



Parameterization of the hydration free energy computations for organic solutes in the framework of the implicit solvent model with the nonuniform dielectric function

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ARTICLE INFO

Article history:

Received 24 September 2012

Received in revised form 19 December 2012

Accepted 19 December 2012

Available online 5 January 2013

Keywords:

Hydration free energy

Implicit solvent models

Polarizable continuum model

ABSTRACT

An earlier developed Smooth Boundary Continuum Model (SBCM) which allows to consider the solution in inhomogeneous media has been parameterized for the calculation of hydration free energy. The traditional (for implicit models of solvent influence) decomposition ΔG_{solv} on polar, nonpolar and hydrophobic components for implicit models of solvent has been used. The peculiarity of SBCM appears as a position-dependent dielectric permittivity function, which is applied for a computation of the electrostatic component of ΔG_{solv} in the frame of solving the pertaining Poisson equation. By this means non-uniformity of medium environment for a solute particle can be simulated. This feature distinguishes the present approach from its conventional counterparts based on standard uniform electrostatic schemes.

Two hundred and three molecular species, covering most important classes of neutral organic molecules, have been considered for the parameterization. The comparison of calculated and experimental ΔG_{solv} for these species results the root mean square deviation value that is quite comparable with literature data and equal to 0.76 kcal/mol. The current status and the perspectives of developing the SBCM is discussed.

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1. Introduction

Implicit solvation approaches are among important and widely used applications of the theoretical chemistry. They are based on relatively simple theoretical background and extensive parameterization. By this means a large amount of experimental material can be explained at a semi-empirical level with little computation effort. Many approximate schemes of this sort are reported. According to the basic and general idea the combined solvation system is spatially subdivided into its solute and solvent parts by separating a cavity which corresponds to the solute excluded volume. The solute/solvent interaction is then formulated in terms of a continuum model assumed for the external solvent space. The water solvent remains to be under conventional consideration. Electrostatic interaction dominates for such material, and it reveals as a consequence of the external medium polarization, with uniform dielec-

tric permittivity, by the solute charge distribution embedded in the internal cavity volume. The solvation free energy emerges then after solving the Poisson equation in which a specific choice of the cavity shape defines its boundary conditions. The simplest approach with a spherical cavity goes back to seminal works of Born, Kirkwood and Onsager. Its recent conventional modifications, better adapted to real molecular solutes, invoke more complicated cavities [1,2] for which a treatment of the Poisson equation requires numerical solutions [3–6]. Originally, exact algorithms with the pertaining boundary conditions were applied but various simplifying approximations were also suggested [5–8]. Several approximations were additionally introduced for treating non-electrostatic interactions at a continuum level. In applications, the resulting computational schemes require a careful and extensive parameterization [9–20]. The present status of this widely extended research field is surveyed in several reviews [6,21–24].

The distinctive feature of the present approach is the new methodology for treating the electrostatic component of the solvation energy. We invoke here the recently developed computational

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procedure, called SBCM (Smooth Boundary Continuum Model [25,26]) which was addressed for treating most complicated solvation systems with non-uniform solvent environment around the solute molecule. Therefore, the position-dependent dielectric constant is applied within the continuum electrostatic computation based on the exact solution of the Poisson equation. Although such a complication seems to be unnecessary in ordinary applications but it cannot be avoided in special cases, such as several non-aqueous solvents [25,27], binary solvent mixtures [27–29] and nanoparticle models [30]. It is also expected to be useful as applied to biologically important large molecular systems. With this perspective in mind, we performed in the present work the extensive parameterization of the SBCM scheme.

The main strategy is borrowed from the earlier publication [20], in which standard PCM (Polarizable Continuum Model [24]) was applied to treat the electrostatic interactions. As usually, the total solvation energy is separated into the electrostatic and non-electrostatic parts. The SBCM is used for the electrostatic computation. The second non-electrostatic component of the solvation free energy is subdivided into van der Waals and cavitation (or hydrophobic) parts, for which the pertaining computational techniques were elaborated earlier [20].

Only water solvent was considered. The input data for a computation of the hydration energy are molecular structures and charge distributions for the solute particles. They were calculated by standard quantum-chemical methodologies combined with the PCM scheme [31] in order to account for solvation effects at this preliminary stage.

2. Calculations methods

2.1. The method for computing the hydration free energy ΔG_{solv}

The ΔG_{solv} values were calculated as [20]:

$$\Delta G_{solv} = \Delta G_{el} + \Delta G_{cav} + \Delta G_{vdW} \quad (1)$$

where ΔG_{el} , ΔG_{cav} and ΔG_{vdW} – are electrostatic, hydrophobic and nonpolar components of the hydration free energy. The ΔG_{el} component is calculated according to the SBCM [25] as:

$$\Delta G_{el} = \frac{1}{2} \iint d^3r d^3r' \rho(\vec{r}) \frac{1}{4\pi\epsilon^2(\vec{r})} \frac{\nabla\epsilon(\vec{r})\nabla\psi_0(\vec{r}')}{|\vec{r} - \vec{r}'|} \quad (2)$$

where ρ and ψ_0 – are the density and the potential created by the solute charges, ϵ – is the distance-dependent dielectric constant of the solvent (water in the frame of this investigation). Integration is carried out outside the molecular volume. The shape of $\epsilon(\vec{r})$ can be illustrated here by the simplest case with a spherical solute cavity of excluded volume:

$$\begin{aligned} \epsilon(r) &= 1 + 4\pi\{\chi_\infty z(r) + \chi_0 z(r)\Phi[z(r)]\}; \\ z(r) &= 1 + \exp(-2\alpha r) - 2\exp(-\alpha r) \quad (r > 0) \\ \Phi(z) &= \exp((z-1)/z_0) \end{aligned} \quad (3)$$

Here r is the distance between the space point outside the cavity and the cavity surface, $z(r)$ is the solvent density normalized to 1 ($z = 1$ far away from the solute and $z = 0$ inside the cavity). It is modeled as Morse function with damping parameter α , whereas $\Phi(z)$ with parameter z_0 is the nonlinearity correction. (See the full algorithm for $\epsilon(\vec{r})$ in non-spherical general case in the original paper [25]). The optical (χ_∞) and inertial (χ_{in}) permittivities can be combined to give the static dielectric constant $\epsilon_0 = 1 + 4\pi(\chi_\infty + \chi_0)$ for the case $z(r) = 1$. The value $\epsilon_0 = 78$ for water was assumed.

It should be noted that the present realization of the SBCM scheme does not include the self-consistent reaction field connection (the iterative SCRF procedure) between the solution of the

purely electrostatic Poisson problem (i.e. the potential $\psi_0(\vec{r})$ in (2)) and the regular quantum-chemical computation of solute charge distributions (i.e. those appearing as $\rho(\vec{r})$ in (2)). This is why the required SCRF charge distributions were extracted, as already noted above, from a preliminary standard SCRF/PCM computation [31].

The hydrophobic component was calculated as [20]

$$\Delta G_{cav} = \theta \ln \frac{\theta}{\theta - 1} \rho_w k_B T V \quad (4)$$

where $\rho_w = 0.034$ molecule/Å³ is the number density for water at 298 K, $\theta = 1.3$ is a dimensionless parameter, V is the cavity volume, T is the temperature.

The nonpolar component was calculated as

$$\Delta G_{vdW} = \sum_I \sum_{i \in I} A_i^{(6)} \Phi^{(6)}(r_i) + A_i^{(12)} \Phi^{(12)}(r_i) \quad (5)$$

where

$$\Phi^{(m)}(r_i) = \int d^2r \frac{((\vec{r}_i - \vec{r}), \vec{n}(\vec{r}))}{|\vec{r} - \vec{r}_i|^m} \quad (6)$$

In Eqs. (5) and (6) $\vec{n}(\vec{r})$ – is the unit normal vector to molecular surface \vec{r}_i – is the radius-vector of i th atom, $A_i^{(6)}$, $A_i^{(12)}$ – are parameters to the atom of type I . The sum (5) is carried over all atoms of the molecule, each of them belonging to a certain type.

2.2. The parameterization scheme

The set of atomic parameters is defined to calculate the components of the hydration free energy as described in [20]. The atomic radii are needed to perform integrations in (2)–(6) and to calculate the molecular volume in (3). The van der Waals $A_i^{(6)}$, $A_i^{(12)}$ parameters are necessary for ΔG_{vdW} calculations. Besides, according to the SBCM, the ΔG_{el} term depends on two parameters $z_0 = 0.5$ and $\alpha = 3 \text{ \AA}^{-1}$ [25,28,29]. They are common for all types of atoms and define the changes of position-dependent dielectric permittivity.

The types of atoms and their parameters are shown in Table 1. Four parameters are introduced for each type: the electrostatic solute radius R , vdW parameters $A_i^{(6)}$, $A_i^{(12)}$ and the solvent radius $R_S = 1.4 \text{ \AA}$, common for all types. There are two levels of atomic types in the frame of the present approach. Types of the first level are based only on the number of corresponding element taken from the Periodic Table. The second level of type specification is additionally based on the chemical environment of atoms and their hybridization. For the calculation of the electrostatic component

Table 1

Specification of the atomic types and parameters: basic electrostatic radii R (Å), vdW parameters $A_i^{(6)}$, $A_i^{(12)}$ in (kcal(mol)·Å³ and (kcal(mol)·Å⁹ respectively. Parameters for types signed as (*) are not specified in the present work.

No.	R	$A_i^{(6)}$	$A_i^{(12)}$	Specification of type, symbol type
<i>The first level</i>				
1	1.25	−0.34	27.0	H
2	1.65	−11.7	1440.0	C
3	1.72	−14.5	1440.0	N
4	1.65	−11.7	1440.0	O
5	1.9	−11.7	1440.0	F
6	1.9	−11.7	1440.0	Br
7	1.9	−11.7	1440.0	Cl
<i>The second level</i>				
8	0.95	−0.2	27.0	Hydrogen in H–N
9	1.25	−0.34	27.0	Hydrogen in H–O
10	1.8	−9.4	1440.0	=C*
11	1.75	−11.7	1440.0	–N=
12	1.8	−10.0	1440.0	=O
13	2.0	−11.7	1440.0	Oxygen in O= in amides
14	1.5	−10.7	1440.0	Oxygen in O–H

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