

# Ab initio study of ionic solutions by a polarizable continuum dielectric model

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## Abstract

A new implementation of a recently developed formalism to describe chemical systems in ionic solutions is presented. It allows ab initio calculations at the Hartree–Fock and density functional levels on closed and open shell systems, taking into account the ionic atmosphere effects at not too large concentrations. Test calculations on simple systems are compared to experimental data and to values obtained by numerical integration of the Poisson–Boltzmann equation. A more complex system, namely the glycine radical in aqueous solution, is also analyzed. © 1998 Elsevier Science B.V.

## 1. Introduction

An effective strategy for the description of chemical systems in solution with accuracy comparable to that for isolated molecules is based on the continuum dielectric approach [1–3]. In this kind of model a target subsystem, the “solute” (possibly supplemented by a few strongly interacting solvent molecules), is described by advanced ab initio techniques, whereas the “solvent” is modeled as an infinite polarizable continuum. In the quantum mechanical version of the continuum model, use is made of an effective Hamiltonian where the solute–solvent interactions are described by a reaction potential operator  $\hat{V}_R$  coupled to the solute Hamiltonian  $\hat{H}^0$ :

$$\begin{aligned} \hat{H}^0\Psi^0 &= E^0\Psi^0 && \text{in vacuo} \\ \left[ \hat{H}^0 + \hat{V}_R \right] \Psi &= E\Psi && \text{in solution} \end{aligned} \quad (1)$$

Among the several approaches exploiting such strategy, we are interested in those expressing  $\hat{V}_R$

in terms of an apparent surface charge (ASC) distribution: in fact, ASC methods permit the reaching of a greater accuracy than other approaches. One of the most powerful ASC solvation methods is the so-called polarizable continuum model (PCM), which has been applied to a great number of systems in aqueous and non aqueous solutions. An effective PCM version [4,5] allowing fast and reliable calculations of the energy and energy gradients for closed and open shell molecules at the Hartree–Fock (HF) and density functional (DF) levels, has been coded in the Gaussian94 package [6]: this version exploits the numerous procedures existing in Gaussian94 for the study of electronic properties and for the optimization of molecular geometries. Another interesting approach, based on the description of the solvent as a polarizable conductor medium [7,8] has been recently implemented in a form similar to PCM [9]: in the following we shall refer to these methods as D-PCM and C-PCM (i.e. dielectric and conductor PCM, respectively). The C-PCM method can be

applied to polar solvents and provides energies and energy gradients with limited computational times, exploiting the same features cited above for D-PCM.

The present Letter reports on the implementation of a new formulation of PCM, based on an integral equation formalism (IEF) [10,11]. The IEF-PCM procedure allows the *ab initio* study of different systems: ordinary isotropic solvents (which are already treatable by D-PCM and C-PCM), anisotropic solvents like nematic liquid crystals and ionic solutions. Some years ago a PCM treatment of anisotropic solutions, based on a different approach, was implemented for HF calculations on closed shell systems [12]: the present formulation is more effective and it is extended to DF calculations and to open shell molecules. However, ionic solutions are studied in most cases [13–17] (for less recent examples, one can refer to the exhaustive review by Davis and McCammon) [18] by numerical integration of the Poisson–Boltzmann equation on 3D grids, with a considerable computational burden, whereas in the present formulation the treatment is nearly as effective as for isotropic solvents. Other boundary element methods solving the linearized Poisson–Boltzmann equation by means of apparent charges spread on the solute–solvent interface have been proposed by Yoon and Lenhoff [19], Juffer et al. [20] and Wilson et al. [21]

In the following we present some applications of IEF-PCM to ionic solutions at different ionic strengths, deferring the analysis of anisotropic solutions to further work. A reliable *ab initio* description of ionic strength effects on energies and electronic properties is particularly important for bio-chemical molecules: let us recall that the recent advances in *ab initio* techniques are making quantum calculations feasible also on systems with hundreds of atoms. Moreover, D-PCM, C-PCM and IEF-PCM models can make use of a specific procedure to build the solute cavity allowing the calculation of solvation free energies ( $\Delta\mathcal{E}_{\text{solv}}$ ) with chemical accuracy (mean errors with respect to experimental  $\Delta\mathcal{E}_{\text{solv}}$ s lower than 0.2 kcal/mol for neutral and about 1 kcal/mol for charged solutes) for a large number of chemical systems both at the HF and at the DF levels [22]. Such a good agreement between calculated and experimental  $\Delta\mathcal{E}_{\text{solv}}$ s makes a reliable computation of ionic strength effects even more desirable.

As explained below, the IEF formalism for ionic solutions is based on the linearized Poisson–Boltzmann equation, thus being more suited for low charge electrolytes at low concentrations: even in these conditions the effect of the ionic atmosphere on the thermodynamics and kinetics of chemical processes is often not negligible.

The IEF-PCM procedure has been recently implemented in the GAMESS [23] package: the present implementation in Gaussian94 extends the applicability of this procedure to open shell molecules and to density functional methods and in particular to large biochemical system for which *ab initio* calculations are becoming feasible, thanks to the recent advances in quantum chemistry techniques. Lastly the present implementation, like the D-PCM and the C-PCM cited above, is particularly easy to use also for those researchers not directly involved in the elaboration of computer codes: this aspect is becoming more and more important, as the increased reliability of the computational methods and the reduction of computational costs nowadays make this kind of procedures accessible to a large portion of the chemical community.

## 2. Computational method

Like in other continuum solvation models, the solute molecule is embedded in a cavity surrounded by a polarizable medium, with the dielectric constant of the considered solvent. The cavity has molecular shape: it is formed by fused spheres, centered on solute atoms or atomic groups, according to the GEPO algorithm [24].

The IEF-PCM procedure is based on operators largely exploited in the theory of integral equations, not familiar in computational and theoretical chemistry. The mathematical foundations are given in Refs. [10] and [11] and some examples of chemical applications can be found in Ref. [10]. A detailed derivation of the method is out of the scope of the present Letter: here we limit ourselves to stressing a few points.

Inside the cavity the electrostatic potential  $V$  obeys the Poisson equation:

$$-\nabla^2 V = 4\pi\rho \quad (2)$$

where  $\rho$  is the solute electronic and nuclear charge density, whereas in the bulk of the solvent  $V$  obeys the (linearized) Poisson–Boltzmann equation:

$$-\epsilon \nabla^2 V + \epsilon \kappa^2 V = 0 \quad (3)$$

where  $\epsilon$  is the dielectric constant and  $\kappa$  the inverse of the so-called Debye length:

$$\kappa = \frac{8\pi IF}{\epsilon RT} \quad (4)$$

where  $I$  is the ionic strength of the solution and  $F$  the Faraday constant. The usual boundary conditions on the cavity surface hold:

$$V_e = V_i \quad (5)$$

$$\nabla V_e \cdot \hat{n} = \frac{1}{\epsilon} \nabla V_i \cdot \hat{n} \quad (6)$$

where the suffixes  $e, i$  refer to the regions outside and inside the cavity, respectively and  $\hat{n}$  is the unit vector normal to the surface.

The solvent reaction field is described by an apparent, or polarization charge distribution appearing on the cavity surface: the surface is partitioned into small domains, called tesseræ and the apparent surface charge density is represented by suitable point charges, one per tessera. The polarization point charges are determined by the matrix equation

$$\mathbf{C}\mathbf{q} = -\mathbf{g} \quad (7)$$

$\mathbf{q}$  is a vector containing the polarization charges on tesseræ,  $\mathbf{C}$  is a “geometrical” matrix

$$\mathbf{C} = (\mathbf{I}/2 - \mathbf{D}_e)\mathbf{S}_i\mathbf{A}^{-1} + \mathbf{S}_e(\mathbf{I}/2 + \mathbf{D}_i^\dagger)\mathbf{A}^{-1} \quad (8)$$

where  $\mathbf{I}$  is the unit matrix,  $\mathbf{A}$  is a diagonal matrix collecting tesseræ areas and  $\mathbf{D}_e$ ,  $\mathbf{D}_i$ ,  $\mathbf{S}_e$  and  $\mathbf{S}_i$  depend on tesseræ positions, on the solvent dielectric constant and, in the case of ionic solutions, on the ionic strength (their explicit expressions are given in Ref. [10]). Lastly  $\mathbf{g}$  is a vector whose elements are combinations of the electrostatic potential and of the electric field exerted by the solute nuclei and electrons on the tesseræ (see Ref. [10] for more details). Notice that Eqs. (7) and (8) are put in a form slightly different from those used in Ref. [10], to highlight the formal equivalence with our previous implemen-

tations of the D-PCM (Ref. [4]) and C-PCM (Ref. [9]) approaches.

The molecular free energy in solution can be written as a sum of four contributions:

$$\mathcal{G} = \mathcal{G}_{\text{el}} + \mathcal{G}_{\text{cav}} + \mathcal{G}_{\text{dis}} + \mathcal{G}_{\text{rep}} \quad (9)$$

The electrostatic contribution,  $\mathcal{G}_{\text{el}}$ , is

$$\begin{aligned} \mathcal{G}_{\text{el}} &= \langle \Psi | \hat{\mathcal{H}}^0 + 1/2 \hat{\mathcal{V}}_R | \Psi \rangle \\ &= \langle \Psi | \hat{\mathcal{H}}^0 | \Psi \rangle + \frac{1}{2} \sum_k^{\text{tesseræ}} q_k V_k \end{aligned} \quad (10)$$

where  $V_k$  is the electrostatic potential due to the solute nuclei and electrons and  $q_k$  is the polarization charge on tessera  $k$ .

$\mathcal{G}_{\text{cav}}$  corresponds to the work needed to build the solute cavity and is calculated by a classical hard sphere approach:

$$\mathcal{G}_{\text{cav}} = \sum_I^{\text{spheres}} \mathcal{G}_I^{\text{HS}} \frac{A_I}{4\pi R_I^2} \quad (11)$$

where the sum runs over the spheres forming the cavity:  $\mathcal{G}_I^{\text{HS}}$  is the cavitation energy for an isolated hard sphere of radius  $R_I$  according to Pierotti’s approach [25], and  $A_I$  is the area of the sphere  $I$  actually exposed to the solvent, i.e. not buried by other spheres.

$\mathcal{G}_{\text{dis}}$  and  $\mathcal{G}_{\text{rep}}$  describe the solute–solvent dispersion and repulsion interactions, respectively. These latter terms are calculated classically using the atom–atom interaction potentials proposed by Caillet et al. [26], with the procedure illustrated in Ref. [27]. Notice that the cavitation, dispersion and repulsion terms do not modify the solute Hamiltonian: therefore they affect the solute free energy but not its wavefunction.

Clearly, IEF differs from the other PCM-like approaches only for  $\mathcal{G}_{\text{el}}$ : in particular, in ionic solutions the ionic atmosphere affects the electrostatic solute–solvent interactions only.

Some attention must be paid to the definition of the solute cavity, in particular to the radii of the spheres put around the atoms and the atomic groups. The strict agreement between PCM and experimental solvation energies, mentioned in the Introduction, can be achieved by a specific procedure, called

UATM (united atoms topological model) [22], that has been applied in all the IEF calculations reported below. In the UATM procedure the H atoms are always included in the same spheres of the heavy atoms they are bonded to, and the atomic and group radii depend on the molecular topology: the reader is addressed to Ref. [22] for the details of the method. We recall that in the IEF version implemented in Gaussian94 a specific routine automatically assigns the proper UATM radii: as in all PCM-like models [1,4] the atomic radii have to be multiplied by 1.2 when electrostatic solvation energies are calculated.

### 3. Results and discussion

The reliability of the IEF-PCM description of ionic solutions has been tested by calculating the free energy of simple systems in aqueous solution at

Table 1

Logarithm of the activity coefficient for dilute solutions of  $\text{Na}^+$ , calculated by IEF at the HF/6-31G(d) level and by numerical integration of the Poisson–Boltzmann equation

$I$ (M)	$\ln \gamma$	
	IPBECF (numerical PB)	IEF
$10^{-7}$	$-0.37 \times 10^{-3}$	$-0.38 \times 10^{-3}$
$5 \times 10^{-7}$	$-0.53 \times 10^{-3}$	$-0.54 \times 10^{-3}$
$10^{-6}$	$-1.17 \times 10^{-3}$	$-1.19 \times 10^{-3}$
$5 \times 10^{-6}$	$-2.62 \times 10^{-3}$	$-2.65 \times 10^{-3}$
$10^{-5}$	$-3.70 \times 10^{-3}$	$-3.75 \times 10^{-3}$
$5 \times 10^{-5}$	$-8.24 \times 10^{-3}$	$-8.37 \times 10^{-3}$
$10^{-3}$	$-11.62 \times 10^{-3}$	$-11.82 \times 10^{-3}$
$5 \times 10^{-3}$	$-25.65 \times 10^{-3}$	$-26.22 \times 10^{-3}$
$10^{-3}$	$-35.90 \times 10^{-3}$	$-36.87 \times 10^{-3}$

different ionic strengths. First we considered dilute solutions of a monovalent ion  $\text{Na}^+$ , studied at the HF level with the 6-31G(d) basis set: the results are most

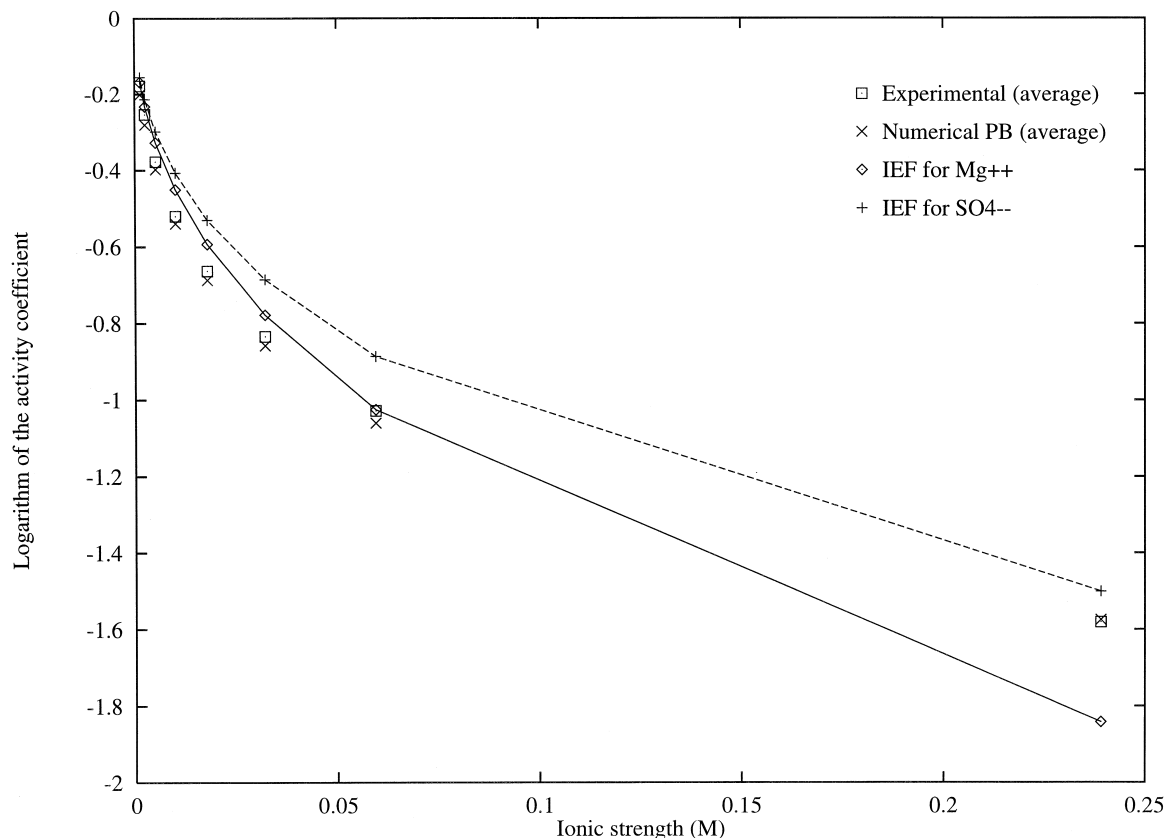


Fig. 1. Logarithm of the activity coefficient for  $\text{Mg}^{2+}$  and  $\text{SO}_4^{2-}$  calculated by IEF at the HF/6-31G(d) level, compared to average values obtained by IPBECF (numerical integration of PB equation) and to experimental average values.

clearly expressed by comparing the molecular free energy at finite ionic strength  $I$  to the “ideal” free energy at  $I = 0$ , defining the activity coefficient  $\gamma$ :

$$\ln \gamma = \frac{\mathcal{E}_{el}(I) - \mathcal{E}_{el}(0)}{RT} \quad (12)$$

where  $R$  is the gas constant ( $1.98 \times 10^{-3}$  kcal mol $^{-1}$  K $^{-1}$ ) and  $T$  the absolute temperature. In Table 1 we compare IEF results to  $\ln \gamma$ s calculated by numerical integration of the full (non-linearized) Poisson–Boltzmann (PB) equation, performed by the IPBEC program [28]: the agreement is good up to  $I = 0.001$  M.

The results for a divalent system, namely MgSO $_4$ , over a more extended range of concentrations are shown in Fig. 1. In this case IEF calculations at the HF/6-31G(d) level are compared to experimental

[29] and numerical full PB data: in the numerical integration, performed by the IBPECP program, the two divalent ions are described as charged spheres, whose radius is optimized at the value of 4.1 Å (in Ref. [29] the dependence of these results on the sphere radius was estimated, for example, by repeating the calculations at 3.6 Å: the calculated  $\ln \gamma$ s changed by about 5%).

Though some discrepancies appear for concentrated solutions, IEF results show a remarkably good behaviour even for  $I > 0.01$  M: notice, moreover, that in experimental data one cannot distinguish between cation and anion contributions, and that the numerical PB integration gives the same value of  $\ln \gamma$  for Mg $^{2+}$  and SO $_4^{2-}$ , since the ions are described as charged spheres with the same radius.

Also the  $pK$  of weak acids depends on the ionic

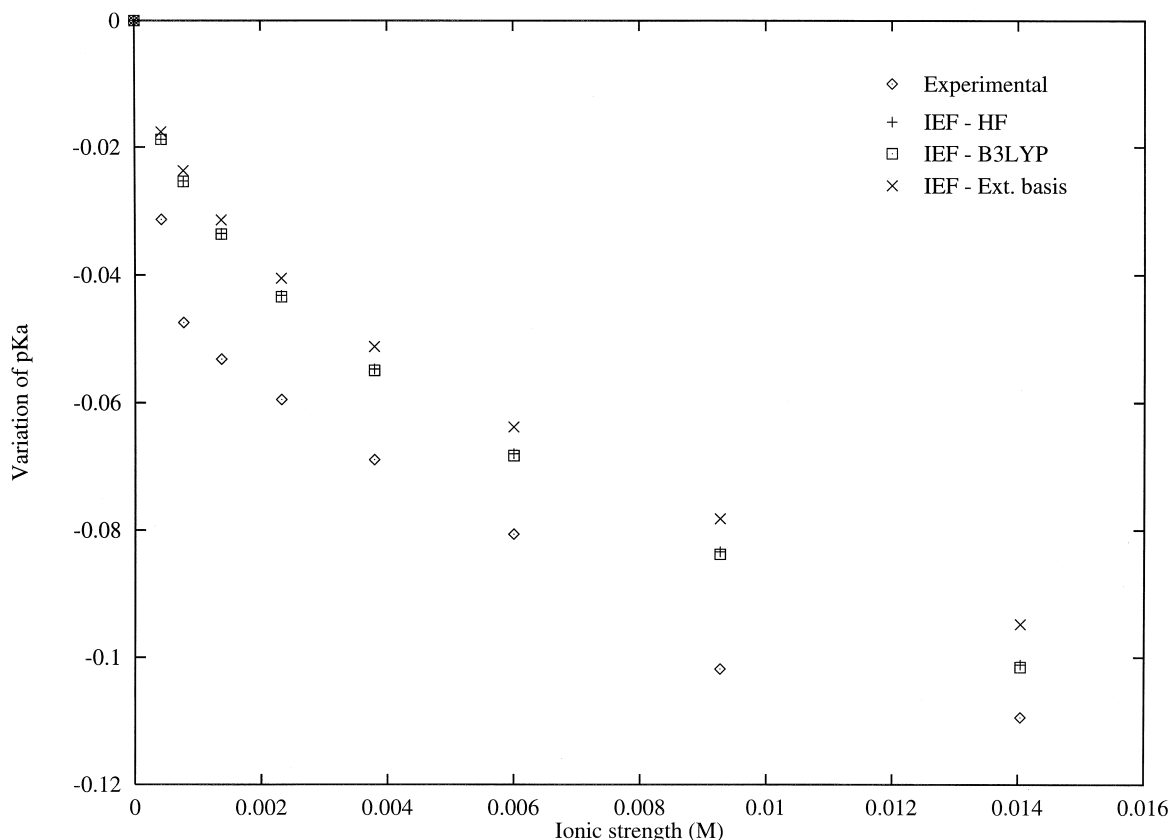
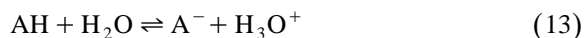


Fig. 2.  $\Delta pK_a$  with respect to zero ionic strength for cyanacetic acid calculated by IEF at the HF/6-31G(d), HF/6-311 + G(d,p) and B3LYP/6-31G(d) levels, compared to experimental values.

strength: we can calculate the free energy variations related to the ionization process



$$\Delta \mathcal{G}_{\text{ion}}(I) = \mathcal{G}(\text{A}^-, I) + \mathcal{G}(\text{H}_3\text{O}^+, I) - \mathcal{G}(\text{AH}, I) - \mathcal{G}(\text{H}_2\text{O}, I) \quad (14)$$

and the corresponding  $\text{p}K_a$ :

$$\text{p}K_a(I) = - \frac{\Delta \mathcal{G}_{\text{ion}}(I)}{RT} \quad (15)$$

The accurate evaluation of  $\text{p}K_a$ s is a delicate task, since the calculated values dramatically depend on the basis set quality and on the calculation level: then, to highlight the ionic strength effects we considered the quantity

$$\Delta \text{p}K_a = \text{p}K_a(I) - \text{p}K_a(0) \quad (16)$$

In Fig. 2 we report the experimental [30]  $\Delta \text{p}K_a$

values for cyanacetic acid,  $\text{CN}-\text{CH}_2-\text{COOH}$ , compared to IEF results obtained at the HF/6-31G(d), DF/6-31G(d) and HF/6-311 + G(d,p) levels (using in DF calculations the so-called B3LYP hybrid functional [31], which combines Hartree–Fock and Becke [32] exchange with the Lee–Yang–Parr [33] correlation functional).

Though the calculated  $\text{p}K_a$  variations are systematically lower than their experimental counterparts, the IEF procedure is able to reproduce a large part of the ionic atmosphere effect on this quantity. The disagreement with experimental data is greater with the extended basis set: a tentative explanation is related to the fraction of the solute electronic cloud lying outside the cavity. In fact, the electrostatic solute–solvent interactions can be described by a simple surface charge distribution only if the whole solute charge is inside the cavity: however, with the

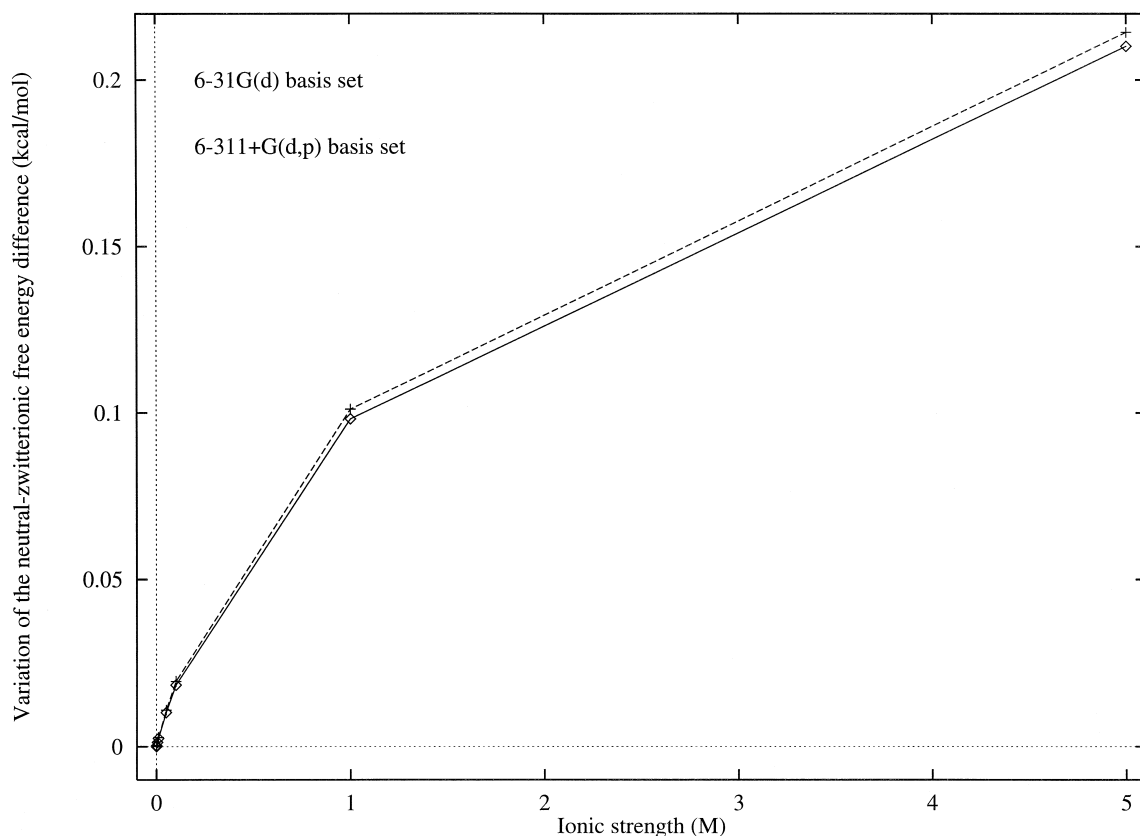
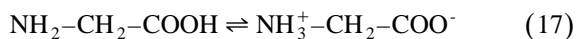


Fig. 3. Ionic strength effects on the energy difference (kcal/mol) between the neutral and the zwitterionic forms of glycine radical calculated at the B3LYP/6-31G(d) and B3LYP/6-311 + G(d,p) levels.

cavities used in actual calculations, a non negligible fraction of the solute electrons can often be found outside the cavity. D-PCM, C-PCM as well as IEF-PCM for solutions at zero ionic strength are provided with procedures to compensate the effect of such escaped charge [34]: these techniques are not directly applicable to IEF calculations for ionic solutions and this is a possible source of errors, especially for anions and with extended basis sets. However, IEF-PCM (for usual isotropic solutions) and C-PCM are significantly less dependent on escaped charged effects than D-PCM [34,35]

Then we applied the IEF procedure to a more complex system, that could not be treated by classical approaches, namely the equilibrium between the neutral and the zwitterionic forms of the glycine radical:



This system is involved in a long time study performed by our group, concerning the relative stability, the spectroscopic constants and the reactivity of this kind of radical in aqueous and non aqueous solutions [36]: it is of interest to investigate the effect of finite ionic strength on the calculated energies and properties. At infinitely low concentration, i.e.  $I = 0$ , the neutral form of glycine radical is more stable than the zwitterionic form by 24.78 kcal/mol at the B3LYP/6-31G(d) level and by 23.66 kcal/mol at the B3LYP/6-311 + G(d,p) level. In Fig. 3 we report the correction due to the ionic atmosphere at different salt concentrations.

Notice that the calculation at  $I = 5$  M, though correct from a mathematical point of view, is out of the range of validity of the Poisson–Boltzmann description: we report it to test the behaviour of the algorithm for high values of  $I$ , but clearly some physical sense must drive the applications of such methods. Nevertheless it is not unusual to find in the literature calculations exploiting Poisson–Boltzmann equations up to  $I = 10$  M or even higher.

It is noteworthy that this radical, unlike the parent molecule, is more stable in the neutral form even in aqueous solution, though the energy gap is slightly reduced by increasing the ionic strength: this is consistent with the lowering of  $\mathcal{E}_{\text{el}}$  induced by the ionic atmosphere in the systems mentioned above: clearly such an effect is more pronounced for the

zwitterionic form of the radical. Moreover, expanding the basis set has little effect for what concerns the ionic strength dependence of the calculated quantities. This agrees with the general finding that reliable solvation effects can be computed at a level less advanced than that required for accurate calculations on isolated molecules. Then one can devise a sort of G2 protocol for the study of systems in solution, resorting to high level calculations on isolated molecules and adding solvation (and ionic atmosphere) effects obtained at a lower ab initio level, with considerable CPU time savings. In this context, we are confident that also the escaped charge effects mentioned above are markedly reduced, since one only considers the differences with respect to zero ionic strength values, which are computed with refined compensation techniques.

#### 4. Conclusions

We have presented a new implementation of the integral equation formalism version of the PCM solvation method. This implementation exploits a number of techniques for the analysis of the energies and electronic properties of closed and open shell molecules at the Hartree–Fock and density functional levels, like the similar implementations of standard D-PCM and of C-PCM, previously elaborated by our group.

Test calculations have shown that the ionic atmosphere effects are correctly reproduced on simple spherical ions in aqueous solution: an application to the neutral and zwitterionic forms of the glycine radical reveals a small but not negligible ionic strength influence on the energy difference between the two isomers.

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