A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics

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A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics

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We present a new integral equation formulation of the polarizable continuum model (PCM) which allows one to treat in a single approach dielectrics of different nature: standard isotropic liquids, intrinsically anisotropic medialike liquid crystals and solid matrices, or ionic solutions. The present work shows that integral equation methods may be used with success also for the latter cases, which are usually studied with three-dimensional methods, by far less competitive in terms of computational effort. We present the theoretical bases which underlie the method and some numerical tests which show both a complete equivalence with standard PCM versions for isotropic solvents, and a good efficiency for calculations with anisotropic dielectrics. © *1997 American Institute of Physics.* [S0021-9606(97)51432-2]

I. INTRODUCTION

The reaction field method has been widely used to study solvent effects in chemical and biological systems. In this method the solvent is represented by a homogeneous continuum medium which is polarized by the solute placed in a cavity. The solute–solvent interactions are described in terms of a solvent reaction field which can be partitioned into many contributions of different physical origin, related to dispersion, repulsive and electrostatic forces between solute and solvent molecules.[1]

In the quantum-mechanical (QM) version of the method the solute molecule is studied *ab initio* and the interactions with the solvent are taken into account through a reaction potential $\hat{V}_R$ which acts as a perturbation on the solute Hamiltonian:

$$\hat{H}^\circ \Psi^\circ = E^\circ \Psi^\circ \quad in\ vacuo,$$

$$[\hat{H}^\circ + \hat{V}_R]\Psi = E\Psi \quad \text{in solution}, \tag{1}$$

where $\hat{H}^\circ$ is the Hamiltonian of the solute *in vacuo* (including nuclear repulsion terms), Ψ° and Ψ are the solute wave functions *in vacuo* and in solution, respectively.

Among the QM reaction field methods, the polarizable continuum method (PCM)[1–3] has spread out since its introduction in 1981 because of its adaptability and accuracy. Within this framework belonging to the class of apparent surface charges (ASC) or boundary element methods (BEM), the electrostatic component of the reaction potential to be added to $\hat{H}^\circ$ in order to get the effective Hamiltonian, is described in terms of a set of induced point charges $\{q_i\}$ placed at the center of small surface elements (tesserae) covering the cavity in the dielectric medium, where the solute is embedded.

Generally, the reaction field methods are considered as almost exclusively limited to deal with linear isotropic homogeneous dielectrics (LIH description). Actually, the introduction of inhomogeneities in continuum solvation models has a long history,[4,5] but only recently quantum mechanical models have been proposed. Such models describe the local disturbances (cybotactic effects) in terms of dielectric functions based on the local value of the electric field $\mathbf{E}$, $\epsilon(\mathbf{E})$, or on the distance from the solute, $\epsilon(\mathbf{r})$.[6–9] In this context a large attention has been paid to models in which the medium is described as a set of nonoverlapping dielectrics, each one with a different constant value of ϵ: These models describe both cybotactic effects and large scale inhomogeneities due to the occurrence of separate phases.[10–13]

On the contrary, not much attention has been paid to the large scale anisotropies due to the intrinsic structure of the liquid medium, as in the case of molecular solutes in liquid crystals and biomembranes. Here the scalar dielectric constant ϵ has to be replaced by a tensorial quantity $\boldsymbol{\epsilon}$ and an additional apparent charge distribution of volume type, $\rho_b(\mathbf{r})$, has to be taken into account by a finite element method (FEM). The most direct computational procedure to treat this problem of large interest in many fields such as, for example, NMR measurements of orientational order in nematic mesophases, is a combined BEM/FEM technique, as that recently implemented in the PCM framework.[14,15] Here ASC charges coming from BEM are supplemented by volume point charges given by FEM, and both sets are then used to define $\hat{V}_R$ and to get the electrostatic contribution to the solvation free energy.

The present paper accounts for a new formulation of the PCM method, which allows one to treat media of different nature, such as standard isotropic liquids but also intrinsically anisotropic dielectrics with a tensorial permittivity, by direct use of a single ASC procedure without need of any

additional FEM step. To arrive to this formulation, which reduces the dimensionality of the problem to the surface, the standard Poisson operator formalism generally in use in electrostatic formulations is replaced by the use of other operators derived from the theory of integral equations.[16]

II. THEORY

Before going deeper inside the new mathematical formalism, it is worth recalling some main characteristics of the standard PCM procedure.

The electrostatic problem of the evaluation of the interaction energy between solute and solvent, including also mutual polarization effects, is solved by introducing an apparent charge distribution σ spread on the cavity surface. In the computational practice this continuous distribution is discretized by point charges $\{q_i\}$, each associated with a small portion (tessera) of the cavity surface, and defined through a set of linear equations written in the following matrix formulation:

$$\mathbf{q} = \mathbf{\Sigma}\boldsymbol{\sigma} = -\mathbf{\Sigma}\mathbf{D}^{-1}\mathbf{E}_n. \qquad (2)$$

Here $\mathbf{\Sigma}$ is a diagonal square matrix with elements given by the areas of the surface tesserae and $\mathbf{E}_n$ is the column vector containing the normal components of the electric field due to the solute. $\mathbf{D}$ is a nonsymmetric square matrix with dimension equal to the number of tesserae, whose elements depend on geometrical cavity parameters and on the dielectric constant.

The procedures for the calculation of solute energy and wave function with the PCM method have been reported in several papers,[1,3] and we skip here all the details. Suffice it to say that, in order to get solvation quantities, one has to resort to a direct minimization of the functional of the free energy G of the whole solute–solvent system.

For a closed-shell solute, described by an SCF wave function with orbitals expanded over a finite basis set, the variational condition $\delta G = 0$ leads to the following equation:

$$\widetilde{\mathbf{F}}\mathbf{C} = \mathbf{S}\mathbf{C}\boldsymbol{\varepsilon}, \qquad (3)$$

where the tilde stresses that the Fock matrix contains terms accounting for the presence of the solvent field; namely we have

$$\widetilde{\mathbf{F}} = \mathbf{h} + \tfrac{1}{2}(\mathbf{j} + \mathbf{y}) + \mathbf{G}(\mathbf{P}) + \mathbf{X}(\mathbf{P}). \qquad (4)$$

Here $\mathbf{h}$ and $\mathbf{G}(\mathbf{P})$ collect the usual one- and two-electron integrals over the basis set used for the vacuum SCF calculation, while $\mathbf{P}$ is the one-electron density matrix; the matrices $\mathbf{j}$, $\mathbf{y}$, and $\mathbf{X}(\mathbf{P})$ collect the one- and two-electron integrals to be added when the interactions with the polarized dielectric medium are explicitly taken into account within the PCM framework. More details on these matrices can be found elsewhere.[3]

Now we may turn to the new formalism; an important aspect to be stressed from the very beginning is that the following derivation, even if it is here applied to the physical system of a charge distribution located inside a cavity surrounded by an anisotropic dielectric, is completely general. As a matter of fact, the method we are presenting can treat with equal efficiency structurally very different dielectric systems: standard isotropic liquids, as well as intrinsically anisotropic media, and ionic solutions; for the most general formulation of the method the reader is referred to a parallel more theoretical work.[17]

Let us start our analysis by considering two charge distributions, ρ and ρ', carried by the solute molecule and both located inside the cavity Ω_i. Their electrostatic interaction energy is given by

$$E_I(\rho,\rho') = \int_{R^3} \rho'(x)V(x)dx, \qquad (5)$$

where the electrostatic potential V created by ρ satisfies the Poisson equation:

$$-\text{div}(\boldsymbol{\epsilon}(x)\cdot\nabla V(x)) = \rho(x), \qquad (6)$$

with

$$\boldsymbol{\epsilon}(x) = \begin{cases} \boldsymbol{\epsilon}_i & \text{if } x \in \Omega_i \\ \boldsymbol{\epsilon}_e & \text{if } x \in \Omega_e, \end{cases}$$

where $\boldsymbol{\epsilon}_i$ is the unit 3×3 tensor, $\boldsymbol{\epsilon}_e$ a positive 3×3 symmetric tensor, and Ω_e the outer domain. Without loss of generality, we can always choose a set of orthonormal coordinates of the real space so that $\boldsymbol{\epsilon}_e$ is diagonal:

$$\boldsymbol{\epsilon}_i = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

$$\boldsymbol{\epsilon}_e = \begin{pmatrix} \epsilon_1 & 0 & 0 \\ 0 & \epsilon_2 & 0 \\ 0 & 0 & \epsilon_3 \end{pmatrix}.$$

We denote by G_i and G_e the Green's functions of the operators $-\Delta$ and $-\text{div}(\boldsymbol{\epsilon}\cdot\nabla V)$, respectively, and we define the function

$$G(x,y) = \begin{cases} G_i(x,y) = 1/4\pi|x-y| & \text{if } x \in \Omega_i \\ G_e(x,y) = 1/4\pi\sqrt{\det \boldsymbol{\epsilon}_e(\boldsymbol{\epsilon}_e^{-1}\cdot(x-y))\cdot(x-y)} \\ \qquad\qquad\qquad\qquad \text{if } x \in \Omega_e. \end{cases} \qquad (7)$$

We also write the following operators which are three of the four components of the so-called Calderon projector (we refer the reader to any convenient mathematical textbook[16] for the definition and the basic properties of such operators):

$$(S_i \cdot u)(x) = \int_\Gamma G_i(x,y)u(y)dy,$$

$$(D_i \cdot u)(x) = \int_\Gamma \partial_y G_i(x,y)u(y)dy,$$

$$(D_i^* \cdot u)(x) = \int_\Gamma \partial_x G_i(x,y)u(y)dy, \qquad (8)$$

where $\partial_y G(x,y) = \nabla_y G_i(x,y) \cdot n(y)$, $\partial_x G(x,y) = \nabla_x G_i(x,y) \cdot n(x)$, $u(x) \in L^2(\Gamma)$, and $x \in \Gamma$, being Γ the cavity boundary and $n(y)$ the outward pointing normal at y. The operator S_i is self-adjoint, and D_i^* is the adjoint of D_i. Besides one can prove that $S_i D_i^* = D_i S_i$. In a parallel way we can define two other operators, S_e and D_e, by replacing G_i of Eq. (8) with the corresponding function G_e defined in the outer space. In this case the derivative operator means $\partial_y G_e(x,y) = (\epsilon_e \cdot \nabla_y G_e(x,y)) \cdot n(y)$.

By introducing the electrostatic potential $\phi'(x)$ generated by the distribution ρ' in the vacuum, and a function $f(x)$ such as

$$\phi'(x) = \int_{R^3} G_i(x,y)\rho'(y)dy,$$

$$f(x) = \int_{R^3} G(x,y)\rho(y)dy, \qquad (9)$$

we may define an ''apparent'' potential $W = V - f$, and rewrite the interaction energy of Eq. (5) as

$$E_I(\rho, \rho') = E_1 + E_2$$

$$= \int_{R^3} \rho'(x)f(x)dx + \int_{R^3} \rho'(x)W(x)dx. \qquad (10)$$

The first term E_1 is easy to be computed since we suppose that both charge distributions are supported in Ω_i: this is in fact the expression of the electrostatic energy in the vacuum. The point is to compute the second term: In Appendix A we show that it can be rewritten by introducing the quantity $\sigma = S_i^{-1} \cdot W_i$, which has the dimension of a surface charge, so that

$$E_2 = \int_\Gamma \sigma(x)\phi_i'(x)dx. \qquad (11)$$

The problem is thus completely solved if we manage to compute the equivalent surface charge σ. The latter is the unique solution to the equation:

$$A \cdot \sigma = g \qquad (12)$$

with

$$A = \left(\frac{I}{2} - D_e\right)S_i + S_e\left(\frac{I}{2} + D_i^*\right) \qquad (13)$$

and

$$g = -\left(\frac{I}{2} - D_e\right)f_i - S_e \cdot \partial f_i. \qquad (14)$$

The proof of Eq. (12), which contains some mathematical technicalities, can be read in Ref. 17.

It is worth remarking that, when ϵ_e is a scalar (i.e., when the dielectric is isotropic), we have $S_e = S_i/\epsilon_e$, $f_e = f_i$, and $D_e = D_i$. Denoting by $\partial f_i = -E_n$, the normal component of the electric field created by ρ in the vacuum and using the relation $(I/2 - D_i) \cdot f_i + S_i \cdot \partial f_i = 0$,[17] Eq. (12) then becomes

$$S_i\left[\left(\frac{I}{2} - D_i^*\right) + \frac{1}{\epsilon_e}\left(\frac{I}{2} + D_i^*\right)\right] \cdot \sigma = -\frac{\epsilon_e - 1}{\epsilon_e} S_i \cdot E_n. \qquad (15)$$

After multiplication by $(\epsilon_e/\epsilon_e - 1)S_i^{-1}$, we obtain

$$\left(\frac{\epsilon_e + 1}{\epsilon_e - 1}\frac{I}{2} - D_i^*\right) \cdot \sigma = -E_n, \qquad (16)$$

which is exactly the operatorlike form of the matrix equation (2) obtained above for the standard PCM procedure. This is a very important point as it clearly shows that the new integral formulation approach reduces to that of PCM when the anisotropy of the medium disappears.

III. EFFECTIVE COMPUTATION

As in the standard PCM procedure, we can exploit a tessellation of the boundary Γ (i.e., the cavity surface) into K tesserae (T_k) with $1 \leq k \leq K$, and approximate the charge density σ by a piecewise constant function (i.e., a function constant on each tessera). In this approximation, Eq. (12) amounts to a linear system of order K denoted

$$\mathbf{A} \cdot \boldsymbol{\sigma} = \mathbf{g}, \qquad (17)$$

where $\boldsymbol{\sigma}$ is the column vector containing the approximated value of the density on the single tesserae, $\mathbf{A}$ is a $K \times K$ matrix, and $\mathbf{g}$ a column vector depending on the charge distribution ρ. We obtain for all $1 \leq k$, $k' \leq K$

$$A^{kk'} = \int_{T_k} dx \int_\Gamma dy \int_{T_{k'}} \kappa(x,y,z)dz, \qquad (18)$$

with

$$\kappa(x,y,z) = \left(\frac{\delta(x-y)}{2} - \partial_y G_e(x,y)\right)G_i(y,z)$$

$$+ G_e(x,y)\left(\frac{\delta(y-z)}{2} + \partial_y G_i(y,z)\right)$$

and

$$g^k = -\int_{T_k} dx \int_\Gamma dy\left[\left(\frac{\delta(x-y)}{2} - \partial_y G_e(x,y)\right)f_i(y)\right.$$

$$\left. + G_e(x,y)\partial f_i(y)\right]. \qquad (19)$$

In standard PCM, the tessellation of the cavity is built with the GEPOL procedure.[1,18] We briefly recall here the main characteristics of this procedure: The molecular cavity is formed by interlocking spheres centered on the solute nu-

clei (in some cases groups of atoms can be put in a single sphere); each sphere is then subdivided into triangular tesserae, corresponding to the projections on the surface of the faces of a pentakisdodecahedron inscribed in this sphere. Tesserae completely buried by some other spheres are discarded, while those cut by intersections with one or more other spheres are replaced by new polygonal tesserae whose areas are calculated using the Gauss–Bonnet theorem.[19]

We have noticed through numerical tests that such a tessellation is not adapted to the new formalism. Indeed, in some cases, the GEPOL procedure gives birth to cut polygonal tesserae which are either very small compared to the uncut ones (the observed area ratio can reach 1/10 000) or of bad shape in the sense that they present very acute angles. Both cases are known to lead to numerical instabilities for boundary element methods. However, standard PCM gives good results even with such meshes; this specific behavior comes from the spectral properties of the operator D_i. On the contrary, a mesh generated with GEPOL gives unstable results when used for the new method. That is why we have chosen another procedure for building a tessellation with better geometrical properties. The chosen procedure presently manages to treat, as the most complex cases, cavities formed by spheres having no more than two separate intersections with the others but it is a short-term goal for us to extend this new meshing procedure to other cases of intersected spheres. This procedure is an extension of the meridian and parallel-like division and reduces to this simple case for a single sphere cavity. The tessellation obtained in this way has much better geometrical properties in the sense mentioned above than that obtained with GEPOL. Indeed, it gives final tesserae with almost the same shape and area.

The immediately following aspect to be analyzed is the numerical computation of the various surface integrals in Eqs. (18) and (19).

Let us compare the numerical choices made for the standard PCM and the new method. In the standard PCM we need to compute the normal component of the electric field created by the surface density σ, which is here represented by K point charges $\{q_k\}$ located at the representative points $\{\bar{y}_k\}$ of the tesserae T_k. At $\bar{y}_k$ the normal component of the electric field generated by the apparent charge $q_{k'}$ for $k' \neq k$ reads

$$\mathbf{E}_{k'}(\bar{y}_k) \cdot \hat{n}_k = \frac{(\bar{y}_k - \bar{y}_{k'}) \cdot \hat{n}_{k'}}{|\bar{y}_k - \bar{y}_{k'}|^3} q_{k'}.$$

This expression can be understood as a single point integration rule. As for the part of the electric field generated at $\bar{y}_k$ by the charge q_k itself, we resort to Gauss theorem:

$$\mathbf{E}_k(\bar{y}_k) \cdot \hat{n}_k = 2\pi \frac{q_k}{a_k} (1 - \xi_k), \tag{20}$$

where $\hat{n}_k$ is the outward normal unit vector to the cavity at point $\bar{y}_k$, a_k the area of the tessera, and ξ_k an extrapolated correction factor due to the curvature of the tessera ($\xi_k = 0$ for a flat tessera).

Let us now turn to the new method. When Γ is piecewise smooth, and this is the case for the tessellation described above, one can prove that, for fixed x the singularities of the kernels $G_i(x,y)$, $G_e(x,y)$, $\partial G_i(x,y)$, and $\partial G_e(x,y)$ are almost everywhere in $1/|x-y|$. Therefore these singularities are integrable almost everywhere on this surface.

As a first guess, when T_k and $T_{k'}$ are different, one can also exploit a single-point integration rule, which gives for instance for S_i

$$S_i^{kk'} = \frac{a_k a_{k'}}{4\pi |\bar{y}_k - \bar{y}_{k'}|}.$$

However, numerical experiments have shown that it is better to use a more accurate integration rule. Usually, ten well-chosen integration points per tessera are widely enough.

A sharper analysis is needed for the diagonal terms of the various matrices involved in Eqs. (18) and (19); here it is not possible to exploit simple relations such as that of Eq. (20), since the matrix $\mathbf{A}$ is formed by contributions of different electrostatic origins. The procedure we have implemented to evaluate those terms is based on the reduction of the surface integral expressions (18) and (19) to line integrals along the edges of the tessera; the interested reader can find a detailed description of the method in Appendix B.

IV. NUMERICAL RESULTS AND DISCUSSION

The results reported below can be divided in two groups; the first one regards comparative tests between standard PCM and the implementation of the new formalism presented above, while the second group is a direct application of the new procedure to real anisotropic dielectrics.

In the following tables we report a selection of results for some molecular solutes in water ($\epsilon = 78.5$) for the preliminary comparative tests, while for the second part concerning anisotropic media, we consider the liquid crystal 7CB (4-n-heptyl-4'-cyanobiphenyl), which is nematic at room temperature ($T_{NI} = 312$ K). The principal values of its permittivity tensor are

$$\epsilon_{\perp} = 5.54, \quad \epsilon_{\parallel} = 17.1,$$

where $\epsilon_{\parallel}$ is the permittivity along the direction of preferential alignment of solvent molecules, and $\epsilon_{\perp}$ the correspondent value in the plane normal to this direction. The following results are obtained choosing the reference coordinate frame such that $\epsilon_1 = \epsilon_2 = \epsilon_{\perp}$ and $\epsilon_3 = \epsilon_{\parallel}$, where indices 1,2,3 stands for x,y,z Cartesian components, respectively.

We have examined five solutes: an ion (H^-), three dipolar neutral molecules (HF, H_2CO, CH_3CN), and a donor–acceptor complex (NH_3BH_3), using for all of them two basis sets: a standard DZP basis set for the anisotropic solvent calculations and a DZP plus diffuse functions for the test calculations in water. The DZP basis set derives from Dunning's[20] $4s2p(2s)$ contraction of Huzinaga's $9s5p(4s)$ primitive set,[21] supplemented by a set of polarization functions (d type for heavy atoms, and p type for H) with exponents 0.85 for O, 0.8 for C and N, 0,7 for B, and 1.0 for H. The diffuse functions, introduced to amplify the

effects due to the fraction of solute charge outside the cavity (see the following subsection for an analysis of this problem), are of dsp type for the heavy atoms and of sp type for hydrogen, their exponents are 1/3 of the smallest exponents of the correspondent DZP functions.

As already said, the solutes are contained within cavities in the dielectric medium defined in terms of interlocking spheres. In the simplest polyatomic system HF the spheres are centered on the nuclei, with radii equal to 1.2 times the corresponding van der Waals radii;[22] namely we have: $R_H = 1.44$ Å, $R_F = 1.62$ Å. For the other systems we have exploited cavities in which the interlocking spheres can contain more than one nucleus; namely we have: for H_2CO two spheres, one of radius $R_{CH_2} = 2.34$ Å centered on C atom and enveloping the CH_2 group, and the other of radius $R_O = 1.692$ Å centered on the O atom; for CH_3CN three spheres, one (radius $R_{CH_3} = 2.4$ Å) centered on the C atom and containing the methyl group, and the remaining centered on the other C ($R_C = 2.04$) and N ($R_N = 1.8$ Å) atoms, respectively; finally for NH_3BH_3 complex two equal spheres ($R = 2.124$ Å) centered on the N and B atoms, respectively, and each one containing also the three bonded hydrogens. For the single sphere case (i.e., for the H^- anion) a radius $R = 1.68$ Å has been used. All the numerical results reported below have been obtained by using implementations of both standard PCM and the new method within the GAMESS package.[23]

A. Comparison with standard PCM

Let us first focus on the comparison between the results obtained with the standard PCM procedure and those obtained within the new method, with the three principal values of tensor ϵ_e put equal. As we have already underlined, in this limit case the two formalisms are exactly equivalent from a theoretical point of view. We thus need to check that the two methods give the same results, apart from numerical approximations.

The test chosen as a first important requirement to state the reliability of the new method, and at the same time as an effective term of comparison with respect to standard PCM, derives from simple electrostatic considerations.

If we consider an isotropic dielectric of permittivity ϵ_e, according to Gauss theorem there is a simple relation between the solute charge Q_M^d and the integral of the corresponding apparent charge distribution σ^d, where d indicates the type of charges we are taking into account, i.e., total, nuclear, or electronic charges:

$$\int_\Gamma \sigma^d(x)dx = -\frac{\epsilon_e - 1}{\epsilon_e} Q_M^d. \tag{21}$$

This formal relation is no more exactly fulfilled when we introduce the discretized representation of the surface integrals in terms of piecewise functions that are constant on the tesserae; namely, the rougher is the way this approximation is performed, the greater is the difference between the two quantities of Eq. (21).

For the preliminary comparative analysis three different versions of the standard PCM have been exploited. These three versions, below indicated as ic0, ic2, and ic3, are characterized by the different approaches exploited to solve the problem of the inequality between the total apparent charge one can get in the calculation and the theoretical value defined by Gauss theorem [see Eq. (21)]. Actually, the so-called ic0 version does not take into account this eventual error and uses the apparent charge as it is obtained by computation; on the contrary, the other two methods exploit two different processes of renormalization of the apparent charges defined in Eq. (2), such as to bring the renormalized $\bar{q}_k^d$ to satisfy the condition

$$\sum_k \bar{q}_k^d = -\frac{\epsilon_e - 1}{\epsilon_e} Q_M^d. \tag{22}$$

Separating the apparent charges into nuclear and electronic contributions, $\mathbf{q}^N$ and $\mathbf{q}^e$, obtained through two equivalents of Eq. (2) in which the column matrix $\mathbf{E}_n$ of the electric field due to the solute charge distribution is limited to its nuclear or electronic component, respectively, the ic2 version corrects the two sets of charges through two separate factors f^N and f^e, such that $\bar{q}_k^d = f^d q_k^d$, for all k. The parallel renormalization procedure used in the ic3 version needs a short digression.

In the previous analysis we have omitted to say that the Gauss relation (21) when $d = e$ cannot be fulfilled for reasons of physical origin; indeed the solute electronic charge distribution has always tails spreading outside the cavity.[24] This usually small portion of charge should be taken into account as a further source of apparent charges, this time placed in the volume of dielectric, to be added to the surface ones. Actually, what is done in the so-called ic3 version of PCM[25] is a little different; here the ''escaped'' solute charge is numerically quantified and its effects are evaluated by introducing an extra apparent surface charge (called ''effective''), σ_{eff}, obtained through the Green–Ostrogradski formula. This additional charge distribution is treated exactly in the same way as σ, and replaced by a finite set of point charges $\{q_{eff}(\bar{y}_k)\}$ to be added to that related to σ.

We may note that each $q_{eff}(\bar{y}_k)$ contributes only to the electronic component q^e; in addition, these effective apparent charges are produced by the solute field (or better the solute electronic charge) only; hence the numerical error due to the calculation of the other apparent charge interactions in terms of single-point integration techniques, which affects both q^N and q^e, does not apply to them. In this framework, the renormalization factor f^e applied to the standard q^e charges is obtained as

$$f^e \sum_k q_k^e = -\frac{\epsilon - 1}{\epsilon} Q^{in} = -\frac{\epsilon - 1}{\epsilon} Q_M^e - \sum_k q_{eff}(\bar{y}_k). \tag{23}$$

As a last preliminary note we add that in the new integral equation formulation (in the following indicated as ''IEF'') no renormalization techniques are used nor are additional ''effective'' charges introduced.

TABLE I. Solvation data for H$^-$ in water obtained with four PCM versions. Charges are in a.u., energies in kcal/mol.

	ic0	ic2=ic3	IEF
$Q_T^d(th)$		$-0.9873/1.9745^a$	
Q_T^N		-0.9916	-0.9890
Q_T^e		1.5939	1.9079
Q_M^{out}		-0.3520	
ΔG_{sol}	-53.24	-87.40	-81.32
ΔG	-28.08	$+6.08$	

^{a}The two values of $Q_T^d(th)$ refer to nuclear and electronic components, respectively.

The notations introduced in the next tables are the following: $Q_T^d(th)$ and $Q_T^d = \Sigma_k q_k^d$, theoretical [i.e., as defined by the Gauss theorem, see Eq. (21)] and computed apparent charge, where d stands for nuclear (N) or electronic (e), respectively; Q_M^{out} solute electronic charge spreading outside the cavity; ΔG_{sol} electrostatic free energy of solvation: $\langle \Psi | \hat{H}^\circ + \hat{V}_R/2 | \Psi \rangle - \langle \Psi^\circ | \hat{H}^\circ | \Psi^\circ \rangle$; $\delta \Psi$ index measuring the variation of the wave function with respect to the value in vacuo: $\langle \Psi | \hat{H}^\circ | \Psi \rangle - \langle \Psi^\circ | \hat{H}^\circ | \Psi^\circ \rangle$; δG solvation free energy difference between IEF and the various PCM versions.

All charge values are in a.u., while energies are in kcal/mol.

Tables I–III show some important characteristics of the new procedure when implemented in the PCM framework.

First of all it is worth stressing the completely comparable quality of the approximations used to calculate the total nuclear apparent charge Q_T^N in the two methods (for standard PCM we report a single value as all the three versions give the same unrenormalized apparent charge): The differences with respect to the Gauss-theorem value $Q_T^N(th)$, are almost equal and always smaller than 0.1%. This behavior can be safely taken as the definite proof of the good reliability of the tessellation procedure chosen for the IEF method, and, even more important, of the integration techniques used in the evaluation of **A** and **g** matrices.

On the contrary, not negligible differences between the two methods can be observed on the total electronic apparent charge Q_T^e: IEF values differ from those calculated with any of the standard PCM versions of about 0.6% in HF, 0.4% in H$_2$CO, 2.2% in NH$_3$BH$_3$, and 1% in CH$_3$CN. A much larger

effect is present in the case of H$^-$: here the difference between the two methods is of about 20%. Let us try to understand the reasons for this behavior.

As already noted, the evaluation of electronic charges is a very delicate point in PCM; the presence of fractions of the solute charge outside the cavity can affect the result in a quite sensitive way; as a general rule we may state that the more diffuse the basis set functions used in the calculation, the larger the error in the calculation of Q_T^e. The calculations below are performed with a quite diffuse basis set, DZP $+(spd/sp)$, which gives a fraction of escaped charge not always negligible (in the neutral solutes it ranges from about 0.067 a.u. in HF to 0.336 a.u. in NH$_3$BH$_3$, while for H$^-$ is 0.352 a.u.). The immediate consequence is that in all the three standard PCM versions the error on the electronic apparent charge is always larger than that on the nuclear component. Indeed, for the latter the error is due to numerical approximations only, while Q_T^e is affected also by this neglect of electronic tails. The results are different for the IEF method; here the value of the total apparent charge Q_T^d of both the electronic ($d=e$) and nuclear ($d=N$) set, differs from the theoretical one, $Q_T^d(th)$, for quantities which are almost equal (only in the case of the anionic solute the error on Q_T^e is rather larger than that on Q_T^N); as an important consequence the IEF error on the electronic apparent charges is always smaller than that found in the PCM procedure.

The reasons for this good behavior of IEF can be derived from electrostatic considerations on simple spherical cases. By assuming a radial symmetric electron density it can be shown that the potential calculated on the cavity surface is almost by an order of magnitude less sensitive to the problem of the escaped charge than the electric field;[26] hence as IEF exploits both potential-type and electric field-type operators [see Eqs. (7) and (8)], while standard PCM exploits only the latter ones, the errors that the IEF methods give on apparent charges because of the escaped charge, are smaller with respect to the PCM method. Nevertheless the remaining apparent charge defect, which can be large for anions, still affects the final result as we can see from data reported in Table I. In this case in fact, as the spherical symmetry allows an exact renormalization of the charges, we may take the results obtained with both ic2 and ic3 (exactly equal) as the best ones; with respect to them IEF gives an ''error'' of

TABLE II. Solvation data for HF and H$_2$CO in water obtained with four different PCM versions, see text for their definitions. Charges are in a.u., energies in kcal/mol.

	HF				H$_2$CO			
	ic0	ic2	ic3	IEF	ic0	ic2	ic3	IEF
$Q_T^d(th)$		± 9.8726				± 15.7962		
Q_T^N		-9.8771		-9.8811		-15.8000		-15.8014
Q_T^e		$+9.8122$		$+9.8750$		$+15.7264$		$+15.7949$
Q_M^{out}		-0.0672				-0.0733		
ΔG_{sol}	-4.81	-5.01	-5.32	-5.31	-4.91	-5.09	-5.30	-5.25
$\delta \Psi$	0.51	0.55	0.61	0.60	1.04	1.14	1.23	1.20
δG	-0.68	-0.35	$+0.02$		-0.34	-0.16	$+0.05$	

TABLE III. Solvation data for NH_3BH_3 and CH_3CN in water obtained with four different PCM versions, see text for their definitions. Charges are in a.u., energies in kcal/mol.

	NH_3BH_3				CH_3CN			
	ic0	ic2	ic3	IEF	ic0	ic2	ic3	IEF
$Q_T^d(th)$		± 17.7707				± 21.7197		
Q_T^N		-17.7795		-17.7761		-21.6380		-21.7174
Q_T^e		$+17.3548$		$+17.7441$		$+21.4978$		$+21.7062$
Q_M^{out}		-0.3357				-0.1397		
ΔG_{sol}	-11.01	-10.22	-14.72	-14.79	-5.89	-6.10	-7.21	-7.26
$\delta\Psi$	1.32	1.15	2.96	2.64	1.09	1.30	1.86	1.80
δG	-3.78	-4.57	-0.07		-1.37	-1.16	-0.05	

about 7% on the free energy, which nevertheless has to be compared with the by far larger 40% of error obtained with the parallel PCM method not exploiting renormalization procedures (ic0).

All these considerations, which could appear, on the one hand, a little abstract and, on the other, too technical, have an important effect on the quantity that gives the fundamental check with the experiments: the free energy of solvation and this is the reason why it is worth examining this point. Actually the ΔG_{sol} data reported in Tables I–III refer to the electrostatic component only, other contributions related to repulsion and dispersion-type interactions and to cavitation, here neglected, should be considered in order to have a reliable comparison with experimental measurements; anyway to our scopes these partial values are enough. What is worth stressing is that IEF values are very similar to those obtained with the version of standard PCM (ic3) which is considered to be the most refined one. In fact previous tests have clearly shown that the introduction of a set of additional effective charges which takes explicitly into account the escaped charge gives a by far better description of the whole system with respect to that obtained with a version (ic2) which exploits a renormalization performed *a posteriori* and with constant factors, or, *a fortiori*, with a nonrenormalized procedure (ic0).

B. Calculations for anisotropic dielectrics

Once we have analyzed the computational aspects of the new method, and compared its performances with those of standard PCM, let us consider its application to an anisotropic solvent, namely the nematic liquid crystal 7CB. In the following tables we report a selection of numerical results obtained with the IEF method for the four neutral solutes described above. For each molecule we have performed four different calculations: two in the hypothetical isotropic media with permittivity equal to the smallest ($\epsilon_e = \epsilon_{min} = 5.54$) and the largest ($\epsilon_e = \epsilon_{max} = 17.1$) component of the 7CB dielectric tensor, respectively, and two in the real liquid crystal. The latter two refer to the same solute–solvent system, but with the solute oriented with its principal axis along the x Cartesian direction (along which $\epsilon = \epsilon_\perp = 5.54$) and the z direction (along which $\epsilon = \epsilon_\parallel = 17.1$), respectively. In fact,

because of the anisotropy of the liquid crystal, the two possible orientations can be stabilized in different ways by the solvent.

The specific effects of the anisotropic medium, and their comparison with the limiting isotropic equivalents, are here evaluated in terms of different quantities. In Tables IV and V we report the already defined total apparent charges, and their correspondent theoretical values (for the anisotropic cases the reported value is not the real theoretical equivalent but only what we should obtain for an isotropic dielectric with permittivity equal to the geometric average of the tensorial components), the solute dipole moment (in debye), and the electrostatic solvation free energy (in kcal/mol).

As one could expect, both the electrostatic solvation free energy and the dipole moment are larger (in absolute value) when the direction of the solute principal axis coincides with the z axis along which the tensor ϵ_e has the greatest value. This preferential orientation is here due to electrostatic interactions only.

In an effort to give some, at least qualitative, explanations we may describe the solute charge distribution in terms of a multipole expansion approach: In the presence of the reaction field due to the polarizable surrounding medium the solute's positive and negative charges will move with respect

TABLE IV. Solvation data of HF and H_2CO in three different dielectrics. Charges are in a.u., dipoles in debye, and free energies in kcal/mol.

	ϵ_{min}	Along x	Along z	ϵ_{max}
		HF		
$Q_T^d(th)$	± 8.1949	± 8.7603		± 9.4152
Q_T^N	-8.2028	-8.8148	-8.7716	-9.4234
Q_T^e	8.2072	8.8162	8.7738	9.4222
μ	2.2204	2.2353	2.2382	2.2532
ΔG_{sol}	-4.41	-4.81	-4.90	-5.30
		H_2CO		
$Q_T^d(th)$	± 13.1119	± 14.0164		± 15.0643
Q_T^N	-13.1224	-14.0922	-14.0552	-15.0710
Q_T^e	13.1294	14.0949	14.0571	15.0685
μ	3.3113	3.3645	3.3709	3.4269
ΔG_{sol}	-4.03	-4.48	-4.53	-4.99

TABLE V. Solvation data of NH_3BH_3 and CH_3CN in three dielectrics. Charges are in a.u., dipoles in debye, and free energies in kcal/mol.

	ϵ_{min}	Along x	Along z	ϵ_{max}
		NH_3BH_3		
$Q_T^d(th)$	± 14.7509	± 15.7685		± 16.9474
Q_T^N	-14.7554	-15.8685	-15.7464	-16.9525
Q_T^e	14.7810	15.8749	15.7546	16.9399
μ	6.4297	6.4924	6.5067	6.5698
ΔG_{sol}	-12.36	-13.39	-13.62	-14.66
		CH_3CN		
$Q_T^d(th)$	± 18.0289	± 19.2726		± 20.7134
Q_T^N	-18.0285	-19.4027	-19.2080	-20.7116
Q_T^e	18.0407	19.4075	19.2124	20.7084
μ	4.9779	5.0514	5.0679	5.1426
ΔG_{sol}	-5.34	-5.83	-5.93	-6.43

to each other. Even if we limit our analysis to the first term only (the dipole), it should be clear that, because of the positive anisotropy ($\Delta\epsilon = \epsilon_\parallel - \epsilon_\perp > 0$) of this liquid crystalline solvent, the greatest polarization effects, and consequently the most solvent-stabilized situation, are given by the solute orientation indicated as ''along z.''

The analysis reported above is clearly quite limited, and the reported results account for electrostatic interactions only; a better evaluation of the ordering mechanism in nematic phases, including also cavitation term, is easily obtainable within PCM framework,[15] but it is not performed here as it is out of the scope of the paper.

In Tables VI and Tables VII the analysis is extended to other, more specific, quantities, such as the energy values of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and their differences $\Delta\varepsilon$ (all values are in a.u.), the Mulliken derived atomic charges (Q_A), and the bond order index (b_{AB}) as obtained from Mayer analysis.[27] These properties have been chosen as

TABLE VI. Solvation data of HF and H_2CO in three different dielectrics. All values are in a.u.

	ϵ_{min}	Along x	Along z	ϵ_{max}
		HF		
HOMO	-0.6489	-0.6485	-0.6490	-0.6485
LUMO	0.2239	0.2266	0.2267	0.2295
$\Delta\varepsilon$	0.8728	0.8751	0.8757	0.8780
Q_F	-0.44797	-0.45040	-0.45094	-0.45336
Q_H	0.44797	0.45040	0.45094	0.45336
b_{HF}	0.825	0.822	0.822	0.820
		H_2CO		
HOMO	-0.4458	-0.4451	-0.4450	-0.4444
LUMO	0.1160	0.1169	0.1171	0.1180
$\Delta\varepsilon$	0.5618	0.5620	0.5621	0.5624
Q_H	0.10889	0.11212	0.11225	0.11555
Q_C	0.16487	0.16471	0.16526	0.16528
Q_O	-0.38264	-0.38895	-0.38976	-0.39638
b_{HC}	0.927	0.927	0.927	0.927
b_{CO}	2.014	2.009	2.008	2.003

TABLE VII. Solvation data of NH_3BH_3 and CH_3CN in three different dielectrics. All values are in a.u.

	ϵ_{min}	Along x	Along z	ϵ_{max}
		NH_3BH_3		
HOMO	-0.4400	-0.4375	-0.4385	-0.4356
LUMO	0.1568	0.1601	0.1596	0.1631
$\Delta\varepsilon$	0.5968	0.5976	0.5981	0.5987
Q_H	0.33952	0.34154	0.34227	0.34458
Q_N	-0.58264	-0.58457	-0.58451	-0.58661
Q_B	-0.13528	-0.13853	-0.13803	-0.14146
Q_H	-0.10021	-0.10077	-0.10142	-0.10189
b_{HN}	0.880	0.879	0.879	0.877
b_{NB}	0.630	0.634	0.636	0.640
b_{BH}	0.997	0.997	0.997	0.997
		CH_3CN		
HOMO	-0.4734	-0.4729	-0.4731	-0.4726
LUMO	0.1849	0.1857	0.1857	0.1866
$\Delta\varepsilon$	0.6583	0.6586	0.6588	0.6592
Q_H	0.18231	0.18392	0.18414	0.18595
Q_C	-0.36605	-0.36780	-0.36743	-0.36949
Q_C	0.09126	0.09590	0.09714	0.10184
Q_N	-0.27214	-0.28012	-0.28212	-0.29019
b_{HC}	0.952	0.951	0.951	0.950
b_{CC}	0.909	0.910	0.910	0.911
b_{CN}	3.115	3.114	3.114	3.113

they can give an immediate chemical description of the changes induced in the solute distribution by solvents with quite different structures.

Results reported in Tables VI and VII confirm what derived from dipole and solvation free energies values of the previous tables from a quite different point of view.

In fact, even if the variations we are trying to analyze are quite small (as we have to expect from the small dielectric anisotropy here considered, which is common to all the most used liquid crystals), we can see that almost all the quantities calculated in 7CB have different values for the solutes in the two orientations; this shows that if one neglects the anisotropic nature of the solvent, for example by replacing its dielectric tensor with an averaged scalar permittivity, the results one obtains are surely incomplete as, for example, they cannot give account for this preferential alignment ''along z.''

This specific characteristic of anisotropic media, here only briefly introduced as a test, can be further exploited in order to get hints on some other interesting results, such as those we have obtained in a preliminary study on chemical reactions conducted in liquid crystals; we are not able to give more details yet, as calculations are still in progress. On the other hand, even more interesting results could be derived from calculations of other molecular properties, which are more affected by the anisotropic nature of the medium; a very promising group is given by electric response functions, such as static and dynamic polarizabilities and hyperpolarizabilities, and by their magnetic counterparts; developments in this direction have already began.

V. CONCLUSION AND FUTURE TRENDS

In the previous sections we have shown that integral equation methods are still efficient in the extension of the PCM framework to solvents with intrinsic dielectric anisotropy such as liquid crystal, but also solid matrices with symmetry less than cubic. Besides, a further extension to treat ionic solutions described in terms of the so-called linearized Poisson–Boltzmann equation:

$$-\operatorname{div}(\boldsymbol{\epsilon}(x)\cdot\nabla V(x))+\epsilon(x)\kappa(x)^2 V(x)=\rho(x), \qquad (24)$$

where the constant $1/\kappa$ is the Debye length, is possible; first numerical results can be read in Ref. 17. In all these cases, integral equation methods are much more efficient than the three-dimensional (3D) methods, finite difference and/or finite element methods used so far: indeed, the computational effort is by far lower and no approximations are made to account for boundary conditions. Moreover, and even more important, it is easier to compute analytical derivatives of the energy with respect to physical parameters, as the temperature in the case of ionic solutions, or the orientation of the molecule with respect to the principal directions of the dielectric tensor $\boldsymbol{\epsilon}_e$ in the case of liquid crystals; the latter kind of analysis can give very useful information on structural and dynamical characteristics of nematic mesophases, to be successively used in a large number of spectroscopic measurements. Analytical derivatives with respect to nuclear coordinates, exploited in geometry optimization procedures, are more difficult to be computed, but seem nevertheless accessible. This further extension is in progress at the moment.[28]

ACKNOWLEDGMENTS

APPENDIX A

Proof of Eq. (11).
The ''apparent'' potential $W=V-f$ satisfies the following relations:

$$\begin{cases} -\Delta W=0 & \text{in } \Omega_i, \\ -\operatorname{div}(\boldsymbol{\epsilon}_e\cdot\nabla W)=0 & \text{in } \Omega_e. \end{cases}$$

Hence if we apply the relation

$$W(x)=\int_\Gamma G_i(x,y)\partial W_i(y)dy-\int_\Gamma W_i(y)\partial_y G_i(x,y)dy, \quad (A1)$$

which is true for all $x\in\Omega_i$ (see Ref. 17), we obtain

$$E_2=\int_\Gamma \partial W_i(y)\left(\int_{R^3}\rho'(x)G_i(x,y)dx\right)dy$$

$$-\int_\Gamma W_i(y)\left(\int_{R^3}\rho'(x)\partial_y G_i(x,y)dx\right)dy$$

$$=\int_\Gamma \partial W_i(y)\phi'(y)dy-\int_\Gamma W_i(y)\partial\phi'(y)dy. \qquad (A2)$$

If we now apply twice the relation: $\forall x\in\Gamma$,

$$\tfrac{1}{2}u_i(x)=\int_\Gamma G_i(x,y)\partial u_i(y)dy-\int_\Gamma u_i(y)\partial_y G_i(x,y)dy$$

$$-\int_{\Omega_i} G_i(x,y)\Delta u(y)dy \qquad (A3)$$

first with $u=W$, and then with $u=\phi'$, we may write:

$$S_i\cdot\partial W_i-D_i\cdot W_i=W_i/2,$$

$$S_i\cdot\partial\phi_i'-D_i\cdot\phi_i'=-\phi_i'/2. \qquad (A4)$$

The relations above are then exploited in order to get the expressions of ∂W_i and $\partial\phi_i'$ to be used in Eq. (A2); in such a way we obtain:

$$E_2=\int_\Gamma S_i^{-1}(I/2+D_i)\cdot W_i(y)\phi'(y)dy$$

$$-\int_\Gamma W_i(y)S_i^{-1}(-I/2+D_i)\cdot\phi'(y)dy$$

$$=\int_\Gamma(I/2+D_i^*)S_i^{-1}\cdot W_i(y)\phi'(y)dy$$

$$-\int_\Gamma(-I/2+D_i^*)S_i^{-1}\cdot W_i(y)\phi'(y)dy. \qquad (A5)$$

By introducing the quantity $\sigma=S_i^{-1}\cdot W_i$, which has the dimension of a surface charge, the equality above may be written as

$$E_2=\int_\Gamma \sigma(y)\phi_i'(y)dy$$

which is exactly Eq. (11).

APPENDIX B

We have to compute

$$I=\int\int_{T\times T} G(x,y)dx\,dy, \qquad (B1)$$

where T is a tessera drawn on a sphere and G is one of the four kernels G_i, G_e, ∂G_i, or ∂G_e. We first notice that the function

$$x\mapsto\int_T G(x,y)dy \qquad (B2)$$

is regular. So we are allowed to use a classical Gaussian integration scheme to compute the outer integral. Thus

$$I \simeq \sum_j \, w_j \int_T G(x_j, y) dy, \qquad (B3)$$

where the x_j are Gauss points and w_j the associated weights. Using polar coordinates centered at x_j, the integral $\int_T G(x_j, y) dy$ reduces to the integral over ∂T of a regular function ϕ. The integral over ∂T is evaluated with a Gauss rule. As for the function ϕ, it has an analytical expression when $G = G_i$ or $G = \partial G_i$. In most cases, it has no simple analytical expression for $G = G_e$ and $G = \partial G_e$, but this function can be nevertheless easily computed numerically as a one-dimensional integral of a regular function.

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