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A combined discrete/continuum solvation model: Application to glycine

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A new solvation model that combines discrete and continuum descriptions of the solvent has been developed. The discrete solvent molecules are represented by effective fragment potentials (EFP), while the continuum is represented by the Onsager model. This (EFP+Onsager) model has been applied to the relative stabilities of the neutral and zwitterionic forms of glycine. Other supermolecule-continuum calculations were also performed, using quantum mechanical discrete waters and the isodensity polarizable continuum model (IPCM) or solvation model 5.42R (SM5.42R) for the continuum. It is shown that the Onsager model provides a poor description of the solvent in the supermolecule-continuum calculations. On the other hand, more sophisticated models can predict the correct energy order of the glycine isomers. Thus, the development of mixed methods that combine sophisticated continuum models with the discrete EFP model appear to be promising. © 2000 American Institute of Physics. [S0021-9606(00)50527-3]

I. INTRODUCTION

A realistic treatment of the electronic structure of molecules in solution is one of the most important issues in theoretical chemistry, since most chemical reactions take place in solution. It is highly desirable that electronic structure and chemical reactivity in solution be described with a similar level of accuracy to that used for the gas phase. A major roadblock is that *ab initio* quantum mechanical calculations that include even a modest number of solvent molecules is impractical from a computational point of view. A reasonable alternative for modeling solvent effects is to treat the solvent classically while treating the solute quantum mechanically. The two basic choices for a classical description of the solvent are the discrete approach¹ and the dielectric continuum approach^{2,3} although there have been efforts to describe the solvent by the statistical mechanical RISM theory⁴ and by a collection of dipoles.⁵

In the discrete approach, solvent molecules are treated explicitly, so that specific interactions between solute and solvent are taken into account. However, the size of the configuration space of the solvent increases dramatically with the number of solvent molecules, so this can become a computational bottleneck. On the other hand, in the dielectric continuum model, the solvent is described as an infinite, isotropic dielectric in which the solute is embedded. In this model, the solute polarizes the solvent via its dielectric constant. The solvent in turn polarizes the solute. The “reaction field” of the solvent is calculated either analytically or numerically depending upon the complexity of the electrostatic problem. The latter is a function of the shape of the cavity and the solute charge distribution. Various cavities have been considered ranging from regular shapes like spheres and ellipsoids to molecular shapes such as a cavity constructed from interlocking spheres surrounding the atoms of the solute.²

The continuum model has been the most popular choice for describing solvents in the context of electronic structure theory. However, the continuum model neglects the specific interactions between solute and solvent molecules. It is desirable to develop a model that includes both discrete interactions between solute and nearby solvent molecules and the average interaction between solute and solvent molecules that are further away from the solute. Such a model would incorporate both discrete and continuum descriptions of the solvent. One approach would be to treat several solvent molecules as well as the solute with *ab initio* quantum mechanics, while treating the bulk solvent as a continuum.⁶ However, an *ab initio* description of a sufficient number of explicit solvent molecules will generally be computationally intractable. A more tractable approach would be to use three different layers to describe the system. In such a method, one would treat the solute, perhaps plus a small number of solvent molecules using *ab initio* quantum mechanics. The remaining explicit solvent molecules would be treated with a model potential, and the outer layer would be a continuum. Van Duijnen and co-workers explored this idea and developed a three layer model⁷ by representing the explicit solvent molecules as a combination of point charges and atomic polarizabilities.

In this work we present a new three layer model in which the second layer of solvent molecules is represented by effective fragment potentials (EFP).⁸ It has been shown for several applications that EFP calculations give very similar results to *ab initio* RHF calculations.⁹ The continuum that is interfaced with the EFPs is described by a multipole expansion up to the dipole term in a spherical cavity. For simplicity hereafter this continuum model will be referred as the Onsager model. Since this is the simplest continuum model, it is useful to assess the viability of such an approach. The three layer model will be referred to as EFP+Onsager. The new model is tested by studying the relative stabilities of the two isomers (neutral and zwitterion) of glycine in water. These calculations are compared with analogous ones in

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which the solvent molecules are treated with *ab initio* methods. In addition to the EFP+Onsager approach, other *ab initio* supermolecule-continuum calculations are performed with more sophisticated continuum models, the isodensity polarizable continuum model (IPCM),¹⁰ and solvation model 5.42R (SM5.42R).¹¹ Thus, this work examines the performances of both the EFP+Onsager model and more general supermolecule-continuum calculations.

Glycine has been the subject of a number of studies in the gas phase¹² and in solution.^{13,14} It is known that the zwitterionic (Z) form is more stable than the neutral (N) in aqueous solution. However, at the Hartree–Fock level only sophisticated solvation models^{2,13} can predict the correct energy order of the two isomers. In a recent study, Tortonda *et al.*¹⁴ have shown that a continuum model, having an ellipsoidal cavity and multipolar expansion up to the sixth order, fails to give the correct energy order at the HF level. In the present work, we explore two issues: (a) How is the prediction of the relative stabilities of N and Z glycine in a continuum solvent affected by the quality of the continuum model? (b) How are these predictions affected by the introduction of explicit solvent molecules?

The present paper is arranged as follows. The theory and computational methods are described in Sec. II. In Sec. III details of the calculation for glycine are described. Section IV consists of results and discussions. Conclusions and summary are presented in Sec. V.

II. THEORY AND COMPUTATIONAL METHODS

In the first part of this section, the effective fragment model is briefly described. Readers are referred to the original literature⁸ for details. In the second part, working equations of the EFP+Onsager model are presented.

A. The effective fragment method

In the EFP model, the interactions between the fragment and the quantum mechanical solute and those between the fragments are evaluated by considering the fundamental intermolecular interactions. In the case of solute-fragment interactions, one-electron terms are added to the *ab initio* Hamiltonian of the solute, representing electrostatic (Coulombic), polarization and exchange-repulsion plus charge-transfer interactions. For the μ th fragment molecule, the effective fragment potential is given by

$$V_{\text{el}}(\mu, s) = \sum_{k=1}^K V_k^{\text{Elec}}(\mu, s) + \sum_{l=1}^L V_l^{\text{pol}}(\mu, s) + \sum_{m=1}^M V_m^{\text{rep}}(\mu, s), \quad (1)$$

where s represents the electronic coordinates. The three terms on the right-hand side of Eq. (1) represent the electrostatic, polarization, and exchange-repulsion plus charge transfer interactions, respectively. The electrostatic potential is expressed in terms of the distributed multipolar analysis (DMA)¹⁵ of the solvent charge distributions. K in the first term of Eq. (1) is the number of expansion points (e.g., each atom center and bond midpoint in water). Each expansion is

carried through octupole terms at each point. The exchange repulsion plus charge transfer interactions are modeled by simple Gaussian functions located at the fragment atom centers, denoted by m in the third term of Eq. (1), where M is the number of expansion centers (each atom center and the center of mass of water). The polarization of the solvent molecules by the electric field of the solute molecules is treated self-consistently.¹⁶ In this process the dipole polarizability tensor is expanded into its component bond and lone pair localized orbital dipole polarizabilities centered at the centroids of the L localized valence molecular orbitals.

B. EFP+Onsager model

The electrostatic interaction energy between a solute inside a sphere and the surrounding solvent can be written¹⁷ as

$$E_{\text{int}} = -\frac{1}{2} \sum_l \sum_{m=-l}^l \frac{(l+1)(\epsilon-1)}{[l+\epsilon(l+1)]a^{2l+1}} M_l^m M_l^m, \quad (2)$$

where a is the radius of the spherical cavity, ϵ is the dielectric constant, and M_l^m is the expectation value of the multipole moment m_l^m of the solute,

$$M_l^m = \int d\tau \rho m_l^m, \\ m_l^m = \left(\frac{4\pi}{2l+1} \right)^{1/2} r^l Y_l^m(\theta, \phi),$$

where $Y_l^m(\theta, \phi)$ and ρ are the spherical harmonics and the charge density of the solute, respectively. Extracting the first two terms from Eq. (2) gives

$$E_{\text{int}}^{(1)} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) (1/a) Q^2$$

and

$$E_{\text{int}}^{(2)} = -\frac{1}{2} \frac{2(\epsilon-1)}{(2\epsilon+1)a^3} \mu^2,$$

where Q and μ are the charge and dipole moment of the solute, respectively. The energy of the system is then given by

$$E = E_0 - \frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) (1/a) Q^2 - \frac{1}{2} g \mu^2, \quad (3)$$

where $g = [2(\epsilon-1)/(2\epsilon+1)]/(1/a^3)$ and E_0 is the energy of the quantum mechanical solute plus the fragments. The second term on the right-hand side of Eq. (3) is additive. So, the energy functional in the EFP+Onsager model is given by

$$L = E_0 - \frac{1}{2} g \mu^2 - W(\langle \Psi | \Psi \rangle - 1), \quad (4)$$

where W is a Lagrange multiplier ensuring normalization of the wave function. The total dipole moment of the system μ , has three contributions,

$$\mu = \mu_{ab} + \mu_{efp} = \mu_{ab} + \mu_{efp}^s + \mu_{efp}^i. \quad (5)$$

The three terms on the right-hand side of Eq. (5) represent the dipole moment of the *ab initio* part, the static dipole moment of the fragments and the induced dipole moment of

the fragments, respectively. Taking the variation of the functional in Eq. (4) with respect to the wave function parameters and setting it to zero gives

$$\delta L = \delta E_0 - g \mu \delta \mu - W \delta \langle \Psi | \Psi \rangle + cc = 0, \quad (6)$$

where “cc” denotes the complex conjugate of the terms given. Explicit expressions for δE_0 are given in Ref. 8. Here, we focus our attention on the second term on the right-hand side of Eq. (6),

$$\begin{aligned} \delta \mu = & \delta \mu_{ab} + \delta \mu_{efp} = \delta \langle \Psi | \hat{\mu}_{ab} | \Psi \rangle + \mu_{\text{nuclear}} \\ & + \delta \left(\sum_j \alpha_j \langle \Psi | \hat{F}_j | \Psi \rangle + F_{j,\text{nuclear}} \right. \\ & \left. + F_{j,efp}^s + F_{j,efp}^i \right), \end{aligned} \quad (7)$$

where the α_j are the polarizabilities of the fragments defined at the points j . \hat{F}_j is the *ab initio* electric field operator, and, $F_{j,\text{nuclear}}$, $F_{j,efp}^s$, $F_{j,efp}^i$ are the electric fields due to the *ab initio* nuclei, static dipole of the fragments, and induced dipole of the fragments, respectively. Taking the variations in Eq. (7) explicitly and inserting the result into Eq. (4) gives the following Schrodinger equation:

$$\left[H_0 - g \mu \cdot \hat{\mu}_{ab} - g \mu \cdot \sum_j \alpha_j \hat{F}_j \right] | \Psi \rangle = W | \Psi \rangle, \quad (8)$$

where μ is the total dipole moment of the system as defined in Eq. (5). $\hat{\mu}_{ab}$ is the dipole moment operator for the *ab initio* part.

For a neutral molecule the total energy of the system is given by

$$\begin{aligned} E = & W + \frac{1}{2} g \mu \mu - g \mu \mu_{efp}^s - g \mu \left[\sum_j \mu_j^{\text{tot}} \right. \\ & \left. - \sum_j \alpha_j \langle \Psi | \hat{F}_j | \Psi \rangle \right], \end{aligned} \quad (9)$$

where μ_j^{tot} is the total induced dipole moment of the fragments at point j . As discussed previously,⁸ the expectation value of the functional in Eq. (4) is not equal to the energy given in Eq. (3) due to the nonlinear nature of the Schrodinger equation. This is reconciled by adding the extra terms to W in Eq. (9) to get the total energy. The above equations have been coded and implemented in the electronic structure code GAMESS.¹⁸

III. APPLICATION TO GLYCINE

There are two issues which need to be addressed in a supermolecule-continuum calculation. The first is the number of solvent molecules to be used in the calculation, and the second is how to sample the nuclear degrees of freedom of the explicit solvent molecules. Although it is difficult to determine a definitive answer to the first question, it seems reasonable that adding waters to the hydrophilic parts of the solute should give a reasonable approximation to the first solvation shell. With this philosophy, it is found that at least eight water molecules are necessary to fill hydrophilic areas of glycine and act as a “first solvation shell.” Hence, in the

present work, eight explicit water molecules are included. In this study, the configuration space of the eight water molecules was not exhaustively sampled. Instead, full geometry optimizations were performed for reasonably chosen glycine-water cluster structures. For more comprehensive studies it would be necessary to sample the configuration space of the explicit waters. Since the primary focus of the present work is to assess the interface between discrete and continuum methods, it is assumed that optimized well chosen structures are sufficient.

Details of the calculation. The main objective of the present study is to compare continuum with supermolecule-continuum calculations. For this reason, three sets of calculations were performed. First, bare N and Z glycine were optimized in solution with the 6-31++G** basis set using the Onsager model. The cavity radii for the optimizations were taken as 3.62 and 3.74 Å for N and Z, respectively. These radii were obtained by calculating the molecular volume using GAUSSIAN94.¹⁹ Two other solvation models, IPCM/6-31++G** and SM5.42R/6-31G*, were also used to calculate the energies of these two optimized structures. Second, N(H₂O)₈ and Z(H₂O)₈ were optimized using effective fragment waters with the RHF/6-31++G** method for N and Z. Finally, the effect of the bulk solvent was taken into account by embedding the clusters in a continuum. The Onsager description of the continuum was used with the EFP waters, while *ab initio* waters at the EFP geometries were used when the continuum was described by the IPCM and SM5.42R models. The calculations were performed using GAMESS,¹⁸ GAUSSIAN94,¹⁹ and GAMESOL.²⁰

IV. RESULTS AND DISCUSSIONS

A. Calculation for bare N and Z

The optimized structures of the N and Z forms of glycine in the Onsager continuum are shown in Figs. 1(a) and 1(b), respectively. Our structure for Z agrees with that obtained by Ding *et al.* at the HF/6-31++G** level.²¹ The energy differences between the optimized N and Z isomers at the Onsager, SM5.42R, and IPCM levels are shown in Table I, along with the gas phase energy difference. For the calculation of the gas phase energy difference, the Onsager optimized geometry of Z was used. Since there is no defined SM5.42R model for 6-31++G** basis set, a smaller basis set was used for this model. All three continuum methods predict a significant stabilization of Z relative to N, but all three still find N to be slightly more stable than Z. One reason for these results is that the three models assume that the polarization of the solvent is linearly proportional to the electric field of the solute. However, for the zwitterion, nonlinear effects in the polarization of the solvent become important due to the charges present at the two ends of the solute.²² Only the SM5.42R model includes nonelectrostatic terms, so it is of interest to determine the difference in the nonelectrostatic terms for the neutral and zwitterion. The nonelectrostatic contribution (the so-called CDS term) is -5.0 kcal/mol for N but only -2.66 kcal/mol for Z. This suggests that with only the electrostatic contribution to solvation, SM5.42R model favors Z by ~ 1.35 kcal/mol.

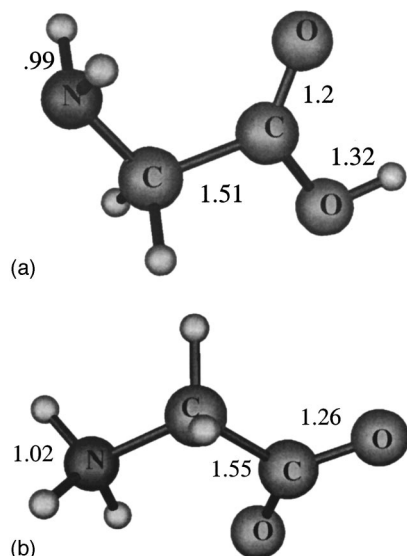


FIG. 1. (a) Optimized structure of neutral isomer of glycine in solution in the RHF/6-31++G** level using Onsager as the continuum model. All unlabeled atoms are hydrogens. The numbers represent the bond lengths in angstroms. (b) Optimized structure of zwitterion isomer of glycine in solution at the RHF/6-31++G** level using Onsager as the continuum model. All unlabeled atoms are hydrogens. The numbers represent the bond lengths in angstrom.

B. Optimization of the glycine clusters

In the next step of the calculation, $N(H_2O)_8$ and $Z(H_2O)_8$ were optimized at the RHF/6-31++G** level with the effective fragment waters. The optimized structures are shown in Figs. 2 and 3 for the N and Z clusters, respectively (the full geometries are included as supplementary material²³). The hydrophilic sites of both N and Z are filled by the explicit waters.

Analogous calculations were carried out at the RHF/6-31G* level where the waters are described by *ab initio* quantum mechanics. Table II shows the N–Z energy difference between the clusters with the EFP waters and with the quantum mechanical waters. The results differ by only 1.4 kcal/mol. The addition of eight waters stabilizes Z relative to N, but $N(H_2O)_8$ is still predicted to be more stable than $Z(H_2O)_8$. It is interesting to consider the relative order of the dipole moments in the two isomers. In the gas phase, Z has a much higher dipole moment (13.4 D) than N (1.3 D) at the RHF/6-31++G** level. But $Z(H_2O)_8$ has a smaller dipole moment (3.5 D) than $N(H_2O)_8$ (5.3 D). Since the Onsager model considers only the dipole moment of the solute, it is clear that $N(H_2O)_8$ will be more stabilized than $Z(H_2O)_8$

TABLE I. Energy difference (in kcal/mol) between N and Z isomers of glycine in gas phase and in solution.

Environment	Method	$E(N) - E(Z)$
Gas phase	RHF/6-31++G**	-30.0
	Onsager/6-31++G**	-2.8
Solution	IPCM/6-31++G**	-3.2
	SM5.2R/6-31G**	-1.0

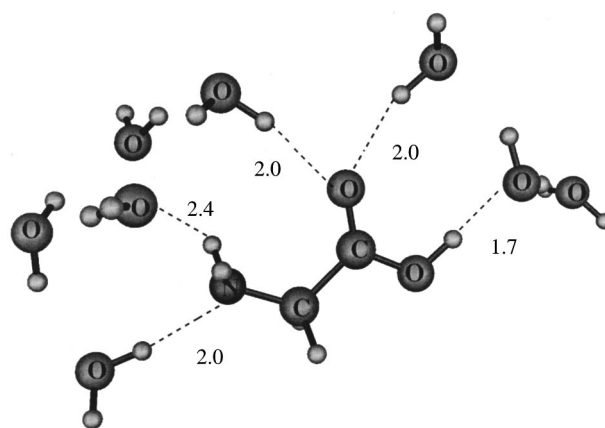


FIG. 2. Optimized structure of $N(H_2O)_8$ at the RHF/6-31++G** level with effective fragment waters. N is the neutral isomer of glycine. All unlabeled atoms are hydrogens. The dotted lines represent hydrogen bonding and the numbers represent the hydrogen bond distances in angstrom.

in this model, contrary to the stabilization of bare N and Z in the Onsager model.

C. Effects of the continuum

The effect of the bulk solvent is taken into account by surrounding the clusters with a continuum, using the EFP+Onsager model, as well as all three continuum models with *ab initio* waters. The results of the calculations are shown in Table III. The IPCM calculations are carried out by employing a $0.001e$ isodensity surface. The volumes of the cavities for $N(H_2O)_8$ and $Z(H_2O)_8$ in the IPCM model are found to be 1460.53 bohr^3 and 1848.70 bohr^3 , respectively. As suggested above, the Onsager model stabilizes the N cluster more than the Z cluster due to the larger $N(H_2O)_8$ dipole moment.

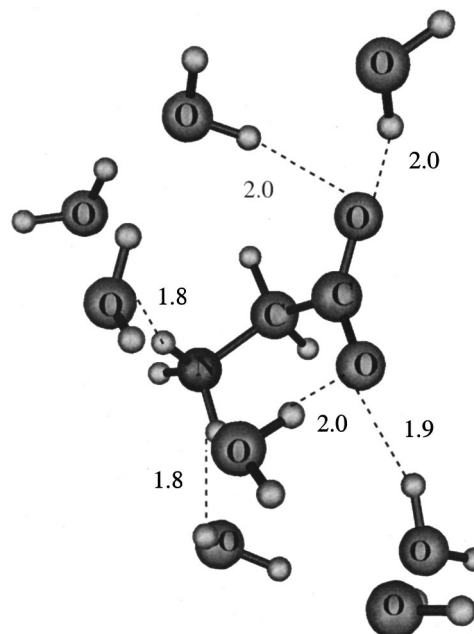


FIG. 3. Optimized structure of $Z(H_2O)_8$ at the RHF/6-31++G** level with effective fragment waters. Z is the zwitterionic form of glycine. All unlabeled atoms are hydrogens. The dotted lines represent hydrogen bonding and the numbers represent the hydrogen bond distances in angstrom.

TABLE II. Comparison of EFP and full quantum calculations for $N(H_2O)_8$ and $Z(H_2O)_8$: $E(N) - E(Z)$ (in kcal/mol).

Method	$E(N) - E(Z)$
RHF/6-31++G** (EFP waters)	-4.6
Full quantum (RHF/6-31G*)	-3.2

$N(H_2O)_8$ is more stable than $Z(H_2O)_8$ by 5.8 kcal/mol (without the continuum the energy difference is 4.6 kcal/mol, see Table II). The relative stabilization of N using 8 *ab initio* waters is similar. The Onsager model with only a dipole term must be viewed with some caution in such a case, since higher order multipole terms may have a significant effect on the predicted outcome. The other two models, which have more sophisticated treatments of the solute-solvent interactions, perform better than Onsager. In the SM5.42R model, N and Z clusters are very close in energy, though N is still more stable by 1.1 kcal/mol. This energy difference is almost the same with the continuum only calculation (see Table I). The SM5.42R continuum stabilizes the $Z(H_2O)_8$ cluster by 2.1 kcal/mol. The IPCM model clearly favors the Z cluster, by 8.6 kcal/mol. So, the IPCM continuum stabilizes the $Z(H_2O)_8$ cluster by ~ 11.8 kcal/mol. A more definitive study of these effects would involve a systematic sampling of configuration space as a function of the number of water molecules.

The most meaningful calculated quantity is

$$\Delta(\Delta E) = \Delta(\text{gas}) - \Delta(\text{solution}),$$

where

$$\Delta(\text{gas}) = E_N - E_Z,$$

$$\Delta(\text{solution}) = E'_N - E'_Z + G_N - G_Z.$$

E_N and E_Z are the internal energies of N and Z clusters in the gas phase and E'_N and E'_Z are the internal energies of N and Z clusters in solution, respectively. G_N and G_Z are the solvation free energies of N and Z clusters, respectively. If the difference between the internal energies in gas phase and in solution is approximately the same, then $\Delta(\Delta E)$ essentially represents the difference in the free energy of solvation between N and Z in solution. The values $-\Delta(\Delta E)$ can be seen

TABLE III. Energy differences between Z and N on solvation using supermolecule-continuum calculations and energy difference relative to the isolated cluster, $E(N) - E(Z)$ /(kcal/mol).^a

Method	Energy difference	Energy difference relative to the isolated cluster
EFP+Onsager(6-31++G**)	-5.8	-1.2
<i>Ab initio</i> +Onsager(6-31G*)	-4.3	-1.1
<i>Ab initio</i> +SM5.2R(6-31G*)	-1.1	2.1
<i>Ab initio</i> +IPCM(6-31G*)	8.6	11.8

^aEFP waters were used with the EFP+Onsager model. For other calculations *ab initio* waters were used.

from Table III, where it is again clear that a sophisticated continuum treatment is needed to obtain a clear preference for Z.

It is important to attempt to put these computations in the context of what is known from experiment. Such a comparison can, of course, only be approximate, given the nature of the approximations in the computational methods. These include the use of Hartree-Fock level electronic structure theory, approximate continuum solution methods and small clusters. With these caveats we compare the SM5.42R and IPCM values with the experimental free energy change, $N \rightarrow Z$ in solution, of 7.67 kcal/mol favoring Z.²⁴ Although the IPCM model takes into account only the electrostatic part of the solvation free energy, these results suggest that the combination of a small number of explicit waters and a sophisticated continuum model will be an effective tool for the study of N-Z equilibria.

V. SUMMARY AND CONCLUSION

A unifying condensed phase model (EFP+Onsager), which describes the system of interest in three layers, quantum solute, explicit solvent molecules (using EFP potentials) and the bulk solvent as continuum (using the Onsager model) has been developed. The EFP+Onsager model has been applied to the relative stabilities of the two forms of glycine. Supermolecule-continuum calculations have also been performed using the SM5.42R and IPCM descriptions of the continuum with quantum mechanical waters. Effects of the explicit waters have been investigated by performing the same calculation with Onsager, IPCM, and SM5.42R models using the bare glycine isomers.

It has been found that with the bare glycine isomers none of the continuum models used can predict the correct energy order. The addition of explicit waters, to represent the first solvation shell, changes the scenario depending upon the solvation model used. The EFP+Onsager and *ab initio*+Onsager models perform poorly because the simple dipole interaction term in the Onsager model does not capture the important physics. The SM5.42R and IPCM models provide improved results in comparison with experiment. The IPCM model does predict the correct energy order of the two isomers of glycine in the presence of the explicit waters. The zwitterion is predicted by this method to be 8.5 kcal/mol more stable than the neutral isomer, very close to the experimental observation of 7.67 kcal/mol free energy change for the process $N \rightarrow Z$ in solution favoring Z. The results obtained with the SM5.42R method suggested non-electrostatic terms are not negligible and that the calculations are not converged with respect to the number of explicit waters.

In this work the configuration space of the explicit waters were not sampled exhaustively. The sampling would be necessary to comment more definitively on the relative performance of the IPCM and SM5.42R models. However, in combination with a sophisticated continuum model, supermolecule-continuum calculations should be an excellent tool to study molecular processes in solution. We are now in the process of developing interfaces between the EFP method and more sophisticated continuum models, in order to further explore the three layer method.

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