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A Multiscale Procedure for Predicting the Hydration Free Energies of Polycyclic Aromatic Hydrocarbons

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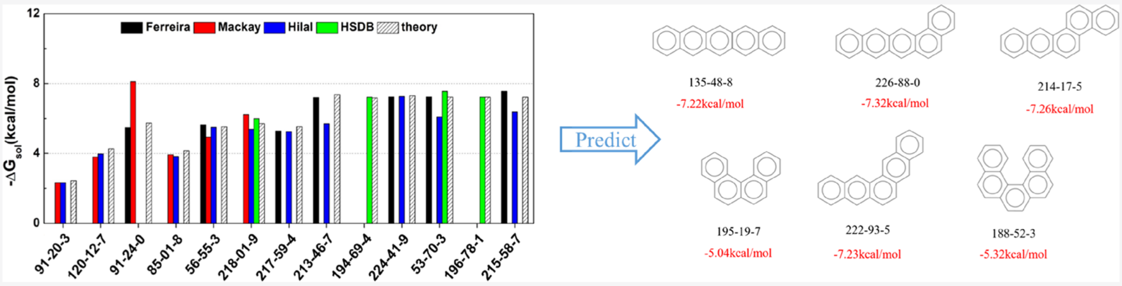

ABSTRACT: Polycyclic aromatic hydrocarbons (PAHs) are organic compounds consisting of fused or condensed benzene rings that mostly have adverse environmental effects. The interaction of PAHs with water molecules plays an important role in understanding their aqueous behavior. Despite the ubiquitous presence of such compounds in nature, experimental data for the solvation properties of PAHs are rarely available or incomplete because of their extremely low solubility in water, yet conventional thermodynamic methods to estimate such properties are often unreliable. Here, we demonstrate that the hydration free energies and the solvation structures of PAHs can be quantitatively predicted by a combination of the first principles and the classical density functional theory calculations. The theoretical procedure may serve as a useful alternative to the missing experimental data and, importantly, provides microscopic insights into absorption and degradation of PAH compounds in aqueous environments.

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs), also known as polynuclear aromatic hydrocarbons (PNAs), can readily be generated from incomplete combustion of diverse carbon sources and exist pervasively in nature, from the atmosphere, volcanic ashes to interstellar space.[1−5] Despite their ubiquitous presence in the environment, the hydration behavior of PAHs remains poorly understood due to extremely low solubility in water. The existing knowledge is mostly established from experimental measurements[6,7] and molecular simulations[8−11] of naphthalene−water systems that may not provide a faithful representation of PAHs interacting with water. Because many PAHs are carcinogenic or mutagenic agents, a direct experiment is hampered by concerns over harmful effects to humans and other living organisms.

Computational methods provide a valuable route to predicting the thermophysical properties of chemical systems that are too difficult or inconvenient to be measured experimentally. With ever-increasing computer power, one can in principle predict molecular configurations and intermolecular interactions accurately based on quantum mechanical (QM) calculations and, subsequently, thermodynamic properties including solvation free energies from molecular dynamics (MD) or Monte Carlo (MC) simulations. While reliable thermodynamic data can be obtained from first-principles predictions, the multiscale procedure is computationally expensive, and quantitative predictions are mostly limited to relatively small systems. For practical purposes, in particular for high-throughput predictions, approximate methods are inevitable to eschew the computational burden. Toward that end, we often rely on lower-level QM methods or semi-empirical force fields to describe intermolecular interactions and use liquid-state theories to predict thermodynamic properties.

In previous work,[12,13] we demonstrated that a combination of QM and classical density functional theory (cDFT) calculations can be used to predict the hydration free energies for a large library of organic compounds. The theoretical performance of the multiscale procedure depends not only on approximations in the cDFT calculations but also on the selection of QM methods to predict the molecular structure and the force-field parameters. It was shown that the optimal

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computational procedure reflects not only the accuracy of theoretical predictions at individual scales but, often more importantly, a reliable linkage between different theoretical methods for electronic structure and atomic representations in order to attain the best overall performance. Here, we follow a similar procedure to study the hydration behavior of PAHs. We first calibrate QM/cDFT predictions for the hydration free energies of 13 PAHs with known experimental data. The calibrated multiscale method is then used to predict the solvation structure and hydration free energies of six additional PAHs. Furthermore, we analyze contributions to the hydration free energy from two types of ring arrangements, namely, "linearized" and "surrounded" PAH structures. For PAHs with a "linearized" arrangement of aromatic rings, the hydration free energies show linear dependence of the hydration free energy on the number of rings. However, "surrounded" PAHs do not exhibit such a linear relationship. Given the same number of rings, the hydration free energy of a "linearized" PAH is larger than that of a "surrounded" PAH, implying the significance of the solvation shell volume effect in the hydrophobic interactions.

■ THEORETICAL METHODS

The theoretical methods for solvation free energy calculations have been reported in our previous work.[14,15] Briefly, solvation free energy is defined as the reversible work to transfer a solute molecule from a vacuum into the pure solvent at fixed temperature T and pressure. The thermodynamic conditions can be equivalently specified by temperature and the corresponding chemical potential of the solvent molecules μ. For a given conformation of the solute molecule, $\varpi \equiv \{\mathbf{r}_{i=1,2,\cdots M}\}$, where $\mathbf{r}_i$ stands for the position of the solute atom i (or interaction site), the solvation free energy can be related to the change in the grand potential of the pure solvent upon inserting a solute molecule at constant temperature and the solvent chemical potential[14]

$$F_s[\rho(\mathbf{x})] = \Omega[\rho(\mathbf{x})] - \Omega_0 \tag{1}$$

where $\rho(\mathbf{x})$ stands for the density profile of the solvent molecules near the solute, $\mathbf{x}$ is the solvent configuration, and Ω_0 is the grand potential of the pure solvent in the bulk phase. Like chemical potential, the solvation free energy is an intensive thermodynamic quantity independent of the system size.

For a solute with a rigid molecular conformation, the grand potential $\Omega[\rho(\mathbf{x})]$ can be directly calculated from cDFT by its minimization with respect to the density profile of the solvent molecules. If the solute takes multiple conformations, the overall solvation free energy is given by

$$\beta F_s = -\ln\langle \exp[-\beta F_s] \rangle_0 \tag{2}$$

where $\beta = 1/(k_B T)$ with k_B being the Boltzmann constant, $\langle \exp[-\beta F_s] \rangle_0$ denotes an ensemble average of all solute conformations in a vacuum. PAHs are rigid organic molecules each with a fixed conformation. Accordingly, eq 1 is used for all calculations discussed in this work.

The grand potential $\Omega[\rho(\mathbf{x})]$ can be calculated from that for an inhomogeneous system of the pure solvent with the solute–solvent interaction treated as an effective external potential. The solvation free energy is given by

$$\begin{aligned}\beta F_s[\rho_i(\mathbf{r})] = &-\frac{1}{M_s}\sum_i \int \mathrm{d}\mathbf{r}\, \Delta\rho_i(\mathbf{r}) \\ &+ \frac{1}{2}\sum_{i,j} \iint \mathrm{d}\mathbf{r}\, \mathrm{d}\mathbf{r}'\, c_{ij}(|\mathbf{r}-\mathbf{r}'|)[\rho_i(\mathbf{r})\rho_j(\mathbf{r}') - \rho_i^0\rho_j^0] \\ &+ \beta F^B[\rho_i(\mathbf{r})] - \sum_i \int \mathrm{d}\mathbf{r}\, \rho_i(\mathbf{r}) B_i(\mathbf{r})\end{aligned} \tag{3}$$

where M_s stands for the number of interaction sites for the solvent molecule and $\Delta\rho_i(\mathbf{r}) = \rho_i(\mathbf{r}) - \rho_i^0$ represents the deviation of the local atomic density for the solvent atom i $\rho_i(\mathbf{r})$ from the bulk value ρ_i^0; $c_{ij}(r)$ denotes the direct correlation function (DCF) between atoms i and j for the bulk system, $F_B[s_i(\mathbf{r})]$ stands for the bridge functional, and $B_i(\mathbf{r})$ is the bridge function of site i

$$B_i(\mathbf{r}) \equiv \delta F_B/\delta\rho_i(\mathbf{r}) \tag{4}$$

Following the universality ansatz proposed by Rosenfeld,[16] we conjecture that the bridge functional of the molecular system can be approximated by that of an effective hard-sphere (HS) reference system. Approximately, the effective HS diameter is close to the solvent diameter. The expression for F_B and the selection of an effective hard-sphere diameter for the reference system can be found in our previous publications.[12,17]

In addition to the site–site DCFs and the bridge functional for the pure solvent, our cDFT calculation requires as the input the molecular structure for the solute and a semi-empirical force field for both solvent–solvent and solute–solvent interactions. While a large number of molecular models are available for water, the molecular model for the solute is more specialized and, in general, must be derived from quantum mechanical (QM) calculations for the electronic structure in combination with a semi-empirical force field for van der Waals interactions. To predict the hydration free energies of PAHs, we select a multiscale procedure that yields the best prediction of the hydration free energies of hydrophobic chemical species.[18] Specifically, the SPC/E[19] model is used for water, and the solute structure is determined using the Hartree–Fock (HF) method by energy minimization in a vacuum.[20] The GAFF[21] force-field parameters are chosen to describe the van der Waals (VDW) interactions between solute and solvent molecules, and the atomic charges are assigned according to AM1-BCC[22] charge distributions. All QM calculations are based on the ORCA ab initio quantum chemistry package.[23] The density profile of the solvent molecules near the solute and solvation free energy can be obtained with the homemade program.

■ RESULTS AND DISCUSSION

Our theoretical calculations are focused on solvation of about 20 polycyclic aromatic hydrocarbons (PAHs) in liquid water at ambient conditions (298 K and 1 atm). The number of aromatic rings in these PAHs ranges from two to five as most commonly observed in the environment. Because aromatic rings represent a common feature of all these PAHs, we set the effective hard-sphere (HS) diameter for the bridge functional according to the hydration free energy of benzene, which is −0.844 kcal/mol at room temperature.[24] With the SPC/E model for water and the GAFF force field for benzene, cDFT predicts a hydration free energy of −0.753 kcal/mol by setting the effective HS diameter to 2.915 Å in the hard-sphere bridge functional. The same value is used without further optimization for all theoretical predictions discussed in this work.

We first calibrate the QM/cDFT procedure for hydration free energy predictions established in our previous work.[18] Figure 1 shows the molecular structures of 13 PAHs for which we can find experimental Henry's constants from literature.[24] Henry's constant is related to the solvation free energy by

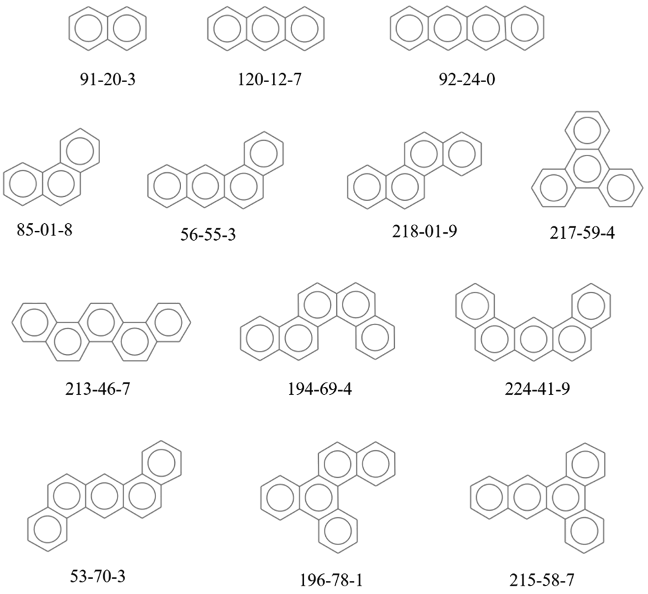

Figure 1. Molecular structures of 13 PAHs with known experimental data for Henry's constants at ambient conditions. Underneath each structure is the Chemical Abstracts Service (CAS) number.

$$\beta F_s = -\ln(H \cdot RT) \tag{5}$$

where H represents Henry's constant in experimental units of mol·liter^{-1}·atm^{-1} and R = 0.082 liter·atm·mol^{-1}·K^{-1} is the gas constant. With two to five aromatic rings in different configurations, these PAH compounds provide an excellent benchmark for the calibration of the theoretical predictions.

Figure 2 compares the theoretical results with experimental data for the hydration free energies of 13 PAHs. To validate the QM/cDFT predictions objectively, we include in this figure four independent sets of experimental results from literature. Overall, the theoretical results reproduce the experimental data well. The averaged unsigned error (AUE) is less than 0.5 kcal/mol, which is comparable to the experimental uncertainty. Interestingly, Mackay reported that the hydration free energy is −8.11 kcal/mol for tetracene (CAS 92-24-0), which is 2 kcal/mol larger than Ferreira's measurement and the theoretical prediction. In light of the excellent agreement between theory and experiment for other compounds, we conjecture that the hydration free energy from Mackay's measurement is most likely inaccurate.

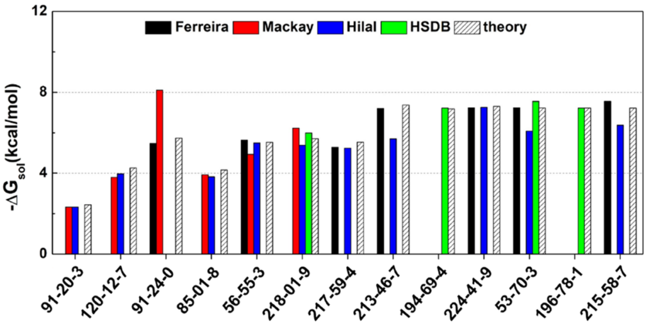

Figure 2. Hydration free energies compared with the experimental data (all experimental data come from Sander's compilation of Henry's law constants; Ferreira, Mackay, and Hilal are the authors who contributed the data; and HSDB stands for Hazardous Substances Data Bank).

While a true first-principles procedure requires no experimental data for validation of theoretical predictions, a comparison between theory and experiment is essential from a practical perspective because the performance of approximate methods is radically different in multiscale calculations of different chemical systems. After calibration with the hydration free energies for a relatively large number of PAHs, we then apply the QM/cDFT calculations to predict the hydration behavior of pentacene and its isomers with different arrangements of the aromatic rings. Figure 3 shows six PAH molecules that we select to study the configuration effects on hydration. Among them, pentacene (CAS 135-48-8) is a highly conjugated compound widely used as a conductor in organic electronic devices.[25] Benzo[c]phenanthrene (CAS 195-19-7) and pentahelicene (CAS 188-52-3) are members of helicenes commonly used in conformational analysis[26] and chemical sensors.[27] Despite their technological importance, no experimental data can be found for the hydration free energies of these PAHs. Therefore, our cDFT/QM predictions provide useful estimates of such properties and insights into the conformational effects on the hydration energy.

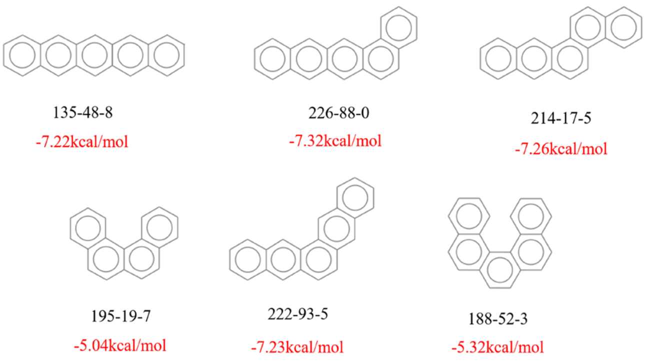

Figure 3. Structure, Chemical Abstracts Service (CAS) numbers, and the predicted hydration free energies of six PAHs that lack experimental data for Henry's constant.

Figure 4 shows the variation of the hydration free energy with the number of aromatic rings in the PAH molecules. Here, the aromatic rings are connected with two types of configurations, namely, "linearized" and "surrounded" structures, as shown in Figure 4a. In Figure 4b, we present the hydration free energies with the number of rings increasing from two to five. PAHs with a linearized structure show a perfect straight line with a slope of −1.623 kcal/mol, which agrees perfectly with the additive hydrophobic model proposed by Wu and Prausnitz,[28] as shown in Figure 4c. From the hydrophobic potential between benzene rings, it is easy to calculate the free energy of hydration for linearized PAH molecules. For example, the black line in Figure 4c predicts that the free energy of hydration for pentacene (CAS: 135-48-

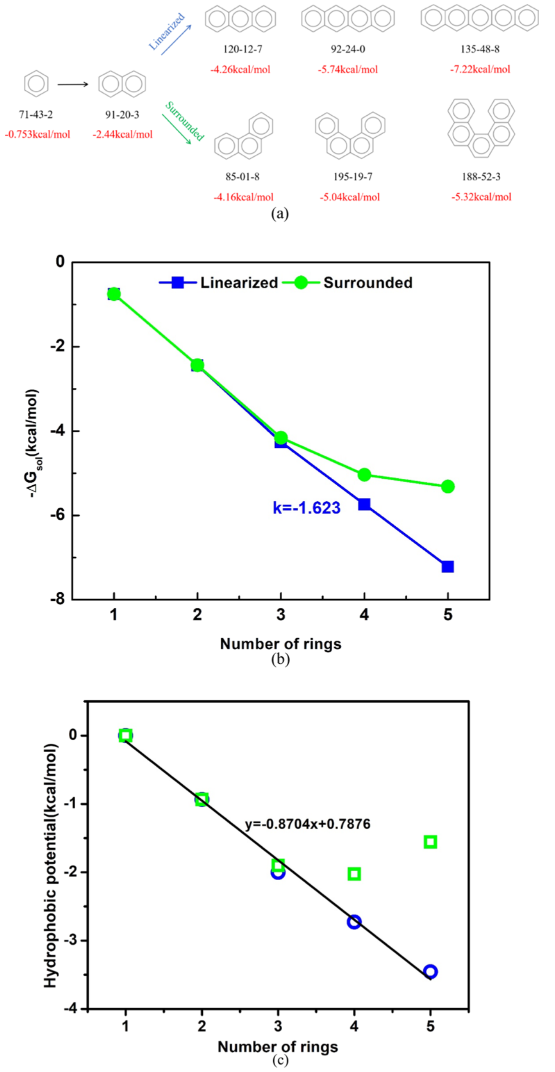

Figure 4. (a) Hydration free energies for two types of PAH structures, namely, "linearized" and "surrounded" types. (b) Hydration free energies versus the number of benzene rings. (c) Hydrophobic potential among benzene rings in "linearized" and "surrounded" PAH molecules.

Table 1. First Solvation Shell Volume and the "Overlap Volume" Corresponding to Fusion of Benzene Rings to Form the Two Types PAHs[a,b]

CAS/linearized	71-43-2	91-20-3	120-12-7	92-24-0	135-48-8
volume of first solvation shell	237.2	318	394.6	475.3	543.9
overlapped volume	0	156.4	317	473.5	642.1
hydrophobic potential	0	−0.934	−2.001	−2.728	−3.455
CAS/surrounded	71-43-2	91-20-3	85-01-8	195-19-7	188-52-3
volume of first solvation shell	237.2	318	394.3	460.1	522.1
overlapped volume	0	156.4	317.3	488.7	663.9
hydrophobic potential	0	−0.934	−1.901	−2.028	−1.555

[a] The units of volume and hydrophobic potential are Å^3 and kcal/mol, respectively. [b] Volume of first solvation shell = volume within solvent-accessible surface − excluded volume. The volume within the solvent-accessible surface and excluded volume are calculated using tool pdbvol from python library pdbremix. The carbon atom is considered as a sphere with 3.9 Å diameter with the hydrogen atom ignored, and the solvent is considered as a sphere with 2.8 Å diameter.

8) is $5 \times (-0.753) + (0.7876 - 5 \times 0.8704) = -7.33$ kcal/mol, showing good agreement with −7.22 kcal/mol from experimental data. Besides, the proportionality constant A = 9.89 nm^{-3} can be calculated from the overlapped volume in Table 1, which is not far from that for n-alkanes (9.01 nm^{-3}). The hydration free energies of "surrounded" PAHs do not exhibit such a linear relationship because of the additional overlap of the solvation shells of the neighboring benzene rings. Given the same number of rings, the hydration free energy of a "linearized" PAH is higher than that of a "surrounded" PAH when each ring interacts with multiple neighbors.

The QM/cDFT calculations also allow us to examine variation of the hydration structure with the number of aromatic rings. Figure 5(a−f) shows the density profiles of an oxygen atom from the water molecule near linearized and surrounded PAHs with three to five aromatic rings. While the solvation free energy is mostly dominated by water molecules within the first layer of the hydration shell, it is clear that the PAH molecules have significant effects on the local structure of water molecules up to the nanometer scale. The long-range distributions of water molecules within the hydration shell were discussed in our previous studies.[29] Interestingly, the local density of water molecules is noticeably enhanced near the hydrophobic pockets of "surrounded" PAHs. The increased local water density may be attributed to the slight increase in water molecules near a hydrophobic surface and the excluded volume effects.

■ CONCLUSIONS

In this work, we applied a multiscale strategy to predict the hydration free energies of polycyclic aromatic hydrocarbons (PAHs) using classical density functional theory (cDFT) for thermodynamic calculations and quantum mechanical method (HF) for structure optimization, in combination with GAFF force-field parameters, AM1-BCC charge sets, and SPC/E water model. We demonstrated that the bridge functional for water can be approximated by that of a hard-sphere system with the effective diameter obtained from the hydration free energy for benzene from experimental data. The multiscale procedure predicts the hydration free energies of 13 PAH molecules in good agreement with experimental data. It was also used to predict the hydration free energies of six PAH molecules that lack experimental data but might be of interest for practical applications.

The solvation free energies for different PAHs were analyzed in terms of two types of ring arrangements, namely, "linearized" and "surrounded" structures. For PAHs with the "linearized" arrangement, the hydration free energies show a linear relationship with the number of benzene rings in excellent agreement with the Wu−Prausnitz model. Given the same number of rings, the hydration free energy of a "linearized" PAH is higher than that of a "surrounded" PAH because of the additional overlap among the solvation shells of neighboring benzene rings. While the hydration free energy is mostly dominated by water molecules within the first solvation shell, the local density of water molecules exhibits significant inhomogeneous distribution near PAH solutes up to the nanometer scale.

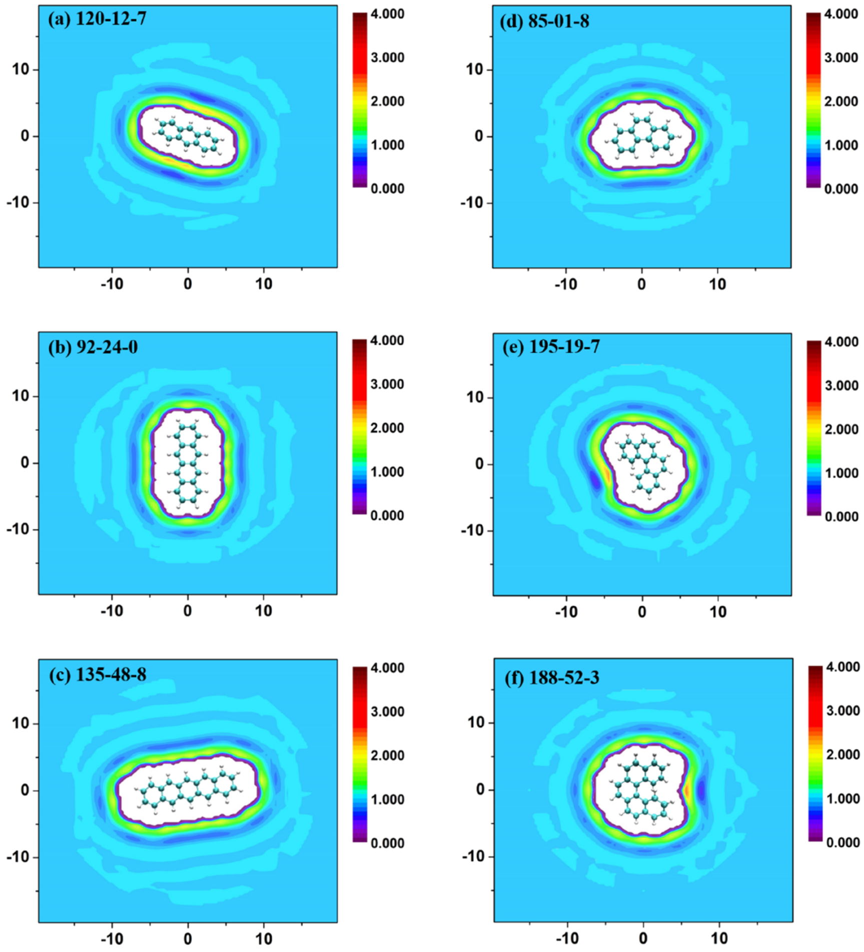

Figure 5. Density profiles of water molecules near (a–c) "linearized" and (d–f) "surrounded" PAHs.

Experimental measurement of Henry's constant requires sophisticated devices and careful experimental skills. Besides, the measurement is subject to health concerns due to the toxicity of solutes such as PAHs. This work demonstrates that the multiscale procedure provides a valuable alternative to experiment to attain Henry's constants and related solvation properties. While conventional first-principles methods and molecular simulations are time-consuming for predicting solvation free energy, cDFT calculations can be accomplished within 30 min for each solute even without any effort to optimize the computer program. We expect that the drastic improvement of computational efficiency is important for high-throughput and customized industrial applications.

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Notes

The authors declare no competing financial interest.

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