, and the energy parameters are $\epsilon_1=1.25\epsilon_{\text{solvent}}$, $\epsilon_2=1.5\epsilon_{\text{solvent}}$, and $\epsilon_3=2\epsilon_{\text{solvent}}$. The gross variations in the various solute chemical potentials for this system are consistent with the ternary and binary mixtures. The results are summarized in Figure 12, which plots the solute chemical potential for the $\sigma_{\text{solute}}=3\sigma_{\text{solvent}}$ and $\epsilon_{\text{solute}}=1.5\epsilon_{\text{solvent}}$ species as a function of its density for the binary, ternary, and quaternary mixtures. The overall effect is the expected increase in the chemical potential of a given species as the overall density of the system is increased. If the system also includes a simultaneous increase in the number of components, proportional to the increase in density of the individual solute, then this forces the chemical potential as a function of the individual solute density to a steeper increase. The effect is slightly smaller on going from three to four overall components, relative to the increase in going from two to three overall components.

The different mixtures examined were constructed to examine the effects on solubilities of different solute species as a function of the number of constituents in the system. Since the total solute density is the same for each case, some of the variation in the solubility of the differing solutes comes as a function of the number of differing solute species.

We find two results due to the increase in the number of and variations between constituents. First, we observe that, at a given individual concentration, there is a concerted shift upward of the solvation free energy of a given solute due to the increase in the total number of constituents (or total solute density) and that the degree of this shift is composition-dependent. We expect that, in principle, the demixing point for the more complex mixtures will also shift relative to the corresponding binary mixture as a function of composition.

The second result shown is that size disparity between species in a mixture can induce crossover in their respective solvation free energies, such that the preferred, lower energy solute for a given solution depends on the total solute density. This is the result in Figure 11. We find that size dispersion is the most significant contribution in the Lennard-Jones mixtures to the crossover effect between the solubilities of the different solution compositions, whereas energy variations between solutes can change the free energy gap but not bridge it in the range examined.

This result is complementary to the long-time solvation dynamics crossovers observed by Ladanyi and co-workers for benzene–acetonitrile and water–methanol mixtures. The element that connects our equilibrium measures with the dynamical measures of Ladanyi et al. is that the long-time tail components, which, interpreted via kinetic theory, imply a free-energy barrier to solvation.^{35–37} The equilibrium chemical potential is the solvation work surface, averaging the work done over all transitions. While this washes out the details of particular events, the total work done to solvate a particular molecule and the crossover effects observed in both total (equilibrium) and local (dynamical) work surfaces are consistent with each other. Here, we do not have the contributions of polar intermolecular potentials, so the comparison is not complete in detail, but our results are encouraging and suggest further work to complete the picture in terms of mechanism.

CONCLUSIONS

For this work, we examined the chemical potential for Lennard-Jones model fluid systems, both single-component and mixtures. We calculated the chemical potential in concert with the HNCH2 and HNCH3 integral equation theories to first investigate the pure Lennard-Jones fluid. We found that, as for the other thermodynamic results previously examined, HNCH2 and HNCH3 significantly and systematically improved the chemical potential predictions for the model fluid in comparison to simulation. Furthermore, we found that, while the HNCH2 approximation was insufficient to predict gas–liquid coexistence, the HNCH3 approximation qualitatively predicted gas–liquid coexistence and the critical region of the pure Lennard-Jones fluid in agreement with known simulation results, although more quantitative results will require further computational work focused strictly on phase transitions.

We then turned to mixtures of Lennard-Jones fluids. Here, we used the HNCH2 approximation to investigate binary, ternary, and quaternary mixtures in which the solutes were varied with respect to energy while keeping relative sizes constant and then in which sizes were varied while keeping interaction energies constant. For solutes, we chose to focus on relative solute sizes around $3\sigma_{\text{solvent}}$. These are coarse models of nanoscale solute molecules with a water-scale solvent molecule.

We found small, increasing solubility shifts due to energy dispersity between different solutes in binary mixtures. We then used ternary and quaternary mixtures to examine the solubility effects due to variation of both energy and size dispersity. From the energy variations, we found that the solubility curves in the more complex mixtures vary with crowding. The degree of variance is measurable but small for solute energy variations, and

the precise composition of the mixture determines the solubility variations. On changing solute sizes, we found that the solubility curves can be qualitatively shifted, with dramatic alterations caused by the size dispersity of solutes. In particular, the solute size change induced crossover between the solubilities of the different solutes in a ternary mixture as a function of total solute concentration, so identifying which solute species might be called solvophobic in relation to the other constituents depends on the concentration.

The results of this work suggest reasonable avenues for future investigation. For aggregation and self-assembly, one of the principle experimental necessities is the search for solvent conditions that allow for fine control of the molecular details of nano- and mesoscale targets. This work suggests that both the particular structure of self-assembled constructs and their solution-state stability can be controlled by targeting the distribution of intramolecular states that are accessible by the building-block solute molecules as a clustering process takes place. Future work will extend these results to take into account whether and how particular cosolvents and salts may inhibit or enhance the general solvation process. A particularly interesting result for further work is that not only is the relative magnitude of the size distribution significant but also so are aspects relative to a given solute energy. We suggest that, to the extent that the observations scale to higher complexity, this result will have particular utility for different forms of crowded systems.

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APPENDIX

Many routes to the chemical potential and equation of state are known.³⁸ Some are proven to be path-independent,³⁹ and some depend on the thermodynamic path taken.⁴⁰ The chemical potential route found by Attard chooses a path for the particular form of the $\beta\mu^{\text{ex}}$ charging integral used. Following that work, we begin with the standard charging integral⁴¹

$$\begin{aligned} -\beta\mu^{\text{ex}} &= \rho \int \int d\lambda \, d\mathbf{r} \, (-\beta u(r)) g(r, \lambda) \\ &= \rho \int_0^1 d\lambda \int d\mathbf{r} \, y(r, \lambda) \partial_e(r, \lambda) \end{aligned} \quad (11)$$

where $y = \exp(t + b)$ is the cavity function, we use the closure, and in the second line we follow Singer and Chandler and Attard and write the energy as the λ derivative of the e-bond, $e(r) = \exp(-\beta u(r))$, using the operator notation

$$\partial = \frac{\partial}{\partial \lambda}$$

and

$$\partial^{-1} = \int_0^1 d\lambda \quad (12)$$

for the λ derivative and antiderivative, respectively. We follow convention and assume here that $\beta\mu^{\text{ex}}$ is not a function of r , i.e., λ is independent of r throughout and $d/d\lambda = \partial/\partial\lambda$ is the exact differential.

We proceed from eq 11 by writing the λ integrals as (suppressing for the moment the $\int d\mathbf{r}$ integrals)

$$\begin{aligned} \partial^{-1} y \partial e &= \partial^{-1} [y \partial e + e \partial y - e \partial y] \\ &= \partial^{-1} [\partial h - e \partial y] \end{aligned} \quad (13)$$

from which we find the Attard solution in compact form as

$$\beta\mu^{\text{ex}} = \rho \int d\mathbf{r} \left[\frac{1}{2} h(r) (h(r) - c(r)) - c(r) + b(r) + \sum_n \frac{n}{n+1} h(r) b^{(n)}(r) \right] \quad (14)$$

where $b(r) = \sum_n b^{(n)}(r)$ is the bridge diagram series ordered by the n number of bonds in any given diagram that connect to the root point labeled 1. This follows from Leibniz' rule applied term by term to each diagram in bh and yields the $n/n(n+1)$ symmetry factor in eq 14.

An alternative thermodynamic path may be derived by simply scaling the operators symmetrically by N and considering that the e -bond subscripts 1 and 2 label the open root points of a given diagram

$$\begin{aligned} \partial^{-1} \partial h - \partial^{-1} e \partial y &= N \partial^{-1} \frac{1}{N} \partial h - N \partial^{-1} e_{12} \frac{1}{N} \partial y \\ &= \partial_{12}^{-1} \partial_{12} h - \partial_{12}^{-1} e_{12} \partial_{12} y \end{aligned} \quad (15)$$

where

$$\partial^{-1} \partial = N \partial^{-1} \frac{\partial}{N} = \partial_{12}^{-1} \partial_{12} \quad (16)$$

and the labeled operators are

$$\frac{\partial}{N} = \partial_{12} \quad (17)$$

by particle indistinguishability, and

$$N \partial^{-1} = \partial_{12}^{-1} \quad (18)$$

by substitution. The labeled operator ∂_{12} is the λ derivative with respect to the λ_{12} parameter alone for any diagram in the series representation of $g(r)$, and, similarly, ∂_{12}^{-1} is the antiderivative with respect to λ_{12} alone. The labeled operators ∂_{12} and ∂_{12}^{-1} are the derivative and antiderivative, respectively, with respect to the λ_{12} root point parameter of any given diagram in $g(r)$ while holding the field point λ parameters constant.

Thus, we may hold the λ values in the field points, λ_{1n} , $n = 2$, constant ($= 1$) while differentiating and integrating over λ_{12} .

Using the diagrammatic properties of $t(1, 2)$, $b(1, 2)$, and $y(1, 2)$, all of which by construction contain no elementary root bonds, $e_\lambda(1, 2)$ or $f_\lambda(1, 2)$, dependent on λ_{12} , we find the excess chemical potential in closed form as

$$-\beta\mu^{\text{ex}} = \rho \int d\mathbf{r} \int_0^1 d\lambda_{12} (-h(r) \partial_{12} (h(r) + b(r) - c(r)) - \partial_{12} (b(r) - c(r)))$$

or

$$= -\rho \int d\mathbf{r} \left(\frac{1}{2} h^2(r) - \frac{1}{2} h(r) c(r) - c(r) + b(r) \right) \quad (19)$$

since

$$\begin{aligned} \partial_{12} y &= 0 \\ \partial_{12} t &= 0 \text{ so that } \partial_{12} h = \partial_{12} c \\ \partial_{12} b &= 0 \end{aligned}$$

and

$$\begin{aligned} \int d\lambda_{12} h(r) \partial_{12} b(r) &= h(r) b(r) - \int d\lambda_{12} b(r) \partial_{12} h(r) \\ &= h(r) b(r) - \int d\lambda_{12} \partial_{12} (b(r) h(r)) = 0 \quad (20) \end{aligned}$$

The $ht/2$ term follows from the OZ relation in Fourier space and the symmetry of the Fourier transform. Parseval's relation and the convolution theorem reduce the r -dependent integral over a 3-point function to the k -dependent integral over a 2-point function, without effect on the λ dependence since λ is not a function of r .

The difference between eqs 19 and 14 is summarized numerically for the LJ fluid in Figure 2, where the $\beta\mu^{\text{ex}}$ results are calculated for the HNCH3 theory, both with and without the $(n/(n+1))hb$ integral, eqs 14 and 19, respectively. Similar results hold for the HNCH2 theory. We observe by direct computation that, following the analysis above, $\beta\mu$ for the LJ fluid at the HNCH2 and HNCH3 approximation is best approximated in comparison with the simulation results by the integrals without the hb term in eq 19.

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Figure 1.

Comparison among the total chemical potentials, $\beta\mu = \beta\mu^{\text{ex}} + \ln \rho^*$, as calculated from eq 9, for the first three HNCHn theories, for the pure Lennard-Jones fluid at $T^* = 1.0$, and for the results from simulation. The black triangles are the simulation results from Attard, the red circles are the HNC results, the green squares are the HNCH2 results, and the blue diamonds are the HNCH3 results.

Figure 2.

Comparison among the different routes for calculating the chemical potentials of the Lennard-Jones fluid for the HNCH3 level theory and for the results for simulation and HNC theory. The black diamonds are the simulation results as for Figure 1, the red circles are the HNC results, the dark blue diamonds are the results of the HNCH3 theory using eq 9, and the light blue (cyan) diamonds are the results of the HNCH3 theory from eq 14, i.e., including the $(hb)n/(n + 1)$ integrals.

Figure 3.

Temperature dependence of the total chemical potential for the Lennard-Jones fluid in the HNCH2 approximation, for temperatures $T^* = 1.08, 1.18$, and 1.38 (red circles, green squares, and blue diamonds, respectively). The dotted lines are fitted for convenience of the eye. The HNCH2 approximation shows no gas–liquid coexistence in these results.

Figure 4.

Total chemical potential, $\beta\mu(\rho^*)$, for the Lennard-Jones fluid in the HNCH3 approximation, at $T^* = 1.25, 1.45$, and 1.85 (black circles, red squares, and green diamonds, respectively). The dotted lines are fitted for convenience of the eye. The discontinuous region around $\rho^* \simeq 0.35$ in the $T^* = 1.25$ curve corresponds to the accepted critical density for the LJ fluid, $\rho^c \simeq 0.35$, and was not found to be numerically stable for the HNCH3 theory. As well, the critical temperature region ($T^c \simeq 1.35$ for the LJ fluid is commonly accepted) is indicated by regions of both $T^* = 1.25$ and 1.45 curves where $\beta\mu(\rho^*)$ is double-valued (which also confirms gas-liquid coexistence for the HNCH3 approximation), whereas for $T^* = 1.85$, $\beta\mu(\rho^*)$ remains monotonic throughout.

Figure 5. Isothermal compressibilities of the phase diagram for the LJ fluid as for Figure 4 in the HNCH3 approximation, with corresponding symbols. This details the mechanical measure of the system (χ_T), as a companion to the compositional description ($\beta\mu$) in Figure 4. The discontinuous region occurs in $T^* = 1.25$ and $\simeq \rho^* = 0.35$.

Figure 6.

Comparison between excess chemical potential of simulation and the HNCH2 and HNC theories in a binary Lennard-Jones mixture, as described in the text. The circles are the large LJ species; the squares are the small LJ species. The lines are drawn to aid the eye. The black symbols/lines are the simulation results of Kunor and Taraphder, the red symbols/lines are the HNCH2 results, and the green symbols/lines are the HNC results. The black and red circles/lines directly overlay each other; in this comparison, the large LJ species was chosen as the reference.

Figure 7.

Comparison between simulation and theory, with the mean value of the simulation excess chemical potentials at $T^* = 1.29$ chosen as the reference and the large species kept constant in excess chemical potential to match simulation. The symbol types are the same as those in Figure 6.

Figure 8.

Total solute chemical potential for three different binary mixtures of Lennard-Jones fluids with the solvent density held fixed throughout at $\rho_{\text{solvent}}^* = 0.7$ and $T^* = 1.0$, in the HNCH2 approximation. The potential parameters are $\sigma_{\text{solute}} = 3\sigma_{\text{solvent}}$ for all systems, and $\epsilon_{\text{solute}} = 2\epsilon_{\text{solvent}}$, $1.5\epsilon_{\text{solvent}}$, and $1.25\epsilon_{\text{solvent}}$ for the green, red, and black curves, respectively.

Figure 9. Solvent chemical potentials for the three different binary Lennard-Jones mixtures as given in Figure 8, with the line types being the same.

Figure 10. Isothermal compressibility, κ_T , for the three different binary Lennard-Jones mixtures, as given in Figure 8. The line colors are the same as those in Figure 8.

Figure 11.

Variation in solute chemical potentials for the ternary mixtures investigated. The dashed lines are for the ternary system where the two solute types differ only in energy; $\sigma_{\text{solute}} = 3\sigma_{\text{solvent}}$ for both, whereas $\epsilon_1 = 1.25\epsilon_{\text{solvent}}$ is the black dashed line, and $\epsilon_2 = 1.5\epsilon_{\text{solvent}}$ is the green dashed line. The solid lines are for the ternary system where the two solute types differ only in size; $\epsilon_{\text{solute}} = 1.25\epsilon_{\text{solvent}}$ for both, whereas $\sigma_1 = 3\sigma_{\text{solvent}}$ is the solid black line, and $\sigma_2 = 2\sigma_{\text{solvent}}$ is the solid red line. ρ_{solute}^* here is the number density of the individual solute in each mixture, not the total of all solutes. The maximum numerically stable (single) solute density for the energy-disperse system is $\rho_{\text{solute}}^* = 0.0078$; for the size-disperse system, it is $\rho_{\text{solute}}^* = 0.012$.

Figure 12.

Chemical potential for the same solute in binary, ternary, and quaternary mixtures (black, red, and green lines, respectively), as a function of the individual solute density, ρ_1^* . The solute is the $\sigma_{\text{solute}} = 3\sigma_{\text{solvent}}$ and $\epsilon_{\text{solute}} = 1.5\epsilon_{\text{solute}}$ model. ρ_{solute} here is the number density of the individual solute in each mixture, not the total of all solutes.