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REGULAR ARTICLE

Shells theory of solvation and the long-range Born correction

Josefredo R. Pliego Jr

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Abstract A new solvation model, named shells theory of solvation, is proposed. In this approach, the solvent is divided in two regions, the S_1 shell, close to the solute and describing specific solute–solvent interactions, and the S_2 shell, representing the remain solvent and accounting for the long-range interaction contribution. A simple theoretical equation can be derived which allows the computation of the solvation free energy using two-point thermodynamic integration and configurations generated from molecular dynamics simulation. The discrete/continuum version of this theory provides rigorous theoretical foundations for the popular long-range Born correction and presents a new reliable expression for including this contribution. Further, it converges to the full discrete representation of the solvent when the number of solvent molecules goes to infinity. The method can be easily applied when the solute–solvent interaction (S_1 shell) is treated by full quantum mechanics, while the S_2 shell is described by a dielectric continuum solvation method. A simple test of the theory was done for solvation of fluoride ion in benzene solution. The S_1 shell was composed of the fluoride ion plus 32 benzene molecules, and the interaction with the S_2 shell was calculated at Hartree–Fock level with the MINI basis set and using the polarizable continuum model.

Keywords Solvation free energy · QM/MM · Hybrid discrete/continuum · Molecular dynamics · Thermodynamic integration · ab initio · Linear response

J. R. Pliego Jr (✉)
Departamento de Ciências Naturais,
Universidade Federal de São João del-Rei,
36301-160 São João del-Rei, MG, Brazil
e-mail: pliego@ufsj.edu.br

1 Introduction

Interaction of a solute molecule with the surround medium may have a profound effect on chemical stability and reactivity [1–5]. From a theoretical viewpoint, introducing the solvent effect, either through explicit molecules or using an approximate method like dielectric continuum model, is essential for describing many processes in condensed phase. These considerations have induced a lot of research in theory and modeling of solvation phenomenon.

The first line and most popular approach for describing solvation is the use of continuum solvation models [6–8]. The polarizable continuum model (PCM) has been developed for almost third years [9–20] and its reliable quantum mechanical description of the solute electron density combined with shaped solute cavity provides a good description of solute–solvent interaction in many different problems. Other popular continuum model is the SMx family of Cramer and Truhlar [21–23], which make use of molecular shaped cavity and reliable solute atomic charges. The most recent version, named SMD, true quantum mechanical electron density of the solute has been used [24, 25]. Despite its successful, continuum solvation models can fail in many situations. One interesting example is the stability of hydroxylamine isomers in water solution [26].

The approach based on explicit solvent molecules using Molecular Dynamics or Monte Carlo methods coupled with free energy perturbation or thermodynamic integration has become more interesting as the computer power is increasing each year [27–40]. The most popular approach is the use of classical force-fields based on effective pair potentials [41, 42]. In recent years, it has become more evident that polarization effects can be very important in some problems [43–46]. Therefore, combined quantum mechanical/molecular mechanics methods and even full quantum mechanical description of interaction potential is the most reliable approach, mainly in the description of chemical processes in solution [47–52].

A midway approach for describing solvation is the combination of discrete and continuum solvation models. In the past 10 years, there has been an increased interest in hybrid discrete/continuum solvation models [53–71]. An advantage of using such approach is the possibility of introducing the solvent features present in the first solvation shell as well as full quantum mechanical treatment of solute–solvent interaction. However, once someone decides to treat solvation through this approach, arises the question on how to combine both the explicit solute with implicit part represented by the dielectric continuum. One approach is the cluster–continuum model [54], where the solute and some strongly bound solvent molecules are considered a chemical species. This approach has been successfully applied for pK$_a$ prediction [53, 72] and for some important ionic reactions in aqueous solution [73, 74]. A similar approach is the quasi-chemical theory of solvation of Pratt and co-workers [62, 65, 68]. In this case, the solvation can be seen as an equilibrium involving clusters of the solute and a variable number of solvent molecules. Both the quasi-chemical theory and the cluster–continuum model are closely related [55]. Several authors have also used mixed discrete/continuum approaches, although in some situations a more rigorous theoretical foundations of the method for calculating the solvation free energy is lacking.

Despite the fact these hybrid approach are very useful, an evident problem of the quasi-chemical-related theories is that the interaction of the solute with the first solvation shell may not be enough strong and the solvent molecules should experience a high mobility which is not adequately described by these theories. Similarly, the solvent molecules in the second and more external solvation shells are not bound to the central solute. Therefore, the solvation free energy may not convergence to the true value when the number of solvent molecules goes to infinity. A more reliable approach is need, which should work for different solutes, irrespective on how strong the solute–solvent interaction is. Other possibilities for combining discrete and continuum solvation are the dynamical hybrid methods [58–60, 71, 75]. The aim of this paper is to present a new dynamical hybrid discrete/continuum solvation method, able to converge toward a full discrete representation of the solvent. The main contribution from this report is the development of the theory. A simple application for solvation of the fluoride ion in benzene solution is also reported. In this example, it was calculated the long-range solvation contribution and compared it with the simple Born correction.

2 Shells theory of solvation

Lets consider a solute "A" interacting with the solvent and to divide the solvent in two shells: S_1, in close contact with the solute, and S_2, a more distant shell. We can define the following interaction terms:

U_{AS_1} → interaction energy of the solute A with the S$_1$ shell

U_{AS_2} → interaction energy of the solute A with the S$_2$ shell

$U_{AS_1S_2}$ → many body effects in the interaction of the solute A with the S$_1$ and S$_2$ shells

U_{S_1} → interaction energy among the S$_1$ shell molecules

U_{S_2} → interaction energy among the S$_2$ shell molecules

$U_{S_1S_2}$ → interaction energy between the S$_1$ and S$_2$ shells

Considering the solute and the solvent molecules as rigid structures, the free energy of solvation is given by the equation:

$$\Delta G_{solv}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1}+U_{AS_2}+U_{AS_1S_2})}e^{-\beta(U_{S_1}+U_{S_2}+U_{S_1S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_1}+U_{S_2}+U_{S_1S_2})}\mathbf{dr}_1\mathbf{dr}_2} \tag{1}$$

The solute and the S_1 shell can be considered a "supersolute" and Eq. 1 can be rearranged for:

$$\Delta G_{solv}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1}+U_{AS_2}+U_{AS_1S_2}+U_{S_1}+U_{S_1S_2})}e^{-\beta(U_{S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_1}+U_{S_2}+U_{S_1S_2})}\mathbf{dr}_1\mathbf{dr}_2} \tag{2}$$

and written as:

$$\Delta G_{solv}(A) = -RT\ln\left[\frac{\int e^{-\beta(U_{AS_1}+U_{AS_2}+U_{AS_1S_2}+U_{S_1}+U_{S_1S_2})}e^{-\beta(U_{S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_2})}\mathbf{dr}_2} \times \left(\frac{\int e^{-\beta(U_{S_1}+U_{S_2}+U_{S_1S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_2})}\mathbf{dr}_2}\right)^{-1}\right] \tag{3}$$

The first ratio in Eq. 3 is related to the solvation of the solute A and the S_1 shell by S_2, whereas the last ratio is related to the solvation of only the S_1 shell. Thus, we can write:

$$e^{-\beta\Delta G_{solv}(AS_1)} = \frac{\int e^{-\beta(U_{AS_2}+U_{AS_1S_2}+U_{S_1S_2})}e^{-\beta(U_{S_2})}\mathbf{dr_2}}{\int e^{-\beta(U_{S_2})}\mathbf{dr_2}} \tag{4}$$

$$e^{-\beta\Delta G_{solv}(S_1)} = \frac{\int e^{-\beta(U_{S_1S_2})}e^{-\beta(U_{S_2})}\mathbf{dr_2}}{\int e^{-\beta(U_{S_2})}\mathbf{dr_2}} \tag{5}$$

The terms $\Delta G_{solv}(AS_1)$ and $\Delta G_{solv}(S_1)$ are the free energy of solvation of AS_1 and S_1 due to S_2 shell. Thus, two new relations can be obtained:

$$\int e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1 = \frac{\int e^{-\beta(U_{S_1}+U_{S_2}+U_{S_1S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_2})}\mathbf{dr}_2} \tag{6}$$

$$\int e^{-\beta(U_{AS_1}+U_{S_1}+\Delta G_{solv}(AS_1))}\mathbf{dr}_1 = \frac{\int e^{-\beta(U_{AS_1}+U_{AS_2}+U_{AS_1S_2}+U_{S_1}+U_{S_1S_2})}e^{-\beta(U_{S_2})}\mathbf{dr}_1\mathbf{dr}_2}{\int e^{-\beta(U_{S_2})}\mathbf{dr}_2} \tag{7}$$

and Eq. 3 becomes:

$$\Delta G_{solv}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1}+U_{S_1}+\Delta G_{solv}(AS_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{8}$$

With a new rearrangement, we can write:

$$\Delta G_{solv}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1}+\Delta G_{solv}(AS_1)-\Delta G_{solv}(S_1))}e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{9}$$

This is a key equation and it says we can compute the free energy of solvation of solute A considering its interaction with the S_1 shell through direct insertion of the solute inside this solvation shell. The S_2 shell affects indirectly the configurations of the S_1 shell (the $e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}$ term) and the $(\Delta G_{solv}(AS_1)-\Delta G_{solv}(S_1))$ term includes the interaction of the solute with the S_2 shell.

The goal of separating the solvent between S_1 and S_2 shells is describing these shells in different levels. The S_1 shell is in close contact with the solvent and should be described in high level, whereas the S_2 shell has a minor importance and could be described using a lower level. Modeling the solvation by a dielectric continuum is very attractive because of its lower computational cost and direct introduction of long-range contribution. Therefore, a natural implementation of the developed solvation theory is using explicit solvent molecules for the S_1 shell, whereas the S_2 shell could be described by the dielectric continuum.

2.1 Separation between attractive and repulsive terms

Direct use of Eq. 9 requires computing the free energy for cavity formation for the supersolute ($A + S_1$) inside the S_2 shell. This task is very hard for large S_1 shell, and it would be useful to single out the cavity contribution of the solute A. For attaining this goal, we can define an auxiliary repulsive potential between each atom of the solute A and each atom of the solvent molecules, which is close to the real potential in the repulsive region. In this way, we can define a free energy of solvation only considering this repulsive potential:

$$\Delta G_{solv,Rp}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp}(AS_1)-\Delta G_{solv}(S_1))}e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{10}$$

Thus, Eq. 10 is the solvation free energy of the solute A considering only the auxiliary repulsive potentials $U_{AS1,Rp}$ and $U_{AS2,Rp}$. It represents the cavity formation contribution for the free energy. In the next step, we can combine Eqs. 9 and 10 to obtain:

$$\Delta G_{solv}(A)-\Delta G_{solv,Rp}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1}+\Delta G_{solv}(AS_1)-\Delta G_{solv}(S_1))}e^{-\beta(U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp}(AS_1)-\Delta G_{solv}(S_1)+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{11}$$

The full interaction potential can be divided in repulsive, using the auxiliary repulsive potential (*Rp*), and the remaining electrostatic-dispersion-repulsion term (EDR) for solute–solvent and solvent–solvent interactions:

$$U_{AS_1} = U_{AS_1,Rp} + U_{AS_1,EDR} \tag{12}$$

$$U_{AS_2} = U_{AS_2,Rp} + U_{AS_2,EDR} \tag{13}$$

$$U_{S_1S_2} = U_{S_1S_2,Rp} + U_{S_1S_2,EDR} \tag{14}$$

Using these decompositions, Eq. 11 can be rewritten as:

$$\begin{aligned}\Delta G_{solv}(A) - \Delta G_{solv,Rp}(A) &= -RT\ln\frac{\int e^{-\beta(U_{AS_1,EDR}+\Delta G_{solv,EDR,EDR}(AS_1)-\Delta G_{solv,EDR,EDR}(S_1))}e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp,Rp}(AS_1)-\Delta G_{solv,Rp,Rp}(S_1)+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp,Rp}(AS_1)-\Delta G_{solv,Rp,Rp}(S_1)+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}\\ &\quad - RT\ln\frac{\int e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp,Rp}(AS_1)-\Delta G_{solv,Rp,Rp}(S_1)+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp}+\Delta G_{solv,Rp}(AS_1)-\Delta G_{solv}(S_1)+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}\end{aligned} \tag{15}$$

where:

$$\Delta G_{solv}(AS_1) = \Delta G_{solv,Rp,Rp}(AS_1) + \Delta G_{solv,EDR,EDR}(AS_1) \tag{16}$$

$$\Delta G_{solv}(S_1) = \Delta G_{solv,Rp,Rp}(S_1) + \Delta G_{solv,EDR,EDR}(S_1) \tag{17}$$

The subscript "*Rp*, *Rp*" ("EDR, EDR") refers to solvation involving repulsive (electrostatic-dispersion-repulsion) interactions of $A + S_1$ with S_2, while the subscript "*Rp*" ("EDR") refers to corresponding solvation interactions between A and $S_1 + S_2$. Using Eq. 17, the integral in the denominator of the third line of Eq. 15 can be written as:

$$\begin{aligned}&\int e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp}(AS_1) - \Delta G_{solv}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1 \\ &\quad = \int e^{-\beta(\Delta G_{solv,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,EDR,EDR}(S_1))} \\ &\quad \times e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1\end{aligned} \tag{18}$$

Substituting (18) into (15) leads to:

$$\begin{aligned}\Delta G_{solv} - \Delta G_{solv,Rp} = {}& -RT\ln\frac{\int e^{-\beta(U_{AS_1,EDR} + \Delta G_{solv,EDR,EDR}(AS_1) - \Delta G_{solv,EDR,EDR}(S_1))} e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1} \\ & -RT\ln\frac{\int e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(\Delta G_{solv,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,EDR,EDR}(S_1))} e^{-\beta(U_{AS_1,Rp} + \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}\end{aligned} \tag{19}$$

In the next step, we can introduce the approximation:

$$\Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(S_1) \cong \text{constant} \tag{20}$$

and defining:

$$\begin{aligned}&\Delta G_{solv,Rp}(AS_1) - \Delta G_{solv,Rp,Rp}(AS_1) - \Delta G_{solv,EDR,EDR}(S_1) \\ &\quad = -\Delta G_{solv,EDR,EDR}(S_1(S_{2,A}))\end{aligned} \tag{21}$$

Equation 19 can be simplified for:

$$\Delta G_{solv} - \Delta G_{solv,Rp} = -RT\ln\frac{\int e^{-\beta(U_{AS_1,EDR} + \Delta G_{solv,EDR,EDR}(AS_1) - \Delta G_{solv,EDR,EDR}(S_1))} e^{-\beta(U_{AS_1,Rp} + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(-\Delta G_{solv,EDR,EDR}(S_1(S_{2,A})))} e^{-\beta(U_{AS_1,Rp} + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{22}$$

The $\Delta G_{solv,EDR,EDR}(S_1(S_{2,A}))$ term has a simple interpretation. It is the solvation of S_1 molecules by S_2 molecules placed in the position of solute A. This term is small, and we can introduce one more approximation:

$$\Delta G_{solv,EDR,EDR}(S_1(S_{2,A})) \cong \text{constant} \tag{23}$$

Substituting (23) into (22) leads to:

$$\begin{aligned}&\Delta G_{solv}(A) = \Delta G_{solv,Rp}(A) - RT\ln \\ &\times \frac{\int e^{-\beta(U_{AS_1,EDR} + \Delta G_{solv,EDR,EDR}(AS_1) - \Delta G_{solv,EDR,EDR}((A)S_1))} e^{-\beta(U_{AS_1,Rp} + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp} + U_{S_1} + \Delta G_{solv}(S_1))}\mathbf{dr}_1}\end{aligned} \tag{24}$$

where:

$$\begin{aligned}\Delta G_{solv,EDR,EDR}((A)S_1) = {}& \Delta G_{solv,EDR,EDR}(S_1) \\ & - \Delta G_{solv,EDR,EDR}(S_1(S_{2,A}))\end{aligned} \tag{25}$$

The $\Delta G_{solv,EDR,EDR}((A)S_1)$ term is the solvation of S_1 shell excluding any S_2 solvent molecule from the position of solute A. *Equation* (24) *is the fundamental equation of the shells theory of solvation and it is very similar to Eq.* 9. The difference is that Eq. 9 is equivalent to the particle insertion method [76–78], while the second term of the right side of Eq. 24 can be seen as a single perturbation step from the solute with its auxiliary repulsive potential to the full potential. Someone should notice the solvation terms with EDR, EDR means the solvation free energy excludes the cavity formation contribution. Thus, it is not need to create a large cavity into the S_2 shell to insert $A + S_1$. Only the cavity contribution for the solute A needs to be calculated, maybe by an approximated method or even classical simulation coupled with free energy perturbation or thermodynamic integration.

2.2 Two points thermodynamic integration

Equation 24 provides the pathway for calculating the free energy of solvation. However, a simplification of the final expression is required in order to set a practical method. This is specially important if the goal is calculating quantum–mechanical solute–solvent interactions. The use of two-point thermodynamic integration method is very attractive because it is a good approximation and requires less evaluations of the interaction energy. Thus, we can define the EDR contribution to the free energy of solvation of solute A as:

$$\Delta G_{solv,EDR}(A) = -RT\ln\frac{\int e^{-\beta(U_{AS_1,EDR}+\Delta G_{solv,EDR,EDR}(AS_1)-\Delta G_{solv,EDR,EDR}((A)S_1))}e^{-\beta(U_{AS_1,Rp}+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,Rp}+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{26}$$

Introducing the coupling parameter λ and using the thermodynamic integration formula leads to:

$$\Delta G_{solv,EDR}(A) = \int_0^1 \left\langle \frac{\partial(U_{AS_1,EDR}(\lambda)+\Delta G_{solv,EDR,EDR}(AS_1,\lambda)-\Delta G_{solv,EDR,EDR}((A)S_1,\lambda))}{\partial\lambda}\right\rangle_{S_1,\lambda} d\lambda \tag{27}$$

where the angular brackets are given by:

$$\langle f(\mathbf{r}_1,\lambda)\rangle_{S_1,\lambda} = \frac{\int f(\mathbf{r}_1,\lambda)\, e^{-\beta(U_{AS_1,EDR}(\lambda)+\Delta G_{solv,EDR,EDR}(AS_1,\lambda)-\Delta G_{solv,EDR,EDR}((A)S_1,\lambda)+U_{AS_1,Rp}+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1}{\int e^{-\beta(U_{AS_1,EDR}(\lambda)+\Delta G_{solv,EDR,EDR}(AS_1,\lambda)-\Delta G_{solv,EDR,EDR}((A)S_1,\lambda)+U_{AS_1,Rp}+U_{S_1}+\Delta G_{solv}(S_1))}\mathbf{dr}_1} \tag{28}$$

Choosing a simple relation with λ, we can write:

$$\begin{aligned} &U_{AS_1,EDR}(\lambda)+\Delta G_{solv,EDR,EDR}(AS_1,\lambda) \\ &\quad -\Delta G_{solv,EDR,EDR}((A)S_1,\lambda) \\ &\quad =\lambda[U_{AS_1,EDR}+\Delta G_{solv,EDR,EDR}(AS_1) \\ &\quad -\Delta G_{solv,EDR,EDR}((A)S_1)] \end{aligned} \tag{29}$$

Substituting Eq. 29 into 27 and performing the integral while assuming the λ dependence of the ensemble average is linear in λ, we arrive to:

$$\begin{aligned} \Delta G_{solv,EDR}(A) =&\frac{1}{2}\left(\langle U_{AS_1,EDR}\rangle_{S_1,\lambda=1}+\langle U_{AS_1,EDR}\rangle_{S_1,\lambda=0}\right) \\ &+\frac{1}{2}\langle \Delta G_{solv,EDR,EDR}(AS_1)-\Delta G_{solv,EDR,EDR}((A)S_1)\rangle_{S_1,\lambda=1} \\ &+\frac{1}{2}\langle \Delta G_{solv,EDR,EDR}(AS_1)-\Delta G_{solv,EDR,EDR}((A)S_1)\rangle_{S_1,\lambda=0} \end{aligned} \tag{30}$$

Equation 30 is a very simple expression. The first term is the contribution of the S_1 shell, obtained through direct interaction of the solute with the S_1 solvent molecules with the EDR potential. The calculations are performed in the geometries generated by the repulsive potential ($\lambda = 0$) and including the full potential ($\lambda = 1$). The second term is the contribution of the S_2 shell for $\lambda = 1$, whereas the third term is the contribution of the S_2 shell for $\lambda = 0$. As a final comment, the two-point thermodynamic integration is equivalent to full Linear Response approximation [31].

3 Dynamically coupled discrete/continuum shells theory of solvation

A problem with Eq. 30 is that configurations generated for the S_1 shell depend on the influence of the S_2 shell, and it should be calculated for each new simulation step. Therefore, we could make a decoupling between the shells and introduce *on the fly* coupling between them, i.e., dynamical coupling. The idea is to perform a simulation using low level of theory and a simulation box for generating the configurations. In the next step, some molecules in closest contact with the solute are selected to compose the S_1 shell and to calculate the interaction energy. The effect of S_2 shell is also calculated for selected configurations. So, this is an approximated theory and the proposed final expression for the discrete/continuum shells theory of solvation is:

$$\begin{aligned}\Delta G_{solv}(A) = \Delta G_{cav}(A) &+ \frac{1}{2}\left(\langle U_{AS_1}\rangle_{\lambda=1} + \langle U_{AS_1}\rangle_{\lambda=0}\right)\\ &+ \frac{1}{2}\langle \Delta G_{solv}(AS_1) - \Delta G_{solv}((A)S_1)\rangle_{\lambda=1}\\ &+ \frac{1}{2}\langle \Delta G_{solv}(AS_1) - \Delta G_{solv}((A)S_1)\rangle_{\lambda=0} \qquad (31)\end{aligned}$$

The first term is the free energy for cavity formation. This term could be calculated using a simple analytical theory or empirical expression and it will not be explored in this work. The second term is a simple two-point thermodynamics integration using configurations generated from the simulation box and low level of theory, for example, classical force-field calculations. Then, the complete classical potential is used for $\lambda = 1$, whereas the electrostatic terms are excluded for $\lambda = 0$. In the next step, for each selected configuration, n solvent molecules in closest contact with the solute are selected, and the interactions between them are obtained from full quantum mechanical calculations for both λ values. The third and fourth terms are the S_2 contribution. They can include electrostatic, dispersion, and repulsion contributions for solute–solvent and solvent–solvent interactions. However, because these terms involve a difference, the dispersion-repulsion contribution for solvent–solvent interaction cancels out and only the solute-S_2 shell interaction remains. In the case of electrostatic contribution, the polarization of solvent molecules is different when the solute is present or absent and as a consequence, a full calculation must be done. In addition, if the S_1 shell is large, the solute-S_2 shell dispersion term does not need to be calculated because it is short range and its inclusion will have a minor effect on the solvation free energy. Thus, the contribution of the S_2 shell is calculated using a reliable continuum solvation model like PCM (polarizable continuum model). Because in this paper the S_2 shell involves more distant molecules, only electrostatic contributions are included.

The $\Delta G((A)S_1)$ term means the cavity of the solute A is present in the continuum calculations, although the solute is absent. In this point, we can notice this S_2 contribution is similar to the long-range Born correction. However, *the simple Born formula only sees a central ion with an extended radius due to the* S_1 *shell. The shells theory of solvation includes details of the solvent structure around the solute as well as the charging state* (λ *value*) *of the solute. In addition, the effect of solute's higher multipoles is included. The present theory allows the use of any number of solvent molecules in the* S_1 *shell and converges for full discrete representation of the solvent for n going to infinity. Therefore, it provides a much more general and theoretically sound formula for including the long range contribution.*

In this point, it can be noted that other dynamical discrete/continuum solvation methods have been proposed. Roux and co-workers have proposed the surface boundary potential [71, 75], whereas Brancato et al. have proposed a mean field approach [58–60]. However, the method presented in this paper is different from these previous developments, and the expression for the long-range contribution proposed in this paper has been presented for the first time.

4 Application of discrete/continuum shells theory of solvation for long-range correction

In this section, the Long-Range contribution from Eq. 31 will be applied for solvation of fluoride ion in a simulation box with 32 benzene molecules. The 32 benzene molecules will constitute a large S_1 shell, and a continuum solvation method will represent the S_2 shell. Details of the calculations are presented below.

4.1 Molecular dynamics and long-range contribution calculations

Molecular dynamics calculations were done for one fluoride ion in a cubic box with 32 benzene molecules under periodic boundary conditions. The box was build putting each benzene molecule in a symmetric lattice and the fluoride ion in the center of the box. It was done a long molecular dynamics run using the NPT ensemble and the Berendesen thermostat in order to equilibrate the system using the AMOEBA force-field. A cutoff radii of 8.5

angstron was considered for this force-field interaction and the Modified Beeman Algorithm was used for integration of the motion equations. The production run was done on a time of 200 ps, selecting one structure for energy computation each 10 ps. Two set of molecular dynamics runs were done. In the first one, it was considered the full interaction potential among the fluoride ion and the benzene molecules. In the second run, the charge of the fluoride ion was withdrawn and it was considered only the Lennard-Jones 12–6 contribution for the interaction of fluoride ion with benzene molecules. All the molecular dynamics calculations were done with the TINKER program [79].

The final step of the calculation was to include the dielectric continuum for accounting long-range interaction. It was used the PCM method [16, 18–20, 80], which has a molecular shaped cavity able to introduce the molecular form. It was used the following atomic radii: H (1.20), C (1.70), and F (1.40). All atomic radii were scaled by 1.40, in line with the observations that aprotic solvents require a larger cavity [81]. For these PCM calculations, it was done 20 single point calculations with the 32 benzene molecules using selected structures taken each 10 ps of simulation run. Because these are test calculations, it was used the Hartree–Fock method with the MINI basis set, i.e., it was done PCM/HF/MINI calculations.

A problem that someone needs pay attention is the formation of holes inside the explicit solvent, which could be occupied by the dielectric continuum. These holes introduce error in the solvation calculations, because the apparent surface charge method considers that no dielectric is present inside the solute [82]. In addition, the equations derived in this paper consider that the hole is not occupied by the S_2 shell. To avoid this problem, it was included a neon atom in the fluoride ion position in the calculation of the solvation of 32 benzene molecules without the fluoride ion. This procedure has a minimum effect on the solvation free energy. All PCM/HF/MINI calculations were done with the GAMESS program [83].

5 Results and discussion

Table 1 presents the solvation free energy contribution of the S_2 shell, determined by the PCM method for 20 selected

Table 1 Interaction energies and dielectric continuum solvation for $\lambda = 1$ and $\lambda = 0$

Structure	$\lambda = 1$			$\lambda = 0$		
	ΔG_{solv} ($F^-(C_6H_6)_{32}$)	ΔG_{solv} ($Ne(C_6H_6)_{32}$)	$\Delta\Delta G^{a}_{solv}$	ΔG_{solv} ($F^-(C_6H_6)_{32}$)	ΔG_{solv} ($Ne(C_6H_6)_{32}$)	$\Delta\Delta G^{a}_{solv}$
1	−10.69	−1.32	−9.37	−12.24	−1.60	−10.64
2	−10.37	−1.33	−9.04	−15.11	−1.73	−13.39
3	−11.32	−1.81	−9.51	−12.61	−1.63	−10.98
4	−10.42	−1.44	−8.98	−13.25	−1.76	−11.49
5	−10.81	−1.62	−9.19	−13.31	−1.85	−11.46
6	−10.37	−1.33	−9.04	−16.58	−1.81	−14.77
7	−10.83	−1.50	−9.34	−10.87	−1.64	−9.23
8	−11.06	−1.49	−9.57	−12.00	−1.47	−10.52
9	−10.96	−1.51	−9.44	−15.86	−1.72	−14.14
10	−10.89	−1.45	−9.44	−15.52	−1.67	−13.84
11	−10.46	−1.58	−8.87	−14.66	−1.75	−12.91
12	−10.83	−1.49	−9.34	−13.55	−1.44	−12.11
13	−11.46	−1.56	−9.90	−15.78	−1.77	−14.01
14	−10.97	−1.50	−9.46	−13.92	−1.59	−12.34
15	−10.50	−1.36	−9.15	−11.92	−1.58	−10.34
16	−11.15	−1.57	−9.58	−16.74	−1.73	−15.01
17	−10.37	−1.39	−8.98	−12.93	−1.94	−10.99
18	−10.82	−1.51	−9.31	−16.62	−1.74	−14.89
19	−10.66	−1.57	−9.09	−15.24	−1.69	−13.55
20	−11.04	−1.63	−9.41	−11.70	−1.82	−9.88
Average			−9.30			−12.32
δ			0.25			1.76

Units of kcal/mol

Dielectric continuum contribution: $\Delta\Delta G_{solv} = \Delta G_{solv}(F^-(C_6H_6)_{32}) - \Delta G_{solv}(Ne(C_6H_6)_{32})$

configurations. The calculations include either the fluoride ion or the neon atom (filling the hole), and the difference between them is the S_2 shell contribution to the solvation free energy ($\Delta\Delta G_{solv}$). As someone can notice, the fluctuation is small and as few as 20 structures lead to small error, suggesting that even a small sampling could produce reliable values of S_2 contribution to the solvation free energy. The λ value has an important effect on the S_2 shell contribution to the solvation free energy. In fact, for $\lambda = 0$, the $\Delta\Delta G_{solv}$ contribution is -12.3 kcal/mol, whereas in the case of $\lambda = 1$ this contribution becomes -9.3 kcal/mol, a difference of 3.0 kcal/mol. For an accurate work, this is a large variation and the difference can be explained by the different orientations of the benzene molecules in $\lambda = 0$ and $\lambda = 1$ states. Based on Eq. 31 and the results of Table 1, we can calculate the S_2 contribution to the solvation free energy is -10.8 kcal mol^{-1}.

Theoretical studies of ion solvation require the inclusion of long-range electrostatic interactions that take place between the ion and the solvent molecules. Many studies make use of cutoff radius for ion–solvent interaction and a simple Born correction is introduced for account the long-range interaction [84]. Essentially, the idea is to include the effect of remaining molecules beyond a cutoff point, considering the solute plus the S_1 shell are a large ion. Thus, it uses the simple Born model (Eq. 32), although no rigorous theoretical justification has been provided for this correction.

$$\Delta G_{solv} = -\frac{1}{2}\frac{1}{4\pi\varepsilon_o}\frac{q^2}{R}\left(1 - \frac{1}{\varepsilon}\right) \tag{32}$$

Other approach like extrapolation for infinite solvent box was also proposed [85] and a very usual procedure is the Ewald summation method and correction for self-interaction [86]. In the present paper, it was provided a more rigorous derivation on how to introduce the contribution of the S_2 shell, through the relation $\Delta\Delta G_{solv} = \Delta G_{solv}(F^-(C_6H_6)_{32}) - \Delta G_{solv}((F^-)(C_6H_6)_{32})$. In the discrete/continuum shells theory, this contribution is calculated by $\Delta\Delta G_{solv}$ evaluated at $\lambda = 1$ and $\lambda = 0$ and taking the average. It is interesting making a comparison with the prediction made by the Born model. Considering that the box with the fluoride ion and the 32 benzene molecules have an average volume of 4.9×10^3 Å^3, this translates to a spherical radii of 10.5 Å. On this way, using the Born formula results in $\Delta\Delta G_{solv}$ of -8.8 kcal/mol, in good agreement with the more reliable value of -10.8 kcal/mol calculated from Table 1. The deviation of only 2 kcal/mol suggests the Born model is a reasonable correction for the long-range solute–solvent interaction contribution, at least for apolar solvents. Nevertheless, it is reasonable that for accurate work, the Born model should be replaced by the present expression for the long-range. A detailed study in water solution will be published elsewhere.

6 Conclusion

A new theoretical approach for solvation free energy calculation, using dynamical hybrid discrete/continuum method, was proposed. Any number of solvent molecules can be used in the S_1 shell, with configurations generated by molecular dynamics calculations based on classical force-fields or even quantum mechanical, whereas the interaction energy can be calculated by full quantum mechanical methods. The remained solvent, represented by the S_2 shell, is treated by a dielectric continuum method like PCM. The theory provides a justification for the Born correction and presents more theoretically sound expression for including the long-range contribution. In the present application, the S_1 shell was described by 32 benzene molecules and the PCM method used for the S_2 shell. It was found an error of 2 kcal mol^{-1} for the Born correction.

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