Thermodynamics of association of water soluble fullerene derivatives [C₆₀(OH)_n, n = 0, 2, 4, 8 and 12] in aqueous media

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Abstract. The thermodynamics of association of fullerene [C₆₀] and water-soluble fullerene derivatives, *i.e.*, fullerols [C₆₀(OH)_n, where, n = 2, 4, 8, 12] in aqueous solutions have been studied using molecular dynamics simulations. The potentials of mean force (PMFs) bring out the tendency of aggregation of these nanostructures in water. The extent of hydroxylation seems to have a minor effect on the depth of the contact minima (the first minimum in the PMFs). The positions of the subsequent minima and maxima in the PMFs change with the size of the solute molecules. Higher stability of the contact state of highly hydroxylated fullerols is due to the van der Waals interactions whereas intermolecular solute-solvent hydrogen bonding nearly flattens the PMFs beyond the 2nd minima for higher fullerols. The solvent contributions to the PMFs for all the solute particles studied here are positive. Entropic and enthalpic contributions to the association of solute molecules are calculated in the isothermal-isobaric (NPT) ensemble. We find that the contact pair formation is governed by entropy with the enthalpic contributions being highly unfavorable, whereas the solvent assisted and solvent separated configurations show entropy-enthalpy compensation.

Keywords. Fullerene; fullerol; potentials of mean force; entropy; enthalpy.

1. Introduction

Fullerene C₆₀ and its water soluble derivatives have been the subject of intense research, both for their unique chemistry and technological significance.^{1–7} Fullerene and its aqueous solutions are being used extensively in biochemistry, molecular sensing devices,^{8–11} for inhibiting HIV protease,^{12,13} cleaving DNA,¹⁴ delivering drugs¹⁵ and in environmental science. They are also being used as light-activated antimicrobial agents.¹⁶ Since fullerenes are considered for applications related to biological activity, a detailed understanding of solvation structures is crucial. In the case of fullerene, solute-solvent interactions are dominated mostly by van der Waals forces. One of the major issues that hampers the application of fullerenes in the biomedical and medicinal field is their poor solubility in aqueous media which is related to its hydrophobic character. Fullerenes are soluble in organic solvents (*e.g.*, toluene, piperidine, pyrrolidine, etc.)¹⁷ but these solvents are not appropriate to be introduced into biological systems; so several ways have been found to solve this problem of the low solubility of fullerene in aqueous media.

Thus for fullerenes to be used in biomedical applications, its hydrophobic character must be reduced and functionalization of fullerene surface with hydrophilic substituents is the easiest way to enhance its solubility in aqueous media. There are many hydrophilic substituents which have been attached to the fullerene surface to increase its solubility in water.^{18–22} According to the results obtained on the solubility of fullerols in aqueous media, Chiang and co-workers²³ reported that fullerols with less than 12 hydroxyl groups exhibit very poor water solubility, whereas fullerols with more than 16 hydroxyl groups are highly soluble in water.^{24,25} Solubility of fullerols in aqueous media is dependent on the number of hydroxyl groups as well as the position of the hydroxyl groups.^{26,30,31} Labille *et al.*, observed that pristine fullerene can acquire sufficient hydrophilic character by surface hydroxylation in the presence of a solvent.³² These are some of the most interesting derivatives in fullerene chemistry. They have found applications in aqueous solution chemistry, electrochemistry and biochemistry. Their antitumor, antioxidant, antimicrobial and anticancer activities have been reported in the literature.^{32–38} Fullerols are also used in pharmaceuticals,³⁹ polymer-based solar cells^{40,41} drug delivery,⁴² proton conductors^{43,44} and electrodeposited

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films.⁴⁵ Their high water solubility, dispersing nature as single carbon nanoparticles and varied biochemical properties are very attractive from the viewpoint of materials chemistry. Therefore, it is important to acquire a deep knowledge of the solvation structure of such macromolecules. Structural arrangements and dynamics of fullerene in solutions via molecular dynamics simulations have been studied in detail by many authors.^{7,46–70} The association of fullerene in aqueous media is dominated by the strong van der Waals attraction between the fullerenes.^{46–49} Li *et al.*, studied the repulsive solvent-induced interaction between C₆₀ fullerenes in water.^{46,47} Cao *et al.*, performed molecular dynamics simulation of fullerene C₆₀ in ethanol solution.⁶⁷ MD simulations of fullerene in aqueous solutions are studied in detail by Choudhury and co-workers.^{50–52} Makowski *et al.*, determined the potential of mean force for the association of two fullerene molecules in TIP3P water at room temperature.⁵³ Fileti and co-workers studied the solvation of fullerene in different solvents.^{7,54–56} A large number of theoretical,^{71,72} computational^{7,46–70} and experimental studies,^{73,74} have been devoted to the understanding of structural properties of fullerenes in different solvents. Although in the past few decades, several works have been reported to study the formation mechanism, structural and electronic properties of fullerols and association of fullerols in aqueous media have not been studied in detail.^{30,75–88} The interactions of fullerene and fullerols with solvents (particularly water) is of prime interest because in many applications such as optical, electrochemical, medicinal and biochemical field water is used as the dominant solvent. The biological and medical interactions and effects of fullerenes and modified fullerenes are dependent upon the nature of their hydrophobic hydration and hydrophobic interaction in aqueous environments. There are only few experimental studies on the solubility of fullerols in aqueous media. Recently, we have studied the hydration thermodynamics of fullerols in water as a function of the number of hydroxyl groups. Molecular dynamics, in this case, is a powerful tool to predict molecular and thermodynamic properties of fullerols in solution. It can be used to describe the hydration and association behavior of fullerols, allowing us to characterize the microscopic structure of solvation around the solute. The association of modified fullerene *i.e.*, fullerols in water is not explored much. Because of surface hydroxylation in fullerols, one might expect a different behavior of these hydrophobic-hydrophilic solutes in water. In order to gain an insight of the association of fullerols in aqueous media, we have performed computer simulations of fullerols in aqueous media. Aiming at the characterization of fullerol association in water, we determine

the potentials of mean force (PMFs) for each pair of fullerol as a function of the distance between the center of mass (COM). We would like to know how the association of fullerols changes as a function of the number of hydroxyl groups attached to the fullerene surface. In the present work, we have studied the binary aggregation of fullerene and C₆₀(OH)_n [n = 2, 4, 8, 12] in water. The systems under study are shown in Figures 1(a) to 1(e). Section 2 describes the methodology used in the present work. Results and discussions are given in Section 3, followed by conclusions in Section 4.

2. Computational models and methodologies

The mean forces between two solute molecules in the present work are calculated using constrained molecular dynamics. In this method, two solute molecules [compound (i) to (v)] are held at a fixed separation by imposing constraints on them. The initial configurations of the system are generated using Packmol.⁸⁹ Each solution is prepared with 2137 water molecules and two solute molecules [compounds (i) to (v)] in cubic boxes of box length 40 Å, using periodic boundary conditions. The classical molecular dynamics simulations for these systems are performed using the GROMACS package (version 4.5.4).⁹⁰ The extended simple point charge (SPC/E)⁹¹ potential model is used to describe the interactions of the water molecules. In the case of solute molecules, the force field parameters are taken from GROMOS53a6 force field.⁹² The geometrical and force field parameters of the solvent molecule are given elsewhere.³¹ All the bonds of the solute and solvent molecules were kept fixed using the LINCS algorithm.⁹³ Thus, the solute molecules were treated as rigid species in our simulations. To model all the solute-solute, solute-solvent and solvent-solvent interactions we have adopted the pair-wise additive potentials, $U_{ij}(r)$ as a sum of short range Lennard-Jones and long range Coulombic terms. The potential is represented as,

$$U_{ij}(r) = \frac{A_{ij}}{r^{12}} - \frac{B_{ij}}{r^6} + \frac{q_i q_j}{r} \quad (1)$$

where, i and j denote a pair of interaction sites on different molecules, q_i is the charge located at site i and q_j is the charge located at site j and r is the site-site separation. The combination rules used for the Lennard-Jones cross interactions are as follows,

$$A_{ij} = 4 \times (\varepsilon_{ij}) \times (\sigma_{ij})^{12} \quad (2)$$

$$B_{ij} = 4 \times (\varepsilon_{ij}) \times (\sigma_{ij})^6 \quad (3)$$

whereas, ε_{ij} and σ_{ij} are calculated using the Lorentz-Berthelot mixing rules.⁹⁴

$$\varepsilon_{ij} = (\varepsilon_i \times \varepsilon_j)^{1/2} \quad (4)$$

$$\sigma_{ij} = \left(\frac{\sigma_i + \sigma_j}{2} \right) \quad (5)$$

Figure 1. Systems under study: (a) C₆₀, (b) C₆₀(OH)₂, (c) C₆₀(OH)₄, (d) C₆₀(OH)₈, and (e) C₆₀(OH)₁₂.

As a general trend, half of the box length is used as the cut off for Lennard–Jones forces. The long range electrostatics were treated using the particle mesh Ewald (PME).⁹⁵ A cut off of 1.5 nm is used for non-bonded van der Waals interactions. The edge effects are minimized using the periodic boundary conditions (PBC) along with the minimum image criterion.⁹⁶ The neighbor list was updated every 10 steps. The temperature of the systems was kept constant at 298 K using the velocity rescaling thermostat⁹⁷ (coupling constant of 0.1 ps) and the pressure was fixed at 1 bar using the Berendsen barostat (coupling constant of 1.0 ps).⁹⁸ Leapfrog algorithm with a time step of 2 fs was used to solve the classical equations of motion.⁹⁹ To obtain quantitative information about the association process of fullerene and fullerols in water, we calculated potentials of mean force (PMF). PMF describes how free energy between two solute molecules varies as we increase the distance between their centers. We used the constrained mean force approach which was proposed by Ciccotti and his co-workers to calculate the PMFs. This technique requires a number of constraints be applied at specific positions on the reaction coordinate (in this case the distance between the centers of mass of fullerols) so that all regions are appropriately sampled. Each specific constraint position consists of a simulation window. In this work, for each solute pair, we conducted a series of 111 simulation windows, where the

separation between the center of mass was increased from 0.9 to 2.00 nm with 0.01 nm increments. Each simulation was 15 ns long, giving a total time of 1665 ns for each solute pair. For simulations in vacuum (*i.e.*, for the direct angle averaged pair potential), we use only two fullerenes/fullerols. Parrinello-Rahman barostat¹⁰⁰ was used for the calculation of the mean force. The individual PMFs were calculated by integrating the mean forces over the solute separation distance, while the entropic force due to the increase in phase space with solute separation was added to the mean force after the integration. Uncertainties in the mean force values were estimated from the limiting values of the block averages. The mean force is the sum of the solute-solute direct force and ensemble average of the solute-solvent force. That is,

$$F(r) = F_d(r) + \Delta F(r) \quad (6)$$

where, $\Delta F(r) = \langle F(r, t) \rangle$ and $F(r)$ is the mean force between solutes at distance r . The angular brackets denote the ensemble average.

During the constrained molecular dynamics simulations of solute molecules at infinite dilution, the distance between the centres of mass of solute molecules is kept constant. However, the individual Cartesian coordinates of the solute molecules are not fixed. With this procedure, two non-interacting masses will already experience an entropic force that pulls them apart,

as the available phase space depends on the length of the constraint r . The entropic force due to the increase in phase space with solute-solute separation is taken care of by adding the logarithmic term.^{101–103} The entropic force is given by,

$$-\frac{d}{dr} \left[-k_B T \log(4\pi r^2) \right] = \frac{2k_B T}{r} \quad (7)$$

where, k_B is the Boltzmann constant and T is the temperature. To obtain the effective pair potential between two solute molecules, we have to add the entropic term to the constraint force,

$$\frac{-dW(r)}{dr} = F(r) - \frac{2k_B T}{r} \quad (8)$$

Integration of equation (8) yields the potential of mean force, $W(r)$,

$$W(r) = W(r_0) - \int_{r_0}^r F(r) dr + 2k_B T \ln \left(\frac{r}{r_0} \right) \quad (9)$$

The choice of $W(r_0)$ is required to be done in such a way that the calculated mean force potential matches the macroscopic Coulombic potential at long distances.

$$W(r_0) = \frac{q_i \times q_j}{\epsilon_r r_0} \quad (10)$$

where, ϵ_r is the dielectric constant of the solvent. For Coulombic systems, we need to use equation 10. For uncharged solutes, the value of $W(r_0)$ is already close to zero beyond $r_0 = 2.0$ nm. The value of r_0 is taken to be 2 nm for all the systems. The dependence of the results on the choice of r_0 is very weak. The depths of PMFs change by ~ 0.1 kJ/mol; the solute-solute association (positions of contact minima, solvent assisted minima, solvent separated minima, barrier heights) remains the same and is independent of the choice of r_0 .

3. Results and Discussion

3.1 Potentials of mean forces (PMFs)

The aggregation of fullerene and other related nanoparticles in water has been examined in several earlier studies.^{7,46–70} To investigate the stability of aggregated fullerenes and fullerols in water, we have calculated the potentials of mean force (PMFs) between the centers of masses (COMs) of these molecules. These are shown in Figure 2. The relative stabilities of the solute molecules at different intersolute separations are reassessed by trailing the trajectories. In these simulations, the constraint between the solute molecules is released at various intersolute separations for a fixed period of time (5 ns) and the trajectory is expressed in terms of the residence time vs. interionic separation r . The residence time is an approximate measure of the length of time that the solute molecules reside at a particular distance.

Figure 2. Potentials of mean force between the COMs of compounds (a) C_{60} , (b) $C_{60}(OH)_2$, (c) $C_{60}(OH)_4$, (d) $C_{60}(OH)_8$, and (e) $C_{60}(OH)_{12}$ in water.

The residence time is defined as,

$$Residence\ time(r) = \frac{\Delta t}{n_T} \left(\sum_{l=1}^{n_T} \sum_{i=1}^N \delta_{r,r(i\Delta t)} \right) \quad (11)$$

where n_T is the total number of initial configurations (111 in number), ranging from an initial distance $r_{initial} = 0.90$ nm to 2.00 nm with a constant interval of 0.01 nm, Δt is the simulation time step, here 0.25 fs, N is the number of steps (20000000) in a given simulation, and $\delta_{r,r(i\Delta t)}$ is the Kronecker delta which is equal to 1 whenever $r = r(i\Delta t)$ and zero otherwise. The summation over l corresponds to the initiation of the trajectories starting at different initial values of the ion-ion separation. The residence times of solute molecules [compound (i) to (v)] are shown in Figure 3.

PMFs are characterized by three distinct minima. In contact configurations (first minima), neither a solvent molecule nor even a part of it comes in between the solute molecules. In solvent assisted configurations (second minima), a part of one or more solvent molecules comes in between the solute molecules. In solvent separated pairs (third minima), the first solvation shells of both the solutes do not share any common solvent molecule. A representative picture of these three different states is given below (Figure 4).

We have calculated uncertainties in PMF curves in several cases. The differences between PMFs obtained from three sets of 5 ns simulations are less than 0.1 kJ/mol. The locations of the maxima and minima of PMFs of systems under study are given in Table 1. The barrier heights from contact minima and solvent assisted minima to the first transition state are given in Table 2.

Figure 3. Residence times of pairs of molecules (a) C_{60} , (b) $C_{60}(OH)_2$, (c) $C_{60}(OH)_4$, (d) $C_{60}(OH)_8$, and (e) $C_{60}(OH)_{12}$ in water. Insets in the Figure shows the region corresponding to the solvent assisted (bottom inset) and solvent separated (top inset) configurations.

The depth of the first (contact) minimum between the solute pairs provides a measure of the solvophobic hydration in water.¹⁰⁴ Both the position and strength of interaction of C_{60} molecules in water are in good agreement with the previous results obtained by Scheraga *et al.*⁵³ The first minimum in the PMF for C_{60} occurs near 1.00 nm (between centers of mass two solute particles),

which is comparable to the previous PMF calculations of fullerene in water and ethanol.⁶⁹ Locations of the first minima shift to larger distances as we go from C_{60} (1.00 nm) to $C_{60}(OH)_{12}$ (1.04 nm). The depths of contact minima change from -15.4 to -16.9 kJ/mol. From Figure 2 we see that as we go from fullerene to water soluble fullerene derivatives, aggregated conformations become marginally more stable. This is because of the dominance of the van der Waals interactions rather than hydrogen bonding interactions between $C_{60}(OH)_n$ s (as will be seen in a later section). As noticed in Figure 2, the increase in the number of hydroxyl groups in the fullerene surface results in a much slower increase in the depth of the contact minima than could be anticipated on the basis of increasing hydrophilic regions.

The first maximum in the PMF curves between the contact and solvent-separated minima is referred to as the transition state (TS) and it is observed in all cases. As seen from Figure 2, the positions and heights of these maxima change according to the size of the solute. There is a significant shift in the position of the first transition state as we go from C_{60} (1.20 nm) to $C_{60}(OH)_{12}$ (1.32 nm). Transition states also get stabilized as we go from C_{60} (2.2 kJ/mol) to $C_{60}(OH)_{12}$ (-0.5 kJ/mol).

Apart from the first minima, there are two additional shallow minima at distances 1.33 nm and 1.61 nm respectively. The second minimum which occurs

Figure 4. Representative pictures of contact minima, solvent assisted minima and solvent separated minima and transition states.

Table 1. Characteristics of PMFs ($W(r)$ in kJ mol^{-1}) of solutes.

Solute	$r_{\min 1}/\text{nm}$	$W(r)$	$r_{\max 1}/\text{nm}$	$W(r)$	$r_{\min 2}/\text{nm}$	$W(r)$	$r_{\max 2}/\text{nm}$	$W(r)$	$r_{\min 3}/\text{nm}$	$W(r)$
C_{60}	1.00	-15.4	1.21	2.2	1.33	-1.9	1.48	0.52	1.62	-0.74
$\text{C}_{60}(\text{OH})_2$	1.01	-16.3	1.23	0.8	1.34	-1.4	1.49	0.37	1.62	-0.67
$\text{C}_{60}(\text{OH})_4$	1.02	-16.5	1.25	0.3	1.34	-1.1	1.50	0.29	1.62	-0.62
$\text{C}_{60}(\text{OH})_8$	1.03	-16.6	1.28	-0.3	1.35	-0.5	1.54	0.21	1.64	-0.18
$\text{C}_{60}(\text{OH})_{12}$	1.04	-16.9	1.34	-0.5	1.46	-0.6	1.64	-0.21	1.82	-0.04

Table 2. Barrier heights for contact minima and solvent assisted minima ΔE (in kJ/mol).

Solute	ΔE (TS1 - Contact minima)	ΔE (TS1 - Solvent assisted minima)
C_{60}	17.6	4.1
$\text{C}_{60}(\text{OH})_2$	17.1	2.2
$\text{C}_{60}(\text{OH})_4$	16.8	1.4
$\text{C}_{60}(\text{OH})_8$	16.3	0.2
$\text{C}_{60}(\text{OH})_{12}$	16.4	0.1

Table 3. The number of intermolecular water-fullerol hydrogen bonds and fullerol-fullerol hydrogen bonds.

Solute	Solute	1st minima	1st maxima	2nd minima	2nd maxima	3rd minima
Solute-Solute	$\text{C}_{60}(\text{OH})_2$	0.006	0.005	0.004	0.0	0.0
	$\text{C}_{60}(\text{OH})_4$	0.034	0.014	0.006	0.0	0.0
	$\text{C}_{60}(\text{OH})_8$	0.044	0.024	0.002	0.0	0.0
	$\text{C}_{60}(\text{OH})_{12}$	0.144	0.088	0.002	0.0	0.0
Solute-Solvent	$\text{C}_{60}(\text{OH})_2$	1.146	1.131	1.181	1.178	1.192
	$\text{C}_{60}(\text{OH})_4$	2.086	2.041	2.156	2.144	2.178
	$\text{C}_{60}(\text{OH})_8$	3.978	3.721	4.004	3.996	4.108
	$\text{C}_{60}(\text{OH})_{12}$	6.467	6.312	6.848	6.541	6.872

around 1.32 to 1.44 nm, is commonly known as the solvent assisted minimum. The depths and positions of solvent assisted minima follow the same trend as in contact minima. The depth of the solvent assisted minimum changes from -1.9 (C_{60}) to -0.6 kJ/mol ($\text{C}_{60}(\text{OH})_{12}$). The depths of solvent assisted minima indicate that the formation of hydration shell between the solute molecules is more favorable for fullerene than that for fullerols. The third minima that occur near 1.62 nm for C_{60} , $\text{C}_{60}(\text{OH})_2$ and $\text{C}_{60}(\text{OH})_4$ are the solvent separated minima. For the other two solutes, the third minima are very shallow. For solvent separated minima, the depths do not change significantly [-0.74 kJ/mol (C_{60}) and -0.62 kJ/mol ($\text{C}_{60}(\text{OH})_4$)]. It is clear from the above figure that contact minima are more stable than solvent assisted minima or solvent separated minima.

From Table 2, it is seen that the energy difference between contact minima and first transition states

is more than that between solvent assisted minima and the first transition states. Thus, the contact minimum is the most favorable configuration for fullerene and fullerols. It is also seen that the transition barriers from the contact configurations to the solvent separated configurations are not affected much by the addition of $-\text{OH}$ groups on fullerene. This is due to the dominance of the solute solvent interactions over solute solute interactions as described below.

Hydrogen bonding between solute-solute and solute-solvent at various intersolute separations can be used to explain the stability of solvent assisted and solvent separated configurations of fullerols in aqueous media. The total number of intermolecular water-fullerol hydrogen bonds and fullerol-fullerol hydrogen bonds and the average number of hydrogen bonds in the bulk are given in Table 3.

From Table 3, we note that for fullerols with n less than 12, there are hardly any solute-solute hydrogen bonds. It is also seen that the intermolecular solute-solute hydrogen bonding which is of some significance for $n = 12$ fullerol, decreases from contact configuration to solvent assisted configurations (from 0.144 to 0.002 in the case of $C_{60}(OH)_{12}$). In the solvent separated configurations, when the solutes are far away from each other, there are no intermolecular hydrogen bonds formed between solutes, instead, the shell water molecules are now rearranged in a lower energy state forming hydrogen bonds with the solute molecules.

For all the solute molecules, the number of solute-solvent hydrogen bonds increases with increasing number of hydroxyl groups. Of interest is that these numbers show small but significant fluctuations as we move from the contact states to solvent separated states. The number of hydrogen bonds in the desolvation barrier is always less compared to those in the contact, solvent assisted or solvent separated configurations. As we go from contact configuration to the 1st transition state, the number of solute-solvent hydrogen bonding decreases and then it increases in the solvent assisted configuration. The intermolecular water-fullerol hydrogen bonding shows a decrease as we go from contact minima to 1st transition state. It increases by $\sim 7\%$ from 1st transition state to 2nd minima *i.e.*, solvent assisted minima and this increase in intermolecular hydrogen bonding results in the stability of solvent assisted configurations. The water molecules in the transition states are frustrated because of the enhanced solvent-solvent repulsion in the vicinity of the solutes (because of the partial vacuum created between the solutes) and hence they cannot form many hydrogen bonds with the neighboring water molecules. The numbers of intermolecular water-fullerol hydrogen bonds, as well as fullerol-fullerol hydrogen bonds, increase with an increase in the number of hydroxyl groups. The gradual flattening of the PMFs for large n for $r > 1.4$ nm is due to the individual fullerols forming a nearly steady number of intermolecular hydrogen bonds.

From Figure 3, we observe that an intense peak appears near 1.00–1.04 nm in water, which confirms the presence of aggregated fullerol molecules *i.e.*, the contact minima. It is also observed that the position of the first peak shifts to the right with an increase in the number of $-OH$ groups. Two small broad peaks (near 1.33–1.46 nm and near 1.62–1.82 nm) in the residence times graphs are also seen. These confirm the presence of solvent assisted and solvent separated configurations. For $C_{60}(OH)_8$ and $C_{60}(OH)_{12}$, we see that the peaks corresponding to solvent assisted minima and

solvent separated minima are not very strong. This is because the stability of solvent assisted and solvent separated configurations in $C_{60}(OH)_8$ and $C_{60}(OH)_{12}$ is much less than the thermal energy at room temperature (~ 2.47 kJ/mol). The results obtained from residence times (unconstrained MD) are in agreement with the PMFs (constrained MD).

In order to investigate the extent of solvent contributions, we calculated the potential of mean force of two solute molecules in vacuum, and the solvent-induced contribution was obtained from subtracting the direct interaction in vacuum from the PMF of solute molecules in water. The results are shown in Figure 5.

It is seen that angle averaged direct potentials in vacuum have the characteristic shapes like the Lennard-Jones potentials. We see that depths and positions of the contact minima change according to the size of the solute. The deepest minimum in vacuum is observed for $C_{60}(OH)_{12}$, with the depth in potential being about -38.7 kJ/mol (at 1.03 nm). All the solute molecules have deeper minima in vacuum than in water. It is observed that solvent water has a positive contribution to the PMFs at contact distance for all the solute particles over the entire distance range. It can be seen that the contribution to the PMF by water is purely a repulsion effect which is in agreement with Smith's work on C_{60} in water,^{46,47} as well as Choudhury and Pettitt's work on graphene in water.^{105,106} The highest solvent contribution to the PMF is obtained in the case of the largest solute particle $C_{60}(OH)_{12}$. The depth of the minima of the vacuum PMFs and the depths of the contact minima of the PMFs in water are given in Table 4.

It is seen from the above table that solvent contribution to the PMF at the contact configuration increases with increase in the size of the solute and the direct interaction between the solute particles decreases with increase in the size of the solute. The direct interactions between the fullerene and fullerols cause the total PMFs at contact configuration to be negative despite the positive contribution from the solvent induced interactions. Since the solvent repulsions do not exceed the solute-solute attractions on increasing the number of $-OH$ groups, the contact configurations get stabilized by the addition of $-OH$ groups.

3.2 Entropy and enthalpy contribution to PMFs

We have analyzed the contributions of the thermodynamic parameters to the PMFs. The changes in entropy and enthalpy of the association have been calculated

Figure 5. Contributions to the potentials of mean force between the COMs of compounds (a) C_{60} , (b) $C_{60}(\text{OH})_2$, (c) $C_{60}(\text{OH})_4$, (d) $C_{60}(\text{OH})_8$, and (e) $C_{60}(\text{OH})_{12}$.

from the temperature derivatives of the PMFs via a finite temperature difference method.¹⁰⁷ PMF is the change in free energy to bring two solute molecules close together

from an infinite distance. In the NPT ensemble, the analogous quantity of potentials of mean force ($W(r)$) is the Gibbs free energy.

Table 4. Depths of the contact minima between the solute molecules in vacuum and in water and solvent contributions to the depths of the PMFs.

Solute	Contact minimum depth (kJ/mol)		
	<i>In vacuo</i>	In water	Solvent contribution
C ₆₀	−30.7	−15.4	15.2
C ₆₀ (OH) ₂	−32.7	−16.3	16.3
C ₆₀ (OH) ₄	−34.9	−16.5	18.3
C ₆₀ (OH) ₈	−36.6	−16.6	20.0
C ₆₀ (OH) ₁₂	−38.7	−16.9	21.8

$$G(N, P, T) = A(N, V, T) + PV$$

$$= -k_B T \ln Q(N, P, T) = W(r) \quad (12)$$

The method used to calculate the entropy and enthalpy of association is the finite temperature difference method based on the relationship,

$$\left(\frac{\partial \Delta G}{\partial T} \right)_{N,P} = -\Delta S \quad (13)$$

where, ΔS is calculated from free energy simulations at different temperatures i.e., it requires computation of potentials of mean force ($W(r)$) at three different temperatures. MD simulations at 278 K and 318 K are performed in the NPT ensemble to determine the entropy and the enthalpy of association.

$$-\Delta S(T) = \frac{\Delta G(T + \Delta T) - \Delta G(T - \Delta T)}{2\Delta T} \quad (14)$$

In this present study, values of T and ΔT are chosen to be 298 K and 20 K respectively. $\Delta H(r)$ i.e., enthalpy contribution is computed using the equation given below,

$$\Delta H(r) = \Delta G(r) + T\Delta S(r) \quad (15)$$

The entropic ($-T\Delta S(r)$) and enthalpic ($\Delta H(r)$) contributions to the PMF at 298 K for all the systems under study are shown in Figure 6 (a) to 6 (e) along with the PMFs. The uncertainties in the temperature dependent PMFs are around 5%.

The stabilizing effects of entropic and enthalpic contributions to the PMF act in opposite directions to each other, and the relative proportion of the two contributions depends on the inter solute distances. Interesting entropy-enthalpy compensations and oscillations are observed in the curves (Figure 6). The contact configurations and the solvent assisted configurations are stabilized by entropy and the solvent separated configurations are stabilized by enthalpy for all the solute molecules. The oscillations observed in the entropy and enthalpy correlate with the hydrogen bonding of water molecules according to the study of Southall and Dill.¹⁰⁸

We find that the contact configurations are stabilized entirely by entropy for all the systems, whereas the enthalpy at the contact is slightly positive (unfavourable). When the contact configuration is approached from the 1st transition state, the entropy contribution monotonically increases (i.e., $-T\Delta S$ becomes more negative), whereas the enthalpy contribution initially increases and then reaches a local minimum at the contact configuration. When two large nanoscopic particles approach each other to form a contact configuration solvent molecules are released from the solvation shell to the bulk which increases the randomness of the system (i.e., the entropy). The formation of contact configuration between two nanoscopic solutes decreases the solute-water surface area and, hence, increases the entropy. This is in agreement with the results obtained for small hydrophobic particles like methane. In the case of methane, the simulations indicate that the formation of the methane-methane contact pair is driven by an increase in entropy, and is disfavoured by an increase in enthalpy.^{109–117} Voronin and co-workers¹¹⁸ in their recent experimental study have shown that the aggregation of fullerene molecules in aqueous solutions is a predominantly entropically driven process with a negligible enthalpic contribution.

As we move from a contact configuration to the transition state, a partial vacuum is created between the solutes and there is a decrease in the intermolecular potential. Further, there is enhanced solvent-solvent repulsion in the vicinity of the solutes, thereby increasing the enthalpy contribution in the transition state relative to the contact minima.

Stabilities of the solvent assisted states at an inter-solute separation of around ~ 1.33 nm are determined mostly by the stabilizing effect of the entropy, the enthalpic contribution at this separation being unfavourable.

With increasing solute-solute separation, the entropic stabilization decreases in magnitude. At larger separations, corresponding to those near the 2nd minima i.e., the solvent assisted minima, the enthalpy is slightly unfavourable. In contrast to entropy, the enthalpic contribution is unfavourable up to distances of approximately 1.52 Å with its highest value observed at solute-solute separations corresponding to the 1st transition state. At larger separations, as the excluded volume between the solute pair becomes increasingly accessible to sampling by water molecules, the enthalpic contribution is relatively more favourable. The enthalpic contribution displays a minimum at $r \sim 1.62$ – 1.74 nm that stabilizes the solvent separated configurations. The main mechanism accounting for the stabilization of the solvents separated configurations is the

Figure 6. Entropic ($-T\Delta S(r)$) and enthalpic ($\Delta H(r)$) contributions to the PMFs at 298 K for all the systems under study: (a) C_{60} , (b) $\text{C}_{60}(\text{OH})_2$, (c) $\text{C}_{60}(\text{OH})_4$, (d) $\text{C}_{60}(\text{OH})_8$ and (e) $\text{C}_{60}(\text{OH})_{12}$.

rearrangement of shell water molecules into a lower energetic state. Solute-solvent enthalpic stabilization of the solvent separated configurations in aqueous media is caused by preferential interactions (basically hydrogen bonding interactions) between water the hydroxyl groups of the fullerols (Table 3). At solvent assisted and solvent separated configurations, enthalpy and entropy contributions are quite close to each other in magnitude.

4. Conclusions

In this paper, we have performed computer simulations with the goal of understanding the thermodynamics of association of water soluble derivatives of fullerene *i.e.*, fullerols. Concerning the relations between the number of hydroxyl groups attached to the fullerene surface and the depth of the contact minima, we observed that the hydroxyl group substitution has a little effect on the association structure. However, the number of hydroxyl groups affects the PMF profile beyond second minima (solvent assisted minima) for higher hydroxylated fullerols [$C_{60}(OH)_8$ and $C_{60}(OH)_{12}$]. The attractive interaction is found to be purely entropic for all the solute molecules. In fact, enthalpy favors the dissociated state *i.e.*, the solvent separated state because there are more hydrogen bonds formed between the solute and solvent molecules. A very interesting result in our opinion is the flattening of the PMFs for $C_{60}(OH)_8$ and $C_{60}(OH)_{12}$ which is attributed to the favorable intermolecular solute-solvent hydrogen bonding. It would be of great interest to further study the association of higher hydroxylated fullerols [$C_{60}(OH)_n$, $n > 12$]. Since to the best of our knowledge, there are no experimental results to characterize the thermodynamics of association of fullerols in water, we believe that the results presented here will be useful for both future experimental predictions and the development of new computational investigations on these species. This thermodynamic analysis will be helpful in explaining aggregation of fullerols in other solvents. In future, one can study the effects of pressure, temperature, salt concentration, presence of osmolytes on the PMFs to have a more clear picture of the association of water soluble derivatives of fullerene *i.e.*, fullerols in aqueous media as well as in other solvents. Recently it has been established that imidazolium ionic liquids help in the dispersion of fullerene in aqueous media so we can also study the effect of ionic liquids on the association and dispersion of fullerols.¹¹⁹ These results will widen our understanding of the nature of factors stabilizing fullerene and fullerols in aqueous solution.

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