# Hydration Free Energies of Linear Alkanes: Evaluating and Correcting Classical Force Field Predictions with Different Water Models

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**Abstract**

Common force fields tend to overestimate the hydration free energies of hydrophobic solutes, leading to an exaggerated hydrophobic effect. We compute the hydration free energies of linear alkanes from methane to eicosane ($C_{20}H_{42}$) using free energy perturbation with various three-site (SPC/E, OPC3) and four-site (TIP4P/2005, OPC) water models and the TraPPE-UA force field for alkanes. All water models overestimate the hydration free energies, though the four-site models perform better than the three-site ones. By utilizing cavity free energies, we reparameterize the alkane–water well-depth to bring simulation results in agreement with experimental and group-contribution estimates. We find that the General Amber force Field (GAFF) combined with TIP4P/2005 water provides closer estimates of the hydration free energy. The HH-alkane model (a reparameterized TraPPE-UA force field) with TIP4P/2005 reproduces experimental hydration free energies. We also show that applying a shifted

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Lennard–Jones potential leads to systematic deviations in the hydration free energy estimates.

# 1 Introduction

The hydrophobic effect is a fundamental driving force in many chemical and biological processes, including the self-assembly of surfactants and lipids into micelles and membranes, the folding and stability of proteins, binding of ligands into hydrophobic pockets of proteins, and coalescence of oil droplets in water.[1,2] Recent molecular simulation works have noted that the commonly used force fields tend to exaggerate the hydrophobic effect, leading to underestimated critical micelle concentrations of surfactants and overestimated oil-water interfacial adsorption free energies.[3–5] These systematic deviations highlight the need for improved parameterizations of existing force fields.

Alkanes in water serve as a model system to understand the behavior of non-polar species in aqueous environments. A key property of interest is their solubility, which can be quantified by the hydration free energy, or the change in free energy when an alkane transfers from the vapor to the aqueous phase. Hydration free energy can be estimated using molecular simulations, but the accuracy depends both on the choice of molecular force fields and the numerical implementation details. Molecular force fields are often parameterized on pure species thermodynamic properties. The inter-species force field parameters are then obtained by heuristic mixing rules. Lorentz-Berthelot being the most popular among them. The numerical implementation details refer to the chosen spatial potential cut-off and how the interactions are accounted for beyond the cut-off.[6] In this work, we show that various water models overestimate the hydration free energies of linear alkanes (modeled via TraPPE-UA) when standard Lorentz-Berthelot mixing rules are used. Using the cavity free energies of alkanes, we provide a one-step mechanism to adjust the alkane-water well depth parameter to reproduce the experimental values. We also discuss the implications of using

shifted potentials on the absolute values of hydration free energies.

Non-polar species, like alkanes, do not strongly interact with water due to their inability to form hydrogen bonds and charge neutrality. Such species disrupt the molecular arrangement of water in their vicinity, making their dissolution in water unfavorable. Thus, non-polar species tend to aggregate in aqueous environments, which is referred to as the hydrophobic effect.[1] Hydrophobic effect is length-scale dependent.[7,8] At small length-scales, where size of the solute is less than 1 nm, hydrophobic effect is entropically driven[7,9,10] and the hydration free energy is proportional to solute volume.[8] Hydration free energies of small solutes and their aggregation in water are well-described by the observation that water density fluctuations are Gaussian in small observation volumes.[11] For larger solutes, hydrophobic effect is dominated by the enthalpic loss of hydrogen bonds of water in the vicinity, and the hydration free energy scales proportional to the exposed surface area of the solute.[8,12] Near large hydrophobic solutes, the low-density solvent fluctuations are enhanced relative to Gaussian statistics.[13,14] Thus, water near large hydrophobic solutes sits at the edge of a dewetting transition.[15,16] As a result, liquid water, when confined between large non-polar solutes, becomes metastable with respect to its vapor below a critical confinement gap.[17–20] This phenomenon is understood to dictate the hydrophobic self-assembly of large solutes.

The Gibbs free energy of solvation is given by, $\Delta G_{hyd} = \Delta H_{hyd} - T\Delta S_{hyd}$, where $\Delta H_{hyd}$ is the change in the enthalpy when the solute enters the aqueous phase, and $\Delta S_{hyd}$ is the associated change in the entropy. $\Delta H_{hyd}$ comprises of solute-solvent direct interactions $\Delta E_{UV}$ and changes in the solvent-solvent interactions, $\Delta H_{VV}$ $(= \Delta E_{VV} + P\Delta V)$. The $\Delta H_{VV}$ exactly cancels out the solvent's entropic contribution, $T\Delta S_{VV}$.[21] Therefore, the $\Delta H_{hyd}$ is determined entirely by the solute-solvent contribution, that is, $\Delta G_{hyd} = \Delta E_{UV} - T\Delta S_{UV}$.[21] Previous works have shown that the positive (unfavorable) $\Delta G_{hyd}$ of alkanes arise from a near perfect cancellation of the attractive (favorable) solute-solvent interactions, $\Delta E_{UV}$ and the unfavorable solute-solvent entropic term, $T\Delta S_{UV}$.[21] The $\Delta G_{hyd}$ can also be broken down

into the free energy of creating a solute-sized cavity, $\Delta G_{cavity}$, and the energetic contribution from the attractive solute-solvent interactions, $\Delta H_{att}$.[22]

Several experiments have reported the solubility of linear alkanes in water, but reliable estimates are available only up to decane because of the extremely low solubilities of longer alkanes.[23–31] Cabani et al.[32] developed a group contribution method based on the experimentally known solubilities of small alkanes to predict the solubilities of linear- and cyclo-alkanes. This group contribution method was updated for aliphatic and mono-aromatic hydrocarbons, monohydric alcohols, and aliphatic, non-cyclic ketones.[33,34] In a group contribution method, the thermodynamic property of interest is correlated with the number and types of molecular fragments that make up a molecule, allowing estimation of average contribution of each molecular fragment towards that thermodynamic property.

Aqueous solubility of alkanes has been a subject of several molecular simulation studies. Ferguson et al.[35] employed the Transferable Potentials for Phase Equilibria (TraPPE)-United Atom (UA) force field[36] for alkanes and Simple Point Charge Enhanced (SPC/E) water model.[37] Using the incremental Widom insertion technique[38] and a potential cutoff of 9.875 Å for both Lennard-Jones and electrostatic interactions, they determined the aqueous solubility of n-alkanes up to docosane ($C_{22}$). While Ferguson et al.'s[35] calculations matched experimental values, other studies that employed the same molecular potentials reported deviations from the experiments.[39,40]

Ashbaugh and coworkers[40] compared ten different water models for their ability to reproduce experimental temperature-dependence of liquid water density and methane hydration and concluded that the TIP4P/2005 water model performs the best. Ashbaugh et al.[41] calculated the hydration free energy of linear and branched alkanes using the TraPPE-UA + TIP4P/2005 potentials for alkanes and water, respectively, via thermodynamic integration. They concluded that the hydration free energies are overestimated compared to the experimental values when the standard Lorentz-Berthelot mixing rules are used. They adjusted the Lennard-Jones well depth parameter between the alkane united atoms and water

oxygen to match the experimental data. The new model, called HH-Alkane, reduced the deviation of hydration free energy from experiments to 0.25 kJ/mol on average. However, their simulations were performed for alkanes of size up to butane and neopentane.

Chen and Siepmann[42] studied hydration of small alkanes via Gibbs ensemble Monte Carlo simulations using the Optimized Potentials for Liquid Simulations (OPLS) force field[43] for alkanes and the TIP4P model of water. They reported that the hydration free energy of alkanes from the simulations was consistently higher than the experimental values. Similar conclusions were drawn in another study by Siepmann and coworkers[39] where they employed the TraPPE force field for n-alkanes along with different water models: TIP4P, TIP4P/2005, and SPC/E. Interestingly though, they found that the hydration free energies are closer to the experimental values for the SPC/E water model compared to the TIP4P/2005 water model. Singh and Sharma[44] reported large deviations in the hydration free energies of n-alkanes from the experimental values. They employed the General Amber Force Field (GAFF)[45] for alkanes and SPC/E water with a spherical cutoff of 10 Å and the potentials shifted by their value at the cutoff distance.

In this work, we calculate the hydration free energies of linear alkanes up to eicosane ($C_{20}H_{42}$) using the TraPPE-UA force field for alkanes combined with various three- and four-point water models. All tested water models systematically overestimate the hydration free energies. The "Optimal 3-Charge, 4-Point rigid" (OPC) water model[46] and its 3-site counterpart OPC3,[47] designed by optimizing charge distributions to capture bulk electrostatics, yield hydration free energies similar to those from TIP4P/2005 and SPC/E, respectively. This indicates that OPC and OPC3 do not improve predictions for non-polar solutes. By utilizing the free energy of cavity formation, we adjust the alkane-water Lennard-Jones well depth parameter ($\epsilon$) for each model to match experimental values. Remarkably, in all cases, the well-depth parameter needs to be increased by about 5% relative to the Lorentz-Berthelot mixing rule. We further show that the HH-alkane model with TIP4P/2005 water reproduces experimental hydration free energies up to eicosane. Similarly, the General Am-

ber force Field (GAFF) combined with TIP4P/2005 water model provides good agreement with experiments.

Finally, we demonstrate that shifting the Lennard-Jones potential by its value at the spherical cutoff further increases deviations from the experiment. More broadly, these results highlight that molecular force fields parameterized on pure-component thermodynamics often perform poorly for mixtures when heuristic mixing rules like Lorentz-Berthelot are used. For non-polar species like alkanes, accuarate hydration free energies can be obtained by directly calibrating the interaction parameters using cavity-formation free energies.

## 2 Simulation System and Methods

A widely used force field for alkanes is the Transferable Potentials for Phase Equilibria (TraPPE)- United Atom (UA) model.[36] In this model, each alkyl group is represented as a single united atom bead, with distinct sites defined for $CH_4$, $-CH_3$, and $-CH_2$. Beyond alkanes, TraPPE-UA has also been parameterized for alcohols, thiols, ethers, sulfides, aldehydes, ketones, nitriles, cycloalkanes, and aromatics. We evaluate the performance of TraPPE-UA with the General Amber Force field (GAFF)[45] and the HH-alkane model.[41] For water, we employ four commonly used models: SPC/E, OPC3, TIP4P/2005, and OPC. SPC/E and OPC3 are three-site models, while TIP4P/2005 and OPC are four-site models, in which the negative charge is shifted off the oxygen atom onto the $H-O-H$ angle bisector.[46–48]

Hydration free energies of alkanes are calculated using the free energy perturbation (FEP) method.[3,49] Alkane-water interactions are described by a soft-core Lennard-Jones potential (equation 1),[50] with $\alpha = 0.5$ and $n = 2$. The coupling parameter $\lambda$ is varied from 0 to 1 in 40 windows with $\Delta\lambda = 0.025$. Each window is simulated for 6 ns, and ensemble averages are computed from the last 4.5 ns. Accuracy is validated by also tracing the reverse path ($\lambda$ = 1 to 0) with the same protocol. Reported uncertainties are standard deviation over three

independent simulations.

$$V(\lambda, r) = \lambda^n 4\epsilon \left[ \left( \alpha(1-\lambda)^2 + \left(\frac{r}{\sigma}\right)^6 \right)^{-2} - \left( \alpha(1-\lambda)^2 + \left(\frac{r}{\sigma}\right)^6 \right)^{-1} \right] \quad (1)$$

Hydration free energy is calculated in the isothermal-isobaric ensemble using equation 2.[51,52]

$$\Delta G = -k_B T \sum_{i=0}^{n-1} ln \left( \frac{\langle V exp\left( -\frac{U(\lambda_{i+1}) - U(\lambda_i)}{k_B T} \right) \rangle_{\lambda_i}}{\langle V \rangle_{\lambda_i}} \right) \quad (2)$$

The simulation system comprises one alkane molecule in bulk water. Nominal size of the cubic simulation system is selected to ensure that the periodic images of the alkane do not interact with each other (Table S1, Supporting Information). Periodic boundary conditions are applied in all directions. Coulombic interactions between water molecules are calculated using Particle-Particle Particle Mesh Ewald summation with an accuracy of $10^{-4}$. Lennard-Jones and real-space part of the Coulombic interactions between water molecules are truncated at a spherical cutoff of 10 Å. The Lennard-Jones interactions between water-oxygen and alkane atoms have a spherical cutoff of 14 Å as recommended in the TraPPE-UA force field.[53] Unless noted otherwise, the potential functions are not shifted by their value at the spherical cut-off, and long-range/tail corrections to the potential and pressure are applied for Lennard-Jones interactions. The simulations are performed in the isothermal-isobaric ensemble at the temperature $T = 300$ K and the pressure $P = 1$ bar. Temperature and pressure in the system are maintained using the Nose-Hoover thermostat and barostat respectively. All simulations are conducted using the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS).[54] Initial configurations are generated using the PACKMOL package.[55]

# 3 Results and Discussion

Figure 1(a) presents the hydration free energies, $\Delta G_{hyd}$ of alkanes from methane to eicosane, calculated using the TraPPE-UA alkane potential with four different water models (SPC/E, OPC3, TIP4P/2005, and OPC). The results are compared with experimental $\Delta G_{hyd}$ values up to octane and with estimates from the group contribution method[32] for longer alkanes. For all water models, the TraPPE-UA force field overpredicts $\Delta G_{hyd}$. The deviations are larger for the 3-point water models (SPC/E and OPC3) than for the 4-point water models (TIP4P/2005, OPC), and the deviations increase with alkane length. The two 3-point water models yield similar results, as do the two 4-point water models. Our results are consistent with the observation by Kanduč et al.[3] and others[4,5] who report that the currently available atomistic force fields systematically yield stronger adsorption affinities for oil-water interfaces and under-predict the critical micelle concentration. Our $\Delta G_{hyd}$ values match well with the estimates in previous studies as shown in the Table S2 (Supporting Information).

To reconcile the hydration free energies obtained from the TraPPE-UA force field with different water models, we re-parameterize the alkane-water Lennard-Jones well-depth parameter, $\epsilon$. The hydration free energy can be expressed as $\Delta G_{hyd} = \Delta G_{cavity} + \Delta H_{att}$, where $\Delta H_{att} \approx \Delta U_{att}$ corresponds to the alkane-water Lennard Jones interaction energy. Values of $\Delta G_{cavity}$ are taken from previous studies.[44,56] The experimental (or group contribution) estimate of the $\Delta H_{att}$ can then be obtained as $\Delta H_{att}^{exp} = \Delta G_{hyd}^{exp} - \Delta G_{cavity}$. Analogously, $\Delta H_{att}$ can be computed for each alkane + water model combination. For small perturbations to $\epsilon$, the local solvent structure around the alkane is assumed unchanged. Therefore, the updated $\epsilon$ is found as $\epsilon^{updated} = \frac{\Delta H_{att}^{exp}}{\Delta H_{att}} \times \epsilon$. This procedure is demonstrated for the SPC/E water model in Table 1. Interestingly, for all the models, $\epsilon$ needs to be increased by approximately 5% relative to its Lorentz-Berthelot value. Applying it to all the water models yields the updated $\epsilon$ values summarized in Table 2. Figure 1(b) shows that the $\Delta G_{hyd}$ obtained using the updated $\epsilon$ for all the water models have an excellent match with the experiments/group

contribution values, except for OPC3, whch shows some deviation for large alkanes.

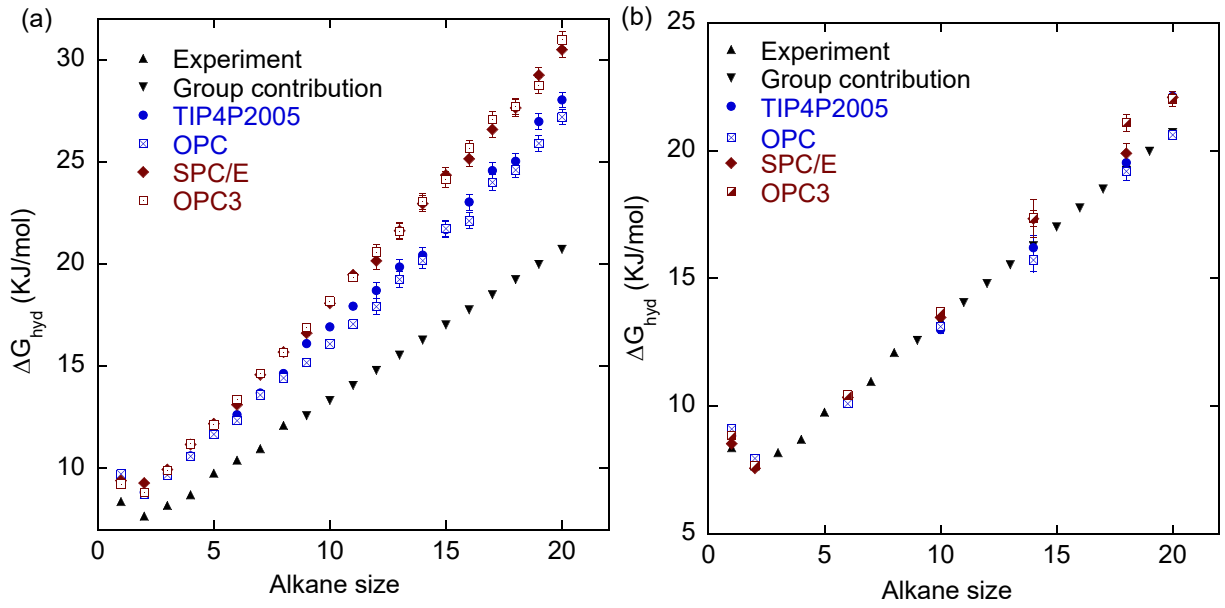


Figure 1: (a) Hydration free energies, $\Delta G_{hyd}$ of alkanes using the TraPPE-UA model and different water models. All models show positive deviation from the experiments/group contribution. The 3-point water models show larger deviation from the experimental/group contribution values compared to the 4-point water models. (b) $\Delta G_{hyd}$ of alkanes using the TraPPE-UA model but with the alkane-water well depth parameter updated via the method discussed in the text. An excellent match with the experimental/group-contribution values is found, except for some deviations observed with the OPC3 model for large alkanes.

Table 1: Comparison of experimental hydration data with TraPPE-UA + SPC/E and updated SPC/E models. The units are in [kJ/mol]. $\Delta G_{hyd}^{SPC/E,pred}$ are the predicted $\Delta G_{hyd}$ values after updating the $\epsilon$. $\Delta G_{hyd}^{SPC/E,sim}$ are the values obtained in the simulations.

| Alkane | $\Delta G_{hyd}^{exp}$ | $\Delta G_{hyd}^{SPC/E}$ | $\Delta G_{cavity}$ | $\Delta H_{att}^{exp}$ | $\Delta H_{att}^{SPC/E}$ | $\Delta H_{att}^{SPC/E,updated}$ | $\Delta G_{hyd}^{SPC/E,pred}$ | $\Delta G_{hyd}^{SPC/E,sim}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 8.37 | 9.39 | 24.52 | -16.15 | -15.12 | -15.96 | 8.56 | 8.53 |
| 2 | 7.66 | 9.28 | 34.87 | -27.21 | -25.59 | -27.01 | 7.86 | 7.57 |
| 3 | 8.18 | 9.94 | 43.85 | -35.67 | -33.91 | -35.78 | 8.07 | |
| 4 | 8.70 | 11.16 | 52.55 | -43.85 | -41.39 | -43.68 | 8.87 | |
| 5 | 9.76 | 12.19 | 61.86 | -52.10 | -49.67 | -52.42 | 9.44 | |
| 6 | 10.4 | 13.11 | 70.34 | -59.94 | -57.23 | -60.40 | 9.94 | 10.34 |
| 8 | 12.1 | 15.69 | 87.72 | -75.62 | -72.03 | -76.01 | 11.71 | |
| 10 | 13.32 | 18.08 | 105.75 | -92.43 | -87.68 | -92.53 | 13.23 | 13.47 |
| 12 | 14.80 | 20.15 | 123.36 | -108.56 | -103.21 | -108.92 | 14.44 | |
| 14 | 16.28 | 22.95 | 140.80 | -124.52 | -117.85 | -124.37 | 16.43 | 17.34 |
| 16 | 17.76 | 25.15 | 157.81 | -140.05 | -132.66 | -140.00 | 17.81 | |
| 18 | 19.24 | 27.64 | 174.72 | -155.48 | -147.08 | -155.21 | 19.51 | 19.90 |

Ashbaugh et al.[41] reported that the TraPPE-UA force field combined with TIP4P/2005

Table 2: Original and updated Lennard-Jones well-depth parameter ($\epsilon$) for $CH_4$-O, $CH_3$-O, and $CH_2$-O for different water models in [kJ/mol]. The sigma ($\sigma$) parameter was not modified.

| | $CH_4$-O | | $CH_3$-O | | $CH_2$-O | |
|---|---|---|---|---|---|---|
| | $\epsilon$ | $\epsilon^{updated}$ | $\epsilon$ | $\epsilon^{updated}$ | $\epsilon$ | $\epsilon^{updated}$ |
| SPC/E | 0.8942 | 0.9436 | 0.7276 | 0.7679 | 0.4985 | 0.5261 |
| OPC3 | 0.9172 | 0.9668 | 0.7464 | 0.7867 | 0.5114 | 0.5390 |
| OPC | 1.0467 | 1.0841 | 0.8517 | 0.8822 | 0.5835 | 0.6044 |
| TIP4P2005 | 0.9765 | 1.0169 | 0.7946 | 0.8274 | 0.5444 | 0.5669 |

water overestimates the hydration free energies of small alkanes. To address this, they proposed the HH-alkane model, in which the alkane-water interaction parameters were re-parameterized. Their study validated the HH-alkane model against experimental data for alkanes up to butane and neopentane.[41] Here, we extend their analysis by calculating the hydration free energies of linear alkanes up to eicosane using the HH-alkane + TIP4P/2005 water model. As shown in Figure 2, the resulting $\Delta G_{hyd}$ values are in excellent agreement with both the experimental/group-contribution data and our re-parameterized TraPPE + TIP4P/2005 force field combination.

We also calculated the $\Delta G_{hyd}$ using the General Amber Force Field (GAFF) with both the SPC/E and TIP4P/2005 water models. Figure 3 compares the $\Delta G_{hyd}$ obtained from GAFF with those from TraPPE-UA. The alkane-water interactions are determined using the Lorentz-Berthelot mixing rules in both cases. GAFF yields smaller deviations from the experimental and group contribution values compared to TraPPE-UA. Specifically, GAFF + SPC/E combination systematically overestimates the $\Delta G_{hyd}$ by roughly 1 to 1.6 kJ/mol. GAFF+TIP4P/2005 tends to overestimate $\Delta G_{hyd}$ for small alkanes but underestimates it for larger alkanes. Our results align with those of Luz et al.,[4] who report that GAFF + SPC/E show too strong affinity of polyethoxylated alkyl ethers ($C_8EO_m$) to a heptane-water interface.

Lastly, we study the impact of potential shift on the $\Delta G_{hyd}$ calculations. Often, molecular interaction potentials are shifted by their value at the spherical cutoff so that the potential

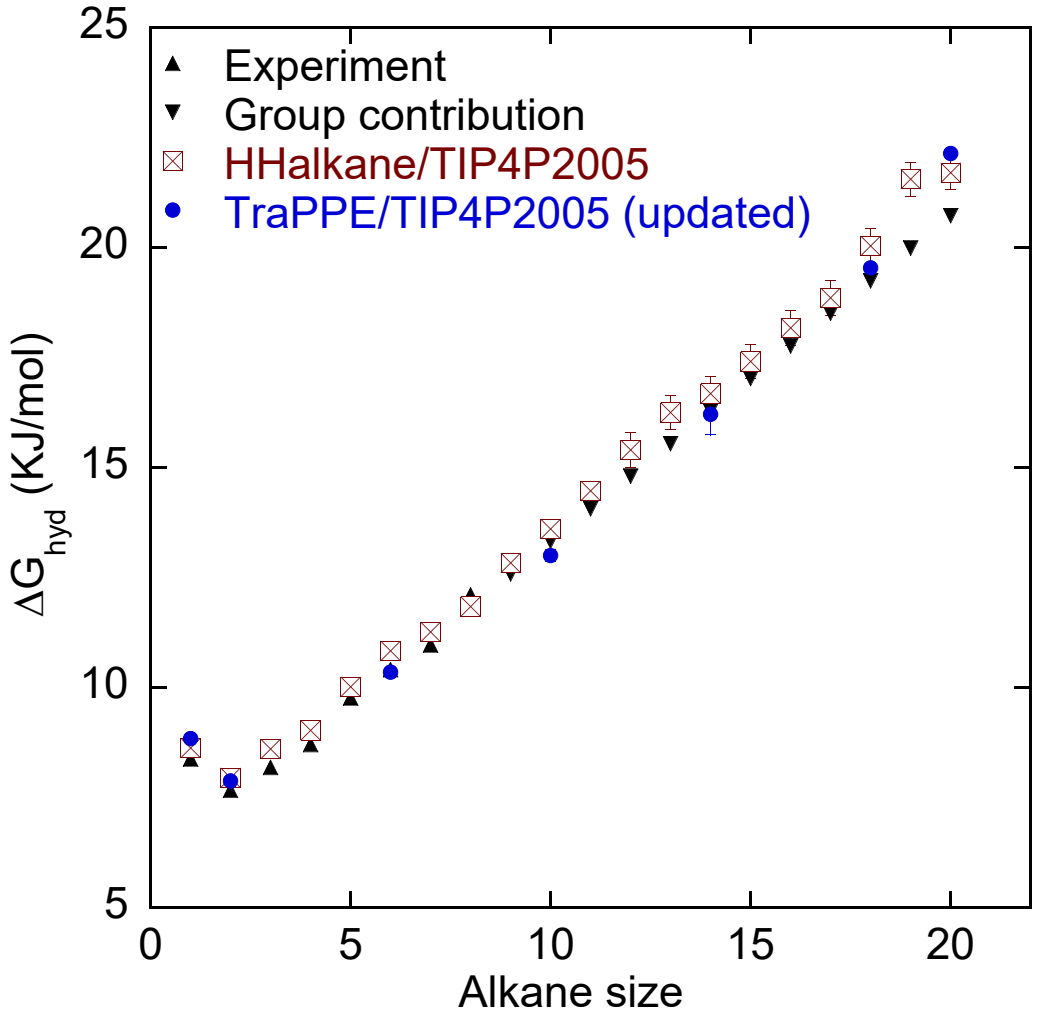


Figure 2: Hydration free energy of alkanes calculated using the HH-alkane model is compared with the TraPPE-UA force field and the experimental/group-contribution values. TIP4P/2005 water model is employed. The HH-alkane model matches the experimental/group contribution values well up to $C_{20}$.

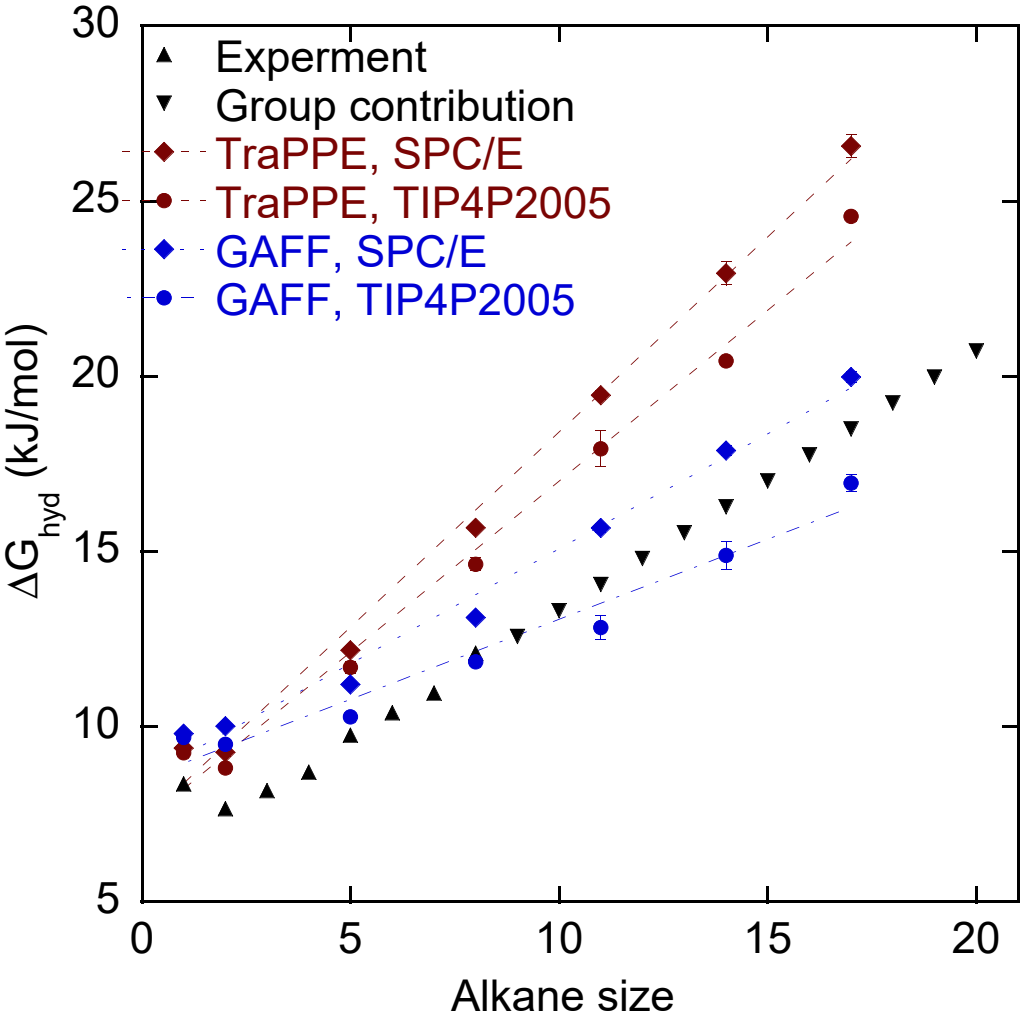


Figure 3: Hydration free energies of alkanes calculated using the General Amber Force Field (GAFF) all-atom model of alkanes and two different water models: SPC/E and TIP4P/2005. The results are compared with the TraPPE-UA model and experimental/group contribution values. Overall, results using GAFF are closer to the experimental/group contribution values compared to TraPPE. GAFF, SPC/E overestimates the $\Delta G_{hyd}$ values. GAFF, TIP4P/2005 overestimates the $\Delta G_{hyd}$ for small alkanes ($\leq C_5$) but underestimates the $\Delta G_{hyd}$ for large alkanes. Lines are guide to the eyes.

becomes zero at the cutoff, $r_c$. Shifted potential functions are given by,

$$u_{shift}(r_{ij}) = \begin{cases} u(r_{ij}) - u(r_c), & r_{ij} \leq r_c \\ 0, & r_{ij} > r_c \end{cases} \tag{3}$$

For the "unshifted" potentials, the contribution of the potential (which remains non-zero) beyond the $r_c$, called long-range or tail correction, is included for energy and pressure calculations. It should be noted that in molecular dynamics only the forces matter. So whether a potential function is shifted or not and whether a tail correction is applied or not does not influence the dynamics and final trajectories, except through pressure calculations, which could affect the NPT ensemble.

For molecules belonging to different species (for example, an alkane molecule in water), the expression for ensemble averaged interaction energy is given by,

$$\langle E \rangle = N_{alkane} \rho_{water} \int_0^\infty 2\pi r^2 g(r) u(r) dr \tag{4}$$

Where, $N_{alkane}$ is the number of united atoms in the alkane molecule, $\rho_{water}$ is the number density of water, and $g(r)$ is the alkane-water radial distribution function. Change in the energy due to the shifting of the potential by $u(r_c)$ is given by:

$$\langle \Delta E \rangle = N_{alkane} \rho_{water} u(r_c) \int_0^{r_c} 2\pi r^2 g(r) dr \tag{5}$$

Equation 5 can be approximated as,

$$\langle \Delta E \rangle = N_{alkane} \rho_{water} u(r_c) \left[ \frac{2}{3}\pi \left( (r_c - \sigma)^3 - (\tilde{N}_{alkane} - 1)\sigma^3 \right) \right] \tag{6}$$

In equation 6, the first term in the brackets assumes $g(r) = 1$ for $r > \sigma$ and 0 for $r < \sigma$. The second term accounts for the excluded volumes of other alkane united atoms. $\tilde{N}_{alkane}$ refers to the number of alkane united atoms that are within the $r_c$ distance of one united atom.

For small alkanes, $\tilde{N}_{alkane} = N_{alkane}$. For the spherical cutoff, $r_c = 1.4$ nm, $\tilde{N}_{alkane} = 11$.

The tail contribution to the energy in the case of "unshifted" potential is also calculated through equation 4 with the assumption of $g(r) = 1$ for $r > r_c$. The tail contribution of the Lennard Jones interactions between alkane and water is given by,

$$\langle E_{LR} \rangle = N_{alkane} \rho_{water} 8\pi\epsilon\sigma^3 \left[ \frac{\sigma^9}{9r_c^9} - \frac{\sigma^3}{3r_c^3} \right] \tag{7}$$

Figure 4 compares the $\Delta G_{hyd}$ obtained for the unshifted HH-alkane potential (labeled as HHalkane), the shifted HH-alkane (labeled as HHalkane (shifted)), the shifted HH-alkane with the effect of potential shift corrected using the equation 6 and the tail corrections added (labeled as HHalkane (shift adj., tail), and the shifted HH-alkane with only the tail corrections added (labeled as shifted, only tail). The main observation is that the shifted potential exacerbates the deviation from the experimental/group contribution values. The correction for the shifted potential + the tail correction results in a negative deviation from the $\Delta G_{hyd}$ obtained from the unshifted potential, with the largest deviation of 3.1 kJ/mol observed for $C_{19}$. Adding only the tail correction to the shifted potential matches the results of the unshifted potential, but this is just fortuitous.

Figure 5 shows the carbon-oxygen radial distribution functions, $g(r)$ for four different alkane-water systems. The $g(r)$ of $C_{10}$, $C_{14}$, and $C_{20}$ are shifted vertically by 0.1 for ease of visualization. Beyond a weak first peak and a trough, the $g(r)$ is close to 1. Thus, the assumption in equation 6 of $g(r) = 1$ for $r > \sigma$ is justified. Table 3 compares the contribution of the potential shift on the $\Delta G_{hyd}$ calculated using the equations 6 and 5 for the case of HH-alkane with TIP4P/2005 water with a spherical cutoff of 1.4 nm. The table shows that the two estimates are close, justifying the approximation in equation 6.

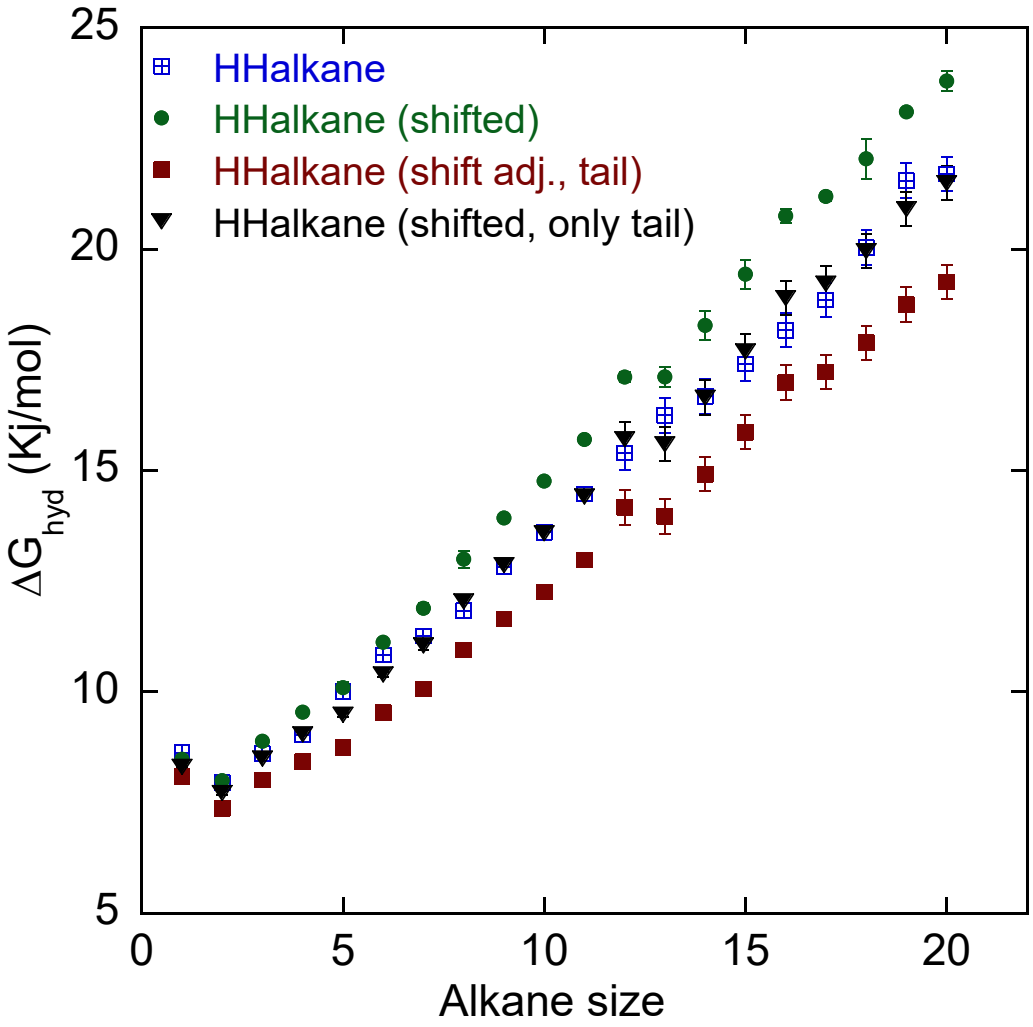


Figure 4: Hydration free energies, $\Delta G_{hyd}$ of alkanes for the unshifted HH-alkane (HHalkane) compared to those obtained for the shifted HH-alkane (HHalkane (shifted)); shifted HH-alkane with the potential shift corrected using equation 6 and tail corrections added (equation 7) (HHalkane (shift adj., tail)); and shifted potential with only tail corrections added (HHalkane (shifted, only tail)).

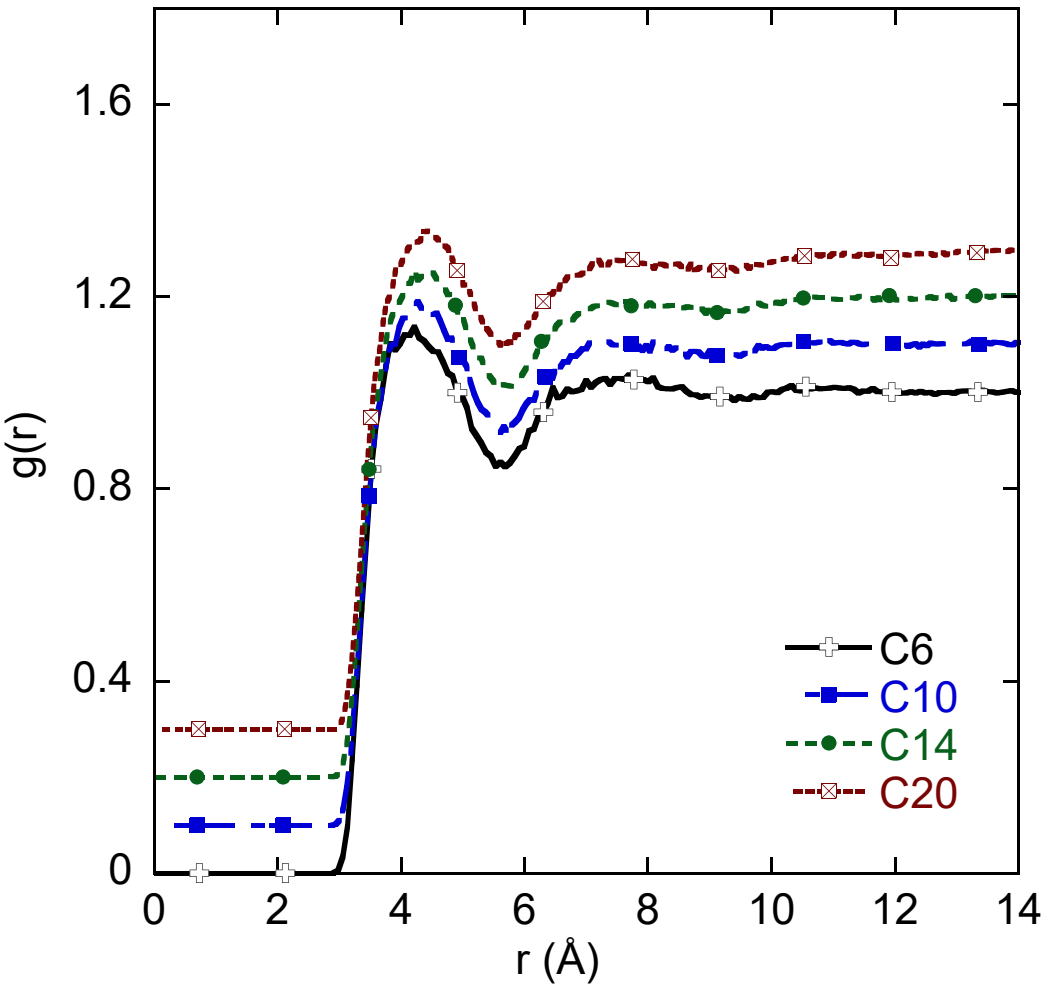


Figure 5: Carbon-oxygen radial distribution function for four different alkanes. The radial distribution functions of $C_{10}$, $C_{14}$, and $C_{20}$ are shifted vertically by 0.1 from the previous graph for ease of visualization.

Table 3: Contribution of the potential shift to the hydration free energies, $\Delta G_{hyd}$ of different alkanes when the HH-alkane force field with TIP4P/2005 water is used with a spherical cutoff of 1.4 nm. The second column is the approximation based on the equation 6. Values in the third column are calculated from the radial distribution functions using the equation 5. The two estimates differ by only 0.33 kJ/mol at most.

| **Alkane** | $\Delta E$ **(eq. 6) (kJ/mol)** | $\Delta E$ **(eq. 5) (kJ/mol)** |
|---|---|---|
| 6 | -0.87 | -0.73 |
| 10 | -1.34 | -1.17 |
| 14 | -1.82 | -1.60 |
| 20 | -2.58 | -2.24 |

# 4 Conclusions

We show that the hydration free energies of linear alkanes from methane to eicosane ($C_{20}H_{42}$) computed using the TraPPE-UA alkane model and four water models (TIP4P/2005, OPC, SPC/E, OPC3) are systematically overestimated relative to experimental/group contribution values when Lorentz-Berthelot mixing rules are applied. Using the cavity free energies of alkanes, we adjust the alkane-water Lennard Jones well-depth parameter ($\epsilon$) to match the hydration free energies to the experimental/group-contribution values. Interestingly, for each water model, the optimal $\epsilon$ is approximately 5% greater than its Lorentz-Berthelot value. The General Amber Force Field (GAFF) all-atom alkane model exhibits smaller deviations from experimental/group contribution values. Finally, we show that applying shifted potential functions increases the deviation of the hydration free energies from the experimental/group contribution values.

# Author Contributions

S.S. conceptualized the project. Y.R. and S.S. designed the methodology. Experiments were performed and analyzed by Y.R. Y.R. and S.S. wrote the original manuscript draft, and performed editing and review. S.S. supervised the project and obtained resources.

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## 5 Conflicts of Interest

The authors have no conflict of interest to declare.

## 6 Data availability

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.15875249.[57]

## 7 Supporting Information

Supporting information is available. Table S1 lists details of the alkane-water simulation systems. Table S2 compares our hydration free energy estimates with those reported in previous studies. Table S3 lists $\Delta G_{hyd}$ from experiments, group-contribution, and all the four water models with alkane-water interaction parameters estimated using the Lorentz-Berthelot mixing rules. Table S4 lists the $\Delta G_{hyd}$ obtained for the four water models with the updated alkane-water well-depth parameter ($\epsilon$). Table S5 lists the $\Delta G_{hyd}$ from GAFF with TIP4P/2005 and SPC/E.

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# Supporting Information: Hydration Free Energies of Linear Alkanes: Evaluating and Correcting Classical Force Field Predictions with Different Water Models

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Table 1: Details of the Alkane-Water Simulation System. Three system sizes are used depending on the alkane length. The simulation system volume fluctuates so as to maintain a constant pressure.

| Alkane | box length [Å] | Number of Water Molecules |
|---|---|---|
| $C_1$-$C_8$ | 36 | 1500 |
| $C_9$-$C_{14}$ | 46 | 3390 |
| $C_{15}$-$C_{20}$ | 56 | 6440 |

Table 2 compares the $\Delta G_{hyd}$ estimated in this work using the TraPPE force field and the TIP4P/2005 and SPC/E water models with the previous estimates by Chen (2000),[1] Xue (2018),[2] and Ashbaugh (2011).[3] Our estimates for TraPPE + TIP4P/2005 match well with those of Ashbaugh (2011) and Xue (2018) with the maximum deviation of 1.65 kJ/mol observed for $C_9$ with Xue (2018). The results from the OPLS + TIP4P are also within 0.7 kJ/mol of our estimates for TraPPE + TIP4P/2005. Our results using the SPC/E water

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model show the largest deviation of 1.5 kJ/mol for $C_8$ when compared to Xue (2018). Overall, this shows that our estimates are in good agreement with the previous studies.

Table 2: Comparison of hydration free energy obtained in this work with previous studies. The estimated error in our calculation, determined from three independent simulations, is 0.05 kJ/mol up to $C_6$, 0.1 kJ/mol up to $C_{11}$, and 0.4 kJ/mol for longer alkanes.

| Alkane | This work | | Chen (2000)[1] | Xue (2018)[2] | | Ashbaugh (2011)[3] |
|---|---|---|---|---|---|---|
| | TraPPE+TIP4P/2005 | TraPPE+SPC/E | OPLS+TIP4P | TraPPE+TIP4P/2005 | TraPPE+SPC/E | TraPPE+TIP4P/2005 |
| 1 | 9.26 | 9.39 | 9.40 | | | 9.33 |
| 2 | 8.82 | 9.28 | 8.20 | | | 8.66 |
| 3 | 9.75 | 9.94 | 9.70 | | | 9.67 |
| 4 | 10.61 | 11.16 | 10.70 | | | 10.33 |
| 5 | 11.69 | 12.19 | | 11.79 | 11.05 | |
| 6 | 12.62 | 13.11 | | 12.99 | 12.12 | |
| 7 | 13.68 | 14.58 | | 14.38 | 13.13 | |
| 8 | 14.64 | 15.69 | | 15.91 | 14.19 | |
| 9 | 16.10 | 16.62 | | 17.75 | 15.30 | |

Table 3: Hydration free energies (kJ/mol) of linear alkanes from methane ($C_1$) to eicosane ($C_{20}$) using different water models with alkane-water interaction parameters calculated using Lorentz-Berthelot mixing rules. The estimated error in our calculation, determined from three independent simulations, is 0.05 kJ/mol up to $C_6$, 0.1 kJ/mol up to $C_{11}$, and 0.4 kJ/mol for longer alkanes.

| Alkane | Experiments | Group Contribution | TIP4P/2005 | OPC | SPC/E | OPC3 | HH-alkane | Shifted HH-alkane |
|---|---|---|---|---|---|---|---|---|
| 1 | 8.37 | | 9.26 | 9.7249 | 9.3933 | 9.2343 | 8.6256 | 8.4752 |
| 2 | 7.66 | | 8.82 | 8.7348 | 9.2782 | 8.8111 | 7.9453 | 7.9936 |
| 3 | 8.18 | | 9.75 | 9.6725 | 9.9414 | 9.9027 | 8.6006 | 8.8800 |
| 4 | 8.70 | | 10.61 | 10.589 | 11.162 | 11.192 | 9.0241 | 9.5404 |
| 5 | 9.76 | | 11.69 | 11.671 | 12.188 | 12.129 | 10.011 | 10.095 |
| 6 | 10.40 | | 12.62 | 12.329 | 13.105 | 13.387 | 10.833 | 11.118 |
| 7 | 10.96 | | 13.68 | 13.589 | 14.578 | 14.642 | 11.258 | 11.886 |
| 8 | 12.10 | | 14.64 | 14.422 | 15.691 | 15.681 | 11.837 | 12.996 |
| 9 | | 12.58 | 16.10 | 15.170 | 16.617 | 16.889 | 12.831 | 13.926 |
| 10 | | 13.32 | 16.92 | 16.089 | 18.078 | 18.186 | 13.598 | 14.759 |
| 11 | | 14.06 | 17.94 | 17.068 | 19.472 | 19.351 | 14.465 | 15.701 |
| 12 | | 14.80 | 18.70 | 17.916 | 20.151 | 20.580 | 15.395 | 17.107 |
| 13 | | 15.54 | 19.85 | 19.245 | 21.628 | 21.608 | 16.245 | 17.112 |
| 14 | | 16.28 | 20.44 | 20.164 | 22.948 | 23.066 | 16.673 | 18.275 |
| 15 | | 17.02 | 21.69 | 21.732 | 24.350 | 24.134 | 17.405 | 19.433 |
| 16 | | 17.76 | 23.03 | 22.113 | 25.149 | 25.677 | 18.171 | 20.750 |
| 17 | | 18.50 | 24.57 | 24.001 | 26.585 | 27.081 | 18.852 | 21.188 |
| 18 | | 19.24 | 25.03 | 24.606 | 27.642 | 27.725 | 20.033 | 22.039 |
| 19 | | 19.98 | 26.97 | 25.912 | 29.246 | 28.745 | 21.548 | 23.097 |
| 20 | | 20.72 | 28.03 | 27.201 | 30.486 | 30.973 | 21.693 | 23.796 |

Table 4: Hydration free energies (kJ/mol) of alkanes with different water models with updated alkane-water well-depth parameter ($\epsilon$).

| Alkane | TIP4P/2005 | OPC | SPC/E | OPC3 |
|---|---|---|---|---|
| 1 | 8.8378 | 9.106 | 8.5273 | 8.8462 |
| 2 | 7.8727 | 7.9507 | 7.5677 | 7.6850 |
| 6 | 10.346 | 10.099 | 10.340 | 10.432 |
| 10 | 12.996 | 13.117 | 13.474 | 13.689 |
| 14 | 16.204 | 15.726 | 17.338 | 17.361 |
| 18 | 19.531 | 19.198 | 19.895 | 21.102 |
| 20 | 22.132 | 20.623 | 22.092 | 22.035 |

Table 5: Hydration free energies (kJ/mol) of alkanes computed using the General Amber Force Field and TIP4P/2005 and SPC/E water models.

| Alkane | TIP4P/2005 | SPC/E |
|---|---|---|
| 1 | 9.696 | 9.802 |
| 2 | 9.5008 | 10.015 |
| 5 | 10.282 | 11.212 |
| 8 | 11.850 | 13.113 |
| 11 | 12.832 | 15.675 |
| 14 | 14.890 | 17.883 |
| 17 | 16.956 | 19.986 |

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