Chemical Physics 443 (2014) 93–106

Contents lists available at ScienceDirect

Chemical Physics

journal homepage: www.elsevier.com/locate/chemphys

Incorporation of the TIP4P water model into a continuum solvent for computing solvation free energy

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ARTICLE INFO

Article history:
Received 16 June 2014
In final form 9 September 2014
Available online 18 September 2014

Keywords:
The first-shell water
Born equation
Excluded solvent volume
Molecular dynamic simulations
Continuum solvent model

ABSTRACT

The continuum solvent model is one of the commonly used strategies to compute solvation free energy especially for large-scale conformational transitions such as protein folding or to calculate the binding affinity of protein–protein/ligand interactions. However, the dielectric polarization for computing solvation free energy from the continuum solvent is different than that obtained from molecular dynamic simulations. To mimic the dielectric polarization surrounding a solute in molecular dynamic simulations, the first-shell water molecules was modeled using a charge distribution of TIP4P in a hard sphere; the time-averaged charge distribution from the first-shell water molecules were estimated based on the coordination number of the solute, and the orientation distribution of the first-shell waters and the intermediate water molecules were treated as that of a bulk solvent. Based on this strategy, an equation describing the solvation free energy of ions was derived.

1. Introduction

Most biomolecules, such as proteins, DNA, and RNA function in an aqueous environment [1]. The behaviors of proteins dissolved in water, such as protein-folding or protein–protein/ligand interactions, are very different than the behaviors of proteins in an air/vacuum or a nonpolar solvent environment [2]. For example, in vacuum, the formation of hydrogen bonds between the donor and acceptor of the biomolecules considerably lowers the electrostatic energy and stabilizes the conformation. However, in a water solvent environment, the hydrogen donors/acceptors of the biomolecules form hydrogen bonds with either the acceptors/donors of the biomolecules or water molecules. The difference in free energy between these two states is small. Therefore, developing a strategy to compute the solvation free energy is crucial for examining the binding affinity of protein–protein/ligand interactions [3–6] and the stability of protein conformations [7–10].

Several strategies have been developed for computing the solvation free energy. These strategies can be classified as explicit [11], hybrid [10,12–19], and implicit [20–27] solvent models. The continuum solvent model is one type of the implicit solvent model. Some strategies, such as the Born equation [28–31], generalized Born equation [32–36], Poisson–Boltzmann equation [25,37,38], two Born radii [39,40], and distance-dependent relative permittivity are derived from the continuum solvent models. The continuum solvent models were conventionally incorporated into the algorithm of quantum mechanics to examine protein function [25,26] or incorporated into docking algorithms for computer-aided drug design [41,42].

The solvation free energy calculated using the continuum solvent model ($-\Delta G^{cal}_{hyd}$) is usually partitioned into two terms, i.e., the charging and non-polar solvation free energy [27,43]. The non-polar component of the solvation free energy depends on (1) the creation of a cavity in the solvent, and (2) the van der Waals (vdW) interaction between the solute and the solvent. Thus, the equations that describe dispersion contribution of the solvation free energy (used to calculate the vdW interaction between the solute and the solvent) were derived [44]. Here, the non-polar free energy can be approximated by the inclusion of the volume and area terms as follows: $\Delta G_{np} \approx \gamma A + pV$ (where γ is a solvent surface tension parameter, A is the surface area of the solute, p is a solvent pressure parameter, and V is the solvent-accessible volume [45–47]). The solvent-accessible radius of a solute atom is the summation of the radius of the solute atom, $-\sigma_i$, and the solvent radius, $-\sigma_s$.

The charging solvation free energy can be calculated by integrating the electrostatic potential $\Phi(q)$ of the solute, which is contributed by the solvent for the solute charge to increase from 0 to Q [28]. Therefore, the ΔG^{cal}_{hyd} can be modeled as,

$$\Delta G^{cal}_{hyd} = \int_0^Q \Phi(q)dq + (\gamma A + pV) \quad (1)$$

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http://dx.doi.org/10.1016/j.chemphys.2014.09.006
0301-0104/

$\Phi(q)$ was estimated using Gauss's law by considering a spherical ion of radius, R_{ion}, (the bare ionic radius) and charge, q, immersed in a solvent with a relative permittivity, ε_r. The ion polarizes the solvent, generating an induced dielectric polarization, $-\boldsymbol{P}(\boldsymbol{r})$, defined by the electric dipole moment per unit volume, $P(r) = q(1 - 1/\varepsilon_r)/(4\pi r^2)$, which makes a contribution of $-q(1 - 1/\varepsilon_r)/(4\pi\varepsilon_0 R_{ion})$ to the electrostatic potential at the ion [48,49]. Substituting the latter into Eq. (1), the free energy of transferring an ion from vacuum to a medium characterized by relative permittivity ε_r is given by:

$$\Delta G_{Born} = -\frac{Q^2(1 - 1/\varepsilon_r)}{8\pi\varepsilon_0 R_{ion}} + (\gamma A + pV) \tag{2}$$

However, ΔG_{Born} overestimates the magnitude of the observed solvation free energy [50,51]. On the other hand, the free energy, calculated using the radius of R_{gmax} (the first peak position in the ion-water radial distribution function) underestimates the magnitude of the observed solvation free energy. Therefore, the "effective" Born radius, $R_{eff} = (R_{ion} + R_{gmax})/2$ was developed, and the corresponding solvation free energy was [51]:

$$\Delta G_{eff} = -\frac{Q^2(1 - 1/\varepsilon_r)}{16\pi\varepsilon_0(R_{ion} + R_{gmax})} + (\gamma A + pV) \tag{3}$$

The Born equation used to compute the charging solvation free energy is based on Gauss' Law. The solution from Gauss' Law yields an induced surface charge on the solute–solvent boundary, and the induced volume charge density is zero outside the boundary region. However, the induced charge distribution calculated from Gauss' Law is considerably different than that calculated from MD simulations [52]. Therefore, the radii of the atoms have been used as parameters to fit the experimental value, $-\Delta G_{exp}$. For a solute composed of n atoms, there are n Born radii parameters but only one ΔG_{exp}. Therefore, numerous sets of Born radii can be adjusted to fit ΔG_{exp}. However, ΔG_{exp} can be expressed as an integration of the solute solvation free energy weighted by the probability of finding the solute in a given conformation over all possible solute conformations. The probability of finding the solute in a given conformation depends on its environment, such as proteins alone or protein–protein/ligand complex structures. Therefore, the n Born radii parameters do not suffice to fit ΔG_{exp} derived from numerous solute conformations unless the function that describes ΔG_{exp} for various solute conformations is sufficiently accurate. Therefore, the macroscopic Gauss' Law was reformulated to incorporate the near-solute solvent structure by considering excluded solvent volume effects [52]. An approximate analytical solution for the hydration free energy of ions is derived by considering the excluded solvent volume effects [39]. The first-shell water was treated as a point dipole at the center of a hard sphere, located at a distance R_{gmax} from a solute atom of charge Q. For a distance greater than $(R_{gmax} + R_w)$ from the solute, the water molecules were treated as bulk water so that the net induced surface charge in the shell at a distance of $(R_{gmax} + R_w)$ from the solute is $-q(1 - 1/\varepsilon_r)$. Hence, the equation describing the solvation free energy using this solvent scheme is [39]

$$\Delta G_{exclud} = -166Q^2\left[\frac{1.85}{R_{gmax}^2} + \frac{(1 - 1/\varepsilon_r)}{R_{gmax} + R_W}\right] + (\gamma A + pV) \tag{4}$$

To mimic the charge distribution surrounding a solute in molecular dynamics (MD) simulations, the dielectric polarization of the first-shell water was modeled as a pair of surface charge layers with a fixed distance between them, but with variable, equal, and opposite charge magnitudes that respond to the electric field on the first-shell water. The water outside the first-shell water is treated as a bulk solvent, and the electric effect of the bulk solvent can be modeled as a surface charge. Based on this strategy, the analytical solution describing the solvation free energy of ions with charge Q is derived [53].

$$\Delta G_{three} = Q\Phi_{water/air} + (\gamma A + pV) - \frac{Q^2}{8\pi\varepsilon_0}\left\{\frac{2R_W C}{[R_{gmax} + s(E_{net})r_{Hb,O}][R_{gmax} + s(E_{net})r_{M,O}]} + \frac{1 - 1/\varepsilon_r}{R_{gmax+R_W}}\right\} \tag{5}$$

$r_{M,O}$ and $r_{Hb,O}$ are the distances between the oxygen atom and M site and the hydrogen bisector center of the TIP4P, respectively. $s(E_{net})$ is the sign of the net electric field on the first-shell water, R_W is the water molecule radius, and $\Phi_{water/air}$ is the electric potential across the water/air interface region. In Eq. (5), C is defined as

$$\frac{1}{C} = \frac{1}{2(r_{Hb,O} - r_{M,O})R_{gmax}}\left[\frac{2r_{Hb,O}R_{gmax} + s(E_{net})R_W^2}{\sqrt{1 + \frac{r_{Hb,O}}{R_W^2}\left(r_{Hb,O} + s(E_{net})\frac{R_W^2}{R_{gmax}}\right)}} - \frac{2r_{M,O}R_{gmax} + s(E_{net})R_W^2}{\sqrt{1 + \frac{r_{M,O}}{R_W^2}\left(r_{M,O} + s(E_{net})\frac{R_W^2}{R_{gmax}}\right)}}\right] + \frac{1}{N_{bulk}\gamma_{mol}} \tag{6}$$

In Eq. (6), N_{bulk} is the bulk solvent molecular density, and γ_{mol} is the solvent molecular polarizability.

The orientation probability distribution of the first-shell water molecule, and the experimental coordination number of the first-shell water, $-N_{coor}$, were considered in this study. The charge distribution of a water molecule is needed for calculating the time-averaged positions and amplitudes of charges from the first-shell waters. A hard sphere water model is needed for including the excluded solvent volume effect when calculating the electric field on the solvent molecule. Taking the charge distribution of TIP4P in a hard sphere water model as an example, the oxygen atom is located at the center of a hard sphere, and the dummy atom with charge, q_M, and two hydrogen atoms with charges q_{H1} and q_{H2} are in this sphere [54]. Considering the oxygen atom of the first-shell water molecule as the rotational center, the oxygen atom is located at the position corresponding to the distance from a solute atom R_{gmax}, and the positions of the time-averaged dummy atom and hydrogen atoms depend on the orientation probability distribution of the water molecules. The orientation probability distribution depends, in turn, on the net electrostatic field, $\boldsymbol{E}_{net}$, on the solvent molecule. The negative and positive surface charge densities are contributed by the dummy and hydrogen atoms of TIP4P, respectively. The positions of the positive and negative surface charges depend on the orientation probability distribution of the hydrogen and dummy atoms in the TIP4P water molecule. The amplitude of the surface charge density is estimated from N_{coor} and R_{gmax}. The water molecules between the first-shell waters and the waters in water/air interface were treated as a dielectric continuum. Based on this strategy, the equation describing the solvation free energy of ions is derived in the Theory section, and the solvation free energies of ions computed from the derived equation and those obtained from experiments were compared in the results/discussions section.

2. Methods

2.1. MD simulations

The system studied in the MD simulation was a one-charged atom fixed at the center of a spherical water cluster with a radius