

Density Functional Theory of Solvation and Its Relation to Implicit Solvent Models[†]

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We describe a density functional theory approach to solvation in molecular solvents. The solvation free energy of a complex solute can be obtained by direct minimization of a density 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 knowledge of the direct correlation function of the pure solvent. After discussing general molecular solvents, we present a generic density functional describing a dipolar solvent and we show how it can be reduced to the conventional implicit solvent models when the solvent microscopic structure is neglected. With respect to those models, the functional includes additional effects such as the microscopic structure of the solvent, the dipolar saturation effect, and the nonlocal character of the dielectric constant. We also show how this functional can be minimized numerically on a three-dimensional grid around a solute of complex shape to provide, in a single shot, both the average solvent structure and the absolute solvation free energy.

1. Introduction

The determination of the solvation free energy of complex solutes in molecular solvents is a problem of primary importance in physicochemistry and biology. On a theoretical point of view, two extreme strategies can be found in the literature. A first class of methods, known as implicit solvent methods,^{1,2} relies on the assumption that the macroscopic laws 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.³ 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 density⁴ or polarization charges^{5,6} free-energy functionals. Several numerically efficient approaches relying on approximate expressions of the electrostatic solvation free energy of a molecule in terms of effective pair interactions are available too. Among the most popular are the generalized-born (GB)^{7,8} and distance-dependent dielectric (DDD)⁹ approaches. There are serious limitations however to a continuum dielectric approach, and first of all the validity of the macroscopic electrostatic laws at microscopic distances and the neglect of the molecular nature of the solvent. The Langevin dipole model developed by Warshel and collaborators^{10–14} has a special status in the sense that induced dipoles placed on a coarse grid can be interpreted as frozen solvent pseudoparticles rather than the discrete representation of a continuous polarization field. That the Langevin dipole model becomes equivalent to continuous electrostatics in the limit of a fine grid is not fully appreciated in the literature, and this property will be shown in the present paper. Efficient semi-implicit solvent models involving mobile polarizable pseudoparticles were introduced recently in refs 15–17.

Another standard route for computing solvation free energies consists of 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 for estimating absolute or relative free energies by molecular simulations,¹⁹ for example, thermodynamic integration methods based on umbrella sampling^{20,21} or generalized constraints.^{22,23} In any case, the precise 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 new implicit solvent 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 the various possible theoretical approaches, one should mention molecular integral equation theories in the site–site^{24,25} or spherical invariants^{26–30} representation, and their implementation around complex solutes,^{31–33} the density functional theory (DFT) of molecular liquids,^{34–39} or Gaussian field theories.⁴⁰ It is noteworthy that David Chandler has contributed in a major way to all those approaches. He has brought a great deal to the theory of molecular liquids with the RISM integral equation formalism (refs 24 and 41–48 to quote a few). He has focused recently on the Gaussian field theory, and he was able to make very important contributions on the nature of hydrophobic interactions^{49–51} and their implications in protein folding.⁵²

The “classical” density functional theory has many points in common with the DFT of electrons in electronic structure

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problems, although its development for chemical applications is still in its infancy. Up to now, it has been used mostly for the description of atomic liquids at interfaces,⁵³ and more recently, it has been used for the description of molecular liquids.^{38,54–56} The essence of DFT is the following: for a fluid submitted to an arbitrary external potential $V_{\text{ext}}(\mathbf{r}, \Omega)$, the grand potential can be written as a functional of the one-particle (position and orientation) density $\rho(\mathbf{r}, \Omega)$ which is a minimum for the thermodynamic equilibrium density. In particular, the so-called excess free-energy contribution, due to the intrinsic interactions within the fluid, appears also as a unique functional of $\rho(\mathbf{r}, \Omega)$, 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 approximations 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 has been done in ref 38 where the authors use a semiphenomenological description of the direct correlation function for the homogeneous system based on integral equation theories. We have shown recently that this function can be extracted accurately from molecular dynamics (or Monte Carlo) simulations of the pure solvent.³⁹

The purpose of this paper is to show the following: (i) The density functional theory of molecular liquids, within the homogeneous reference fluid approximation, provides a universal and flexible tool for devising “implicit solvent” models, with a reduced representation of the solvent in which many microscopic degrees of freedom have already been integrated out. In this context, the conventional implicit solvent models used in the modeling of biomolecules in solution, more particularly the PB-SA method or the Langevin dipole model, can be understood as limiting cases of a more general perspective. (ii) This classical DFT approach can be used in a practical way, as a chemist’s tool, to predict numbers. The numbers in question are indeed important ones: the absolute solvation free energy of molecules, from which many relative quantities such as relative solvation free energies, association constants, or affinities can be deduced.

The outline of the paper is as follows. In section 2, we review briefly the fundamentals of the classical DFT of liquids in the particular context of the solvation of a complex solute in a molecular solvent. We discuss also the “homogeneous reference fluid” approximation which gives a practical way to construct the functional. In section 3, the formalism is limited to dipolar-like electrostatic interactions. In this case, the free energy reduces to a generic functional of $n(\mathbf{r})$, the particle number density, and $\mathbf{P}(\mathbf{r})$, the polarization density. In section 4, we take the limit of a homogeneous solvent and a slowly varying polarization field in order to recover either an electrostatic polarization functional equivalent to the Poisson equation after minimization or a variant of the Langevin dipole model when dipolar saturation effects are kept. Section 5 demonstrates the applicability of the method in order to predict the solvation properties of a small important organic molecule, *N*-methylacetamide, in a molecular solvent of high dielectric constant having some characteristics of water.

2. Density Functional Theory of Solvation

2.1. Exact 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 which, in our case, 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 Ω . For simplicity, we use below the variable $\mathbf{x} \equiv (\mathbf{r}, \Omega)$ to describe the solvent degrees of freedom. The solute itself is described in all microscopic details by a molecular “force field” involving atomic Lennard-Jones and partial charge parameters.

The grand potential density functional for a fluid having an inhomogeneous density $\rho(\mathbf{x})$ in the presence of an external field $V_{\text{ext}}(\mathbf{x})$ can be defined as^{35,36}

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

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

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

Following the general theoretical scheme introduced by Evans,^{34,36,57} the density functional $\mathcal{A}[\rho]$ can be split into three contributions: an ideal term (id), an external potential term describing the interaction between the solvent and the dissolved molecule (ext), and an excess free-energy term accounting for the intrinsic interactions within the fluid (exc)

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

with the following expressions of each term:

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

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

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

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 the density $\rho_\alpha(\mathbf{x}) = \rho_0 + \alpha\Delta\rho(\mathbf{x})$.

The equilibrium condition reads

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

Most of the solvation-free-energy calculations employing molecular simulations are performed at a constant particle number N rather than a constant chemical potential μ_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

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

At equilibrium, $\Delta\mu_s = \mu_s - \mu_0$ gives the solvent chemical potential difference between the inhomogeneous and homogeneous systems and $\mathcal{A}[\rho_{\text{eq}}]$ corresponds to the Helmholtz free-energy difference. When the external potential is created by an embedded solute, $\mathcal{A}[\rho_{\text{eq}}]$ 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.¹⁹ It is also the quantity evaluated directly in implicit solvent methods such as PB-SA^{2,3} or GB-SA.^{7,8}

2.2. 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 of 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 ρ_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 the inhomogeneous direct correlation function can be identified with that of the reference homogeneous fluid. This assumption, that we call the homogeneous reference fluid approximation, corresponds to the HNC approximation in the case of a homogeneous fluid.³⁴ The approximated excess term reads then

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

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

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

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. To manage the inversion problem, it has been shown that both the pair distribution function and the direct correlation function can be expanded in a basis of rotational invariants.²⁶ Blum^{26,27} and later Patey^{28,29} 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.

There are different ways to extract the c -functions corresponding to a given solvent, none of them being easy. As mentioned above, the first one is to use integral equation closures to complement the OZ equation (eq 14). Although a quadrupolar model with already promising features has been developed,³⁰ the integral equation description of water seems still a formidable task. Another approach is to compute the h -functions and their many projections exactly from molecular simulations and to perform a one shot inversion of the OZ equations. This procedure was shown recently to be feasible for a Stockmayer dipolar solvent.³⁹ It remains to be applied to water, with much more rotational invariants to be considered. At last, one can try to infer as much as possible the suitable projections of the direct correlation functions from experimental data such as structure factor and microscopic dielectric properties. This is a promising approach that we are presently exploring, but the road is still long to H-bonding.

3. A Generic Density Functional for a Dipolar Fluid

We now restrict to a dipolar solvent for which each solvent molecule is characterized by only its Lennard-Jones parameters σ_s and ϵ_s and its dipole moment $\mathbf{p}_i = p\Omega_i$, where Ω_i is the unitary orientational vector of the molecule. The interaction of a solvent molecule at position \mathbf{r} and with an orientation Ω with the solute is characterized by the Lennard-Jones interactions with the M solute atomic sites (position \mathbf{r}_i and parameters σ_i and ϵ_i)

$$V_0(\mathbf{r}) = \sum_{i=1}^M 4\epsilon_{si} \left[\left(\frac{\sigma_{si}}{|\mathbf{r} - \mathbf{r}_i|} \right)^{12} - \left(\frac{\sigma_{si}}{|\mathbf{r} - \mathbf{r}_i|} \right)^6 \right] \quad (15)$$

(with the usual combination rules $\sigma_{si} = (\sigma_s + \sigma_i)/2$ and $\epsilon_{si} = (\epsilon_s \epsilon_i)^{1/2}$) and by the interaction of the molecule dipole with the electric field created by the solute atomic charges

$$\mathbf{E}_0(\mathbf{r}) = \sum_{i=1}^M q_i \frac{\mathbf{r} - \mathbf{r}_i}{|\mathbf{r} - \mathbf{r}_i|^3} \quad (16)$$

In the dipolar approximation, following earlier works on the MSA integral equation theory of simple dipolar fluids,^{34,58} we suppose that the direct correlation function can be expressed in terms of the three rotational invariants

$$c(\mathbf{r}_{12}, \Omega_1, \Omega_2) = c_s(r_{12}) + c_\Delta(r_{12})\Phi^{110}(12) + c_D(r_{12})\Phi^{112}(12) \quad (17)$$

where

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

$$\Phi^{110}(12) = \Omega_1 \cdot \Omega_2$$

$$\Phi^{112}(12) = 3(\Omega_1 \cdot \hat{\mathbf{r}}_{12})(\Omega_2 \cdot \hat{\mathbf{r}}_{12}) - \Omega_1 \cdot \Omega_2$$

We have used the original Wertheim notations for the c -components. In this approximation, defining the number density

$$n(\mathbf{r}) = \int d\Omega \rho(\mathbf{r}, \Omega) \quad (18)$$

and the polarization density

$$\mathbf{P}(\mathbf{r}) = p \int d\Omega \Omega \rho(\mathbf{r}, \Omega) \quad (19)$$

it can be shown that the general functional of eqs 3–6 and 12 can be written as a functional of $n(\mathbf{r})$ and $\mathbf{P}(\mathbf{r})$ instead of the much more complex variable $\rho(\mathbf{r}, \Omega)$ (see ref 39 for details):

$$\Delta\Theta[n, \mathbf{P}] = \mathcal{F}[n, \mathbf{P}] - \Delta\mu_s \int d\mathbf{r} n(\mathbf{r}) \quad (20)$$

with again a constraint term with a Lagrange multiplier $\Delta\mu_s$ ensuring a constant number of solvent particles. The Helmholtz free energy can be decomposed into a density part and a polarization part, $\mathcal{F} = \mathcal{F}_d + \mathcal{F}_{\text{pol}}$, with the density part given by

$$\mathcal{F}_d[n] = \beta^{-1} \int d\mathbf{r} \left[n(\mathbf{r}) \ln \left(\frac{n(\mathbf{r})}{n_0} \right) - n(\mathbf{r}) + n_0 \right] - \frac{\beta^{-1}}{2} \int d\mathbf{r}_1 d\mathbf{r}_2 \Delta n(\mathbf{r}_1) c_s(r_{12}) \Delta n(\mathbf{r}_2) + \int d\mathbf{r} n(\mathbf{r}) V_0(\mathbf{r}) \quad (21)$$

where, as before, one can identify an ideal, solvent–solvent, and solute–solvent contribution. The polarization part reads

$$\mathcal{F}_{\text{pol}}[n, \mathbf{P}] = \beta^{-1} \int d\mathbf{r} n(\mathbf{r}) \left(\ln \left[\frac{\mathcal{L}^{-1} \left(\frac{P(\mathbf{r})}{pn(\mathbf{r})} \right)}{\sinh \left(\mathcal{L}^{-1} \left(\frac{P(\mathbf{r})}{pn(\mathbf{r})} \right) \right)} \right] + \frac{P(\mathbf{r})}{pn(\mathbf{r})} \mathcal{L}^{-1} \left(\frac{P(\mathbf{r})}{pn(\mathbf{r})} \right) \right) - \frac{1}{2} \int d\mathbf{r}_1 d\mathbf{r}_2 \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{T}_m \cdot \mathbf{P}(\mathbf{r}_2) - \int d\mathbf{r} \mathbf{P}(\mathbf{r}) \cdot \mathbf{E}_0(\mathbf{r}) \quad (22)$$

In the first ideal term, \mathcal{L} designates the Langevin function and \mathcal{L}^{-1} its inverse; $P(\mathbf{r})$ is the modulus of the polarization vector $\mathbf{P}(\mathbf{r})$. In the second solvent–solvent interaction term, \mathbf{T}_m can be understood as a modified dipolar tensor involving the microscopic orientational c 's

$$\mathbf{T}_m = \frac{1}{\beta p^2} [c_A(r_{12})\mathbf{I} + c_D(r_{12})(3\hat{\mathbf{r}}_{12}\hat{\mathbf{r}}_{12} - \mathbf{I})] \quad (23)$$

where \mathbf{I} is the unit tensor and $\hat{\mathbf{r}}_{12} = \mathbf{r}_{12}/r_{12}$.

The great advantage of the functional above 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 $\rho(\mathbf{r}, \Omega)$. The equilibrium condition is

$$\frac{\delta \mathcal{F}[n, \mathbf{P}]}{\delta n} \Big|_{n_{\text{eq}}, \mathbf{P}_{\text{eq}}} = \Delta\mu_s \quad \frac{\delta \mathcal{F}[n, \mathbf{P}]}{\delta \mathbf{P}} \Big|_{n_{\text{eq}}, \mathbf{P}_{\text{eq}}} = 0 \quad (24)$$

Again, for the problem of a solute in the solvent, the value of \mathcal{F} at equilibrium, $\mathcal{F}[n_{\text{eq}}, \mathbf{P}_{\text{eq}}]$, provides a direct measure of the solute solvation energy. Note that the particle density is present in eq 22, such that the two minimization equations above are not decoupled. If they are artificially decoupled, the density equation can be considered as the equivalent of the surface area term in the PB-SA approach and it contains all solvent–solvent and solvent–solute repulsive and van der Waals contributions as well as a hydrophobic contribution hidden in the excess term of eq 21. In particular, inferring $c_s(r)$ from the experimental structure factor of water leads to correct hydrophobic interaction

for not too large hydrophobic solutes.⁴⁹ As it stands, the polarization part of the functional bears similarities with the Marcus electrostatic polarization functional developed in ref 4. It is the aim of the following sections to draw precisely the connection between this functional and standard implicit solvent approaches such as the Poisson–Boltzmann equation or the Langevin dipole model.

4. Connection to Implicit Solvent Models

4.1. Recovering the Poisson(–Boltzmann) Formulation.

Instead of the conventional approach relying on the Poisson equation for the electrostatic potential, electrostatics can also be formulated in terms of a polarization density free-energy functional^{4,59,60}

$$\mathcal{F}_{\text{el}}[\mathbf{P}(\mathbf{r})] = \frac{1}{2} \int d\mathbf{r} \frac{\mathbf{P}(\mathbf{r})^2}{\chi(\mathbf{r})} - \int d\mathbf{r} \mathbf{P}(\mathbf{r}) \cdot \mathbf{E}_0(\mathbf{r}) - \frac{1}{2} \int d\mathbf{r} d\mathbf{r}' \mathbf{P}(\mathbf{r}) \cdot \mathbf{T}(\mathbf{r} - \mathbf{r}') \cdot \mathbf{P}(\mathbf{r}') \quad (25)$$

Here, $\chi(\mathbf{r}) = (\epsilon(\mathbf{r}) - 1)/4\pi$ is the local electric susceptibility, $\mathbf{P}(\mathbf{r})$ is the polarization density vector, and

$$\mathbf{T}(\mathbf{r}) = -\frac{4\pi}{3} \delta(\mathbf{r}) + r^{-3}(3\hat{\mathbf{r}}\hat{\mathbf{r}} - \mathbf{I})(1 - \delta_r) \quad (26)$$

is the dipolar tensor, where \mathbf{I} is the unit dyadic and $\hat{\mathbf{r}} = \mathbf{r}/r$. In the second term, the scalar δ_r value is 1 for $r = 0$ and zero otherwise. This expression evidences the singularity of the dipolar tensor for $\mathbf{r} = 0$. The space-dependent dielectric constant can be defined phenomenologically as⁴

$$\frac{1}{\epsilon(\mathbf{r})} = \frac{1}{\epsilon_s} + \left(1 - \frac{1}{\epsilon_s}\right) H(\mathbf{r}) \quad (27)$$

where ϵ_s is the solvent permittivity and $H(\mathbf{r})$ is an empirical volume specification function, which takes the value 1 inside the solute and 0 outside. The minimization of the free-energy functional with respect to $\mathbf{P}(\mathbf{r})$ for a fixed charged distribution leads to the constitutive equation of electrostatics (the polarization should be locally proportional to the Maxwell field):

$$\mathbf{P}(\mathbf{r}) = \chi(\mathbf{r}) \mathbf{E}(\mathbf{r}) \quad (28)$$

together with the definition of the Maxwell electric field

$$\mathbf{E}(\mathbf{r}) = \mathbf{E}_0(\mathbf{r}) + \int d\mathbf{r}' \mathbf{T}(\mathbf{r} - \mathbf{r}') \cdot \mathbf{P}(\mathbf{r}') \quad (29)$$

It is a standard exercise to show that solving the preceding equation is equivalent to solving the Poisson differential equation.^{61–63} It is thus equivalent to the implicit Poisson(–Boltzmann) solvent model employed extensively in biomolecular calculations.³ (In fact, the appropriate qualifier here is “Poisson”, since no ionic atmosphere is considered. A general trend in the biosimulation literature however is to use the term Poisson–Boltzmann even at vanishing ionic strength. Furthermore, the present DFT approach can be easily generalized to account for co-ion and counterion densities even beyond the Debye–Hückel limit.^{18,38}) We now show how to derive the electrostatic polarization functional from our more general DFT formalism.

We first suppose that eqs 21 and 22 can be decoupled, and one can solve the density problem first. In this case, minimizing eq 21 with respect to the density gives

$$n(\mathbf{r}) = n_0 e^{\beta \Delta \mu_s / kT} e^{-\beta V_{\text{eff}}(\mathbf{r})} \quad (30)$$

where the effective potential $V_{\text{eff}}(\mathbf{r})$ is connected self-consistently to the density by

$$V_{\text{eff}}(\mathbf{r}_1) = V_0(\mathbf{r}_1) - \int d\mathbf{r}_2 c_S(r_{12}) \Delta n(\mathbf{r}_2) \quad (31)$$

The results depend on the form of the correlations in the solvent and have to be solved self-consistently, or by direct minimization of eq 21.

We then proceed to the next approximation which consists of neglecting dipolar saturation effects and thus of linearizing the ideal term in the polarization functional (eq 22), which leads to

$$\mathcal{F}_{\text{pol}}[n, \mathbf{P}] = \int d\mathbf{r} \frac{\mathbf{P}(\mathbf{r})^2}{2\alpha_d n(\mathbf{r})} \quad (32)$$

where $\alpha_d = \beta p^2/3$ is the usual equivalent polarizability of a rotating dipole p at the temperature β^{-1} . Furthermore, introducing formally the dipolar tensor \mathbf{T} in eq 22, we get

$$\mathcal{F}_{\text{pol}}[n, \mathbf{P}] = \frac{1}{2} \int d\mathbf{r}_1 d\mathbf{r}_2 \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{X}^{-1}(\mathbf{r}_1, \mathbf{r}_2) \cdot \mathbf{P}(\mathbf{r}_2) - \frac{1}{2} \int d\mathbf{r}_1 d\mathbf{r}_2 \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{T} \cdot \mathbf{P}(\mathbf{r}_2) - \int d\mathbf{r}_1 \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{E}_0(\mathbf{r}_1) \quad (33)$$

where $\mathbf{X}^{-1}(\mathbf{r}_1, \mathbf{r}_2)$ is the inverse of a nonlocal susceptibility tensor defined by

$$\begin{aligned} \mathbf{X}(\mathbf{r}_1, \mathbf{r}_2)^{-1} &= \frac{1}{\alpha_d n(\mathbf{r}_1)} \delta(r_{12}) \mathbf{I} - \mathbf{T}_m(\mathbf{r}_1, \mathbf{r}_2) + \mathbf{T}(\mathbf{r}_1, \mathbf{r}_2) \\ &= \left(\left[\frac{1}{\alpha_d n(\mathbf{r}_1)} - \frac{4\pi}{3} \right] \delta(r_{12}) - \frac{c_\Delta(r_{12})}{\beta p^2} \right) \mathbf{I} - \\ &\quad \frac{c_D^0(r_{12})}{\beta p^2} (3\hat{\mathbf{r}}_{12}\hat{\mathbf{r}}_{12} - \mathbf{I}) \end{aligned} \quad (34)$$

We have defined

$$c_D^0(r_{12}) = c_D(r_{12}) - \frac{\beta p^2}{r_{12}^3} (1 - \delta_{12}) \quad (35)$$

where δ_{12} is 1 if $r_{12} = 0$ and zero otherwise. Both $c_D^0(r_{12})$ and $c_\Delta(r_{12})$ are short-ranged nonsingular functions (see ref 39 and the illustration in section 5). Making the macroscopic hypothesis that the polarization field $\mathbf{P}(\mathbf{r})$ varies on a much longer length scale and accounting for the fact that for symmetry reasons

$$\int d\mathbf{r}_2 c_D^0(\mathbf{r}_{12}) (3\hat{\mathbf{r}}_{12}\hat{\mathbf{r}}_{12} - \mathbf{I}) = 0 \quad (36)$$

the first term of eq 34 can be written as

$$\frac{1}{2} \int d\mathbf{r} \mathbf{P}(\mathbf{r})^2 \left(\frac{1}{\alpha_d n(\mathbf{r})} - \frac{4\pi}{3} - \frac{1}{\beta p^2} \int d\mathbf{r}_2 c_\Delta(\mathbf{r}_{12}) \right) \quad (37)$$

which defines a local susceptibility $\chi(\mathbf{r})$ by

$$\frac{1}{\chi(\mathbf{r})} = \left(\frac{1}{n(\mathbf{r})\alpha_d} + \frac{1}{n_0\alpha_c} - \frac{4\pi}{3} \right) \quad (38)$$

α_c can be understood as a polarizability correction due to local dipolar correlation

$$\alpha_c^{-1} = -\frac{4\pi n_0}{\beta p^2} \int_0^\infty dr_{12} r_{12}^2 c_\Delta(r_{12}) \quad (39)$$

α_c turns out to be a positive quantity. For the homogeneous solvent, $\chi(\mathbf{r}) \equiv \chi_s$, eq 38 defines the relation between the solvent susceptibility and the microscopic parameters α_d (connected to the value of the solvent microscopic dipoles) and α_c (connected to dipolar orientational correlations). From this relation, one can derive easily a corrected Clausius–Mossotti equation relating the dielectric constant ϵ_s to α_d and α_c .

$$\frac{\epsilon_s - 1}{\epsilon_s + 2} = \frac{4\pi}{3} \frac{\alpha_d \alpha_c}{\alpha_c + \alpha_d} = \frac{4\pi}{3} \alpha \quad (40)$$

$$= \frac{4\pi \beta n_0 p^2}{9} \left(1 - \frac{4\pi n_0}{3} \int_0^\infty dr r^2 c_\Delta(r) \right)^{-1} \quad (41)$$

The last equality can be identified to the formula proposed by Ramshaw⁶⁴ for the dielectric constant of a dipolar fluid. The previous equations amount in fact to a regular Clausius–Mossotti relation written for an effective polarizability α defined by $\alpha^{-1} = \alpha_d^{-1} + \alpha_c^{-1}$. Note that, with respect to the phenomenological electrostatic definition in eq 27, the local susceptibility is now defined microscopically from the effective solute–solvent interaction potential

$$\chi(\mathbf{r}) = \frac{\chi_s}{1 + \frac{\chi_s}{n_0 \alpha_d} (e^{\beta V_{\text{eff}}(\mathbf{r})} - 1)} \quad (42)$$

which also defines the volume specification function $H(\mathbf{r})$ in eq 27 as

$$H(\mathbf{r}) = \frac{1 - e^{-\beta V_{\text{eff}}(\mathbf{r})}}{1 + \left(\frac{n_0 \alpha_d \epsilon_s}{\chi_s} - 1 \right) e^{-\beta V_{\text{eff}}(\mathbf{r})}} \quad (43)$$

A rather severe approximation made in electrostatic approaches is to assume that the effective potential is simply a hard-sphere exclusion potential felt by solvent spheres of diameter σ_s interacting with the solute atomic spheres of diameter σ_i , that is, with $\sigma_{si} = (\sigma_s + \sigma_i)/2$

$$\begin{aligned} n(\mathbf{r}) &= n_0 e^{-\beta \sum_{i=1}^M V_{\text{HS}}(|\mathbf{r} - \mathbf{r}_i|; \sigma_{si})} \\ &= n_0 \prod_{i=1}^M \Theta(|\mathbf{r} - \mathbf{r}_i| - \sigma_{si}) = n_0 (1 - H(\mathbf{r})) \end{aligned} \quad (44)$$

This implies that $n(\mathbf{r})$ will vanish if at least one site is such that $|\mathbf{r} - \mathbf{r}_i| < (\sigma_i + \sigma_s)/2$ and will be equal to n_0 otherwise. This defines also the volume specification function $H(\mathbf{r})$. This prescription for the solvent-accessible volume is similar to that of Connelly of a solvent sphere rolling at the surface of the molecule. In this case, eqs 42 and 43 simply state that $\chi(\mathbf{r}) = 0$, $\epsilon(\mathbf{r}) = 1$ inside the solute and $\chi(\mathbf{r}) = \chi_s$, $\epsilon(\mathbf{r}) = \epsilon_s$ outside.

We have shown therefore that the electrostatic limit can be obtained from the more general dipolar functional (eqs 20–22) if (i) the dipolar saturation is neglected and the orientational ideal entropy term is linearized, (ii) the short-range behavior of the function c_Δ is replaced by a delta function and incorporated into the definition of the macroscopic dielectric constant. In addition, the derivation gives a clear microscopic definition of the local susceptibility $\chi(\mathbf{r})$ and of the solute intrinsic volume

in terms of the underlying repulsive potentials. Furthermore, the surface area (SA) in the conventional PB-SA approach, which contains both hydrophobic and van der Waals contributions, is replaced in the DFT approach by the definition of the isotropic functional (eq 21). The conventional SA term corresponds to a macroscopic Landau–Ginsburg approximation

$$\mathcal{F}_d[n(\mathbf{r})] = \frac{\gamma}{2} \int d\mathbf{r} (\nabla n(\mathbf{r}))^2 \quad (45)$$

where γ is related to the solvent surface tension. Equation 21 provides a more microscopic definition which will be able to describe hydrophobic effects at microscopic length scales (but will not be able to predict macroscopic behaviors such as a dewetting phase transition). Phenomenological connections between eqs 21 and 45 are possible to describe hydrophobicity at both small and large length scales.^{49,50}

4.2. Recovering the Langevin Dipole Model. Ignoring density effects from the beginning, that is, $n(\mathbf{r}) \equiv n_0$ outside the solute volume, the general polarization functional (eq 22) can be represented on a cubic grid with volume elements Δv with the convention that the grid points overlapping the solute volume are excluded. Noting $\mathbf{P}(\mathbf{r}_i) = \mathbf{p}_i/\Delta v$, the discrete functional reads

$$\mathcal{F}(\{\mathbf{p}_i\}) = n_0 \Delta v k_B T \sum_i \left\{ \mathcal{L}^{-1}(p_i/pn_0\Delta v) \frac{p_i}{pn_0\Delta v} - \ln \left[\frac{\sinh(\mathcal{L}^{-1}(p_i/pn_0\Delta v))}{\mathcal{L}^{-1}(p_i/pn_0\Delta v)} \right] \right\} - \frac{1}{2} \sum_{ij} \mathbf{p}_i \cdot \mathbf{T}_{ij}^m \cdot \mathbf{p}_j - \sum_i \mathbf{p}_i \cdot \mathbf{E}_{0i} \quad (46)$$

with $\mathbf{T}_{ij}^m = \mathbf{T}_m(\mathbf{r}_i - \mathbf{r}_j)$ and $\mathbf{E}_{0i} = \mathbf{E}_0(\mathbf{r}_i)$. Minimizing this functional with respect to the individual induced dipoles \mathbf{p}_i gives a set of self-consistent equations which are reminiscent of those obtained in the Langevin dipole model of Warshel and collaborators:^{12–14}

$$\mathbf{p}_i = p \mathcal{L} \left(\frac{\beta p \mathbf{E}_i}{n_0 \Delta v} \right) \frac{\mathbf{E}_i}{E_i} \quad (47)$$

$$\mathbf{E}_i = \mathbf{E}_{0i} + \sum_j \mathbf{T}_{ij}^m \cdot \mathbf{p}_j \quad (48)$$

with $E_i = |\mathbf{E}_i|$. Note that, with respect to the various models proposed by Warshel, the general model derived here involves the definition of a *modified dipolar tensor* containing the microscopic dipolar correlation functions $c_\Delta(r)$ and $c_D(r)$ of eq 17. Furthermore, the different microscopic parameters of the model are rigorously linked to the macroscopic dielectric constant through eqs 40 and 41. Applying the short-range approximations $c_\Delta(r_{ij}) = \alpha_c^{-1} \delta_{ij}$ and $c_D(r_{ij}) = (1 - \delta_{ij}) \beta p^2 / r_{ij}^3$, the polarization functional becomes

$$\mathcal{F}(\{\mathbf{p}_i\}) = n_0 \Delta v k_B T \sum_i \left\{ \mathcal{L}^{-1}(p_i/pn_0\Delta v) \frac{p_i}{pn_0\Delta v} - \ln \left[\frac{\sinh(\mathcal{L}^{-1}(p_i/pn_0\Delta v))}{\mathcal{L}^{-1}(p_i/pn_0\Delta v)} \right] \right\} + \frac{\mathbf{p}_i^2}{2\alpha_c n_0 \Delta v} - \frac{1}{2} \sum_{i \neq j} \mathbf{p}_i \cdot \mathbf{T}_{ij} \cdot \mathbf{p}_j - \sum_i \mathbf{p}_i \cdot \mathbf{E}_{0i} \quad (49)$$

Minimization with respect to the p_i 's yields now

$$\mathbf{p}_i = p \mathcal{L} \left(\frac{\beta p \mathbf{E}_i}{n_0 \Delta v} \right) \frac{\mathbf{E}_i}{E_i} \quad (50)$$

$$\mathbf{E}_i = \mathbf{E}_{0i} + \sum_{j \neq i} \mathbf{T}_{ij} \cdot \mathbf{p}_j \quad (51)$$

where $\mathcal{L}_m(x)$ is a “modified” Langevin function having the same saturation properties as $\mathcal{L}(x)$ ($\mathcal{L}_m(x) \rightarrow 1$ for $x \rightarrow +\infty$) and defined by its inverse

$$\mathcal{L}_m^{-1}(x) = \mathcal{L}^{-1}(x) + \frac{\alpha_d}{\alpha_c (n_0 \Delta v)^2} 3x \quad (52)$$

with $0 \leq x \leq 1$. This formulation involves the bare dipolar tensor \mathbf{T}_{ij} as in Warshel's Langevin dipole model.¹⁴ Note however that the Langevin function has to be slightly corrected in order to account for dipolar correlation effects. Furthermore, if one considers this model as a phenomenological one, the microscopic parameters cannot be taken independently and they should obey eqs 40 and 41 in order to reproduce the correct dielectric constant of the solvent. Linearizing the inverse Langevin function in eq 49 yields

$$\mathcal{F}(\{\mathbf{p}_i\}) = \sum_i \frac{\mathbf{p}_i^2}{2\alpha_c n_0 \Delta v} - \frac{1}{2} \sum_{i \neq j} \mathbf{p}_i \cdot \mathbf{T}_{ij} \cdot \mathbf{p}_j - \sum_i \mathbf{p}_i \cdot \mathbf{E}_{0i} \quad (53)$$

α is the effective polarizability of eq 40. On account of the Clausius–Mossotti relation between α and the homogeneous susceptibility χ_s (eq 38), the singular character of the discretized dipolar tensor ($\mathbf{T}_{ii} = -4\pi/(3\Delta v)$), and the understanding that solute grid points are excluded, the above expression appears to simply be a discrete representation of the continuous electrostatic functional (eq 25) with sharp dielectric boundaries.

We have thus shown how a Langevin dipole model can be deduced from the discretization of a rigorous microscopic polarization functional. Note that Warshel's motivation was in fact a purely phenomenological one and his model was not designed to represent a polarization functional in the limit of a fine grid but rather to mimic discrete solvent pseudomolecules by induced dipoles placed on a rather coarse grid ($a \approx 3 \text{ \AA}$) with a dipole density close to the water molecule density. He has to define eventually a finer grid close to the solute. This procedure can be rationalized in our formalism as a multiple grid representation of the continuous polarization functional developed above. The advantage of our approach is that the connection between the discrete representation of the solute by local polarizable dipoles and the macroscopic dielectric constant is perfectly defined as a function of the microscopic parameters as well as the (variable) grid size.

5. Application to the Solvation Properties of Charged and Dipolar Solutes

In a previous work,³⁹ we computed from molecular dynamics simulations the direct correlation of a dipolar solvent involving Lennard-Jones and dipole–dipole interactions (the so-called Stockmayer model). The model was adjusted to the properties of water in terms of density (0.029 particles/ \AA^3), particle size ($\sigma_s = 3 \text{ \AA}$), dipole moment ($p = 1.85 \text{ D}$), and macroscopic dielectric constant ($\epsilon_s = 80$). It is clear that water cannot be reduced to a dipolar solvent and that the tetrahedral order due

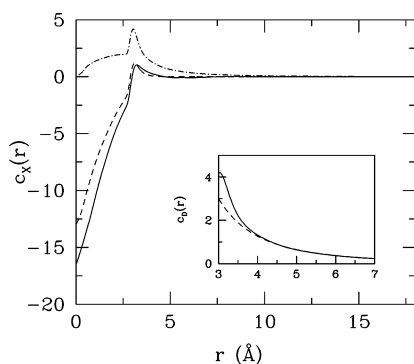


Figure 1. Direct correlation function components of the Stockmayer dipolar liquid studied in ref 39: (solid line) $c_S(r)$; (dashed line) $c_A(r)$; (dot-dashed line) $c_D(r)$. The inset compares $c_D(r)$ (dashed line) to the theoretical asymptotic limit $\beta p^2/r^3$ (solid line).

to H-bonding plays an important role. This microscopic dipolar model goes however well beyond a continuum dielectric description.

The corresponding c -functions are represented in Figure 1. As discussed in the previous sections, it appears that both $c_S(r)$ and $c_A(r)$ are very short ranged and are vanishing beyond $r = r_c \approx 4$ Å. $c_D(r)$ reaches its asymptotic $1/r^3$ limit in the same range. The local dielectric constant approximation proposed above is thus fully justified.

The functional defined by eqs 3–6, being now well defined by the knowledge of the c 's, can be minimized for an arbitrary external field $V_{\text{ext}}(\mathbf{r}, \Omega)$ to yield the equilibrium density profile and equilibrium excess free energy. Practically, the functional is discretized on a three-dimensional cubic grid and minimized with respect to $n(\mathbf{r})$ and the averaged orientation $\Omega(\mathbf{r}) = \mathbf{P}(\mathbf{r})/pn(\mathbf{r})$. The convolution integral appearing in eq 12 for the excess free energy is evaluated using FFT techniques, and the minimizations are carried out with a conjugate gradient scheme. The minimization routine is a constraint 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. Typically the number density $n(\mathbf{r})$ converges rather quickly, in a dozen of iterations, whereas the orientation field is slower to stabilize and requires about 100 conjugate gradient iterations.

We first illustrate the method for the case of a spherical Lennard-Jones particle having the same parameters as the solvent (thus a diameter of 3 Å) and carrying a charge of $q = +e$ at its center. This solute was placed at the center of a cubic box of 36.2 Å, with 64^3 grid points and periodic boundary conditions.

In Figure 2, we display the corresponding radial particle density and the radial polarization density 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 of an ion in the same molecular solvent.³⁹ It should be noted first that the density functional results are doing extremely well in comparison to the “exact” molecular calculations. It is seen that, in contrast to an electrostatic continuum approach, the solvent microscopic structure is fully accounted for and the oscillations of the densities describe the different solvation shells. In Figure 3, we compare the average radial solvent dipole $p(r)$ at a distance r from the ion to the electrostatic uniform dielectric result.

$$p(r) = \frac{pq^2(\epsilon_s - 1)}{4\pi\epsilon_s n_0 r^2} \quad (54)$$

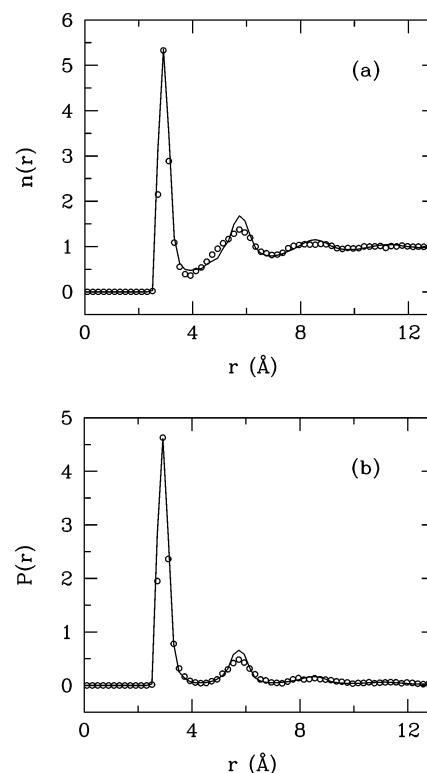


Figure 2. (a) Solvent density $n(r)$ and (b) polarization density $P(r)$ around an ion of charge $+e$: functional minimization results (solid line) compared to the exact molecular dynamics results (circles).

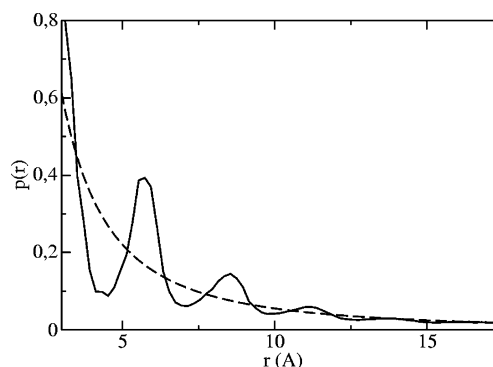


Figure 3. Mean dipole $p(r)$ at a distance r from the charge: DFT results (solid curve) compared to the continuum electrostatic result given by eq 54 (dashed curve).

It is seen that the DFT result oscillates around the “mean-field” electrostatic curve at short distances and matches it perfectly beyond 10 Å. This indicates that the DFT approach is consistent with macroscopic electrostatics but does incorporate more microscopic details.

As a second illustration, we have applied the density functional approach to the solvation of a *N*-methylacetamide (NMA) molecule in our molecular solvent. This molecule constitutes an elementary building block for peptides and proteins, and as such, it serves as a special model for theoretical calculations. This molecule can be found in two isomeric *cis* and *trans* forms corresponding to the isomerization of a peptide bond. The free-energy difference between the two isomers has been determined both experimentally and computationally.

The geometrical configurations of the two isomers are displayed in Figures 4 and 5. We also compare there the solute-atoms/solvent-atom radial distribution functions computed by molecular dynamics to those obtained by minimization of the solvent density functional in the presence of the molecule. In

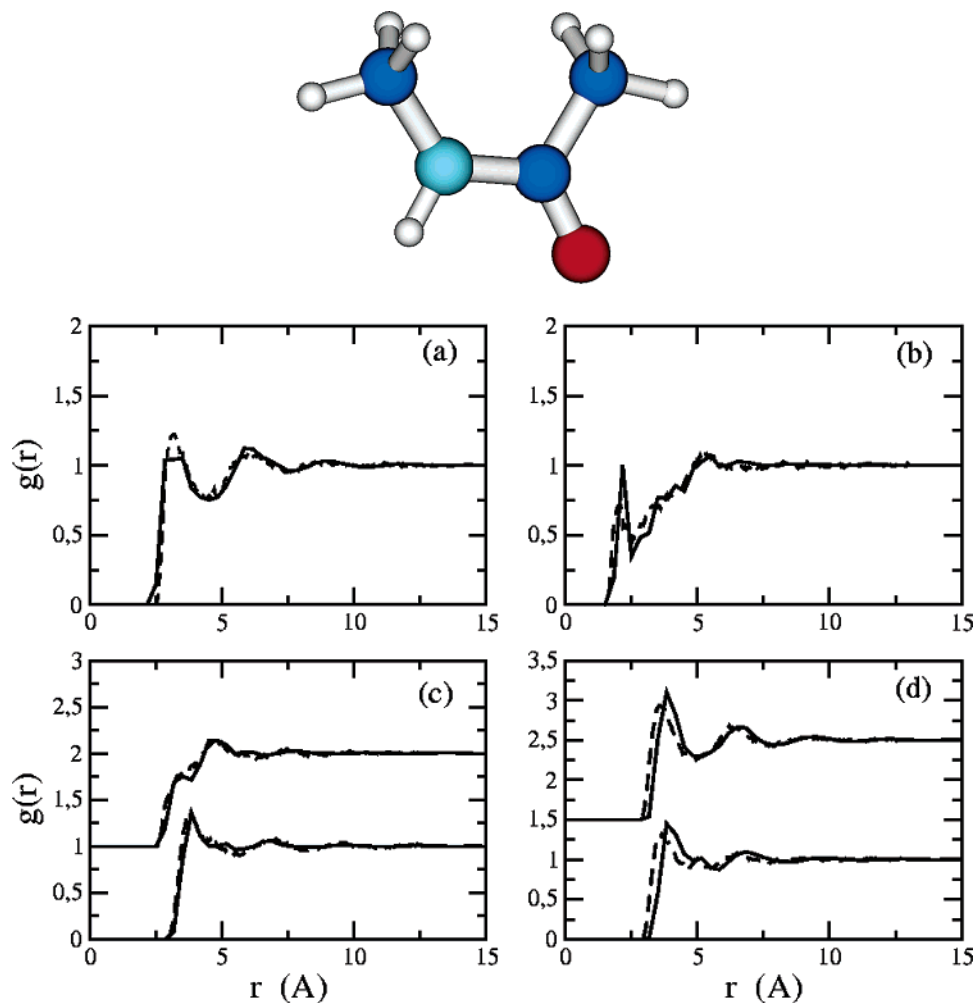


Figure 4. Geometrical configuration of *cis*-*N*-methylacetamide (top) and corresponding atom-solvent radial distribution functions (bottom): (a) oxygen; (b) amide hydrogen; (c) backbone carbon (bottom curves) and nitrogen (top curves, upshifted by 1); (d) C-terminal methyl (bottom) and N-terminal methyl (top, upshifted by 1.5). The solid and dashed lines indicate the DFT and MD results, respectively.

the latter case, the radial distribution functions can be identified to the mean density at a distance r of a given atomic site. The OPLS Lennard-Jones parameters and partial charges for NMA were taken from ref 65; the CH_3 termini are considered as a single effective site. The MD simulations were carried out with one NMA molecule dissolved in 512 solvent particles for a total time of 250 ps. The DFT calculation was performed with a box of grid size of 0.5 Å and 64^3 grid points. It can be seen again in the various figures that the DFT approach is doing quite well. The finite size of the grid does introduce some spurious discretization effects at short distances. Overall, however, the various density peaks are correctly reproduced in both positions and intensities. The most visible discrepancy concerns the first peak of the methyl group radial distribution functions, which appears systematically upshifted by ~ 0.2 Å for both isomers. It is somehow surprising that this largest shift occurs for the “hydrophobic” sites carrying the lowest charge. The atomic site with the highest exposed charge is the amide H. For this site, the first peak appears slightly too high and sharp in the case of the *cis* isomer. The coordination number is well reproduced however: 0.70 for DFT instead of 0.74 for MD. There is almost always a solvent particle stuck to the N–H bond. This is true to even a greater extent for the *trans* isomer. In that case, the H-coordination is found to be very close to 1 (0.98) with both the DFT and MD calculations. The fact that our DFT approach is able to capture correctly the solvent structure around a molecule having a complex three-dimensional shape and charge

distribution is quite encouraging. Recall that the critical conjecture made in section 2.2 is that the solvent direct correlation function $c(\mathbf{r}_1, \Omega_1, \mathbf{r}_2, \Omega_2)$ is unaffected by the solute and can be computed once for good for the pure solvent at given thermodynamic conditions. The range of validity of this assertion is not obvious a priori, since, for a complex solute, the solvent structure near the solute is expected to be notably perturbed (beyond the second-order Taylor expansion regime implied in eq 11). The judiciousness of the conjecture is here demonstrated for a “realistic” molecular solute in a dipolar fluid. It certainly needs further extensive testing for other complex solutes and/or solvents.

At last, to illustrate our goals, and although our solvent model is still a rough representation of liquid water and does not incorporate H-bonding, we have computed the solvation-free-energy difference between the *trans* and *cis* forms and compared the functional minimization results with the Monte Carlo calculations of Jorgensen and Gao⁶⁵ performed with explicit TIP4P water molecules. For consistency and further validation of the conjecture of eq 11, it will be interesting also to compare DFT free-energy calculations to MD thermodynamic integration calculations performed with the same dipolar solvent. These types of comparison are underway.

Thus, for illustration, in correspondence to Jorgensen’s calculation, we have carried successive minimization for a torsional angle Φ varying progressively from the *cis* form (0°) to the *trans* form (180°). It can be seen on Figure 6 that our

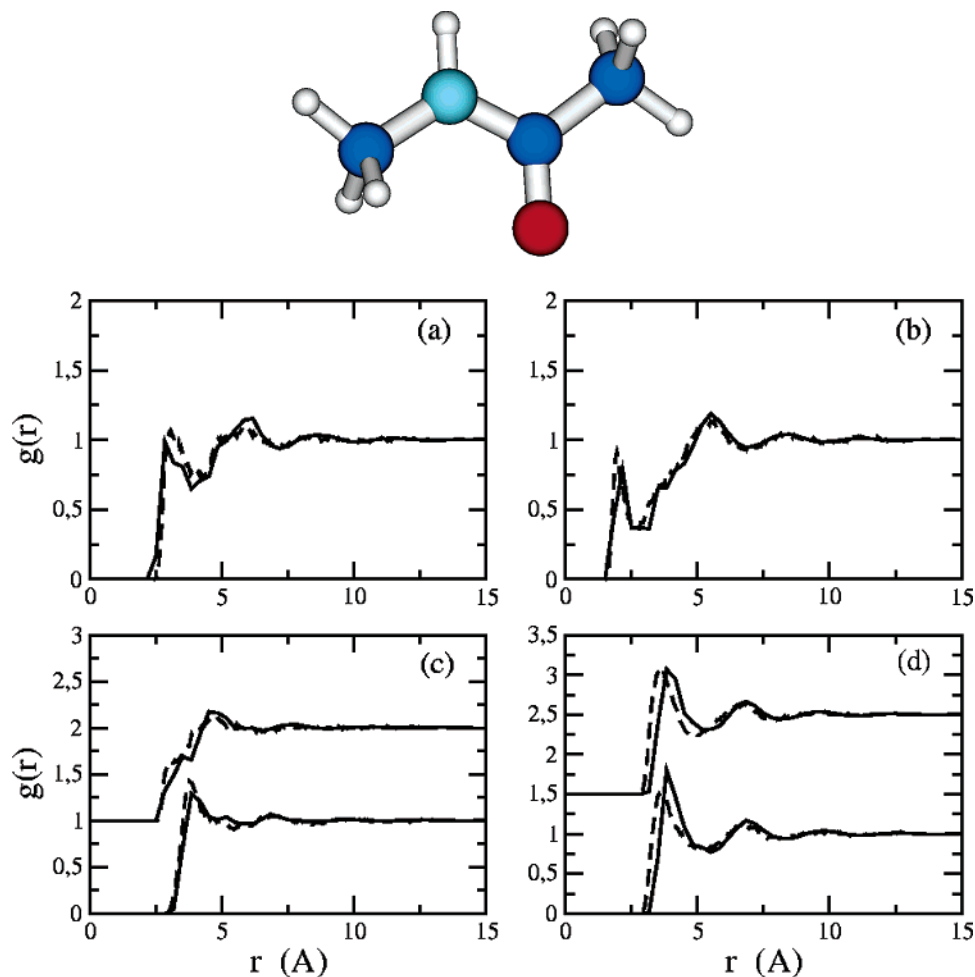


Figure 5. Same as Figure 4 except for *trans*-*N*-methylacetamide.

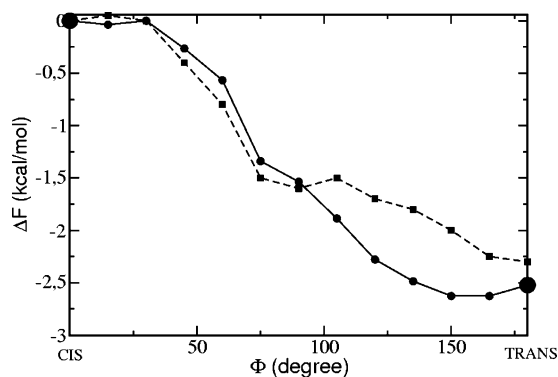


Figure 6. Relative solvation free energy going from the cis isomer to the trans isomer by increments of 15°: (circles and solid line) DFT minimization results; (squares and dashed line) Monte Carlo results of Jorgensen and Gao⁶⁵ using explicit TIP4P water molecules. The two big marks at 0 and 180° recall that only two calculations are necessary to get the overall free-energy difference with density functional minimization, whereas the explicit simulations require the whole thermodynamic path.

DFT free-energy curve follows rather closely the Monte Carlo results and our overall cis–trans free-energy difference of –2.5 kcal/mol only differs by 10% from the one computed by Monte Carlo. Since the solvents are not completely identical, this can be a mark that for this type of small polar molecules dipolar interactions do dominate. Beyond this surprisingly good quantitative agreement however, our main message here is that (i) minimizing a rather detailed microscopic functional around a complex shape solute is numerically feasible at a rather modest

cost (compared to a full MD or MC simulation) and (ii) although we have performed successive DFT minimization for the same angles as those of Jorgensen and Gao for comparison, the great advantage of the functional minimization approach is that the overall free-energy difference does not require any thermodynamic integration scheme, as in explicit simulations, and it can be obtained with only *two* calculations, marked by larger points in Figure 6, one for the starting configuration and one for the final one. Furthermore, both the average solvation structure and the absolute solvation free energy are obtained with a single minimization. Accounting for the flexibility of the solute would be possible by extending the “on-the-fly” minimization procedure of ref 4.

6. Conclusions

In this paper, we have introduced a generic dipolar solvent density functional expressed in terms of the particle density and polarization density fields. We have shown how this functional reduces to the conventional implicit solvent models, that is, the Poisson(–Boltzmann) equation and the Langevin dipole model, when some macroscopic simplifications are made. The functional does include additional features compared to continuous electrostatics, in particular, the solvent microscopic structure, the dipolar saturation, and the nonlocal character of the dielectric constant, which was shown recently to have important effects near a dielectric boundary.⁶⁶ On a practical ground, we have shown also that the functional can be minimized numerically on a three-dimensional grid around a molecular solute of

complex shape to provide, in one single shot, the average microscopic solvent structure and the absolute solvation free energy.

Important features of water, such as the tetrahedral symmetry induced by the H-bonding network, are still lacking in the generic dipolar functional proposed above. Further steps toward a more realistic representation, in terms of quadrupolar^{30,67} or higher-order multipolar interactions,^{68,69} are conceivable for the near future.

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