

# On the use of the quasi-Gaussian entropy theory in the study of simulated dilute solutions

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In a recent paper [M. D'Alessandro, M. D'Abramo, G. Brancato, A. Di Nola, and A. Amadei, *J. Phys. Chem. B* **106**, 11843 (2002)] we showed how to combine molecular dynamics simulations with the quasi-Gaussian entropy theory, in order to model the statistical mechanics and thermodynamics of ionic (water) solutions. In this paper we extend the method to treat nonspherical solutes, describe more thoroughly its theoretical basis and apply it to a set of more complex solute molecules in water (i.e., water, methane, ethane, methanol, and ethanol). Results show that this approach can really provide an excellent theoretical description of solute–solvent systems over a wide range of temperatures. © 2004 American Institute of Physics. [DOI: 10.1063/1.1647530]

## I. INTRODUCTION

The use of molecular simulations for evaluating the statistical mechanics and thermodynamics of liquids is a challenge for theoretical and computational physical chemistry–chemical physics. Usual computational methods (e.g., particle insertion, thermodynamic integration, etc.) although in principle able to provide, for a given Hamiltonian, the “exact” thermodynamics, can be severely affected by their slow convergence and, due to the high computational costs, are typically limited to the evaluation of the excess chemical potential at a few state points. Hence, it would be of great importance in theoretical physical chemistry–chemical physics the use of a largely analytical method, based on a sound theory, providing the thermodynamics of simulated liquid mixtures and solutions at relatively low computational costs, regardless of the complexity of the molecules involved. In a recent paper<sup>1</sup> we extended the quasi-Gaussian entropy (QGE) theory, in combination with molecular simulations, to obtain a complete description of the thermodynamics of dilute ionic solutions. In that paper we showed that this theoretical approach was very efficient for the ionic solutions, but we did not address its applicability and accuracy for treating more complex or apolar solutes. Therefore in this paper we optimize and extend the proposed method to treat nonspherical solutes, investigating its applicability and accuracy for polar and apolar molecules. Moreover, using a water molecule as solute in water and comparing its partial molar properties with those obtained from the molecular properties of (simulated) pure liquid water, we evaluate directly the consistency of the method. The paper is organized as follows. In Sec. II we describe the theoretical basis of our approach

clarifying some relevant derivations (providing a better physical understanding) and extending the theory further to treat nonspherical solutes. In Sec. IV we test the accuracy and applicability of our approach using, as solutes in water, a water molecule and four different types of molecules: methane, ethane, methanol, and ethanol. Finally we summarize the results obtained in Sec. V.

## II. THEORY

In this section we describe in details the derivations of the QGE theory for treating partial molecular properties and to combine this theory with molecular simulation data. We essentially follow the derivations of the previous paper<sup>1</sup> with some relevant extensions and change of notation. Note also that in some equations of the previous paper a few typing errors occurred.

For a fluid state system of  $N$  solute molecules at high dilution, the canonical partition function can be expressed as<sup>2,3</sup>

$$Q = \frac{(8\pi^2 NV)^N}{N!} \times \left( \Theta \int^* e^{-\beta \mathcal{U}'} \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{in} d\mathbf{x} \right)^N \equiv \left( \frac{8\pi^2 V \Theta}{e^{-1}} \int^* e^{-\beta \mathcal{U}'} \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{in} d\mathbf{x} \right)^N, \quad (1)$$

where  $\mathcal{U}'$  is the excess energy (basically the potential energy including the quantum vibrational ground state energy) of a subsystem made of  $n_s$  solvent molecules and a single solute molecule with fixed rototranslational coordinates,  $\mathbf{x}_{in}$  the

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generalized internal (classical) coordinates of the single solute molecule and  $\mathbf{x}$  the (classical) coordinates of the  $n_s$  solvent molecules within the solute molecular volume  $V$ , i.e., the integration limits are defined by  $V$ . Moreover  $\tilde{m}_j$  is the mass tensor of the  $j$ th solvent molecule,  $\tilde{M}$  the mass tensor of the solute (expressed in the basis set which makes it independent of the center of mass position and Eulerian angles), and  $\Theta$  a temperature dependent factor including the quantum corrections,<sup>3</sup>

$$\Theta = \frac{(2\pi kT)^{(d+d_s)/2} Q_{\text{ref}}^{\text{qm}}}{n_s! h^{(d+d_s)} (1+\gamma)(1+\gamma_s)^{n_s}} \quad (2)$$

with  $1+\gamma$  and  $1+\gamma_s$  the symmetry coefficients for the solute and the solvent respectively,  $d$  and  $d_s$  the number of classical degrees of freedom in the solute and  $n_s$  solvent molecules and  $Q_{\text{ref}}^{\text{qm}}$  the quantum vibrational partition function, as defined in previous papers,<sup>3,4</sup> for the molecules within the solute molecular volume  $V$  (note that in this partition function the quantum energy also involves the reference electronic ground state energy). Finally the star denotes an integration only over the accessible configurational space within the solute molecular volume and  $h$  is the Planck's constant. Note that we used the approximation  $N! \cong e^{-N} N^N$ . Defining as reference condition the system at the same temperature and density but without excess energy and hence without any unaccessible configuration, with partition function

$$Q_{\text{ref}} = \frac{(8\pi^2 NV)^N}{N!} \left( \Theta \int \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x} \right)^N \\ \cong \left( \frac{8\pi^2 V \Theta}{e^{-1}} \int \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x} \right)^N \quad (3)$$

we can express the excess (Helmholtz) free energy per solute molecule as<sup>2-6</sup>

$$A' = A - A_{\text{ref}} = \frac{-kT \ln(Q/Q_{\text{ref}})}{N} \\ = -kT \ln \left\{ \frac{\int^* e^{-\beta U'} \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x}}{\int^* \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} (\det \tilde{M})^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x}} \right\} \\ - kT \ln \epsilon \quad (4)$$

$$= -kT \ln \langle e^{-\beta U'} \rangle_{\text{ref}} - kT \ln \epsilon = kT \ln \langle e^{\beta U'} \rangle - kT \ln \epsilon, \quad (5)$$

where  $\epsilon$  is the fraction of available configurational space<sup>6</sup>

$$\epsilon = \frac{\int^* (\det \tilde{M})^{1/2} \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x}}{\int (\det \tilde{M})^{1/2} \prod_{j=1}^{n_s} (\det \tilde{m}_j)^{1/2} d\mathbf{x}_{\text{in}} d\mathbf{x}}. \quad (6)$$

The entropic term due to a possible confinement of the system in configurational space,  $k \ln \epsilon$ , is usually associated with hard-body excluded volume<sup>4</sup> and for molecules with a simple geometry can be obtained in principle by hard body equations of state. Note that the last equations means that the statistical mechanics and thermodynamics of the whole system are fully determined by the subsystem including a single

solute molecule and  $n_s$  solvent ones (thermodynamic elementary system). The ensemble averages in Eq. (5) can also be expressed as

$$\langle e^{-\beta U'} \rangle_{\text{ref}} = \int \rho_{\text{ref}}(U') e^{-\beta U'} dU', \quad (7)$$

$$\langle e^{\beta U'} \rangle = \int \rho(U') e^{\beta U'} dU', \quad (8)$$

where  $\rho_{\text{ref}}(U')$ ,  $\rho(U')$  are the probability distribution functions of the excess energy  $U'$  in the reference and actual conditions, respectively, for the elementary system. The use of  $\rho_{\text{ref}}$  or  $\rho$  is fully equivalent and, for a given model distribution, they provide identical results. We showed in previous papers<sup>4,6-10</sup> that one of the simplest distribution, the gamma distribution, yields a fully physically acceptable theoretical model providing an excellent description of the fluid state thermodynamics over a wide range of temperature and density, including solute-solvent systems. We can rewrite the excess free energy of the elementary system as

$$A'(T) = n_s a'_s + a', \quad (9)$$

where  $a'_s$  is the partial molecular excess (Helmholtz) free energy of the solvent and clearly  $a'$  is the partial molecular excess (Helmholtz) free energy of the solute. It is worth noting that solvent and solute partial molecular excess free energies are obtained at fixed pressure  $p$  for the actual fluid and not in general at fixed pressure for the reference state. This is because the reference state is defined with the same volume and molecules number of the actual condition. Hence, defining with  $n$  the number of solute molecules in the elementary system, which can be considered a continuous variable as the elementary system still contains a huge number of solvent molecules, we have

$$a'_s = \left( \frac{\partial A'}{\partial n_s} \right)_{p,T,n} = \left( \frac{\partial A}{\partial n_s} \right)_{p,T,n} - \left( \frac{\partial A_{\text{ref}}}{\partial n_s} \right)_{p,T,n} \\ = \left( \frac{\partial A}{\partial n_s} \right)_{V,T,n} + \left( \frac{\partial A}{\partial V} \right)_{n_s,T,n} v_s \\ - \left( \frac{\partial A_{\text{ref}}}{\partial n_s} \right)_{V,T,n} - \left( \frac{\partial A_{\text{ref}}}{\partial V} \right)_{n_s,T,n} v_s \\ = \mu'_s - p' v_s, \quad (10)$$

$$a' = \left( \frac{\partial A'}{\partial n} \right)_{p,T,n_s} = \left( \frac{\partial A}{\partial n} \right)_{p,T,n_s} - \left( \frac{\partial A_{\text{ref}}}{\partial n} \right)_{p,T,n_s} \\ = \left( \frac{\partial A}{\partial n} \right)_{V,T,n_s} + \left( \frac{\partial A}{\partial V} \right)_{n_s,T,n} v \\ - \left( \frac{\partial A_{\text{ref}}}{\partial n} \right)_{V,T,n_s} - \left( \frac{\partial A_{\text{ref}}}{\partial V} \right)_{n_s,T,n} v \\ = \mu' - p' v, \quad (11)$$

$$v_s = \left( \frac{\partial V}{\partial n_s} \right)_{p,T,n}, \quad (12)$$

$$v = \left( \frac{\partial V}{\partial n} \right)_{p,T,n_s}, \quad (13)$$

$$\mu'_s = \mu_s - \mu_{\text{ref},s}, \quad (14)$$

$$\mu' = \mu - \mu_{\text{ref}}, \quad (15)$$

$$p' = p - p_{\text{ref}}, \quad (16)$$

where  $p_{\text{ref}}$  is the pressure in the reference state,  $v$  and  $v_s$  the partial molecular volumes of the solute and solvent in the actual fluid (which are in general different from the ones in the reference state), and  $\mu$ ,  $\mu_{\text{ref}}$  the chemical potentials in the actual fluid and in the reference condition, respectively. At high dilution the solvent partial molecular properties and all the intensive thermodynamic properties are virtually identical to the pure solvent ones (hence independent of the solute), and so their derivatives in the solvent molecular number, at fixed pressure, must be virtually zero. Assuming that  $A'$  can be well modeled by a single gamma state,<sup>4</sup> we have

$$A' = U'_0 - T_0 C'_{V0} \Lambda(T) - kT \ln \epsilon, \quad (17)$$

$$\Lambda(T) = \frac{1}{\delta_0} + \frac{T}{T_0 \delta_0^2} \ln\{1 - \delta(T)\}, \quad (18)$$

$$\delta(T) = \frac{T_0 \delta_0}{T(1 - \delta_0) + T_0 \delta_0}, \quad (19)$$

with  $U'_0 = U'(T_0)$  and  $C'_{V0} = C'_V(T_0)$  the excess internal energy and heat capacity of the elementary system at the reference temperature  $T_0$ ,  $k \ln \epsilon$  the entropy term due to configurational confinement, and  $\delta_0$  a dimensionless intensive property<sup>4</sup> independent of the temperature, that in our case (high dilution) is determined by the solvent. The gamma state expressions<sup>4</sup> would then provide any thermodynamic property of the elementary system and hence of the whole macroscopic system. Using the fact that  $(\partial \Lambda / \partial n_s)_{p,T,n} = 0$  (high solute dilution), we then obtain

$$\left( \frac{\partial \Lambda}{\partial n_s} \right)_{p,T,n} = \left( \frac{\partial \Lambda}{\partial \delta_0} \right)_T \left[ \left( \frac{\partial \delta_0}{\partial n_s} \right)_{v,n} + \left( \frac{\partial \delta_0}{\partial V} \right)_{n,n_s} v_s \right] = 0 \quad (20)$$

and hence

$$v_s = - \frac{(\partial \delta_0 / \partial n_s)_{v,n}}{(\partial \delta_0 / \partial V)_{n,n_s}}, \quad (21)$$

$$v = V - n_s v_s = V + n_s \frac{(\partial \delta_0 / \partial n_s)_{v,n}}{(\partial \delta_0 / \partial V)_{n,n_s}}. \quad (22)$$

These last equations clearly show that both the solvent and solute partial molecular volumes are, along the isochore, temperature independent. This result points out a specific feature of the gamma state model at high solute dilution. It is worth noting that the use of the more complex multi gamma state model, introduced in previous papers<sup>6,7,11</sup> and based on the partition of phase space into a set of gamma state regions, may provide temperature dependent partial molecular volumes. Subtracting the solvent partial excess free energy from Eq. (17), we readily obtain

$$\begin{aligned} a' &= A' - n_s a'_s \\ &= \left( \frac{\partial A'}{\partial n} \right)_{v,T,n_s} + \left( \frac{\partial A'}{\partial V} \right)_{n_s,T,n} v = u'_0 - c'_{V0} T_0 \Lambda(T) \\ &\quad - kT \ln \bar{\epsilon}, \end{aligned} \quad (23)$$

where

$$\begin{aligned} u'_0 &= U'_0 - n_s \left[ \left( \frac{\partial U'_0}{\partial n_s} \right)_{v,n} + \left( \frac{\partial U'_0}{\partial V} \right)_{n_s,n} v_s \right] \\ &= \left( \frac{\partial U'_0}{\partial n} \right)_{v,n_s} + \left( \frac{\partial U'_0}{\partial V} \right)_{n_s,n} v, \\ c'_{V0} &= C'_{V0} - n_s \left[ \left( \frac{\partial C'_{V0}}{\partial n_s} \right)_{v,n} + \left( \frac{\partial C'_{V0}}{\partial V} \right)_{n_s,n} v_s \right] \\ &= \left( \frac{\partial C'_{V0}}{\partial n} \right)_{v,n_s} + \left( \frac{\partial C'_{V0}}{\partial V} \right)_{n_s,n} v, \\ \ln \bar{\epsilon} &= \ln \epsilon - n_s \left[ \left( \frac{\partial \ln \epsilon}{\partial n_s} \right)_{v,n} + \left( \frac{\partial \ln \epsilon}{\partial V} \right)_{n_s,n} v_s \right] \\ &= \left( \frac{\partial \ln \epsilon}{\partial n} \right)_{v,n_s} + \left( \frac{\partial \ln \epsilon}{\partial V} \right)_{n_s,n} v, \end{aligned}$$

are temperature independent (as  $v_s$ ,  $v$  are temperature independent) and then at every temperature correspond to the partial molecular excess internal energy  $u'_0$  and heat capacity  $c'_{V0}$ , evaluated at the reference temperature  $T_0$ , and  $-kT \ln \bar{\epsilon}$  to the partial molecular excess free energy due to the confinement. Therefore Eq. (23) also implies  $(\partial \Lambda / \partial n)_{p,T,n_s} = 0$ . Using general thermodynamic relations, the gamma state expressions for the various thermodynamic properties and the fact that the partial molecular volumes are temperature independent, we can obtain any possible thermodynamic property at high dilution, e.g.,

$$\begin{aligned} \left( \frac{\partial U'}{\partial n} \right)_{v,n_s,T} &= \left( \frac{\partial U'}{\partial n} \right)_{p,n_s,T} - \left( \frac{\partial U'}{\partial V} \right)_{n,n_s,T} v \\ &= \left( \frac{\partial \beta \mu'}{\partial \beta} \right)_{v,n,n_s} \end{aligned} \quad (24)$$

or the partial molecular internal energy  $u'$  and heat capacity  $c'_V$

$$\begin{aligned} u' &= \left( \frac{\partial U'}{\partial n} \right)_{p,n_s,T} = \left( \frac{\partial \beta \mu'}{\partial \beta} \right)_{v,n,n_s} \\ &= u'_0 + (T - T_0) \frac{c'_{V0} T_0}{T(1 - \delta_0) + \delta_0 T_0}, \end{aligned}$$

$$c'_V = \left( \frac{\partial C'_V}{\partial n} \right)_{p, n_s, T} = \left( \frac{\partial u'}{\partial T} \right)_{V, n, n_s} \\ = c'_{V0} \left[ \frac{T_0}{T(1 - \delta_0) + \delta_0 T_0} \right]^2.$$

The previous general equations are very suited to be used in combination with simulation data. In fact, Eq. (9) states that we can obtain the whole thermodynamics of a solute–solvent system, at high solute dilution, only using information from simulations of a single solute molecule embedded in the solvent. Assuming a gamma state behavior for the solute–solvent system as well as for the pure solvent, we can parametrize the corresponding gamma state models fitting the average excess (potential) energies in temperature,<sup>1</sup> and hence obtain the solute excess chemical potential, excluding the confinement contribution

$$\mu^* = \mu' + kT \left( \frac{\partial \ln \epsilon}{\partial n} \right)_{V, n_s} = \left( \frac{\partial A^*}{\partial n} \right)_{V, T, n_s} = \Delta A^*, \quad (25)$$

$$A^* = A' + kT \ln \epsilon, \quad (26)$$

where  $\Delta A^*$  is the difference between the excess Helmholtz free energies without the confinement terms (confined ideal reduced Helmholtz free energy<sup>4</sup>) of the solute–solvent system and of the pure solvent one, at fixed volume. Note that from the previous equations, considering that  $\epsilon$  is temperature independent, we have  $\Delta(\beta\mu') = \Delta(\beta\mu^*)$ . The confinement term  $(\partial \ln \epsilon / \partial n)_{V, n_s}$  is determined by the unaccessible phase space regions typically due to hard body contacts. In principle such unaccessible configurations should be characterized by an infinite energy or at least should be separated by the others by an infinite energy barrier. In practice a confinement behavior is found also in systems where no unaccessible regions are strictly present.<sup>6,10</sup> In this case such a term must be regarded as an effective confinement term due to the presence of high energy phase space regions which are virtually unaccessible in the whole temperature range of interest. In the previous article we focused on water–solute systems where the confinement behavior could be well described by a hard sphere model.<sup>1</sup> In this paper we still consider two spherical-like solutes (water and methane) but we also include nonspherical molecules such as ethane, methanol and ethanol. From Eqs. (11), (23), and (25) we also have

$$\mu^* = u'_0 - c'_{V0} T_0 \Lambda(T) + p^* v, \quad (27)$$

$$p^* = p' - \xi T, \quad (28)$$

$$\xi = k \left( \frac{\partial \ln \epsilon}{\partial V} \right)_{n, n_s}, \quad (29)$$

where  $\Lambda(T)$ ,  $p^*$ ,  $p'$ ,  $\xi$ , being intensive properties, are given by the gamma state obtained by the pure solvent simulations (the gamma state expressions for  $p'$  and  $p^*$  are given in previous papers<sup>4</sup>). Fitting, with Eq. (27),  $\mu^*$  as obtained by Eq. (25), we can evaluate  $u'_0$ ,  $c'_{V0}$ , and the partial molecular volume  $v$ . In the infinite temperature limit the excess thermodynamics of the theoretical model we use, will reduce to that of a hard body mixture of the same molar fraction. In the

previous paper<sup>1</sup> we used the Lebowitz equation of state for hard sphere mixtures<sup>12</sup> to obtain the hard sphere radius of the solute once the partial molecular volume is known. In this paper we utilize a more recent and accurate hard sphere mixture equation of state (BMCSL)<sup>13–15</sup> for spherical-like solutes and the recent hard chain equation of state (SC-SPT)<sup>16</sup> to treat homoatomic linear chain solutes (SC-SPT deals with linear chains each made of identical beads). BMCSL has been systematically tested in a rather large density range, including the solute infinite dilution where it provides an excellent agreement with (Monte Carlo) simulation data. Lebowitz's equation of state seems to overestimate the hard sphere radius of the solute and has been tested in a limited range of density not including the solute infinite dilution. This makes BMCSL really more reliable when dealing with large spherical solutes at low dilution. In the case of nonspherical molecules it is obvious that any hard sphere equation of state would be inaccurate and SC-SPT seems one of the most reliable equation of state for hard chain mixtures, although applicable only to homoatomic linear solutes. Other types of nonspherical solutes would require different, and probably more complex, hard body equations of state and so, in this paper, we model their confinement properties simply using at a single temperature thermodynamic integration data (*vide infra*). Note that the confinement properties of the solvent are obtained using the homogeneous Carnahan–Starling hard sphere equation of state.<sup>4,17</sup> The solvent hard sphere radius is evaluated using the Carnahan–Starling model to describe the confinement part of the excess pressure (i.e.,  $\xi T$ ) obtained by the pure solvent simulations. From Eq. (24) we can evaluate the free energy confinement term  $-kT \ln \bar{\epsilon} = -kT(\partial \ln \epsilon / \partial n)_{p, n_s}$  via

$$-kT \left( \frac{\partial \ln \epsilon}{\partial n} \right)_{p, n_s} = -kT \left( \frac{\partial \ln \epsilon}{\partial n} \right)_{V, n_s} - \xi T v, \quad (30)$$

where from the estimate of the solute hard body chemical potential, it is straightforward to obtain the corresponding excess chemical potential  $-kT(\partial \ln \epsilon / \partial n)_{V, n_s}$ . We follow three strategies to obtain the solute hard body excess chemical potential and the other confinement properties. For spherical solutes we directly use the partial molecular volume to evaluate the corresponding hard sphere radius via BMCSL. This is possible since BMCSL is a very accurate and general equation of state which provides rather accurate pressure derivatives of the chemical potential such as the partial molar volume. Hard chain solutes are more difficult to be treated and SC-SPT, although rather efficient, is not quantitatively fully reliable for evaluating pressure derivatives of the chemical potential (we performed tests on this matter). Hence for nonspherical solutes which can be considered as linear chains of identical particles (in this paper ethane), we estimate the bead diameter  $d$  by the corresponding Lennard-Jones  $\sigma$  value, via  $\sigma/\sigma_{\text{ref}} = d/d_{\text{ref}}$ , where  $\sigma_{\text{ref}}$  and  $d_{\text{ref}}$  correspond to the methane values. Finally, for any other nonspherical solutes (in this paper methanol and ethanol) we obtain the confinement properties to be used in our model, simply performing at one temperature a thermodynamic integration calculation to evaluate  $\mu'$ . From such a value the

temperature independent confinement term can be easily obtained from  $(\partial \ln \epsilon / \partial n)_{V, n_s} = (\mu^* - \mu') / (kT)$ , where  $\mu^*$  is again evaluated by the QGE theory.

### III. SIMULATION METHODS

We performed five different sets of molecular dynamics (MD) simulations over a wide temperature range (280–1200 K), using a cubic box of 256 simple point charge (SPC) (Ref. 18) water molecules, at 55.32 mol/l, plus a solute molecule: a water (SPC), a methane,<sup>19</sup> an ethane,<sup>19</sup> a methanol,<sup>20</sup> and an ethanol,<sup>20</sup> respectively. Note that in these models non polar hydrogens are not explicitly present (united atoms approximation). All the simulations were performed using GROMACS software package<sup>21–23</sup> modified to use the isokinetic temperature coupling.<sup>24</sup> This was done in order to obtain results fully consistent with statistical mechanics.<sup>2,25</sup> For all the simulations the number of steps was 3 000 000 with three different time steps: 2 fs for simulations in the range 280–450 K, 1 fs in the range 450–800 K and 0.5 fs in the range 800–1200 K. Hence the corresponding simulation time lengths were about 6, 3, and 1.5 ns and in each simulation the initial 250 000 steps were considered the equilibration and so removed from the analysis. Short range interactions were evaluated within 0.9 nm cut off radius and the long range electrostatics was calculated using the particle mesh Ewald (PME) method,<sup>26</sup> with 34 wave vectors in each dimension and a fourth order cubic interpolation. All the solute molecules were constrained for the internal and rototranslational motions via the rototranslational<sup>2</sup> and bond length<sup>27</sup> constraints, or using the freezing option in GROMACS. Hence in the simulations we treated the solutes as rigid molecules with no rototranslational motions. This procedure, which speeds up the solvent relaxation around the solute, provides the correct statistical mechanics and thermodynamics of the system (SPC plus a rigid solute). In order to compare our QGE results with values obtained by a different, and typically reliable, computational procedure, we used the GROMACS routine to perform thermodynamic integration (TI) calculations (soft core potential with  $\alpha=1.51$ ,  $\sigma=0.3$  nm) on the same systems, at 300 K and 800 K, to evaluate the corresponding solutes excess chemical potentials. For methanol and ethanol the 800 K values were also used to obtain the confinement term in our models (see Theory section). For methane we performed 11 perturbation simulations which were tested to be enough for a good convergence of the excess chemical potential value. Ethane excess chemical potential was obtained from the methane one adding the free energy difference for the ethane to methane transformation (again 11 simulations). In the case of SPC our tests showed that a comparable convergence was obtained using 21 simulations. Methanol excess chemical potential was evaluated from the methane one adding the free energy difference for the methanol to methane transformation, where the latter was obtained performing 21 simulations. Finally ethanol excess chemical potential was obtained from the methanol one adding the free energy difference for the ethanol to methanol change (for this latter perturbation we performed again 11 simulations). All the perturbation simulations (250 ps each,

time step=2 fs at 300 K and 60 ps each, time step=1 fs at 800 K) were performed identically to the ones utilized for QGE calculations except for the use of a simple (group based) 0.9 nm cut off radius for treating molecular interactions. Note that comparison between TI results for Ewald sum or generalized reaction field and group based cut off simulations, shows a complete agreement within the noise.<sup>28,29</sup> In TI calculations we always disregarded the initial part of the simulations (50 ps at 300 K and 10 ps at 800 K) and the free energy error was estimated by propagating the noise of the free energy gradients in the integration. The noise of each free energy gradient was obtained by the standard deviation of the perturbation energy derivative divided by the square root of the number of statistically independent evaluations (obtained using the autocorrelation function). Finally, the pure solvent properties used in the QGE models were obtained by the simulations described in the previous paper.<sup>1</sup>

### IV. RESULTS

We parametrize our theoretical models, described in the theory section, using only the average potential energy (excess internal energy) and pure solvent pressure in the whole temperature range, i.e., by fitting these values with the corresponding theoretical models. The partial molecular properties of the solute are obtained, according to the theory section, via  $\mu^* = \Delta A^*$ . Note that in the calculation of  $\mu^*$  is very important to use exactly the same temperatures for the evaluation of the overall excess free energies of the solute–solvent and pure solvent systems. This is because even a slight systematic error in these two excess free energies would result in an inaccurate  $\mu^*$ . As mentioned in the Theory, in this paper we model the confinement term of the spherical-like solutes using a more recent and accurate hard-sphere mixture equation of state<sup>13–15</sup> than the one used in the previous paper.<sup>12</sup> Interestingly, the new confinement terms we obtain for the ions investigated in that work, provide excess chemical potentials even closer to the ones reported in

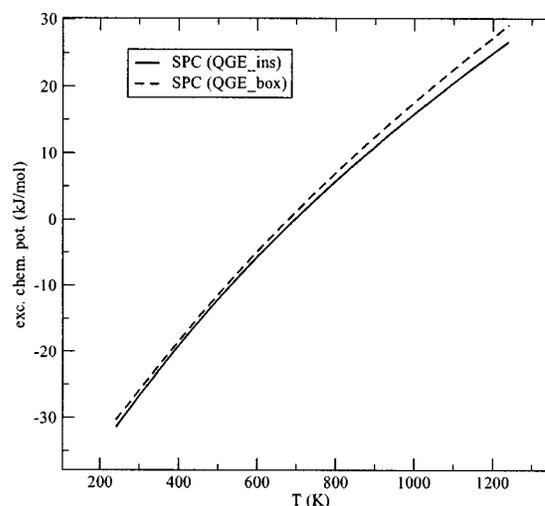


FIG. 1: Excess chemical potential curves of the SPC QGE models. Solid line: values obtained by inserting one SPC molecule as solute in the SPC box; dashed line: values obtained by molecular properties of the SPC box.

TABLE I. Parameters of the QGE theoretical models and corresponding excess chemical potentials at 298 K obtained by molecular properties of pure SPC (256 molecules) at 55.32 mol/l, by inserting one SPC molecule in the previous box, using experimental data of water at 55.32 mol/l, by inserting a methane or an ethane molecule in the SPC box. We also show, between parenthesis, the excess chemical potential error (one standard deviation).

	$d$ (nm)	$v$ (l/mol)	$u'_0$ (kJ/mol)	$c'_{v0}$ (J/mol K)	$\delta_0$	$\mu'$ (kJ/mol)
SPC (box)	0.2426	0.0181	-41.375	46.27	0.6565	-26.0 (0.3)
SPC (ins)	0.2280	0.0165	-43.702	52.58	0.6565	-26.8 (0.6)
Water	0.2700	0.0181	-41.436	49.42	0.5006	-26.8
CH <sub>4</sub>	0.2955	0.0258	-6.659	57.67	0.6565	13.1 (0.6)
C <sub>2</sub> H <sub>6</sub>	0.2991	0.0394	-11.275	69.66	0.6565	12.3 (0.6)

literature using a completely, different method,<sup>30</sup> i.e., thermodynamic integration. In the case of ethane which is in our force field, a linear chain made of two identical pseudo atoms, we use the hard chain model SC-SPT as described in the theory section. For the other nonspherical solutes (methanol and ethanol) we evaluate the confinement properties via TI calculations at a single temperature (800 K). However, with the use of the relation  $\Delta(\beta\mu') = \Delta(\beta\mu^*)$  (see theory section) we may directly compare QGE and TI excess chemical potentials excluding the confinement effect (i.e.,  $\mu^*$ ).

#### A. Water solute in water solvent

In order to ascertain the accuracy of the proposed procedure, we test our method using a water molecule as solute in water. Considering the molecular thermodynamic properties obtained from the QGE theory applied to a pure SPC box of 256 molecules at 55.32 mol/l<sup>1</sup> as the exact molecular properties, we can compare these data with those obtained by inserting in the SPC box an additional SPC molecule as solute and using the procedure described in the theory section to obtain the solute partial molecular properties. In Fig. 1 we show the excess chemical potential curves for these two QGE models. The two curves are in very good agreement in the whole temperature range, with a deviation ranging from about 0.7 to 2.5 kJ/mol. From further analysis of a few temperature points at a close isochore, we could also roughly estimate the standard deviation of the excess chemical potential, obtained by inserting one SPC molecule as solute, to be temperature dependent in the range 0.3–5.0 kJ/mol. Such values are lower than those evaluated in the previous paper

TABLE II. Excess chemical potentials at 300 (upper) and 800 K (lower) for SPC, methane, and ethane as obtained by the QGE theory applied to MD simulation data (first row) and by TI applied to the same solutes (second row). For SPC we provide both the QGE values obtained by insertion (left) or molecular properties (right). All the values are in kJ/mol and we also show, between parenthesis, the excess chemical potential error (one standard deviation).

	SPC		CH <sub>4</sub>	C <sub>2</sub> H <sub>6</sub>
QGE	-26.7 (0.6)	-25.8 (0.3)	13.3 (0.6)	12.5 (0.6)
	5.8 (2.4)	7.1 (1.3)	58.1 (2.4)	74.8 (2.4)
TI	-24.6 (0.5)		12.9 (0.3)	12.4 (0.3)
	10.6 (1.7)		57.8 (1.9)	72.9 (6.0)

TABLE III.  $\Delta(\beta\mu') = \Delta(\beta\mu^*)$  for the 300–800 K transition for SPC, methane, ethane, methanol, and ethanol as obtained by the QGE theory applied to MD simulation data (first row) and by TI applied to the same solutes (second row). For SPC we provide both the QGE values obtained by insertion (left) or molecular properties (right). We also show, between parenthesis, the error (one standard deviation) for TI results.

	SPC		CH <sub>4</sub>	C <sub>2</sub> H <sub>6</sub>	MeOH	EtOH
QGE	11.6	11.4	3.4	6.2	12.4	14.8
TI	11.5 (0.3)		3.5 (0.3)	6.0 (0.9)	11.9 (0.5)	14.0 (0.5)

(10–15 kJ/mol), which were probably overestimated as we did not use as many information as for the SPC solute. In fact, the errors for the solute partial molecular properties at high dilution should be largely determined by the solvent molecules, and hence very close for different solutes. Therefore we consider the previous SPC error estimate as valid also for the other solutes. It is worth noting that these errors could be reduced by augmenting the sample of configurations used to obtain the average potential energies. In this paper we always utilized 2750 MD frames taken every 0.5–2 ps according to the simulation temperature (see Methods). In Table I we report the physical parameters of the two QGE models for SPC (obtained by molecular properties and by insertion of one SPC molecule), together with the corresponding values obtained by the QGE theory applied to experimental liquid water.<sup>4</sup> From the table it is again clear the accuracy of the insertion procedure we use and moreover, the excellent agreement between SPC thermodynamics and the experimental one. In the same table we also report the excess chemical potentials of SPC and experimental water at 298 K, as obtained by QGE models. Our values are very close to the one given in a recent paper<sup>31</sup> where perturbation integration method is used (-26.2 kJ/mol). Interestingly, these values are also very close to the experimental water chemical potential as obtained by vapor pressure data (-26.5 kJ/mol).<sup>32</sup> Finally, in Tables II and III we show the excess chemical potentials at 300 and 800 K and  $\Delta(\beta\mu') = \Delta(\beta\mu^*)$  for the

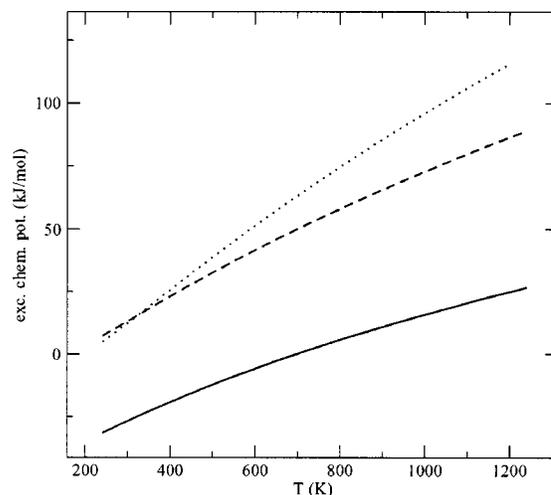


FIG. 2. Excess chemical potential curves of the solutes. Solid line: SPC QGE model obtained by inserting one SPC molecule as solute in the SPC box; dashed line: QGE model of methane in the SPC box; dotted line: QGE model of ethane in the SPC box.

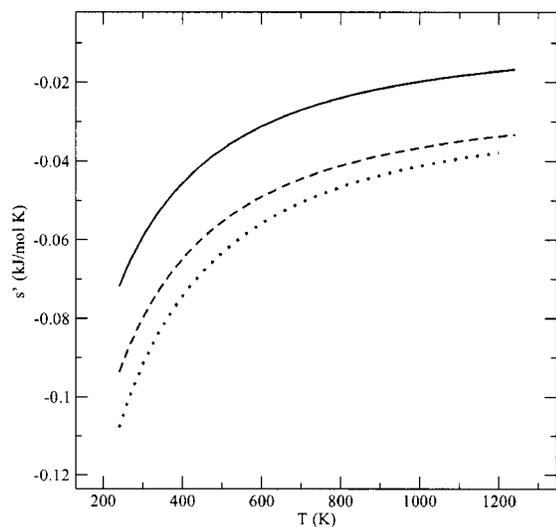


FIG. 3. Excess partial molar entropy of the solutes. Solid line: SPC QGE model obtained by inserting one SPC molecule as solute in the SPC box; dashed line: QGE model of methane in the SPC box; dotted line: QGE model of ethane in the SPC box.

300–800 K transition, as obtained by QGE and TI calculations. From these tables it is evident the complete agreement (within the noise) between QGE and TI SPC results.

## B. Methane and ethane in water

We also evaluate the partial molecular properties of two hydrophobic small solutes in water (SPC): methane and ethane. The physical parameters which define the corresponding QGE models are given in Table I. In Fig. 2 we show the excess chemical potentials of these solutes, together with the excess chemical potential of SPC obtained with the same procedure, i.e., by insertion. From the figure it

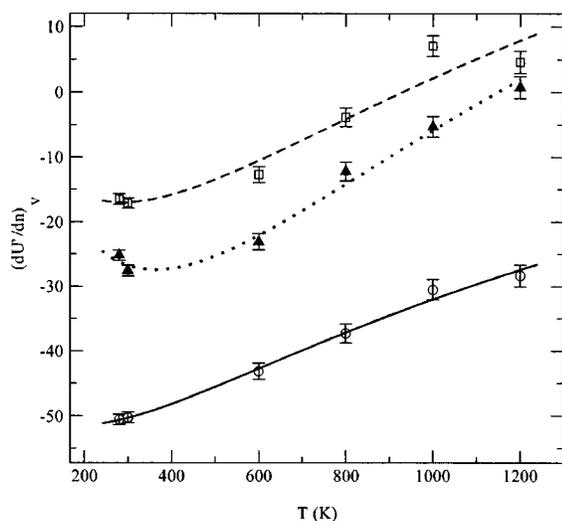


FIG. 4. Isochoric excess internal energy change  $(\partial U'/\partial n)_{V,T,n_s}$  of the solutes. SPC: solid line=QGE model obtained by inserting one SPC molecule as solute in the SPC box; empty circles=MD data. Methane: dashed line=QGE model of methane in the SPC box; empty squares=MD data. Ethane: dotted line=QGE model of ethane in the SPC box; filled triangles=MD data. The errors for the simulation data correspond to a standard deviation.

TABLE IV. Parameters of the QGE theoretical models and corresponding excess chemical potentials at 298 K obtained by inserting a methanol or an ethanol molecule in the SPC box. We also show, between parenthesis, the excess chemical potential error (one standard deviation).

	$v$ (l/mol)	$u'_0$ (kJ/mol)	$c'_{v0}$ (J/mol K)	$\delta_0$	$\mu'$ (kJ/mol)
MeOH	0.0469	-32.625	72.45	0.6565	-14.7 (0.6)
EtOH	0.0662	-33.674	91.72	0.6565	-12.3 (0.6)

is clear that these three molecules have a rather different thermodynamics, implying a different interaction behavior with solvent. From Tables II and III it is clear that, like SPC, methane and ethane QGE values match very well (within the noise) the TI values. In Figs. 3 and 4 we show the partial molar excess entropy and isochoric excess internal energy change  $s(\partial U'/\partial n)_{V,n_s,T}$  of the same three solutes. Methane, ethane, and SPC have not very different excess entropies, which become rather close when we remove the pure entropic confinement terms  $k \ln \bar{v}$ . This means that most of the difference in the solvation entropic cost for these solutes, is due to a simple cavity effect. Finally, the excess internal energy change at fixed volume are compared (Fig. 4). This figure provides a further test for the accuracy of the QGE models as it directly compares the model predictions with simulation data. For all the solutes there is an excellent agreement with the simulation data (the errors shown correspond to a standard deviation of the property).

## C. Methanol and ethanol in water

In order to test further our approach, we also apply it to two different polar nonspherical solutes in water (SPC): methanol and ethanol. The physical parameters which define the corresponding QGE models are given in Table IV. For these heteroatomic solutes we cannot use BMCSL or SC-SPT equations of state and hence we do not provide in the table any bead diameter. As previously described, in this case we obtain the solute confinement properties by TI calcula-

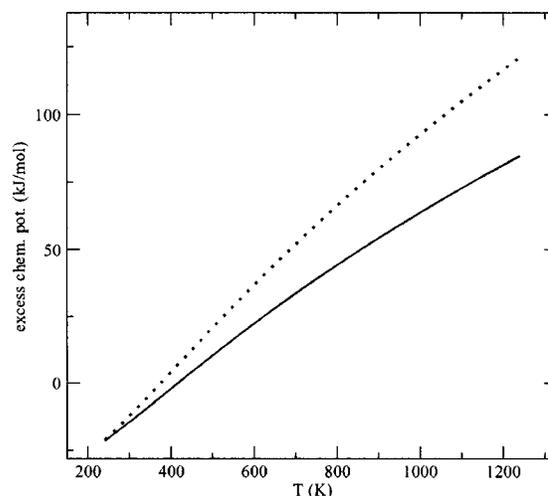


FIG. 5. Excess chemical potential curves of the solutes. Solid line: QGE model of methanol in the SPC box; dotted line: QGE model of ethanol in the SPC box.

TABLE V. Excess chemical potentials at 300 K for methanol and ethanol as obtained by the QGE theory applied to MD simulation data (first row) and by TI applied to the same solutes (second row). All the values are in kJ/mol and we also show, between parenthesis, the excess chemical potential error (one standard deviation).

	MeOH	EtOH
QGE	-14.4 (0.6)	-12.0 (0.6)
TI	-13.0 (0.5)	-9.9 (0.5)

tions at 800 K (evaluation at 300 K is also possible and actually provides close results; however to diminish the temperature propagation of the noise 800 K is preferable). From Fig. 5 where we show the excess chemical potentials of these two solutes as a function of the temperature, it is evident that methanol and ethanol have a rather different behavior. In Table V we compare the QGE excess chemical potentials at 300 K, with the corresponding values obtained by TI calculations. For these solutes we can only compare at one temperature (300 K) as we use the TI values at 800 K to evaluate the confinement terms. From Tables III and V we have, just like for SPC, methane and ethane, that, also for these two non spherical polar solutes, QGE values match very well (within the noise) TI results. In Figs. 6 and 7 we show the partial molar excess entropy and isochoric excess internal energy change of these alcohols. Also in this case most of the difference in the excess entropies is due to the confinement terms, and the isochoric excess internal energy change shows that the QGE models reproduce very well the simulation data (the errors shown correspond to a standard deviation of the property).

## V. CONCLUSIONS

In this paper we show that the combined use of the QGE theory with molecular dynamics (MD) simulations can provide the whole thermodynamics of a solute-solvent system, including all the partial molar properties. We have investigated five different solutes in water (water, methane, ethane,

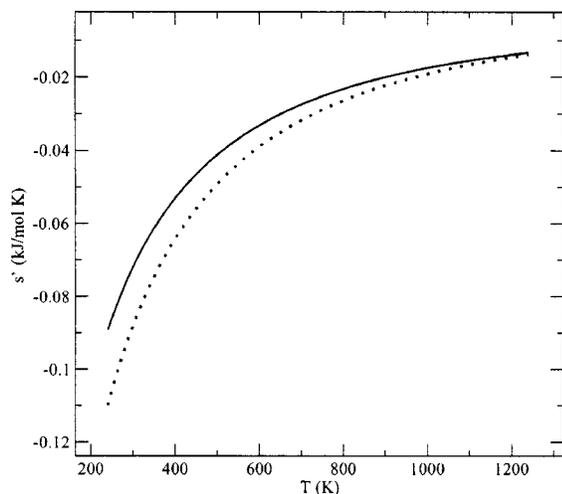


FIG. 6. Excess partial molar entropy of the solutes. Solid line: QGE model of methanol in the SPC box; dotted line: QGE model of ethanol in the SPC box.

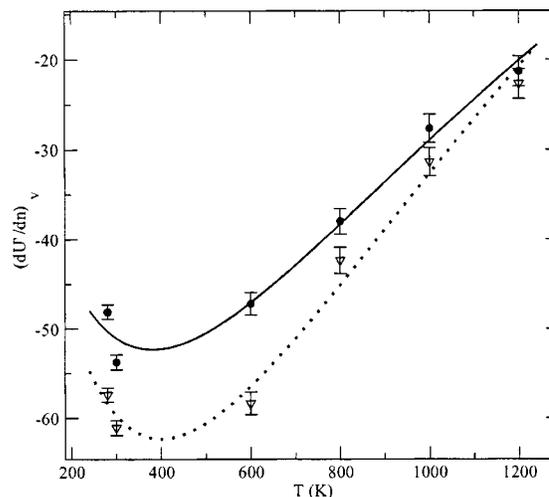


FIG. 7. Isochoric excess internal energy change  $(\partial U'/\partial n)_{v,T,n_s}$  of the solutes. Methanol: solid line=QGE model of methanol in the SPC box; filled circles=MD data. Ethanol: dotted line=QGE model of ethanol in the SPC box; empty triangles=MD data. The errors for the simulation data correspond to a standard deviation.

methanol, and ethanol) at high dilution, along the typical liquid water isochore. Results show that within a wide range of temperature the QGE theoretical models provide a coherent and accurate description of all the partial molar properties of solute and solvent as a function of the temperature. This is demonstrated directly by using a water molecule as solute in water and comparing the excess partial molar properties obtained with the ones given by molecular properties of the pure solvent (SPC box). Moreover, a remarkable agreement between QGE and TI results accuracy is shown for  $\Delta(\beta\mu')=\Delta(\beta\mu^*)$  (Table III) as well as for the excess chemical potentials (Tables II and V), confirming previous results on ionic solutions.<sup>1</sup> It is worth noting that no difficulties were found for ethane, methanol and ethanol showing that nonspherical molecules can be treated properly, although using non-spherical confinement terms.

<sup>1</sup>M. D'Alessandro, M. D'Abramo, G. Brancato, A. Di Nola, and A. Amadei, *J. Phys. Chem. B* **106**, 11843 (2002).

<sup>2</sup>A. Amadei, G. Chillemi, M. A. Ceruso, A. Grottesi, and A. Di Nola, *J. Chem. Phys.* **112**, 9 (2000).

<sup>3</sup>A. Amadei, M. E. F. Apol, G. Brancato, and A. Di Nola, *J. Chem. Phys.* **116**, 4437 (2002).

<sup>4</sup>A. Amadei, M. E. F. Apol, and H. J. C. Berendsen, *J. Chem. Phys.* **106**, 1893 (1997).

<sup>5</sup>M. E. F. Apol, A. Amadei, H. J. C. Berendsen, and A. Di Nola, *J. Chem. Phys.* **111**, 4431 (1999).

<sup>6</sup>A. Amadei, B. Iacono, S. Grego, G. Chillemi, M. E. F. Apol, E. Paci, M. Delfini, and A. Di Nola, *J. Phys. Chem. B* **105**, 1834 (2001).

<sup>7</sup>M. E. F. Apol, A. Amadei, and H. J. C. Berendsen, *J. Chem. Phys.* **104**, 6665 (1996).

<sup>8</sup>M. E. F. Apol, A. Amadei, and H. J. C. Berendsen, *Chem. Phys. Lett.* **256**, 172 (1996).

<sup>9</sup>D. Roccatano, A. Amadei, M. E. F. Apol, A. Di Nola, and H. J. C. Berendsen, *J. Chem. Phys.* **109**, 6358 (1998).

<sup>10</sup>A. Amadei, M. E. F. Apol, G. Chillemi, H. J. C. Berendsen, and A. Di Nola, *Mol. Phys.* **96**, 1469 (1999).

<sup>11</sup>M. E. F. Apol and A. Amadei, *J. Phys. Chem. B* **107**, 1410 (2003).

<sup>12</sup>J. L. Lebowitz and J. S. Rowlinson, *J. Chem. Phys.* **41**, 133 (1964).

<sup>13</sup>T. Boublik, *J. Chem. Phys.* **53**, 471 (1970).

<sup>14</sup>G. A. Mansoori, N. F. Carnahan, K. E. Starling, and T. W. Leland, *J. Chem. Phys.* **54**, 1523 (1971).

- <sup>15</sup>D. Ben-Amotz, *J. Phys. Chem.* **97**, 2314 (1993).
- <sup>16</sup>I. P. Omelyan and D. Ben-Amotz, *J. Chem. Phys.* **114**, 5735 (2001).
- <sup>17</sup>N. F. Carnahan and K. E. Starling, *J. Chem. Phys.* **51**, 635 (1969).
- <sup>18</sup>H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans, "Interaction models for water in relation to hydration," *Intermolecular Forces*, edited by B. Pullmann (Reidel, Dordrecht, 1981), pp. 331–342.
- <sup>19</sup>W. L. Jorgensen, J. D. Madura, and C. J. Swenson, *J. Am. Chem. Soc.* **106**, 6638 (1984).
- <sup>20</sup>W. L. Jorgensen, *J. Phys. Chem.* **90**, 1276 (1986).
- <sup>21</sup>D. van der Spoel, R. van Drunen, and H. J. C. Berendsen, *Groningen MACHine for Chemical Simulations*. Department of Biophysical Chemistry, BIOSON Research Institute, Nijenborgh 4 NL-9717 AG Groningen, 1994.
- <sup>22</sup>D. van der Spoel, A. R. van Buuren, E. Apol, P. J. Meulenhoff, D. P. Tieleman, A. L. T. M. Sijbers, R. van Drunen, and H. J. C. Berendsen, *Gromacs User Manual Version 1.3* (Nijenborgh 4, 9747 AG Groningen, The Netherlands, 1996).
- <sup>23</sup>W. F. van Gunsteren, S. R. Billeter, A. A. Eising, P. H. Hünenberger, P. Krüger, A. E. Mark, W. R. P. Scott, and I. G. Tironi, *Biomolecular Simulation: The GROMOS96 Manual and User Guide* (Hochschulverlag AG an der ETH Zürich, Zürich, 1996).
- <sup>24</sup>D. J. Evans and G. P. Morriss, *Statistical Mechanics of Nonequilibrium Liquids* (Academic, London, 1990).
- <sup>25</sup>M. D'Alessandro, A. Tenenbaum, and A. Amadei, *J. Phys. Chem. B* **106**, 5050 (2002).
- <sup>26</sup>T. A. Darden, D. M. York, and L. G. Pedersen, *J. Chem. Phys.* **98**, 10089 (1993).
- <sup>27</sup>S. Miyamoto and P. A. Kollman, *J. Comput. Chem.* **13**, 952 (1992).
- <sup>28</sup>C. Chipot, C. Millot, and B. Maigret, *J. Chem. Phys.* **101**, 7953 (1994).
- <sup>29</sup>M. Brunsteiner and S. Boresch, *J. Chem. Phys.* **112**, 6953 (2000).
- <sup>30</sup>G. Hummer, L. R. Pratt, and A. E. Garcia, *J. Phys. Chem. B* **100**, 1206 (1996).
- <sup>31</sup>J. T. Slusher, *J. Phys. Chem. B* **103**, 6075 (1999).
- <sup>32</sup>A. Ben-Naim, *Solvation Thermodynamics* (Plenum, New York, 1987).