Properties of 2,2,2-trifluoroethanol and water mixtures

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2,2,2-trifluoroethanol (TFE) is a commonly used cosolvent in experimental studies of peptides and proteins. Although concentration-dependent TFE effects have been well studied experimentally, the exact mechanism by which TFE affects the solubility and stability of peptides is still unclear. Here we report molecular dynamics simulations of TFE/water mixtures of different composition in an attempt to improve our atomic level understanding of the properties of TFE/water mixtures. The trends in most properties—densities, diffusion constants, dielectric constants, and enthalpies of mixing—were well reproduced, although quantitative agreement with experiment was poor. Other thermodynamic properties of the solutions—partial molar volumes, derivatives of activity coefficients, and isothermal compressibilities—were also determined using the Kirkwood–Buff theory of mixtures. The Kirkwood–Buff analysis indicated significant aggregation of TFE molecules in the mixtures, especially at low mole fractions, in agreement with experiment. However, the aggregation of TFE molecules was exaggerated using the current TFE and water models. The results suggest that the combination of simulation data and Kirkwood–Buff theory provides a powerful tool for the investigation of the thermodynamic properties of hydrogen bonding mixtures. © 2001 American Institute of Physics. [DOI: 10.1063/1.1330577]

INTRODUCTION

The addition of cosolvents to solutions of peptides and proteins can result in a variety of effects such as denaturation, increased or decreased solubility, and secondary structure formation.1–6 One such cosolvent is TFE (2,2,2-trifluoroethanol). TFE is known to promote the formation of secondary structure, especially helices, at low concentrations, while higher concentrations can denature proteins.6 The ability of TFE/water mixtures to induce regular structure has resulted in a growing use of TFE in NMR structural studies. However, despite many experimental and theoretical studies, the mechanism by which TFE affects the structure and dynamics of peptides and proteins is still unclear.6

Some of the properties of pure TFE are presented in Table I,7–26 together with the corresponding properties of water and ethanol for comparison. TFE has a lower dielectric constant than water, suggesting that electrostatic interactions will be strengthened in TFE/water mixtures. TFE is approximately four times larger than a water molecule. The presence of the CF3 group indicates a degree of hydrophobic character and this is supported by the much lower solvation free energy of methane in TFE compared to water, although the solvation process is still unfavorable. The inductive effect of the fluoro substituents increases the acidity of the hydroxyl proton in comparison with ethanol, making it a better hydrogen bond donor, but a poorer hydrogen bond acceptor.7 X-ray diffraction studies of the pure liquid suggest that TFE molecules adopt a 50:50 mixture of trans and gauche conformations around the H–O–C–C bond in solution.27 In summary, the presence of TFE in TFE/water mixtures has the potential to effect ionic, hydrogen bonding, and hydrophobic interactions.

Several experimental studies of mixtures of TFE and water have appeared recently, many prompted by the growing use of TFE in protein folding studies. The most interesting property of TFE/water mixtures is the aggregation of TFE molecules, as observed by x-ray scattering and NMR experiments.8,28,29 Aggregation of TFE molecules is more pronounced than that of simple alcohols, such as methanol and ethanol.28 The degree of aggregation is composition-dependent with a maximum around 0.1 mole fraction of TFE (4.3 M or 30% by volume).28 Harris et al. refer to this aggregation as a microheterogeneity which results in TFE-rich regions of the solution.8 However, the exact nature of these clusters is not easily characterized by experimental techniques. The presence of TFE clusters has been used to explain the trend in TFE/water viscosity as a function of TFE concentration, which passes through a maximum at the slightly larger value of 0.2 TFE mole fraction,9 although no such maximum occurs for the dielectric constant or density of TFE/water mixtures. A Kirkwood–Buff analysis of the experimental composition-dependent densities, compressibilities, excess free energies, and partial molar volumes of TFE/water mixtures indicates a maximum in TFE aggregation at 0.15 mole fraction of TFE.30 TFE is considered to be a water structure maker,31 and this effect is also supported by the Kirkwood–Buff analysis of the experimental thermodynamic data.30

Changes in the properties of TFE/water mixtures have been invoked as one of the major reasons for the variable effect of TFE on peptide structure.5,32,33 Any computational studies of such effects must use a TFE (and water) force field capable of reproducing these effects if one expects to have confidence in the results. Here, we test one of the more common TFE force fields. In addition to the normal molecular dynamics (MD) analysis, this study also uses Kirkwood–Buff theory to obtain partial molar volumes, chemical poten-
thermodynamic properties of mixtures. Subsequent ther-
a depletion of species
activity coefficients
f
f
continental


tial and activity derivatives, and isothermal compressibilities
from the simulations for comparison with experiment. This
work expands on a previous study of cosolvent solutions.34

THEORY

Kirkwood–Buff (KB) theory relates fluctuations in particle
densities in the grand canonical (μVT) ensemble to
thermodynamic properties of mixtures.35,36 Subsequent ther-
modynamic transformations produce expressions for partial
molar volumes, isothermal compressibilities, and chemical
potential and activity derivatives at constant pressure (p) and
temperature (T).37 The above thermodynamic properties are
expressed in terms of KB integrals which are defined as35

(1)

Here, G_{ij} is the KB integral between species i and j, and
\text{g}_{ij}(r) \text{ is the corresponding radial distribution function (rdf) in the } \mu VT \text{ ensemble. A KB integral greater than zero indicates an excess of species } j \text{ in the vicinity of species } i \text{ (over a random distribution), while a negative value corresponds to a depletion of species } j \text{ surrounding } i.\)

For a two-component system consisting of water (w) and a cosolvent (c), a variety of thermodynamic quantities can be expressed in terms of the integrals G_{ww}, G_{cw}, and G_{cc}, and the number densities, \rho_w and \rho_c, of water and cosolvent (TFE), respectively. The partial molar volumes of the two components, \bar{V}_w and \bar{V}_c; the isothermal compressibility of the solution, \kappa_T; derivatives of the chemical potential, \mu; derivatives of the activity, \alpha; and derivatives of the activity coefficients f (mole fraction scale, x), are given by37

(2)

Here, \bar{V}_w = \frac{1 + \rho_c (G_{cc} - G_{cw})}{\eta}

(3)

Here, \bar{V}_c = \frac{1 + \rho_w (G_{ww} - G_{cw})}{\eta}, \quad \kappa_T = \frac{\beta \xi}{\eta},

(4)

Here, \eta = \rho_w + \rho_c + \rho_w \rho_c G_{ww} + \rho_c G_{cw} + \rho_w \rho_c G_{cw} + \rho_w \rho_c G_{cc} - 2 G_{cw}, \quad \xi = 1 + \rho_c G_{ww} + \rho_c G_{cc} + \rho_w \rho_c (G_{ww} G_{cc} - G_{cw}^2), \quad \beta = 1/RT,

where R is the gas constant. For real (stable) solutions the values of \eta and \xi must be positive.37

In principle, the combination of theory or simulation with KB theory appears very natural. The required rdfs are easily obtained from simulation (either Monte Carlo or MD) or integral equation theory, and can be used to generate the necessary KB integrals. In practice, the r^2 weighting present

<table>
<thead>
<tr>
<th>Property</th>
<th>Water</th>
<th>Ethanol</th>
<th>TFE</th>
<th>Units</th>
</tr>
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<tbody>
<tr>
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<td>18.02</td>
<td>46.07</td>
<td>100.04</td>
<td>g/mol</td>
</tr>
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<td>Density, \rho</td>
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<td>0.789^b</td>
<td>1.383^c</td>
<td>g/cm^3</td>
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<td>cm/mol</td>
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<td>Diffusion coefficient, D</td>
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<td>10^{-9} m^2/s</td>
</tr>
<tr>
<td>Surface tension, \gamma</td>
<td>72^a</td>
<td>22^a</td>
<td>mN/m</td>
<td></td>
</tr>
<tr>
<td>Isothermal compressibility, \kappa_T</td>
<td>4.63^f</td>
<td>9.91^f</td>
<td>10.64^f</td>
<td>10^{-3} atm^{-1}</td>
</tr>
<tr>
<td>Thermal expansion coefficient, \alpha</td>
<td>0.256^f</td>
<td>1.096^f</td>
<td>1.255^f</td>
<td>10^{-3} K^{-1}</td>
</tr>
</tbody>
</table>

\begin{align*}
\Delta H^\theta & = 43.99^f + 42.31^f + 43.97^e \text{ kJ/mol} \\
\Delta C_p & = 75.35 m + 177.78 n J/mol/K \\
\rho_K & = 15.3^g + 16.0^f + 12.5^f \text{ D} \\
P \rho & = 2.6^{f, r} + 2.46^{o} \text{ D} \\
\text{Dielectric constant, } \varepsilon & = 78^d + 24^d + 27^f \text{ cm}^3 / \text{mol} \\
\text{CH}_4 \text{ solvation, } \Delta G^{\text{rot}} & = 8.4^f + 2.4^f + 10 \text{ kJ/mol} \\
\end{align*}

\begin{align*}
\text{Property} & \quad \text{Water} \quad \text{Ethanol} \quad \text{TFE} \quad \text{Units} \\
\text{Molar mass, M} & \quad 18.02 \quad 46.07 \quad 100.04 \quad \text{g/mol} \\
\text{Density, } \rho & \quad 0.997^a \quad 0.789^b \quad 1.383^c \quad \text{g/cm}^3 \\
\text{Molar volume, } V_w & \quad 18.07^a \quad 58.69^a \quad 72.32^c \quad \text{cm/mol} \\
\text{Shear viscosity, } \eta_s & \quad 0.89^f \quad 1.10^e \quad 1.78^f \quad \text{cp} \\
\text{Diffusion coefficient, D} & \quad 2.3^b \quad 1.1^a \quad 0.6^f \quad 10^{-9} \text{ m}^2/\text{s} \\
\text{Surface tension, } \gamma & \quad 72^a \quad 22^a \quad \text{mN/m} \\
\text{Isothermal compressibility, } \kappa_T & \quad 4.63^f \quad 9.91^f \quad 10.64^f \quad 10^{-3} \text{ atm}^{-1} \\
\text{ Thermal expansion coefficient, } \alpha & \quad 0.256^f \quad 1.096^f \quad 1.255^f \quad 10^{-3} \text{ K}^{-1} \\
\text{Heat of vaporization, } \Delta H^\theta & \quad 43.99^f + 42.31^f + 43.97^e \quad \text{kJ/mol} \\
\text{Heat capacity, } C_p & \quad 75.35 m + 177.78 n \quad \text{J/mol/K} \\
\text{pK}_w & \quad 15.3^g + 16.0^f + 12.5^f \quad \text{D} \\
\text{Dipole moment (g), } \mu^g & \quad 1.85^f \quad 1.69^g \quad \text{D} \\
\text{Dipole moment (l), } \mu^l & \quad 2.6^{f, r} \quad 2.46^{o} \quad \text{D} \\
\text{Dielectric constant, } \varepsilon & \quad 78^d + 24^d + 27^f \quad \text{cm}^3 / \text{mol} \\
\text{CH}_4 \text{ solvation, } \Delta G^{\text{rot}} & \quad 8.4^f + 2.4^f + 10 \quad \text{kJ/mol} \\
\end{align*}

\begin{align*}
\text{Reference} & \quad 8. \quad \text{Reference} \quad 18. \\
\text{Reference} & \quad 13. \quad \text{Reference} \quad 19. \\
\text{Reference} & \quad 10. \quad \text{Reference} \quad 20. \\
\text{Reference} & \quad 11. \quad \text{Reference} \quad 21. \\
\text{Reference} & \quad 14. \quad \text{Reference} \quad 22. \\
\text{Reference} & \quad 9. \quad \text{Reference} \quad 23. \\
\text{Reference} & \quad 15. \quad \text{Reference} \quad 24. \\
\text{Reference} & \quad 16. \quad \text{Reference} \quad 25. \\
\text{Reference} & \quad 17. \quad \text{Reference} \quad 26. \\
\text{Reference} & \quad 12. \quad \text{Reference} \quad 27. \\
\end{align*}
in the KB integrals [Eq. (1)] indicates that long range effects may dominate, which does not always provide a simple picture of the solution behavior in terms of direct molecular associations, and that numerical errors from the simulations may be amplified. In the next section we argue that these factors are not serious impediments to the application of KB theory for the study of TFE/water mixtures using data obtained from computer simulations.

While Kirkwood–Buff theory has been used extensively to determine KB integrals from the relevant experimental data and to describe the mutual solvation of different components in solution mixtures,\textsuperscript{48–43} it is less common to use simulation data to evaluate experimental properties. Most previous evaluations of KB integrals have focused on simulations of Lennard-Jones mixtures,\textsuperscript{44,45} simple (2D) models of water,\textsuperscript{46} the application of Debye–Hückel theory to salt solutions\textsuperscript{46,47} to determine partial molar volumes of hydrocarbons at infinite dilution,\textsuperscript{48} or have used integral equations to determine the appropriate rdfs.\textsuperscript{43,49,50}

The KB integrals are integrals over rdfs corresponding to the μVT ensemble. Unfortunately, most simulations are performed in the NpT, NVT, or NVE ensembles. In these closed systems, the corresponding KB integrals are equal to 0 for unlike pairs and −1 for like pairs, and therefore cannot be used directly.\textsuperscript{37} In principle, one can perform molecular dynamics simulations in the μVT ensemble,\textsuperscript{51,52} but these are nontrivial calculations due to the problems associated with inserting new particles.\textsuperscript{53,54} Here, we take a simpler approach. The μVT radial distribution function (rdf) is approximated by the NpT rdf truncated at a distance $R_c$. This distance is chosen to be the range over which the intermolecular forces dominate the distribution of particles. Under these circumstances, the truncated NpT rdf captures the major features of the μVT rdf and provides a very good approximation to the required KB integrals. The similarity between the rdfs in open and closed systems has been illustrated in previous computational studies.\textsuperscript{55} Also, although the long range behavior of the μVT and NpT rdfs differ by a term of the order of $1/N$,\textsuperscript{56} this is a negligible quantity (for a reasonable $N$ and away from a phase transition) except when the integration over the rdf extends to infinity. This point is discussed in detail by Ben-Naim.\textsuperscript{56} Truncated rdfs obtained from NpT simulations have been used before to obtain partial molar volumes from KB theory,\textsuperscript{48} and for expressing the KB equation in terms of local compositions.\textsuperscript{57} The above approach is simpler and easier than performing constant chemical potential\textsuperscript{51} or Gibbs ensemble simulations\textsuperscript{58} where particle insertion or sampling problems can arise.

The above approximation is equivalent in spirit to the assumption of a correlation volume used to obtain preferential solvation parameters through inversion of KB theory using experimental data obtained at constant $p$ and $T$.\textsuperscript{37,56} The only question remaining is the choice of $R_c$. Experimental estimates of this correlation volume suggest that the sphere of influence of one molecule over another extends for several molecular diameters,\textsuperscript{59,60} although this is somewhat dependent on the density. In this work, a radius of 1.0 nm was used to define the correlation volume for all compositions. For the majority of simulations performed here this represents approximately 25% of the total volume of the system. The practical consequence of this assumption is to reduce the KB upper integration limit [Eq. (1)] from infinity to 1.0 nm.

Before leaving this section we note that for an infinitely dilute cosolvent in a solvent one obtains $\eta = \rho_w^\infty$, $\zeta = 1 + \rho_w^\infty G_{ww}^\infty$, and

\[
\tilde{V}_w^0 = \frac{1}{\rho_w^0}; \quad \tilde{V}_c^0 = \frac{1}{\rho_c^0} + G_{ww}^\infty - G_{cw}^\infty,
\]

\[\rho_w^\infty RT \kappa_w^0 = 1 + \rho_w^\infty G_{ww}^\infty,
\]

\[\frac{\partial \ln f_c}{\partial x_c} \bigg|_{T,p,\rho_c=0} = -\rho_w^\infty (G_{ww}^\infty + G_{cc}^\infty - 2G_{cw}^\infty),
\]

where the superscripts $o$ and $\infty$ refer to the pure solvent or infinitely dilute cosolvent, respectively. The values of $G_{cc}^\infty$ and $G_{ww}^\infty$ can be obtained from the rdfs between a pair of cosolvent molecules in pure solvent, and between cosolvent and solvent from a simulation of a single cosolvent in pure solvent, respectively. The former may be difficult to obtain due to poor sampling. Nevertheless, this is attempted here.

### METHODS

Classical molecular dynamics simulations were performed in the NpT ensemble at 300 K and 1 atm. The temperature and pressure were modulated using the weak coupling technique,\textsuperscript{61} with relaxation times of 0.1 and 0.5 ps, respectively. The initial configuration for each composition was obtained by randomly replacing an appropriate number of waters by TFE molecules in a cubic cell containing 512 equilibrated water molecules. The simulation cell edge length varied between 2.5 (pure water) and 3.0 nm (pure TFE). Periodic boundary conditions were imposed. The nonbonded force field parameters for the SPC/E water model\textsuperscript{62} and the TFE model\textsuperscript{63} used in the present study are listed in Table II. Intramolecular TFE parameters are given in Ref. 63 for the GROMOS potential.\textsuperscript{64} The geometric mean was used for both $\sigma$ and $\epsilon$ in the calculation of both intra- and intermolecular interactions. All bonds were constrained using SHAKE\textsuperscript{65} leading to a timestep of 2 fs for integration of the equations of motion.

<table>
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<tr>
<th>Species</th>
<th>Atom</th>
<th>$q$</th>
<th>$\epsilon$</th>
<th>$\sigma$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O</td>
<td>O</td>
<td>$-0.8476$</td>
<td>0.6506</td>
<td>0.3166</td>
<td>62</td>
</tr>
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<td>H</td>
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<td>TFE</td>
<td>CH$_3$</td>
<td>0.2600</td>
<td>0.4896</td>
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<tr>
<td>H</td>
<td></td>
<td>0.3000</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Symbols are $q$, atomic charge in $|e|$; $\epsilon$ and $\sigma$ Lennard-Jones 6-12 well depth (in kJ/mol) and diameter (in nm), respectively. The geometric mean was used for both $\epsilon$ and $\sigma$ combining rules.

*United atom carbon. Bonded parameters for the TFE model can be found in Ref. 63.*
Electrostatic interactions were modelled by using the Ewald technique\textsuperscript{66} with conducting boundary conditions. This is not the electrostatic method used in the parameterization of either the TFE or the water model used here; and it is known that different truncation methods can affect the resulting properties.\textsuperscript{67} However, for studying peptides and proteins in TFE/water mixtures an inclusion of long range effects is required.\textsuperscript{68,69} Hence, the Ewald approach was adopted here. A real space cutoff of 1.2 nm was used along with a convergence parameter of 2.5 nm\textsuperscript{-2} and lattice vectors with \( n^2 = 49\). Minimization was performed using 100 steps of steepest descent. The system was then sufficiently equilibrated to ensure that there was no drift of potential energies with time. The total simulation time was at least 2 ns for each of the finite concentration simulations (excluding the larger system sizes). Table III summarizes the details of the simulations reported here.

All properties were calculated from configurations saved every 0.1 ps. Data in the final nanosecond of each simulation were used in the calculation of ensemble averaged properties. Standard deviations were estimated by determining properties from four subaverages spanning 250 ps each. The errors so obtained typically provide an upper bound on the real errors in the calculation of properties such as the dielectric constant and shear viscosity, which require several hundred picoseconds to converge. The center of mass of TFE was used for the calculation of the radial distribution functions (rdfs). A value of 0.025 nm was used for the bin width in the calculation of rdfs.\textsuperscript{70} Residence times, diffusion constants, and dielectric constants of the solutions were determined as described previously.\textsuperscript{34,71}

In order to calculate the infinite dilution rdfs between two TFE molecules in water and between two waters in TFE, a half-harmonic potential was used to restrain the center of mass distance between the pair of like molecules \( r \) to less than 1.2 nm in order to improve the inherently poor statistics for these calculations. A potential of the form \( V(r) = (1/2)k(r - r_o)^2 \) was applied for values of \( r > r_o = 1.2\) nm during the trajectories which were performed for a total of 1 ns after 50 ps of equilibration. The parameter \( k \) was set to 5000 kJ/mol/nm\textsuperscript{2}. The density inside this constraining sphere was used to normalize the calculated rdfs after all configurations with intermolecular distances greater than 1.2 nm were excluded. Hence, the biasing potential was zero for all the configurations included in the rdf calculation. This ensured equal weighting for each configuration in the ensemble average.

The excess enthalpy of mixing for a TFE/water solution of TFE mole fraction \( x_c \) was obtained by subtracting the potential energies of the pure components from that of the mixture:

\[
\Delta H_m = U_{\text{mix}} - x_c U_{c,\text{mix}} - x_w U_{w,\text{mix}} + p(V_{\text{mix}} - x_c \tilde{V}_{c,\text{mix}} - x_w \tilde{V}_{w,\text{mix}}),
\]

where \( p \) is the pressure of the solution (=1 atm), \( U \) is the average internal energy per particle \( (N_c + N_w) \), \( \tilde{V} \) is the average volume per particle, and \( \tilde{V} \) is the partial molar volume; the superscript \( o \) denoting values for pure solutions. The pV term was found to be negligible.

In order to determine the isothermal compressibility by numerical differentiation,\textsuperscript{72} the 4.3 M TFE solution was simulated at pressures of 1 atm and 1000 atm, respectively. The partial molar volumes of both TFE and water were also calculated using a finite difference technique by determining the difference in volume between the \( x_c = 0.5 \) (11.0 M) solution and a simulation in which either a TFE or a water molecule was deleted. The trajectories for these calculations were 1.25 ns long.

The properties obtained from the simulations have been compared with experimental data on TFE/water mixtures from the current literature: densities and partial molar volumes from Ref. 10; dielectric constants from Ref. 9; diffusion constants from Ref. 8; enthalpies of mixing and derivatives of the activity coefficient from Ref. 11; isothermal compressibilities from Ref. 12. The experimental data were interpolated whenever the values corresponding to the com-

### Table III. Summary of MD runs for the TFE/water mixtures.\textsuperscript{a}

<table>
<thead>
<tr>
<th>System</th>
<th>( N_c )</th>
<th>( N_w )</th>
<th>( \langle V \rangle ) (nm(^2))</th>
<th>( \rho_c ) (nm(^{-3}))</th>
<th>( C_v ) (mol/L)</th>
<th>( x_c )</th>
<th>( m_c ) (mol/kg)</th>
<th>v/v</th>
<th>( T_{\text{sim}} ) (ns)</th>
</tr>
</thead>
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\textsuperscript{a}All simulations were performed at 300 K and 1 atm in the NpT ensemble. \( N_c \)=number of TFE molecules; \( N_w \)=number of water molecules; \( \langle V \rangle \)=average volume of the solution; \( \rho_c \)=TFE number density in solution; \( C_v \)=TFE molarity; \( x_c \)=TFE mole fraction; \( m_c \)=TFE molar volume; v/v=percentage of TFE by volume in the solution; \( T_{\text{sim}} \)=total simulation time after initial equilibration; ID=infinte dilution.
positions studied here were not reported. The experimental activity coefficient derivative was obtained using an analytical expression for the excess molar Gibbs free energy fitted to experimental data in Ref. 11.

RESULTS

Some of the physical properties of TFE/water mixtures are presented in Fig. 1 for the compositions given in Table III. The trends in most properties as a function of composition are well reproduced, but quantitative agreement was not so good, although this was often due to poor values for the pure solution properties (with the exception of the density). 34 Particularly noticeable were the diffusion constant of TFE, and the enthalpy of mixing. The larger positive excess enthalpy of mixing obtained from the simulations indicated that the current description of TFE/water interactions was not as favorable as it should be. Reasons for this discrepancy will become apparent later on in this section. The gauche/trans ratio for rotation around the C–C–O–H dihedral was independent of composition and remained at 40:60.

Evidence to support our Kirkwood–Buff approach is presented in Fig. 2. Here, the derivatives of the TFE and water chemical potentials, the isothermal compressibility, and the TFE and water partial molar volumes are presented, as generated using KB theory and the center of mass based radial distribution functions obtained from the xTTE/M = 0.1 (4.3 M) TFE simulations. The properties are plotted as a function of the integration distance [Eq. (1)] and no image molecules were included. For all properties except the compressibility a plateau region at intermediate distances in which the derivatives adopt a particular constant value was observed. This region covered the value of 1.0 nm which was adopted as the integration distance in the present calculations. The compressibility was still oscillating in this region, and hence the KB expression for this property displayed a high degree of uncertainty. As a check for any system size dependence, the data obtained from a larger simulation (~2.7 times larger by volume) of the same composition are also included. The data displayed a small system size dependence with a tendency for the smaller systems to underestimate the deviation of each function away from the baseline. In the present study we have ignored these differences as they are small in comparison with the inherent errors in the TFE force field.

In order to determine the infinite dilution activity coefficient derivatives, one requires $G'_{cc}$ and $G'_{cw}$. The latter can be obtained from a simulation of a single cosolvent in a bath of solvent. $G'_{cc}$ can be determined by calculating the rdf

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FIG. 1. Properties of TFE/water mixtures as a function of composition. The solid lines represent the experimental data and the symbols denote simulation data. Properties are: density ($\rho$), relative permittivity ($\varepsilon$), diffusion constant ($D$), residence times ($\tau$), excess enthalpy of mixing ($\Delta H_m$).

FIG. 2. The derivative of the chemical potential, the isothermal compressibility, and the partial molar volumes of water and TFE ($x_t = 0.1$) as a function of the integration distance in Eq. (1). The properties of two systems of the same composition but differing in simulation cell size are also included (see Table IV).
between two cosolvent molecules in a bath of solvent. The rdfs for TFE–TFE, TFE–water, and water–water in pure TFE are presented in Fig. 3 as a function of cosolvent mole fraction. Both molecule pairs displayed a tendency to associate in a bath of the other species. The TFE–TFE rdfs all displayed a favorable contact interaction. This was most pronounced in the $x_c = 0.5$ mixture indicating that a significant degree of aggregation occurred. Aggregation also explains the low solvation of TFE by water at $x_c = 0.5$. The water–water rdfs varied significantly with composition. There was a larger favorable water–water contact interaction at infinite dilution in TFE and at $x_c = 0.5$, with the latter extending over several molecular diameters. The above rdfs have been used to evaluate the corresponding KB integrals at infinite dilution of each species. ($\partial \ln f_c / \partial x_c)_{T,p,r_c \rightarrow 0}$ was determined to be $6 \pm 1$ using Eq. (6). The corresponding value from experiment is $-12.97$.\(^{11}\) ($\partial \ln f_w / \partial x_w)_{T,p,r_w \rightarrow 0}$ obtained using the KB integrals was found to be $2.2 \pm 0.3$ kJ/mol, while the experimental value is $-0.16$.\(^{11}\) Clearly, the agreement with experiment was not good. Longer simulation times and a better TFE model are required. Fortunately, the exact values of these derivatives had only a small effect on the calculated activity coefficients after integration.

Previously, we have performed a KB analysis of the experimental TFE/water data and determined the KB integrals as a function of composition.\(^{30}\) The experimental KB integrals are plotted in Fig. 4, together with the simulated values. The trends in both $G_{cc}$ and $G_{cw}$ were very reasonable with the experimental maxima and minima reproduced qualitatively, although they appear at lower mole fractions of TFE. However, the maximum in $G_{ww}$ appears at far larger mole fractions in the simulations and is several orders of magnitude too large. Hence, excessive clustering between water molecules was observed in the simulations of high TFE mole fractions, even though the simulated pure TFE and pure water KB integrals were very reasonable.

Using the computed KB integrals displayed in Fig. 4 one

![FIG. 3. Radial distribution functions (rdfs) for TFE–TFE, TFE–water, and water–water in TFE/water mixtures of different composition. ID denotes infinite dilution. The first peak in the water–water rdf for an infinitely dilute concentration of water in TFE occurs at a distance of 0.287 nm, with a peak height of 28.9 (this rdf has been truncated to illustrate the major features of all the curves in the bottom panel).](image1)

![FIG. 4. Kirkwood–Buff integrals as a function of TFE mole fraction. The thick lines represent the values calculated from experimental data and symbols denote the simulation data.](image2)
can determine a range of properties for TFE/water mixtures. These are displayed in Fig. 5. In general, the trends in the experimental data were well reproduced with the exception of the compressibility which, as mentioned previously, was sensitive to the integration distance, and the partial molar volume of water which increased in the simulations whereas the experimental data display a decrease. The positive values of $\eta$ and $\zeta$ for all compositions indicated that the solutions were stable. It might seem surprising that the absolute KB integrals were significantly different from the experimental values, whereas the resulting properties displayed good agreement with experiment. This is partly due to the fact that all the properties, except the compressibility (through $\zeta$), depend on differences between KB integrals, and some cancellation can occur.

As a test of the Kirkwood–Buff approach, we attempted to determine the partial molar volumes of TFE and water by comparing the volume of the mixture at $x_c=0.5$ with that of a solution in which a single water or a single TFE molecule were deleted. Values of $25\pm11$ and $75\pm10$ cm$^3$/mol were obtained from the finite difference method for the partial molar volumes of water and TFE, respectively, compared to the corresponding values of $19.6\pm0.3$ and $71\pm1$ cm$^3$/mol, obtained using simulated KB integrals. Both the partial molar volumes obtained from KB theory, as well as those obtained by the finite difference method, are consistent in that they reproduce the observed average volume. However, the finite difference data suffered from large uncertainties even after 1 ns of simulation. Hence, assuming the truncated rdf approach is reasonable, it is possible to generate properties with higher precision than conventional simulation techniques. In contrast, the compressibility of the 4.3 M solution obtained by numerical differentiation ($4.4\times10^{-2}$ atm$^{-1}$) compared well with the experimental value of $4.7\times10^{-5}$ atm$^{-1}$, whereas the value of $\kappa_T$ determined using KB integrals ($90\pm12\times10^{-5}$ atm$^{-1}$) was clearly too high. Again, this was due to the high sensitivity of the simulated $\kappa_T$ KB expression on the integration distance. Although the above data do not conclusively prove that a truncated rdf approach is acceptable, the KB data are consistent with the model independent data (partial molar volumes). This, coupled with the fact that the majority of experimental trends are reproduced, suggests that the truncated rdf approximation provides meaningful data.

It is also interesting to examine the convergence properties of the different KB expressions. In Fig. 6, the running time averages of the chemical potential derivatives and partial molar volumes are displayed as a function of simulation.
time (after equilibration) for the \( x_c = 0.1 \) (4.3 M) system. All the expressions were converged after 1 ns of simulation. However, it should be noted that the observed changes between 0.1 and 1.0 ns were of the order of 10% for the chemical potential derivatives and less than 1% for the partial molar volumes. These values are generally far smaller than the corresponding changes which occur with composition (see Fig. 5). Hence, simulations of a few hundred picoseconds are probably adequate. The same convergence pattern was also observed for the individual KB integrals \( (G_{cc}, G_{cw}, \text{and } G_{ww}) \).

The models of TFE and water used here generally reproduced the major trends in the properties of TFE/water mixtures. While aggregation of TFE molecules was in agreement with experiment, the reason for a lack of a quantitative comparison appeared to be related to an excessive aggregation of both TFE with TFE and water with water observed for the simulated solutions. An indication of the degree of aggregation can be seen in Fig. 7. Here, a configuration from the 4.3 M solution is displayed and one can clearly distinguish well-defined TFE-rich and water-rich regions. Although this resembles a phase separation, the positive values of \( \eta \) and \( \zeta \) indicate that this was a real (stable) solution mixture.

While one can have a high degree of confidence in the properties calculated for the majority of the compositions investigated here, there are problems which arise for very low or very high mole fractions due to the high degree of aggregation observed. The simulation performed at a mole fraction of 0.0186 involved just 9 TFE molecules in 476 waters. Here, the small number of TFE molecules can affect the aggregation process. For instance, there may be too few molecules to form a reasonable hydrophobic core, if that is an important feature of the mixture. This is illustrated in Table IV where a system size comparison has been performed for TFE mole fractions of 0.0186 (1 M) and 0.1 (4.3 M). While the data obtained for the higher mole fraction were reasonably consistent between the two system sizes, there were significant differences for the smaller system. A higher degree of TFE aggregation \( (G_{cc}) \) was observed in the larger 1 M simulation and this affected all the KB properties. The same problems will also arise for simulations involving a small number of water molecules in a large number of TFE molecules. It is difficult to judge how important this factor is for studying nonaggregating systems.

CONCLUSIONS

It has been shown that KB theory and molecular simulations can be used to provide information concerning a variety of thermodynamic properties of solution mixtures. The approximation of a truncated NpT rdf capturing the major features of the \( \mu VT \) rdf appeared to be reasonable based on the fact that: (i) the major trends in the experimental data were reproduced; (ii) the KB partial molar volume data agreed with finite difference calculations, and; (iii) the similarity of rdfs obtained in open and closed systems observed from previous simulation data.\(^{55}\) The truncation represented an interaction or correlation length of 1.0 nm between the molecules. This approach provided valuable thermodynamic data (partial molar volumes and activity derivatives) which are generally inaccessible through normal simulation techniques. It also suggests a route for the improvement of current force fields by providing more experimental data for comparison and refinement. There appeared to be a small system size dependence in the calculated KB properties indicating that a slightly larger system size might lead to results that are in better agreement with experimental data.

The models of TFE and water investigated here were able to reproduce the trends in the properties of TFE solutions, except for very low or high mole fractions. In particular, trends in the activity coefficient with composition could be directly related to an excessive degree of aggregation in the simulations, especially between water molecules at high mole fractions of TFE. On closer inspection, the high degree of aggregation appeared to stem from the larger intermolecular energy between pairs of water molecules in solution. The per molecule intermolecular energies being \(-46.6\) and \(-38.8\) kJ/mol for pure SPC/E water and pure TFE, respectively. This is in contrast to the experimental heats of vaporization which are \(44.0\) kJ/mol for both pure water and pure TFE (see Table I). The major problem, in addition to a relatively poor TFE model, is that the SPC/E model is a polarization corrected model. Here, the polarization correction results in a larger intermolecular energy for water.\(^{62}\) The current TFE force field, and most other force fields used in liquid simulations, did not include this correction. In addition, the lower charge on the hydroxyl group in the TFE model makes it unable to compete with water–water interactions. Therefore, the description of TFE/water mixtures becomes unbalanced. This also helps to explain the inability of the simulations to quantitatively reproduce the excess enthalpy of mixing, and explains the highly

FIG. 7. A representative configuration from the \( x_c = 0.1 \) (4.3 M) TFE/water simulation. Solid spheres and sticks represent the TFE and water molecules, respectively.
favorable association of water pairs at infinite dilution in pure TFE (see Fig. 3).

The SPC/E water model was chosen as it reproduces the enthalpy of vaporization, density, and diffusion constant of pure water correctly.62 It might seem more reasonable to use an uncorrected model for water. However, polarization corrections for different solvents will not cancel as, in general, molecules possess different molecular dipole moments (gas phase and solution) and different polarizabilities (see Table I). Hence, a water model with no polarization correction will not necessarily perform better than SPC/E. What is required is the inclusion of the polarization correction during the development of a TFE force field, or the inclusion of explicit polarization effects using a polarizable model. However, this would require a reparameterization of existing force fields. Finally, it should be noted that this imbalance could also occur when using SPC/E with common force fields developed for peptides or other molecules, and may have been exaggerated by using Ewald electrostatics instead of the cutoff approach originally adopted for the model.

TABLE IV. Comparison of solution properties as a function of system size. \( N_c \) = number of TFE molecules in the simulation; \( N_w \) = number of SPC/E water molecules in the simulation; \( \rho \) = density of the solution in g/cm\(^3\); \( D_c \) = diffusion constant of TFE and \( D_w \) = diffusion constant of water in \( \times 10^{-9} \) m\(^2\)/s; \( \tau_{wc} \) = residence time of water around TFE, and \( \tau_{cw} \) = residence time of water around TFE in ps; \( \epsilon \) = dielectric constant; \( \Delta H_{\text{ex}} \) = excess heat of mixing in kJ/mol, where the average values (per molecule) for the pure solutions are \( U'_{cc} = 131.17 \) kJ/mol, and \( U'_{ww} = -46.57 \) kJ/mol; \( G_{cc} \), \( G_{ww} \), and \( G_{cw} \) are cm\(^3\)/mol; \( \eta \) = in \( \times 10^{-5} \) atm\(^{-1} \); \( \bar{V}_c \) and \( \bar{V}_w \) are in cm\(^3\)/mol. See Eqs. (1)–(4) for definitions of \( G_{cc} \), \( G_{ww} \), \( G_{cw} \), \( \eta \), \( \xi \), \( \kappa_T \), \( \bar{V}_c \), \( \bar{V}_w \), and \( \delta \ln f_c / \delta \alpha_c \). Values in parentheses are estimated errors.

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