Molecular modelling of fullerene C₆₀ and its amino acid derivatives in aqueous medium

V B Krapivin ¹,² and V B Luzhkov ¹,²*

¹ Institute of Problems of Chemical Physics, Russian Academy of Sciences, Acad. Semenov av., 1, Chernogolovka, Moscow Region, 142432, Russian Federation
² Lomonosov Moscow State University, GSP-1, Moscow, 119991, Russian Federation

E-mail: vbl@icp.ac.ru

Abstract. The hydration free energy ΔGₛ of fullerene C₆₀ has been determined using the quantum mechanical methods and continuum solvent models, microscopic free energy molecular dynamics techniques, and compilation of known experimental data. Theoretical calculations using standard parameterization schemes of solvent models have predicted negative values of ΔGₛ(C₆₀) whereas application of the revised parameters, that take into account special features of carbon structures, shifts the computed ΔGₛ(C₆₀) to positive values. Reasonably accurate estimates of the hydration free energies of the neutral and anionic states of functionalized fullerenes were obtained from the generalized Born method. The described data have shown that the calculations of hydration thermodynamics of fullerenes apparently require separate parameterization for the carbon atoms met in these nanomolecules.

1. Introduction

Fullerenes are a widely studied carbon nanomolecules that find numerous chemical and biological applications as separate species and as functional fragments in complex molecular constructs [1−3]. The numerous practical applications of fullerenes determine significant interest in the rational understanding and theoretical prediction of the properties of these molecules in condensed phase and particularly in the aqueous biomolecular medium. The carbon atoms in fullerenes are interconnected in the networks of fused rings and form closed strained spheroid cages lined with the π-electrons of quasi-aromatic centers. Such electron structure and large molecular volume determine specific properties of these molecules in solution. Pristine fullerene have good solubility in the aromatic hydrocarbon, much lower solubility in the aliphatic hydrocarbons and polar organic solvents, and zero solubility in water under usual conditions [4−6]. However, the functionalized derivatives of fullerenes can be soluble in water [3]. In view of the active studies of the biologically active compounds containing pharmacophore of fullerene C₆₀, it is important to have good understanding of the mechanisms of fullerene−water interactions.

Modern theoretical chemistry methods can provide useful and accurate information about different physico-chemical characteristics of molecular systems. The computational techniques can especially be helpful in the studies of molecular properties that are difficult to measure experimentally. Exactly this situation exists for fullerenes where experimental data on hydration thermodynamics are insufficient or not available. The computational modelling of the molecules in solution generally involve either quantum mechanical (QM) calculations with the polarizable continuum model (PCM) of solvent or molecular dynamics (MD) force field (FF) free-energy simulations of microscopic systems.
In this work we consider the calculations of the thermodynamic potentials of fullerene $C_{60}$ in water using the quantum mechanical PCM and free energy MD FF computational approaches. The influence of the special separate parameterization for the fullerene nanomolecules on the results of the modelling is reviewed. In addition, the hydration free energies of selected pentasubstituted amino acid derivatives of fullerene in neutral and multi-charged states are examined using the density functional theory (DFT) calculations with the polarizable continuum and generalized Born models of solvent.

2. Free-energy molecular dynamics simulations of fullerene $C_{60}$ in water

The MD simulations of hydrated fullerene were conducted using the microscopic models with the minimal image periodic boundary conditions (PBC) and spherical boundary conditions (SBC) (Figure 1). The potential energies of the system were computed using the OPLS force field with the OPLS-AA [7] and Bojan–Steele (B-S) [8] parameters for carbons of $C_{60}$ and the TIP3P FF parameters for explicit water molecules. The OPLS-AA FF parameters are focused on reproduction of the properties of liquids while the B-S carbon–water FF parameters are based on the data for graphite–oxygen interactions. The fullerene atoms were not restrained in the PBC MD simulations whereas the treatment of solute–solvent system in the SBC simulations involved using the artificial spherical cavity for fullerene. The harmonic restraining potential applied to water molecules in order to create empty spherical cavity was derived using the radial distribution function of water molecules around fullerene [9]. The more detailed description of the FF for fullerene and simulation setup can be found in [9,10].

The hydration free energy of fullerene $\Delta G_d(C_{60})$ was determined from the alchemical transformation of fullerene into a dummy cage molecule $C_{60} \rightarrow d_{60}$ in water. The end-point $d_{60}$ particle does not interact with the surrounding medium. The resulting free energy of mutation was calculated using the statistical mechanical free energy perturbation (FEP) method [11]

$$\Delta G_{\text{mut,s}}(C_{60} \rightarrow d_{60}) = -RT \ln \left( e^{\frac{-\Delta U(r)/RT}{\Lambda}} \right).$$

(1)

Here, $\Delta U(r)$ is the perturbation potential, $r$ denote the vector of atom coordinates, $T$ is the absolute temperature, $R$ is the gas constant, $\langle \ldots \rangle$ is the ensemble average over configurational space of the reference state $\Lambda$. Only parameters for the non-bonded interactions in the solute topology were changed in the perturbed state. In case of the spherical model, the calculation of $\Delta G_d(C_{60})$ involved a correction $\Delta G_{\text{cav}}$ for the free energy of creation of the spherical cavity for $C_{60}$

$$\Delta G_{\Lambda}(C_{60}) = \Delta G_{\text{cav}} - \Delta G_{\text{mut,s}}(C_{60} \rightarrow d_{60}).$$

(2)

The cavitation free energy $\Delta G_{\text{cav}}$ of $C_{60}$ was calculated using scaled particle theory [12]. For calculation of $\Delta G_d(C_{60})$ we used the cavity radius $R_{\text{cav}} = 5.414$ Å which renders $\Delta G_{\text{cav}} = 144.6$ kJ mol$^{-1}$.
$R_{av}$ was determined as the sum of the distance of fullerene carbons to the center of C$_{60}$ and the calibrated atom radius of atoms C [10].

The FEP/MD calculations using the OPLS- AA and B-S FF parameters for carbons predict sufficiently differing values of $\Delta G_s(C_{60})$ [10]. The $\Delta G_s(C_{60})$ free energies calculated using OPLS-AA have negative values of $-50.2\pm2.6$ kJ mol$^{-1}$ for the SBC and $-50.3\pm1.1$ kJ mol$^{-1}$ for the PBC model. In case of B-S FF, the computed free energies $\Delta G_s(C_{60})$ are positive and equal $33.6\pm1.7$ and $20.1\pm0.7$ kJ mol$^{-1}$ for the for SBC and PBC models, respectively. We can see in this connection that the 7.5-ns PBC multi-step FEP and 3-ns SBC single-step FEP calculations yield quite coherent results. The calculated with the B-S FF free energies well agree with the data from other MD simulations [13,14]. The FEP/MD simulations have also shown that $\Delta G_s(C_{60})$ is determined by the balance between large negative enthalpy and entropy terms [10].

3. Quantum mechanical modelling of fullerene C$_{60}$ and its derivatives in water

3.1. QM PCM calculations of the hydration free energy of fullerene

The quantum mechanical calculations of hydration free energies $\Delta G_s$ were carried out using the ‘united atom’ (UA) [15] and ‘standard model density’ [16] versions of PCM in Gaussian. The computed $\Delta G_s$ for the solute in water cavity include electrostatic $\Delta G_{el}$ and non-polar $\Delta G_{np}$ contributions

$$\Delta G_s(C_{60}) = \Delta G_{el}(C_{60}) + \Delta G_{np}(C_{60})$$  \hspace{1cm} (3)

The electrostatic contribution $\Delta G_{el}$ was obtained from the quantum mechanical calculation using integral equation formalism with the solvent reaction field included in solute Hamiltonian. The non-polar term $\Delta G_{np}$ was determined using empirical schemes. In the PCM(UA) method, $\Delta G_{np}$ includes the solvent cavity $\Delta G_{av}$, electron dispersion $\Delta G_{disp}$ and repulsion $\Delta G_{rep}$ contributions [15]. In the PCM(SMD) method, calculation of $\Delta G_{np}$ is based on the solvent-accessible surface area and surface tension parameters [16]. The calculated $\Delta G_s$ depend on the parameters of PCM for the solute–solvent interactions and on the level of theory employed. The cavity polarizable dielectric is assembled from the overlapping spheres around the atomic centers of the solute. The atomic radii, that define the solvent cavity in PCM, are of crucial importance for obtaining accurate $\Delta G_s$ values. For instance, the computed $\Delta G_s(C_{60})$ changes from negative to positive values upon increase of the atomic radius $R(C)$ (Fig. 2a). It should be mentioned in this respect that the original UA and SMD models do not contain separate parameters for the atom types met in these nanomolecules.

The rational approach to estimate atomic cavity radius of the fullerene carbons $R(C)$ in PCM considered several possible ways to derive $R(C)$ for fullerene C60 [17]. This involved quantitative description of pyramidal hybridization of carbons in fullerene C$_{60}$ and derivation of atomic radii from the constant electron density surfaces (Figure 2b) around the solute. The computed isodensity surfaces qualitatively support using spherical cavity in the MD SBC simulations of C$_{60}$ (Figure 2b). The atomic radii were also calibrated using the thermodynamic cycle of the pK$_s$ changes for dihydrofullerene and saccharin in DMSO and in a toluene–DMSO mixture. Overall, all three applied criteria have shown that the $R(C)$ value in C$_{60}$ exceeds the standard value of 1.725 Å for the aromatic carbon in the UA model [17]. The derived $R(C)$ values from the calibration for pK$_s$ are 1.842 Å for the HF method and 1.864 Å for DFT B3LYP [16].

The calculated values of $\Delta G_s(C_{60})$ are displayed in Table 1. The DFT B3LYP PCM(UA) calculations predict negative $\Delta G_s$ of C$_{60}$ of $-3.7$ kJ mol$^{-1}$ for standard value of $R(C)$ in the united atom model and positive free energy $\Delta G_s = 14.8$ kJ mol$^{-1}$ for the recalibrated for fullerene $R(C)$. The PCM(SMD) method produces negative free energy $\Delta G_s = -31.0$ kJ mol$^{-1}$. The largest contribution to $\Delta G_s(C_{60})$ comes from the non-polar term although there is also present a small polar contribution (Table 1).
Figure 2. a) The hydration free energy $\Delta G_s(C_{60})$ and its contributions as a function of the carbon radius $R(C)$ in the PCM(UA) scheme, b) the 0.002 e/a$_0^3$ contour isodensity (mesh) and solvent accessible (solid) surfaces of fullerene C$_{60}$. The calculations at the HF/6–31G(d) level of theory.

Table 1. The DFT PCM and GB–SA calculations of the hydration free energy of fullerene C$_{60}$. Calculations at the B3LYP/6–31G(d)/B3LYP/6–31+G(d,p) level.

| Model          | Energy contributions, kJ mol$^{-1}$ |
|----------------|-------------------------------------|
|                | $\Delta G_{el}$ | $\Delta G_{np}$ | $\Delta G_s(C_{60})$ |
| PCM(UA, $R(C)$=1.725 Å) | -2.8             | -0.9             | -3.7             |
| PCM(UA, $R(C)$=1.864 Å) | -1.3             | 16.0             | 14.8             |
| PCM(SMD)       | -8.9             | -22.1            | -31.0            |
| GB–SA          | 0.0              | 17.3             | 17.3             |

3.2. Generalized Born calculations of hydration of fullerenes

The free energies of solvation were also determined from the calculations of the solute interactions with a continuum water dielectric using generalized Born (GB) treatment. The GB approach finds broad applications in the FF and QM studies of solvation of small molecules and proteins [18,19]. In this work, the calculations of $\Delta G_s$ of fullerenes were performed by means of the GB method with the fixed atomic charges and with linear dependence of the non-polar $\Delta G_{np}$ contribution to the solvent-accessible surface area (SA) method [18]. We consider Eq.(3) where the polar $\Delta G_{el}$ and non-polar $\Delta G_{np}$ terms are expressed as the sums over solute atoms

$$\Delta G_{el} = -166(1-1/\varepsilon) \sum_i \sum_j q_i q_j f_{ij}^{GB},$$

$$\Delta G_{np} = \sum_i \sigma_i S_A.$$

In these equations, $q_i$ are the partial atomic charges, $f_{ij}^{GB}$ is the function of interatomic distances and the Born radii of atoms, $S_A$ is the solvent-accessible surface area of atom $i$, $\sigma_i$ is an atomic solvation parameter, $\varepsilon$ is the dielectric constant of water [18]. In the calculations of $\Delta G_s$ with Eq. (3–5), we have used the Amber-95 atomic radii and $\sigma_i$=30 J mol$^{-1}$ (for all atom types). The employed Mulliken charges $q_i$ were determined in gas phase at the B3LYP/6–31G(d)//B3LYP/6–31+G(d,p) level. The side groups in the studied compounds 1,2 (Figure 3a) were considered in a single extended conformation optimized in gas phase for uncharged state. The anionic states correspond to deprotonation of the carboxylic acid of side groups. In 2, the oxidation of the more distant from the
fullerene core −COOH group was considered. In computations of hydration free energies we used the partial atomic charges from the QM calculations, but the partial charges from the standard FFs can also be used in GB–SA to assess \( \Delta G_s \) of the model structures.

![Figure 3. a) Chemical formulas of the studied fullerene derivatives, b) \( \Delta G_s \) in water of the neutral and multi-anionic states of 1, 2 from the GB–SA and PCM(SMD) calculations. The numbers at the plots indicate the total electronic charge of the molecules at the corresponding points.](image)

The computed GB–SA value of \( \Delta G_s(C_{60}) \) is 17.3 kJ mol\(^{-1}\) (Table 1) that is close to the result from the PCM(UA) model with the re-calibrated carbon radius. The hydration free energy of \( C_{60} \) in the GB–SA method totally comes from non-polar contribution (Table 1). We have also explored energetics in water for pentasubstituted amino acid fullerene derivatives 1, 2 (Figure 3a). Hydration thermodynamics of these compounds are determined by the solute–water interactions with the central hydrophobic cage of fullerene and the peripheral hydrophilic groups. Step by step deprotonation of the side groups is accompanied by a steep reduction of \( \Delta G_s \) (Figure 3b). Good linear correlations (with the slopes of the plot and correlation coefficients about unity) are observed between the data from the GB–SA model and more accurate PCM(SMD) method (Figure 3b). These results show that despite the simplified treatment of the solute–solvent system the GB–SA method can be useful in the studies of hydration of complex nanomolecules containing fullerene fragments.

4. Compilation of experimental data
The hydration free energy of fullerene \( C_{60} \) has not been measured experimentally (to our knowledge) due to extremely low solubility of this compound in water [5]. However, there are estimates of the aqueous solubility \( S_{aq}(C_{60}) \) of fullerene \( C_{60} \) based on the Hildebrand–Scatchard model and parabolic extrapolation of the solubilities in normal alcohols [5]. The reported value of \( S_{aq}(C_{60}) \) is 1.3\times10^{-11} \text{ ng m}^{-1} [5,6]. There are also experimental data for the vapour pressure \( P_{vap}(C_{60}) \) of pure fullerene in equilibrium between the pure solid and gas phase (\( \log P_{vap}(C_{60}) = -22.6 \)) [6]. Consideration of the triple system ‘solid \( C_{60} \) – gas state of \( C_{60} \) – water solution of \( C_{60} \)’ allows to determine \( \Delta G_s(C_{60}) \) from the thermodynamic data for transitions solid↔gas and solid↔water. The standard hydration free energy \( \Delta G_s^\circ \) of fullerene was determined [10] from the equation

\[
\Delta G_s^\circ(C_{60}) = 2.303RT \times \left( \log \left( \frac{P_{vap}(C_{60})}{P^*} \right) - \log S_{aq}(C_{60}) \right).
\]

In this equation we use standard conditions of \( T = 298 \text{ K} \) and 1 M concentration and the pressure \( P^* \) of an ideal gas of 24.45 atm. The described treatment predicts negative value of \( \Delta G_s^\circ(C_{60}) = -24.5 \text{ kJ} \)
mol$^{-1}$ which follows from the difference of large negative values for log$S_{aq}(C_{60})$ and log($P_{aq}(C_{60})/P^0$) in Eq. (6). However, it was noted that additional consideration of the fullerene size effect via the Flory–Huggins approach reduces the calculated aqueous solubility $S_{aq}(C_{60})$ of fullerene by several orders of magnitude [5]. The estimated from the data of [5] value of log$S_{aq}(C_{60})$ equals in that case $−28.7$. The calculation using this value of log$S_{aq}(C_{60})$ in Eq. (9) shifts Δ$G^\circ_{aq}(C_{60})$ to a positive value of 26.8 kJ mol$^{-1}$. Reverse calculations by Eq. (6) using the computed Δ$G^\circ_{aq}(C_{60})$ and experimental $P_{aq}(C_{60})$ predict extremely low values of $S_{aq}(C_{60})$ in accordance with known practical experience.

5. Conclusions
We discuss in this presentation the calculations of the hydration free energy Δ$G^\circ$ of fullerene $C_{60}$ using the ‘QM/implicit solvent model’ approach and the FF FEP/MD technique with explicit water molecules. The reliable and conclusive experimental data on Δ$G^\circ_{aq}(C_{60})$ are not available. Judging by the hydrophobic properties of this nanomolecule, it would be safe to expect a positive value of Δ$G^\circ_{aq}(C_{60})$. However, theoretical computations using standard parameterization schemes predict negative values of Δ$G^\circ_{aq}(C_{60})$. The application of the revised parameters, that were adjusted to account for some special features of carbon structures, have shifted the computed Δ$G^\circ_{aq}(C_{60})$ to the range of positive values. The found variations of Δ$G^\circ_{aq}(C_{60})$ arise mainly from the non-polar contributions in the models considered. The re-calibrated parameters of the PCM(UA) model had been successfully employed in the calculations of the absolute pK$_a$ values of substituted hydrofullerenes [20]. It was also found in this work that reasonably accurate estimates of the hydration free energies of the neutral and charged states of functionalized fullerenes can be obtained from the generalized Born method. In total, the described calculations have shown that correct calculations of hydration thermodynamics require separate parameterization for the atom types met in nanomolecules.

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