

# Density functional theory of solvation in a polar solvent: Extracting the functional from homogeneous solvent simulations

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In the density functional theory formulation of molecular solvents, the solvation free energy of a solute can be obtained directly by minimization of a functional, instead of the thermodynamic integration scheme necessary when using atomistic simulations. In the homogeneous reference fluid approximation, the expression of the free-energy functional relies on the direct correlation function of the pure solvent. To obtain that function as exactly as possible for a given atomistic solvent model, we propose the following approach: first to perform molecular simulations of the homogeneous solvent and compute the position and angle-dependent two-body distribution functions, and then to invert the Ornstein-Zernike relation using a finite rotational invariant basis set to get the corresponding direct correlation function. This rather natural scheme is proved, for the first time to our knowledge, to be valuable for a dipolar solvent involving long range interactions. The resulting solvent free-energy functional can then be minimized on a three-dimensional grid around a solute to get the solvent particle and polarization density profiles and solvation free energies. The viability of this approach is proven in a comparison with “exact” molecular dynamics calculations for the simple test case of spherical ions in a dipolar solvent.

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## I. INTRODUCTION

The determination of the solvation free energy of complex solutes in molecular solvents is a problem of primary importance in physico chemistry and biology. From the theoretical point of view, two extreme strategies can be found in the literature. A first class of methods relies on the assumption that the macroscopic laws of electrostatics remain valid at a microscopic level, and that solvation free energies can be computed by combining a dielectric continuum description of the solvent outside the solute core and a simple solvent-accessible surface area expression for the nonelectrostatic contributions [1]. For the electrostatic part, the stationary Poisson equation can be solved using sharp definitions of the dielectric boundaries and various efficient numerical techniques [2], including recent methods based on the minimization of polarization density [3] or polarization charges [4] free-energy functionals. There are serious limitations, however, to a continuum dielectric approach; first of all the validity of the macroscopic electrostatic laws at microscopic distances and the neglect of the molecular nature of the solvent. Another standard route for computing solvation free energies consists in using molecular simulation techniques such as molecular dynamics (MD) or Monte Carlo (MC), with an explicit molecular solvent; for example, the SPC or TIP4P models for water. This way, the solute and the solvent are treated in a consistent way, with a realistic molecular force field. There are a number of well-established statistical mechanics techniques to estimate absolute or relative free energies by molecular simulations [5], for example, thermodynamic integration methods based on umbrella sampling [6,7], or generalized constraints [8,9]. In any case, the pre-

cise estimation of free energies by computer simulation remains extremely costly; it requires one to consider a sufficiently large number of solvent molecules around the molecular solute and, for this large system, to average a “generalized force” over many microscopic solvent configurations, and this for a lot of different points along the reversible thermodynamic integration path.

In this context, it is desirable to devise methods which (i) are able to cope with the molecular nature of the solvent, but without considering explicitly all its instantaneous microscopic degrees of freedom, and (ii) can provide solvation properties at a modest computer cost compared to explicit simulations. Among various possible theoretical approaches, one should mention molecular integral equation theories [10–18], and their three-dimensional implementation around complex solutes [19,20], and the density functional theory (DFT) of molecular liquids [21–25], which will be the focus of the present paper. The “classical” density functional theory has many points in common with the DFT of electrons in electronic structure problems. It has been used extensively for the description of atomic liquids at interfaces [26], and more recently of molecular liquids [27–31]. The essence of the theory is the following: For an atomic fluid submitted to an arbitrary external potential  $v(\mathbf{r})$ , the grand potential can be written as a functional of the one-particle density  $\rho(\mathbf{r})$ , which is minimum for the thermodynamic equilibrium density  $\rho_{eq}(\mathbf{r})$ . In particular, the so-called excess free-energy contribution, due to the intrinsic interactions within the fluid, appears also as a unique functional of  $\rho(\mathbf{r})$ , independent of the applied external field, and its knowledge characterizes the fluid completely. Of course, this excess free-energy functional is not known, but valuable approxima-

tions can be proposed. The rigorous definition of the excess functional involves the direct correlation function (the  $c$  function) of the inhomogeneous fluid, which is connected to the pair correlation function (the  $h$  function) through the Ornstein-Zernike (OZ) equation. A tempting approximation is thus to replace the inhomogeneous direct correlation function by that of a homogeneous reference fluid. This was done in Ref. [29] where the authors use a semiphenomenological description of the direct correlation functions in inhomogeneous ionic solutions using homogeneous MSA integral equation expressions. A similar approximation was also developed in Refs. [30,31] for dipolar fluids. There the direct correlation of the isotropic fluid is inferred from RHNC integral equation theory, and then injected into a density functional to predict the phase behavior of the fluid. Instead of approximate integral equations inputs, an exact description of the correlation function can also be achieved by simply extracting it from a fully molecular simulation of the homogeneous solvent at given thermodynamic conditions. This latter strategy has been largely unexplored, except for hard-ellipsoid fluids with short-range anisotropic repulsive interactions [32], and it is the purpose of this work to develop it for polar solvents.

We thus propose the following general scheme. For a given solvent model at given thermodynamic conditions, extensive MD simulations of the homogeneous system are performed and the position- and orientation-dependent pair correlation function is computed. The Ornstein-Zernike integral equation is then inverted to yield the direct correlation function. This function is then injected into the expression of the free-energy functional that describes the solvent particle and orientation density in the presence of any external field, in particular, a dissolved molecule. Minimization of the functional gives the equilibrium solvent density profile around the solute and its solvation free energy. To assess the validity of the method, the functional results can be compared to those of a molecular dynamics simulation of the solvent in the presence of the solute. In this case, the computation of the solvation free energy requires the definition of a reversible thermodynamic path, for example, a gradual growth of the solute inside the solvent.

Although the method is of general content and our ultimate goal is to provide a convincing free-energy functional for liquid water, even in a simplified quadrupolar version [17,33], we begin our project by applying the theoretical scheme described above to the simplest model of a polar solvent, the Stockmayer fluid, and the simplest solutes, namely, spherical ions.

The outline of the paper is as follows. In the next section, we review briefly the fundamentals of the classical DFT of liquids and describe the ‘‘homogeneous reference fluid’’ approximation. We recall how the homogeneous direct correlation can be obtained by inverting the Ornstein-Zernike equation using a spherical invariant basis set. In Sec. III, the formalism is applied to a Stockmayer solvent and it is shown that in the general case of dipolarlike interactions, the expression of the free-energy functional can be greatly simplified and reduced to a functional of  $n(\mathbf{r})$ , the particle number density, and  $\mathbf{P}(\mathbf{r})$ , the polarization density. Section IV de-

scribes the results, the computed  $h$  functions and inverted  $c$  functions, and the comparison between functional minimization results using the MD-based functional and direct MD calculations for the inhomogeneous system. This includes the inhomogeneous particle and polarization density around spherical ions, as well as the solvation free energies. Section V offers some conclusions and perspectives.

## II. THE DENSITY FUNCTIONAL APPROACH

### A. Exact free-energy functional

In this section we begin by recalling the basis of the density functional theory of liquids, and discussing the general problem of a molecular solvent submitted to an external field. In the applications we have in mind, the external field will be created by a molecular solute of arbitrary shape dissolved at infinite dilution in the solvent. The individual solvent molecules are considered as rigid bodies described by their position  $\mathbf{r}$  and orientation  $\mathbf{\Omega}$ . For simplicity we use below the variable  $\mathbf{x} \equiv (\mathbf{r}, \mathbf{\Omega})$  to describe the solvent degrees of freedom.

The grand potential density functional for a fluid having an inhomogeneous density  $\rho(\mathbf{x})$  in the presence of an external field  $V_{ext}(\mathbf{x})$  can be defined as [23,24],

$$\Theta[\rho] = F[\rho] - \mu_s \int \rho(\mathbf{x}) d\mathbf{x}, \quad (1)$$

where  $F[\rho]$  denotes here the total Helmholtz free-energy functional (including the external potential contribution) and  $\mu_s$  is the chemical potential. The grand potential can be evaluated relative to a reference homogeneous fluid having the same chemical potential  $\mu_s$  and the density  $\rho_0 = n_0/8\pi$  (or  $n_0/4\pi$  for linear molecules),  $n_0$  being the particle density:

$$\Theta[\rho] = \Theta[\rho_0] + \mathcal{F}[\rho]. \quad (2)$$

Following the general theoretical scheme introduced by Saam and Ebner [22] and Evans [23,24] (see also Refs. [21,34]), the density functional  $\mathcal{F}[\rho]$  can be split into three contributions: an ideal term, an external potential term, and an excess free-energy term accounting for the intrinsic interactions within the fluid,

$$\mathcal{F}[\rho] = \mathcal{F}_{id}[\rho] + \mathcal{F}_{ext}[\rho] + \mathcal{F}_{exc}[\rho], \quad (3)$$

with the following expressions for each term:

$$\mathcal{F}_{id}[\rho] = \beta^{-1} \int d\mathbf{x}_1 \left[ \rho(\mathbf{x}_1) \ln \left( \frac{\rho(\mathbf{x}_1)}{\rho_0} \right) - \rho(\mathbf{x}_1) + \rho_0 \right], \quad (4)$$

$$\mathcal{F}_{ext}[\rho] = \int d\mathbf{x}_1 V_{ext}(\mathbf{x}_1) \rho(\mathbf{x}_1), \quad (5)$$

$$\mathcal{F}_{exc}[\rho] = \beta^{-1} \int \int d\mathbf{x}_1 d\mathbf{x}_2 C(\mathbf{x}_1, \mathbf{x}_2) \Delta\rho(\mathbf{x}_1) \Delta\rho(\mathbf{x}_2), \quad (6)$$

and  $\Delta\rho(\mathbf{x}) = \rho(\mathbf{x}) - \rho_0$ . The function  $C(\mathbf{x}_1, \mathbf{x}_2)$  is still a functional of  $\rho(\mathbf{x})$  defined by

$$C(\mathbf{x}_1, \mathbf{x}_2) = \int_0^1 d\alpha (\alpha - 1) c^{(2)}([\rho_\alpha]; \mathbf{x}_1, \mathbf{x}_2), \quad (7)$$

where  $c^{(2)}([\rho_\alpha]; \mathbf{x}_1, \mathbf{x}_2)$  is the two-particle direct correlation function evaluated at a density  $\rho_\alpha(\mathbf{x}) = \rho_0 + \alpha \Delta\rho(\mathbf{x})$ .

The equilibrium condition reads

$$\left. \frac{\delta\Theta[\rho]}{\delta\rho} \right|_{\rho=\rho_{eq}} = 0 \Rightarrow \left. \frac{\delta\mathcal{F}[\rho]}{\delta\rho} \right|_{\rho=\rho_{eq}} = 0. \quad (8)$$

Most of the solvation free-energy calculations employing molecular simulations are performed at constant particle number  $N$  rather than constant chemical potential  $\mu_s$ . In this thermodynamic ensemble, one should minimize the functional

$$\Theta[\rho] = \Theta[\rho_0] + \mathcal{F}[\rho] - \Delta\mu_s \int d\mathbf{x} \rho(\mathbf{x}), \quad (9)$$

where  $\Delta\mu_s$  is the Lagrange multiplier corresponding to the constraint  $\int d\mathbf{x} \rho(\mathbf{x}) = N$ . The minimization equation becomes

$$\left. \frac{\delta\mathcal{F}[\rho]}{\delta\rho} \right|_{\rho=\rho_{eq}} = \Delta\mu_s. \quad (10)$$

At equilibrium,  $\Delta\mu_s = \mu_s - \mu_0$  gives the solvent chemical potential difference between the inhomogeneous and homogeneous systems and  $\mathcal{F}[\rho_{eq}]$  corresponds to the Helmholtz free-energy difference. In particular, if the external potential is created by an embedded solute,  $\mathcal{F}[\rho_{eq}]$  provides directly the solute solvation free energy. This thermodynamic quantity is the one which is obtained in molecular simulations by thermodynamic integration techniques where the solute is progressively grown in the solvent at a fixed number  $N$  of solvent molecules [5].

### B. The homogeneous reference fluid approximation

The functional defined by Eqs. (3)–(6) is formally exact but the inhomogeneous direct correlation functions entering the definition of the excess term are unknown. However, simple approximations can be proposed for this quantity. The most natural one consists in retaining only the first term in the Taylor expansion of the direct correlation function  $c^{(2)}([\rho_\alpha]; \mathbf{x}_1, \mathbf{x}_2)$  around  $\alpha=0$ , that is, around the homogeneous density  $\rho_0$ ,

$$c^{(2)}([\rho_\alpha]; \mathbf{x}_1, \mathbf{x}_2) = c^{(2)}([\rho_0]; \mathbf{x}_1, \mathbf{x}_2) = c(\mathbf{x}_1, \mathbf{x}_2). \quad (11)$$

This amounts to assuming that all the inhomogeneous direct correlation functions can be identified with that of the reference homogeneous fluid. This assumption, which we call the homogeneous reference fluid approximation, corresponds to the HNC approximation in the context of integral equations [19,21]. The approximated excess term then reads

$$\mathcal{F}_{exc}[\rho] = -\frac{\beta^{-1}}{2} \int \int d\mathbf{x}_1 d\mathbf{x}_2 c(\mathbf{x}_1, \mathbf{x}_2) \Delta\rho(\mathbf{x}_1) \Delta\rho(\mathbf{x}_2), \quad (12)$$

and the corresponding total functional described by Eqs. (5), (6), and (9) can now be minimized according to Eq. (10), leading to an integral equation for the density:

$$\rho(\mathbf{x}) = \rho_0^* \exp \left[ -\beta V_{ext}(\mathbf{x}) + \int d\mathbf{x}_2 c(\mathbf{x}_1, \mathbf{x}_2) \Delta\rho(\mathbf{x}_2) \right], \quad (13)$$

where  $\rho_0^* = \rho_0 e^{\beta\Delta\mu_s}$ . This equation, together with the normalization condition of  $\rho(\mathbf{x})$ , can be solved iteratively. Alternatively, as will be shown below, one can directly minimize the initial functional with a normalization constraint.

Here, we are faced with the problem of knowing the direct correlation function  $c(\mathbf{x}_1, \mathbf{x}_2)$  of the homogeneous reference fluid. Having in hand an atomistic model for the solvent, this can be done in principle by computing first the pair correlation function  $h(\mathbf{x}_1, \mathbf{x}_2)$  of the homogeneous solvent using “exact simulation methods” such as Monte Carlo or molecular dynamics simulations, and then inverting the Ornstein-Zernike integral equation which relates the functions  $h$  and  $c$ :

$$h(\mathbf{x}_1, \mathbf{x}_2) = c(\mathbf{x}_1, \mathbf{x}_2) + \rho_0 \int d\mathbf{x}_3 h(\mathbf{x}_1, \mathbf{x}_3) c(\mathbf{x}_3, \mathbf{x}_2). \quad (14)$$

A brute force direct resolution of the Ornstein-Zernike equation is precluded, however, since, even when accounting for translational invariance, both functions still depend on nine continuous variables. In order to manage the inversion problem it is thus necessary to take advantage of the symmetries of the homogeneous system. It has been shown that both the pair distribution function and the direct correlation function for an isotropic system can be expanded in a basis of rotational invariants [13],

$$h(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = \sum_{mnl\mu\nu} h_{\mu\nu}^{mnl}(r_{12}) \Phi_{\mu\nu}^{mnl}(\mathbf{\Omega}_1, \mathbf{\Omega}_2, \hat{\mathbf{r}}_{12}), \quad (15)$$

$$c(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = \sum_{mnl\mu\nu} c_{\mu\nu}^{mnl}(r_{12}) \Phi_{\mu\nu}^{mnl}(\mathbf{\Omega}_1, \mathbf{\Omega}_2, \hat{\mathbf{r}}_{12}), \quad (16)$$

where  $\mathbf{r}_{12} = \mathbf{r}_1 - \mathbf{r}_2$  and  $\hat{\mathbf{r}}_{12}$  is the associated unitary vector.  $\Phi_{\mu\nu}^{mnl}(\mathbf{\Omega}_1, \mathbf{\Omega}_2, \hat{\mathbf{r}}_{12}) \equiv \Phi_{\mu\nu}^{mnl}(12)$  is defined as

$$\Phi_{\mu\nu}^{mnl}(12) = f^{mnl} \sum_{\mu' \nu' \lambda'} \begin{pmatrix} m & n & l \\ \mu' & \nu' & \lambda' \end{pmatrix} \times D_{\mu\mu'}^m(\mathbf{\Omega}_1) D_{\nu\nu'}^n(\mathbf{\Omega}_2) D_{0\lambda}^l(\hat{\mathbf{r}}_{12}), \quad (17)$$

where  $D_{\mu\mu'}^m(\mathbf{\Omega})$  are the Wigner rotation matrices, and  $f^{mnl}$  stand for normalization constants.

The elements of the basis to be considered in the expansion are those having the symmetry properties of the fluid under study [13]. For example, in Sec. II we study a polar solvent in which the only possible rotational invariants are those for which  $\mu = \nu = 0$ , and  $m+n, l$  are even numbers.

Furthermore, the expansion can be closed at a certain order. One of the properties of the Ornstein-Zernike equation is to preserve the number of invariants, so that having expanded the function  $h$  up to a certain order  $n, m \leq M$ , the function  $c$  can be determined up to the same order. Blum [13,14], and later Patey [15,16], have shown how to solve the angular dependent OZ equations, projected on a rotational invariant basis set, by making use of Fourier space and Hankel transforms. The set of convolution equations obtained in real space becomes a set of linear equations in Fourier space which can be inverted straightforwardly. This is the basis of the integral equation theory of anisotropic fluids. The difference between our approach and a fully theoretical one as in Refs. [13–16] is that we do not need to couple the OZ relation to a complementary real space closure such as the MSA or HNC relation. Instead, we take the  $h$  functions as granted from a preliminary “exact” calculation of the homogeneous system under study. In this context, obtaining the  $c$ ’s from the  $h$ ’s does not require an iterative process as in the integral equation formulation, but a simple “one-shot” inversion.

### III. THE CASE OF DIPOLAR FLUIDS

#### A. Restricted rotational invariant basis set

We now restrict the present approach to model dipolar fluids composed of spherical particles interacting through a spherically symmetric short-range potential  $u_s(r_{12})$  and a dipole-dipole potential,

$$u_{dd}(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = \frac{1}{r_{12}^3} [\mathbf{p}_1 \cdot \mathbf{p}_2 - 3(\mathbf{p}_1 \cdot \hat{\mathbf{r}}_{12})(\mathbf{p}_2 \cdot \hat{\mathbf{r}}_{12})], \quad (18)$$

where, for each molecule  $i$ ,  $\mathbf{p}_i = p\mathbf{\Omega}_i$ . In this case, the orientation  $\mathbf{\Omega}_i$  is defined as the unitary vector pointing along the dipole direction.

For these “linear” molecules, the rotational invariants to be selected in the expansion of the  $h$  and  $c$  function must satisfy the conditions  $\mu = \nu = 0$  and  $m + n, l$  even. Up to linear order in the orientation vector  $\mathbf{\Omega}$  (that is, for  $m, n \leq 1$ ), the rotational invariants read

$$\Phi^{000}(12) = 1,$$

$$\Phi^{110}(12) = \mathbf{\Omega}_1 \cdot \mathbf{\Omega}_2,$$

$$\Phi^{112}(12) = 3(\mathbf{\Omega}_1 \cdot \hat{\mathbf{r}}_{12})(\mathbf{\Omega}_2 \cdot \hat{\mathbf{r}}_{12}) - \mathbf{\Omega}_1 \cdot \mathbf{\Omega}_2.$$

The normalization constants  $f^{mnl}$  entering in the definition of Eq. (17) are taken here equal to  $1, -\sqrt{3}$ , and  $\sqrt{30}$ , respectively.

Since the interaction between two particles in the fluid can be described in terms of the invariants  $m, n \leq 1$ ,

$$u(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = u^{000}(r_{12})\Phi^{000}(12) + u^{112}(r_{12})\Phi^{112}(12) \quad (19)$$

with  $u^{000}(r_{12}) = u_s(r_{12})$  and  $u^{112}(r_{12}) = -p^2/r_{12}^3$ , it is a reasonable first approximation to also stop the expansion of  $h$  and  $c$  at the same order.

Thus, retaining only the first three elements of the basis, the  $h$  and  $c$  functions can be expressed as

$$h(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = h^{000}(r_{12}) + h^{110}(r_{12})\Phi^{110}(12) + h^{112}(r_{12})\Phi^{112}(12), \quad (20)$$

$$c(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = c^{000}(r_{12}) + c^{110}(r_{12})\Phi^{110}(12) + c^{112}(r_{12})\Phi^{112}(12). \quad (21)$$

The different components of  $h$  can be computed by performing molecular dynamics simulations of the homogeneous dipolar fluid. They are defined as the average of the corresponding spherical invariant over all possible orientations of a pair at a given distance [21]. The Ornstein-Zernike relation can then be solved in the restricted representation. As has been long known, long, the inversion of the OZ relation starting from “computed”  $h$  functions is a nontrivial numerical problem. Even if the  $h$  projections can be determined with high precision using long MD trajectories and a fairly large number of particles, it is still hard to cancel completely the statistical noise at large distances, and even a tiny noise makes the usual inversion of the OZ relation in Fourier space rather unstable. Instead, we have chosen to transform the  $h$  and  $c$  projections into short-range functions [14] and to use the direct-space version of the OZ relation introduced by Baxter [35], in conjunction with the minimization scheme developed by Dixon and Hutchinson for atomic fluids [36]. The details for this solution will be presented in a forthcoming publication [37]. It will be seen in the application section below that the method leads to stable and smooth solutions for the  $c$ ’s, starting from the  $h$ ’s determined by MD.

#### B. The dipolar fluid reduced density functional

We use the expansion of the direct correlation function in terms of the first spherical invariants, Eq. (21), and consider an external potential  $\Phi_{ext}(\mathbf{r})$  and external electric field  $\mathbf{E}_{ext}(\mathbf{r})$ . It is then possible to perform analytically the integrals over the orientations in the different components of the functional defined by Eq. (9). The result is a new functional in terms of the number density

$$n(\mathbf{r}) = \int d\mathbf{\Omega} \rho(\mathbf{r}, \mathbf{\Omega}) \quad (22)$$

and the polarization density

$$\mathbf{P}(\mathbf{r}) = p \int d\mathbf{\Omega} \mathbf{\Omega} \rho(\mathbf{r}, \mathbf{\Omega}). \quad (23)$$

This functional can be written as (see the Appendix for details)

$$\Delta\Theta[n, \mathbf{P}] = \mathcal{F}_{id}[n, \mathbf{P}] + \mathcal{F}_{exc}[n, \mathbf{P}] + \mathcal{F}_{ext}[n, \mathbf{P}] - \Delta\mu_s \int d\mathbf{r} n(\mathbf{r}), \quad (24)$$



where, as before,  $\Delta\mu_s$  is the Lagrange multiplier assuring a constant number of solvent particles, and where the different components read

$$\begin{aligned} \mathcal{F}_{id}[n, \mathbf{P}] = & \beta^{-1} \int d\mathbf{r} n(\mathbf{r}) \ln \left( \frac{n(\mathbf{r})}{n_0} \right) - n(\mathbf{r}) + n_0 \\ & + \beta^{-1} \int d\mathbf{r} n(\mathbf{r}) \left[ \ln \left[ \frac{\mathcal{L}^{-1}(P(\mathbf{r})/p n(\mathbf{r}))}{\sinh(\mathcal{L}^{-1}(P(\mathbf{r})/p n(\mathbf{r}))} \right] \right. \\ & \left. + \frac{P(\mathbf{r})}{p n(\mathbf{r})} \mathcal{L}^{-1} \left( \frac{P(\mathbf{r})}{p n(\mathbf{r})} \right) \right], \end{aligned} \quad (25)$$

$$\begin{aligned} \mathcal{F}_{exc}[n, \mathbf{P}] = & \frac{1}{2} \int d\mathbf{r}_1 [\Delta n(\mathbf{r}_1) \phi_{exc}(\mathbf{r}_1) \\ & - \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{E}_{exc}(\mathbf{r}_1)], \end{aligned} \quad (26)$$

$$\mathcal{F}_{ext}[n, \mathbf{P}] = \int d\mathbf{r}_1 [n(\mathbf{r}_1) \phi_{ext}(\mathbf{r}_1) - \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{E}_{ext}(\mathbf{r}_1)]. \quad (27)$$

In the ideal term,  $\mathcal{L}$  designates the Langevin function and  $\mathcal{L}^{-1}$  its inverse;  $P(\mathbf{r})$  is the modulus of the polarization vector  $\mathbf{P}(\mathbf{r})$ . The excess potential and electric fields are functions of the  $c$  projections:

$$\begin{aligned} \phi_{exc}(\mathbf{r}_1) = & -\beta^{-1} \int d\mathbf{r}_2 c^{000}(r_{12}) \Delta n(\mathbf{r}_2), \\ \mathbf{E}_{exc}(\mathbf{r}_1) = & (\beta p^2)^{-1} \int d\mathbf{r}_2 (c^{110}(r_{12}) \mathbf{P}(\mathbf{r}_2) \\ & + c^{112}(r_{12}) \{3[\mathbf{P}(\mathbf{r}_2) \cdot \hat{\mathbf{r}}_{12}] \hat{\mathbf{r}}_{12} - \mathbf{P}(\mathbf{r}_2)\}). \end{aligned} \quad (28)$$

The great advantage of this functional form is that the minimization can now be performed with respect to the two fields  $n(\mathbf{r})$  and  $\mathbf{P}(\mathbf{r})$  instead of the full density  $\rho(\mathbf{r}, \mathbf{\Omega})$ . The equilibrium condition is:

$$\left. \frac{\delta \mathcal{F}[n, \mathbf{P}]}{\delta n} \right|_{n_{eq}, \mathbf{P}_{eq}} = \Delta\mu_s, \quad \left. \frac{\delta \mathcal{F}[n, \mathbf{P}]}{\delta \mathbf{P}} \right|_{n_{eq}, \mathbf{P}_{eq}} = 0. \quad (29)$$

Furthermore, and again for the problem of a solute in the solvent, the value of  $\mathcal{F}$  at equilibrium,  $\mathcal{F}[n_{eq}, \mathbf{P}_{eq}]$ , provides a direct measure of the solute solvation energy.

## IV. RESULTS

### A. Molecular model and MD simulation

The theoretical approach described above was applied to a Stockmayer solvent, composed of Lennard-Jones particles (parameters  $\sigma, \epsilon$ ) carrying a permanent dipole of magnitude  $p$  at their center. The physical parameters used in the simulations were  $\sigma = 3.024 \text{ \AA}$ ,  $\epsilon = 1.847 \text{ kJ/mol}$ ,  $p = 1.835 \text{ D}$  and the thermodynamic conditions were temperature  $T = 298 \text{ K}$  and density  $\rho = 0.0289 \text{ particles/\AA}^3$ . Those numbers correspond to a set of reduced variables  $\rho^* = \rho\sigma^3 = 0.8$ ,  $T^* = kT/\epsilon = 1.35$ , and  $p^{*2} = p^2/kT\sigma^3 = 2.96$  explored by Pol-

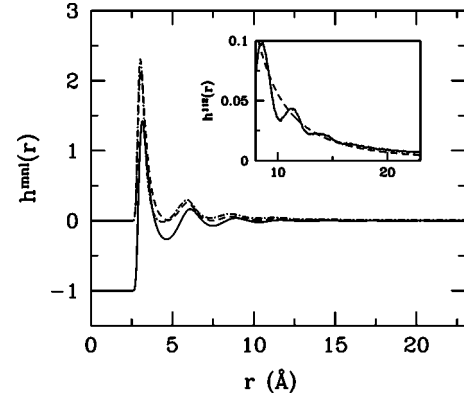


FIG. 1. Pair correlation function components of the Stockmayer liquid for  $\rho^* = 0.8$ ,  $T^* = 1.35$ , and  $p^{*2} = 2.96$  computed by MD simulations:  $h^{000}(r)$ ,  $h^{110}(r)$ , and  $h^{112}(r)$  (solid, dashed, and dot-dashed line, respectively). The inset compares  $h^{112}(r)$  (solid line) to the theoretical asymptotic limit of Eq. (30) (dashed line).

lock and Alder in their study of the dielectric properties of the Stockmayer fluid [38]. For those conditions, they could estimate a static dielectric constant  $\epsilon_s$  close to 80. The MD simulations were performed with the MDMULP program from the CCP5 program library [39]. The Ewald treatment of the Coulombic interactions was employed throughout. For the homogeneous fluid calculations, we have used either 1372 or 2916 particles and a cubic box size of  $36.2 \text{ \AA}$  and  $46.5 \text{ \AA}$ , respectively. The latter choice represents a rather large system according to the usual standards for molecular liquids, and the spherical invariant projections of  $h$ ,  $h^{000}(r)$ ,  $h^{110}(r)$ , and  $h^{112}(r)$  could be computed up to a rather long distance  $R_c = 23.25 \text{ \AA}$ ; they are plotted in Fig. 1. For Ewald boundary conditions, the dielectric constant  $\epsilon_s$  can be computed according to the formula [21]

$$\epsilon_s - 1 = 3y \left( 1 + \frac{4\pi n_0}{3} \int_0^\infty dr r^2 h^{110}(r) \right), \quad (30)$$

with  $y = 4\pi\beta p^2 n_0/9$ . We find  $\epsilon_s = 69.2$ , which is slightly less than the value quoted by Pollock and Alder but our calculations employ a much larger simulation box. It can be seen in the inset of Fig. 1 that the predicted asymptotic behavior of  $h^{112}(r)$ ,

$$h^{112}(r) = \frac{(\epsilon_s - 1)^2}{4\pi\epsilon_s n_0 y r^3}, \quad (31)$$

is correctly described with our computed value of  $\epsilon_s$ . [The slight discrepancy developing close to the box edges is due to the fact that Eq. (30) holds for an infinite system, whereas our simulations use periodic Ewald boundary conditions.]

The projections of the direct correlation function  $c^{000}(r)$ ,  $c^{110}(r)$ , and  $c^{112}(r)$  obtained by solving the OZ equations are displayed in Fig. 2. Again, the theoretical asymptotic behavior relating the direct correlation function and the two-body potential,

$$c(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2) = -\beta u(\mathbf{r}_{12}, \mathbf{\Omega}_1, \mathbf{\Omega}_2), \quad (32)$$

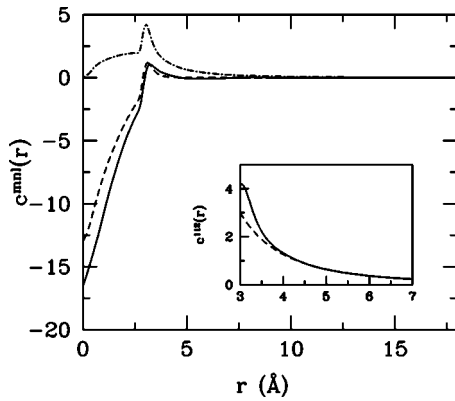


FIG. 2. Direct correlation function components of the Stockmayer liquid, obtained by inversion of the OZ equation:  $c^{000}(r)$ ,  $c^{110}(r)$ , and  $c^{112}(r)$  (solid, dashed, and dot-dashed line, respectively). The inset compares  $c^{112}(r)$  (dashed line) to the theoretical asymptotic limit  $-\beta u^{112}(r)$  (solid line).

which is by no means imposed *a priori*, is shown in the inset for the slowest component  $c^{112}(r)$ , and is seen to be perfectly satisfied. Overall, the observed properties of the computed  $h$  and  $c$  functions give some confidence regarding the convergence of our calculations and the validity of our Ornstein-Zernike inversion method.

### B. Functional minimization and comparison with MD results

The functional defined by Eqs. (25)–(27) being now well defined by the knowledge of the  $c$ 's, can be minimized for any external field  $V_{ext}(\mathbf{r}, \mathbf{\Omega})$  to yield the equilibrium density profile and equilibrium excess free energy. We have studied the special case of a spherical Lennard-Jones particle, with the same parameters  $\sigma, \epsilon$  as the solvent (so roughly a diameter of 3 Å), and carrying a charge  $+q$  at its center. This solute was placed at the center of a cubic box of side 36.2 Å, with periodic boundary conditions. The functional corresponding to this system was discretized on a  $64^3$  three-dimensional grid and minimized with respect to  $n(\mathbf{r})$  and the averaged orientation  $\mathbf{\Omega}(\mathbf{r}) = \mathbf{P}(\mathbf{r})/pn(\mathbf{r})$ . Our experience shows that for the present functional, as well as for the closely related electrostatic polarization density functional used in Ref. [3], a grid spacing of roughly 2 points/Å is sufficient to yield smooth and converged densities around solutes of molecular size.

The convolution integral appearing in Eq. (12) for the excess free energy is evaluated using fast Fourier transform techniques, and the minimizations are carried out with a conjugate gradient scheme. The minimization routine is constrained to preserve the total number of particles and to avoid unphysical negative particle densities. The starting point for the minimization is a homogeneous density  $n_0$  and zero polarization.

In Figs. 3 and 4, we display the radial particle density and the radial polarization density around an ion of charge  $+e$  obtained by minimization. The two quantities are compared to the corresponding ones computed with the same box size and same number of particles by molecular dynamics simulations. For  $n(r)$ , it can be seen that the first peak is ex-

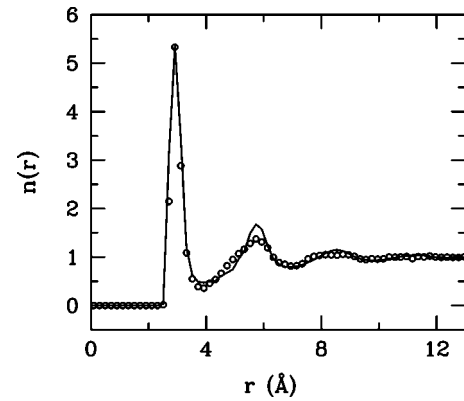


FIG. 3. Solvent density around an ion of charge  $+e$ : Functional minimization results (solid line) compared to MD results (circles).

tremely well reproduced, while the second one is at the correct position but is slightly too high and too narrow. The agreement for the polarization profile  $P(r)$  appears even better, with a correct first peak and correct asymptotic behavior, and only a slightly too high second peak. Overall, the density functional approach is doing extremely well, especially if one accounts for the fact that the fields created by a small particle of charge  $+e$  in the solvent are quite high. As can be expected, the DFT calculations do even better for ions of smaller charges (we checked for  $q=0.1e$  and  $q=0.5e$ ). Note again that the density functional theory calculation relies on two approximations: (i) the homogeneous reference fluid approximation and (ii) the truncation of the spherical invariant expansion of the  $c$  function at the lowest possible order compatible with the interaction potential symmetry. Approximation (i), based on an expansion of the particle density around the homogeneous density  $\rho_0$ , is not expected to work for strong density or orientational gradients, although it has proved to work in particular in the first solvation shell where the density is far from being homogeneous. The validity of the second approximation is hard to assess *a priori* and can only be justified by the results. The approximation seems fine in the present case, although probably responsible for the discrepancies observed in the second peak. It should be tested also for solutes of different symmetries, dipoles, and small molecules of arbitrary shape. We are presently in this process.

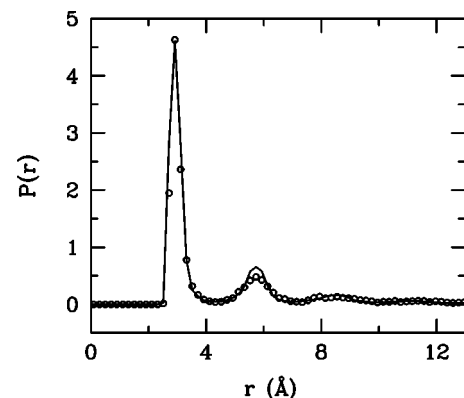


FIG. 4. Same as Fig. 3 for the radial polarization density.

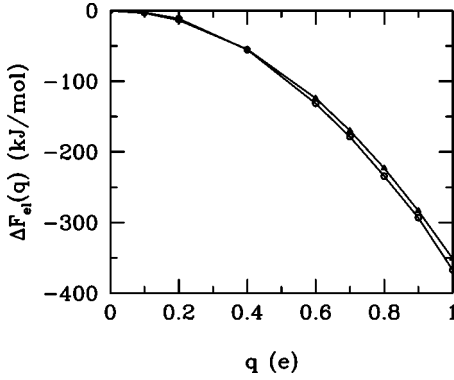


FIG. 5. Electrostatic solvation energy of an ion of charge  $q$  in the Stockmayer solvent: Functional minimization (circles) compared to MD results (triangles).

Finally, since our main motivation is to be able to estimate solvation energies, we display in Fig. 5 the electrostatic solvation free energy of ions of different charges, computed either by direct functional minimization at each value of  $q$  [and subtraction of the neutral Lennard-Jones atom solvation free energy  $\mathcal{F}(q=0)$ ], or by molecular dynamics using the thermodynamic integration formula

$$\Delta F_{el}(q) = \int_0^q d\xi \langle V_{el}(\xi) \rangle, \quad (33)$$

where  $\langle V_{el}(\xi) \rangle$  is the average reaction electrostatic potential exerted by the solvent at the center of the ion for a charge  $q = \xi$ . In practice, a discrete increment of charge of  $0.1e$  was employed to run a series of MD simulations and compute the integral in Eq. (33). The functional minimization was performed for the same set of charges. Again, one can see in Fig. 5 that the DFT calculations do extremely well. As can be expected, the agreement with MD is perfect for small charges (and thus small fields), but slightly degrades for higher charges. The relative error reaches  $\sim 5\%$  for  $q = +e$ . Again, the results are encouraging and the test needs to be extended to more complex solutes.

## V. CONCLUSIONS AND PERSPECTIVES

The position- and angle-dependent direct correlation function is the key quantity entering in the density functional theory description of inhomogeneous molecular fluids submitted to external potentials. In the homogeneous reference fluid approximation, this function is approximated by that of the homogeneous fluid of equal chemical potential, thus in the absence of any external perturbation. We have shown in this paper that, at least for dipolar fluids, the homogeneous direct correlation function can be inferred to a good approximation by first computing “exact” position and angular two-body correlations using MD or MC simulation methods, and then inverting the Ornstein-Zernike equation. To our knowledge, this is the first time that this approach has proved to be possible and valuable for a polar fluid with long-range interactions. The computed  $c$  function was then injected into the definition of a solvent free-energy density functional, and its

validity was tested on the solvation properties of simple spherical solutes in a dipolar solvent. When compared to molecular dynamics, the results of the functional minimization turn out to be very encouraging. Since we have already developed the methodology for representing and minimizing the functional on a three-dimensional grid around the solute, with no symmetry assessment, we are planning to continue our approach for solutes of more complex shape in the same dipolar solvent, as well as in more realistic solvent models reproducing the properties of liquid water, in terms of quadrupolar [17,33] or higher-order multipolar interactions [40,41].

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## APPENDIX: THE DIPOLAR FLUID FREE-ENERGY FUNCTIONAL

Accounting for the definition of the variables  $n(\mathbf{r})$  and  $\mathbf{P}(\mathbf{r})$  in Eqs. (22),(23), the expansion of the  $c$  function in Eq. (16) and of the external potential, and the obvious symmetry requirement that  $\int d\Omega_i \Omega_i = 0$ , a preliminary integration over the angles in the general expression for  $\mathcal{F}_{ext}$  and  $\mathcal{F}_{exc}$  in Eqs. (6) and (12) yields readily the reduced expressions given in Eqs. (26) and (27).

The derivation of the ideal part of the functional is a more subtle task due to the nonlinear term  $\rho(\mathbf{r}, \Omega) \ln \rho(\mathbf{r}, \Omega)$ . We begin by posing

$$\rho(\mathbf{r}, \Omega) = n(\mathbf{r}) \alpha(\mathbf{r}, \Omega), \quad (A1)$$

where  $\alpha(\mathbf{r}, \Omega)$  denotes the conditional probability density for the orientations at fixed  $\mathbf{r}$ , satisfying  $\int d\Omega \alpha(\mathbf{r}, \Omega) = 1$ . With this definition, the ideal term in Eq. (5) can be separated into a density and an orientational contribution:

$$\begin{aligned} \mathcal{F}_{id}[n, \mathbf{P}] = & \beta^{-1} \int d\mathbf{r} \left[ n(\mathbf{r}) \ln \left( \frac{n(\mathbf{r})}{n_0} \right) - n(\mathbf{r}) + n_0 \right] \\ & + \int d\mathbf{r} n(\mathbf{r}) \int d\Omega \alpha(\mathbf{r}, \Omega) \ln [4\pi \alpha(\mathbf{r}, \Omega)]. \end{aligned} \quad (A2)$$

We now use the fact that the formal solution for  $\rho(\mathbf{r}, \Omega)$  is known at equilibrium [Eq. (13)] so that one can calculate the orientational integral in the second term of  $\mathcal{F}_{id}$  above. Performing the angle integration in the exponent of Eq. (13) in the same way as was done for  $\mathcal{F}_{ext}$  and  $\mathcal{F}_{exc}$ , one gets

$$n(\mathbf{r}) \alpha(\mathbf{r}, \Omega) = \rho_0^* \exp[-\beta\Phi(\mathbf{r})] \exp[\beta p \Omega \cdot \mathbf{E}(\mathbf{r})], \quad (A3)$$

where the total potential  $\Phi(\mathbf{r})$  and total electric field  $\mathbf{E}(\mathbf{r})$  are the sums of the corresponding external and excess quantities. Integrating over  $\mathbf{\Omega}$  gives first

$$n(\mathbf{r}) = \rho_0^* \exp[-\beta\Phi(\mathbf{r})] \frac{\sinh[\beta p E(\mathbf{r})]}{\beta p E(\mathbf{r})} \quad (\text{A4})$$

and thus

$$\alpha(\mathbf{r}, \mathbf{\Omega}) = \frac{\beta p E(\mathbf{r})}{\sinh[\beta p E(\mathbf{r})]} \exp[\beta p \mathbf{E}(\mathbf{r}) \cdot \mathbf{\Omega}], \quad (\text{A5})$$

with  $E(\mathbf{r}) = |\mathbf{E}(\mathbf{r})|$ . Next computing the averaged orientation at fixed  $\mathbf{r}$ ,  $\mathbf{\Omega}(\mathbf{r}) = \int d\mathbf{\Omega} \mathbf{\Omega} \alpha(\mathbf{r}, \mathbf{\Omega})$  yields

$$\mathbf{\Omega}(\mathbf{r}) = \mathcal{L}(\beta p E(\mathbf{r})) \frac{\mathbf{E}(\mathbf{r})}{E(\mathbf{r})}, \quad (\text{A6})$$

where  $\mathcal{L}(x) = \coth(x) - 1/x$  is the Langevin function. One can deduce that  $\mathbf{\Omega}(\mathbf{r})$  is parallel to  $\mathbf{E}(\mathbf{r})$ , and that

$$\beta p E(\mathbf{r}) = \mathcal{L}^{-1}(\mathbf{\Omega}(\mathbf{r})), \quad (\text{A7})$$

$$\beta p \mathbf{E}(\mathbf{r}) = \frac{\mathcal{L}^{-1}(\mathbf{\Omega}(\mathbf{r}))}{\mathbf{\Omega}(\mathbf{r})} \mathbf{\Omega}(\mathbf{r}), \quad (\text{A8})$$

where  $\mathcal{L}^{-1}(x)$  is the inverse of  $\mathcal{L}(x)$  and  $\mathbf{\Omega}(\mathbf{r}) = |\mathbf{\Omega}(\mathbf{r})|$ . Injecting these relations into the expression (A5) for  $\alpha(\mathbf{r}, \mathbf{\Omega})$ , and then performing the angle integration in Eq. (A2) yields the final expression for the ideal free energy given in Eq. (25), with  $\mathbf{\Omega}(\mathbf{r}) = \mathbf{P}(\mathbf{r})/pn(\mathbf{r})$ .

Note that the derivation above is done for the equilibrium density, but that in Eq. (25) we make the crucial assumption that the functional form can be extended to polarization fields which are out of equilibrium. This is a reasonable assumption since (i) the functional does yield a minimum corresponding to the correct equilibrium density and (ii) its linearization for small polarization fields yields the correct electrostatic limit, namely,

$$\mathcal{F}_{id}[n, \mathbf{P}] = \int d\mathbf{r} \frac{\mathbf{P}(\mathbf{r})^2}{2\alpha_d n(\mathbf{r})}, \quad (\text{A9})$$

where  $\alpha_d = \beta p^2/3$  is the usual equivalent polarizability of a dipole  $p$  at the temperature  $\beta^{-1}$ . One recognizes the expression for the polarization free energy in a medium with local electric susceptibility  $\chi(\mathbf{r}) = \alpha_d n(\mathbf{r})$ .

Finally, collecting the different terms, and performing the angular integration for the constraint term also, yields the final expressions in Eqs. (24)–(27), with the same definition of the solvent excess chemical potential  $\mu_s^{ex}$ .

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- [1] B. Honig and A. Nichols, *Science* **268**, 1144 (1995).  
 [2] B. Roux, and T. Simonson, *Biophys. Chem.* **78**, 1 (1999).  
 [3] M. Marchi, D. Borgis, N. Lévy, and P. Ballone, *J. Chem. Phys.* **114**, 4377 (2001).  
 [4] R. Allen, J.P. Hansen, and S. Melchionna, *Phys. Chem. Chem. Phys.* **3**, 4177 (2001).  
 [5] P. Kollman, *Chem. Rev.* **93**, 2395 (1993).  
 [6] G.M. Torrie, and J. Valleau, *J. Comput. Phys.* **23**, 187 (1977).  
 [7] J. Valleau, in *Classical and Quantum Dynamics in Condensed Phase Simulations*, edited by B. J. Berne, G. Ciccotti, and D. F. Cocker, (World Scientific, Singapore, 1998), p. 97.  
 [8] E.A. Carter, G. Ciccotti, J.T. Hynes, and R. Kapral, *Chem. Phys. Lett.* **156**, 472 (1989).  
 [9] G. Ciccotti, in *Classical and Quantum Dynamics in Condensed Phase Simulations* (Ref. [7]), p. 159.  
 [10] D. Chandler and H.C. Hendersen, *J. Chem. Phys.* **57**, 1930 (1972).  
 [11] B.M. Pettit and P. Rossky, *J. Chem. Phys.* **84**, 5836 (1986).  
 [12] B.M. Pettit, Martin Karplus, and P. Rossky, *J. Phys. Chem.* **90**, 6335 (1986).  
 [13] L. Blum and A.J. Torruella, *J. Chem. Phys.* **56**, 303 (1972).  
 [14] L. Blum, *J. Chem. Phys.* **57**, 1862 (1972).  
 [15] G.N. Patey, *Mol. Phys.* **34**, 427 (1977).  
 [16] G.N. Patey, *Mol. Phys.* **35**, 1413 (1978).  
 [17] S.L. Carnie and G.N. Patey, *Mol. Phys.* **47**, 1129 (1982).  
 [18] P.J. Rossky, C.M. Cortis, and R.A. Friesner, *J. Phys. Chem.* **107**, 6400 (1997).  
 [19] D. Beglov and B. Roux, *J. Chem. Phys.* **104**, 8678 (1996).  
 [20] D. Beglov and B. Roux, *J. Phys. Chem. B* **101**, 7821 (1997).  
 [21] J. P. Hansen and I. R. McDonald, *Theory of Simple Liquids* (Academic Press, London, 1989).  
 [22] W.F. Saam and C. Ebner, *Phys. Rev. A* **15**, 2566 (1977).  
 [23] R. Evans, *Adv. Phys.* **28**, 143 (1979).  
 [24] R. Evans, in *Fundamental of Inhomogeneous Fluids*, edited by D. Henderson (Marcel Dekker, New York, 1992).  
 [25] D. Chandler, J.D. McCoy, and S.J. Singer, *J. Chem. Phys.* **85**, 5971 (1986).  
 [26] E. Kierlik and M.L. Rosinberg, *Phys. Rev. A* **44**, 5025 (1991).  
 [27] P.I. Teixeira and M.M. Telo da Gama, *J. Phys.: Condens. Matter* **3**, 111 (1991).  
 [28] P. Frodl and S. Dietrich, *Phys. Rev. A* **45**, 7330 (1992).  
 [29] T. Biben, J.P. Hansen, and Y. Rosenfeld, *Phys. Rev. E* **57**, R3727 (1998).  
 [30] S. Klapp and F. Forstmann, *J. Chem. Phys.* **106**, 9742 (1997); **109**, 1062 (1998).  
 [31] S. Klapp and F. Forstmann, *Phys. Rev. E* **60**, 3183 (1999).  
 [32] M.P. Allen, C.P. Mason, E. de Miguel, and J. Stelzer, *Phys. Rev. E* **52**, R25 (1995).  
 [33] D. Lesveque, J.J. Weiss, and G.N. Patey, *Mol. Phys.* **51**, 333 (1984).  
 [34] J. P. Hansen, in *The Physics and Chemistry of Aqueous Ionic Solutions*, edited by M. C. Bellissent-Funel and G. W. Neilson (Kluwer, Dordrecht, 1987).  
 [35] R.J. Baxter, *J. Chem. Phys.* **52**, 4559 (1970).  
 [36] M. Dixon and P. Hutchinson, *Mol. Phys.* **33**, 1663 (1977).  
 [37] R. Ramirez, R. Gebauer, M. Mareschal, and D. Borgis, (unpublished).  
 [38] E.L. Pollock and B. Alder, *Physica A* **102**, 1 (1980).  
 [39] W. Smith, *CCP5 Information Quarterly* **4**, 13 (1982).  
 [40] L. Blum, F. Vericat, and D. Bratko, *J. Chem. Phys.* **102**, 1461 (1995).  
 [41] Y. Liu and T. Ichiye, *J. Phys. Chem.* **100**, 2723 (1996).