

Accurate Estimates of Infinite-Dilution Chemical Potentials of Small Hydrocarbons in Water via Molecular Dynamics Simulation

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The infinite dilution chemical potentials of methane, ethane, propane, and benzene in water are precisely estimated using the single charging integral method [Chialvo, *J. Chem. Phys.* **1990**, 92, 673; Chialvo, *J. Phys. Chem.* **1991**, 95, 6683] in conjunction with molecular dynamics (MD) simulation using simple pair potentials. The method requires the calculation of ensemble averages of derivatives of the potential energy with respect to the model parameters. The derivatives take the form of pairwise virials and energies which are easily obtained with minor modifications to an existing MD code. The present approach is found to be both stable and precise and allows individual contributions of the model parameters to the free energies to be determined. The dependence of the results for the benzene system on the size of the system is investigated, as is the sensitivity of all of the results to the Lorentz–Berthelot combining rules. The importance of including long-ranged corrections in the results is highlighted. The computed chemical potentials for the united atom hydrocarbon models agree with experiment to within 0.7 kJ/mol.

1. Introduction

Solubility and partitioning between two phases are governed by the changes in the chemical potential (μ_i) of a solute as it experiences various physical environments. The ability to describe these changes at a fundamental level, and subsequently to be able to model and predict macroscopic behavior, remains an enormous challenge, the motivation for which is largely driven by applications to industrial separation and biological processes. For example, a knowledge of free energies (and thus Henry's constants) for sparingly soluble solutes in water, such as volatile organics, is essential in the design of separations technology for dilute waste streams.

The use of molecular modeling in the prediction of μ_i for practical purposes is still at an early stage; however, due to advances in both technical methodologies and potential development, we are now at a point where reliable estimates for free energies may be obtained for increasingly complex molecules using molecular simulation techniques. The calculation, rather than measurement of μ_i , is attractive because values may be needed for systems under extreme conditions or in confined systems, where the calculations are feasible but where direct measurement is difficult or impossible.¹ Such calculations also have an important role to play in the understanding of solvation effects on biomolecules.²

Aside from the technical challenges to accurate, sufficient sampling in the calculation of free energy related quantities via molecular simulation, the reasons behind the difficulty in the molecular-based estimation approach are rooted in the realization that transferability at the atomic or united atom level cannot in general be exploited to give quantitative results for mixtures. This appears to be particularly true for systems in which cross hydrogen bonding is dominant, such as alcohol/water mixtures,^{3,4} where the components can both donate and accept

hydrogen bonds. In these mixtures, the use of pairwise additive site–site potentials of the Lennard–Jones + fixed, fractional charges (LJFFC) form, combined with a simple empirical approach to obtain the unlike pair potential parameters (such as the Lorentz–Berthelot (LB) combining rules), is unworkable because of the sensitive balance between repulsion and attraction inherent in the description of the hydrogen bond. This leads to extreme sensitivities in the computed free energies (on the order of the total solvation free energy) to very small deviations ($\approx 1\%$) from the combining rules.⁴ In contrast, for those cases where the solvation free energy is relatively large and dominated by electrostatics, such as partial charge models of biomolecules and simple ionized salts in water, simulation has been shown to be quite successful in predicting solvation free energies.^{2,5,6} In these solutions, although errors might be introduced in the LJ contributions via the empirical combining rules, their effects on the predictions are apparently overshadowed by the magnitude of the electrostatic contribution.

For mixtures in which the unlike interactions are relatively weak, such as hydrocarbon/water solutions, one might expect fewer difficulties in the accurate calculation of mixture properties using models optimized for the pure components. In fact, the residual chemical potential of the prototypical test case, methane in water, has been calculated numerous times^{7–10} in the simple point charge (SPC) model of water using simple pairwise additive potentials which treat the methane as a single united atom spherical interaction site. The results, ranging from (8.5 ± 0.7) kJ/mol to (10.5 ± 1.7) kJ/mol (at ambient conditions), are generally in good agreement with the experimental value (8.4 kJ/mol¹¹), as long as a sufficient number of water solvent molecules is included. Relatively less attention has been given to the possibility of accurately calculating solvation free energies for the larger hydrocarbons, the focus of the present work. In earlier works, the apparent failure of united atom models to perform well for aqueous free energy studies led to development of more complicated, all-atom

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TABLE 1: Final Parameters in the Conversions^a

mutation	ϵ_O/k_b	ϵ_H/k_b	ϵ_{HH}/k_b	σ_O	σ_H	σ_{HH}	l_{OH}	l_{OH}	l_{HH}	λ_1
SPC water	77.92	0.00	0.00	3.166	0.000	0.000	1.000	1.000	1.633	
water \rightarrow methane	147.95	0.00	0.00	3.730	0.000	0.000	1.000	1.000	1.633	σ_O
methane \rightarrow ethane	104.17	104.17	0.00	3.775	3.775	0.000	1.530	1.000	1.633	l_{OH}
ethane \rightarrow propane	59.38	88.06	88.06	3.905	3.905	3.905	1.530	1.530	2.537	l_{OH}
water \rightarrow benzene(6)	55.35	55.35	55.35	3.750	3.750	3.750	2.425	2.425	2.425	l_{OH}
mutation	ϵ_C/k_b	ϵ_H/k_b	σ_C	σ_H	q_C	q_H	λ_1			
benzene(6)	55.35	0.00	3.75	0.00	0.00	0.00				
benzene(6) \rightarrow benzene(12)	35.23	15.10	3.55	2.42	-0.115	0.115				σ_C

^a ϵ_i/k_b in units of K; σ_i and l_i in units of Å.

models.^{12,13} More recent work¹⁴ has demonstrated that very good agreement with experiment for both methane and ethane can be obtained with united atom hydrocarbon and SPC-type water models.

Since the introduction of the Widom test particle method,¹⁵ numerous improvements and alternative approaches have been suggested for calculating free energies in molecular simulation. A current overview of many of these can be found in ref 16. A recently proposed Expanded Ensemble (EE) method⁵ and related methods appear to offer large improvements in efficiency over the test-particle methods, at least for simple solutes. These methods allow the free energy to be estimated from a single simulation run, although appropriate weighting factors must first be quantified with additional runs.¹⁶

In the present work, we use the “single-charging integral” (SCI) method^{17,18} to calculate the infinitely dilute residual chemical potential for methane, ethane, propane, and benzene in water. This approach is based on the Kirkwood coupling parameter concept,¹⁹ and thus relies on a number of separate simulations in which a solute is slowly mutated from one form to another. The approach differs from thermodynamic integration (TI)²⁰ or free energy perturbation (FEP)^{2,21} methods, which utilize a single coupling parameter that varies from 0 to 1, by utilizing a vector of coupling parameters, the elements of which correspond to simple functions of each potential parameter that changes during the mutation. The SCI method thus allows one, in principle, to identify free energy changes with specific features of the model, such as interaction site size, well depth, bond length, or bond angle. The approach also affords more flexibility in dealing with possible singularities, numerical difficulties, or unwanted phase changes which can plague the more “literal” Kirkwood methods such as TI or FEP. Finally, the inclusion of long-ranged LJ corrections and use of the Ewald sum to handle the long-ranged electrostatic interactions are straightforwardly applied in the SCI method. In the following section we provide some details concerning the simulation method.

2. Methodology

The SCI formalism has been previously outlined in detail,^{17,18} with the difference between the residual chemical potential for a solute i infinitely dilute in a solvent j (μ_i^∞)^{res} and that of pure j (μ_j^∞)^{res} given by

$$(\mu_i^\infty - \mu_j^\infty)^{\text{res}} = \sum_{\alpha=1}^k \int_{\lambda_\alpha}^{\lambda_\alpha^i} d\lambda_\alpha \left\langle \frac{\partial U(\vec{\lambda})}{\partial \lambda_\alpha} \right\rangle_{NPT, \lambda_{\beta \neq \alpha}} \quad (1)$$

Here $U(\vec{\lambda})$ is the total potential energy function, k is the number of changing potential parameters, and $\langle \dots \rangle_{NPT}$ represents an isothermal–isobaric ensemble (time) average. Equation 1 may be rewritten as a much more computationally feasible single

integral by parametrizing each of the coupling parameters λ_γ in terms of one arbitrarily chosen parameter, λ_1 :

$$(\mu_i^\infty - \mu_j^\infty)^{\text{res}} = \int_{\lambda_1}^{\lambda_1^i} d\lambda_1 \sum_{\alpha=1}^k c_\alpha \left\langle \frac{\partial U(\vec{\lambda})}{\partial \lambda_\alpha} \right\rangle_{NPT, \lambda_{\beta \neq \alpha}} \quad (2)$$

where $c_\gamma \equiv \partial \lambda_\gamma / \partial \lambda_1 = (\lambda_\gamma^{\text{final}} - \lambda_\gamma^{\text{initial}}) / (\lambda_1^{\text{final}} - \lambda_1^{\text{initial}})$ so that $\lambda_\gamma = c_\gamma (\lambda_1^{\text{final}} - \lambda_1^{\text{initial}}) + \lambda_\gamma^{\text{initial}}$. The reliability of the estimates obtained from eq 2 depends on two factors: (1) the accuracy of the integrands, which is contingent upon adequate sampling of the phase space, and (2) the accurate numerical integration of eq 2. The latter accuracy in turn depends on the behavior of the function $\sum_{\alpha=1}^k c_\alpha \langle \partial U(\vec{\lambda}) / \partial \lambda_\alpha \rangle$ and can be achieved by including enough integrands to allow the function to be accurately fitted to, e.g., a polynomial or cubic spline, which can then be numerically integrated.

The above equations provide a well-defined prescription for calculating the difference in chemical potential between the solute and pure water (or between two different solutes in water) by evaluating ensemble averages of the derivative of the potential energy function with respect to all of the changing potential parameters along a pathway linear in λ_1 . Within the context of LJFFC models under LB combining rules, expressions for the relevant derivatives with respect to the LJ size (σ) and energy (ϵ), partial charges (q), and bond lengths/angles (l) take the form of pairwise energies and virials and are easily evaluated with minor modifications of an existing code. These expressions are straightforwardly derived within the framework of the Ewald summation and have been given elsewhere.^{3,4} In the present work, we used the SPC model²² for water and the OPLS united atom hydrocarbon models.²³ For benzene, the difference between the infinitely dilute chemical potential of the 6-site (benzene(6)) and 12-site (benzene(12))¹³ models was also calculated. By subtracting from the above differences the chemical potential of pure SPC water, (determined in the present work to be -26.2 ± 0.1 kJ/mol using TI and following the same integration pathway chosen by Quintana and Haymet,²⁴) we obtain absolute values for the solvation free energies of the solutes.

The solute mutations start with either a water molecule or the previous solute and follow the conversions outlined in Table 1, which lists the final values, after each mutation, of the parameters associated with the original sites of the oxygen and hydrogens in the water model. For the united atom models, the final values of the partial charges are zero in each case. Each transformation was accomplished via a series of 11–17 simulations of about 200 ps in duration. With the exception of LJ sites which grow from nothing, the coupling parameters λ_γ are all identified with the actual potential parameters. For the former, the coupling parameters associated with the LJ energies were taken as $\epsilon^{1/2}$ to avoid singularities in the derivatives when $\epsilon \rightarrow 0$. In the water \rightarrow benzene(6) conversion, the oxygen and hydrogen

sites of water became “primary” CH sites in the generalized constraint dynamics formalism of Ciccotti et al.,²⁵ while the 3 remaining “secondary” CH sites were grown simultaneously. For the benzene(6) \rightarrow benzene(12) conversion, the explicit hydrogen sites were included as additional secondary sites. The equations of motion for the 12-site model were greatly simplified by treating all of the atomic masses as equal. In these simulations, the 36 coupling parameters were the LJ size and energy parameters and the partial charges associated with all 12 sites.

The equations of motion were solved using *NPT* Nosé–Hoover dynamics²⁶ to fix the temperature and pressure to 298 K and 0.1 MPa, with a noniterative constraint dynamics adaptation²⁷ of the Beeman algorithm²⁸ to fix bond lengths and bond angles, and Ewald summation²⁹ to handle the long-ranged Coulombic forces. In most cases, the simulation cell contained 223 solvent molecules and 1 solute molecule. To check for system size effects, the water \rightarrow benzene(6) calculations were repeated using 499 solvent water molecules. The benzene(6) \rightarrow benzene(12) simulations were likewise performed using 499 solvent molecules. The interactions were cut off at $L/2$, where L is the length of the side of the simulation box, and the Ewald convergence parameter was set to $5.6/L$. Long-ranged corrections to the energy, virial, and to all of the derivatives with respect to the LJ parameters in the charging integrands were included in the usual way,²⁹

$$\langle a(r_{ij}) \rangle^{LRC} = 2\pi\langle\rho\rangle N \int_{r_c}^{\infty} a(r)g(r)r^2 dr \quad (3)$$

where $a(r)$ is a pairwise quantity, $\langle\rho\rangle$ is the average solvent number density, and the value of $g(r)$ is assumed to be unity beyond the cutoff distance, r_c . Long-ranged corrections to the bond length derivatives could not be included as they incorporated direction-dependent terms related to the intermolecular forces.

3. Results and Discussion

An important consideration in free energy calculations is the length of simulation time necessary for convergence of the calculation. This can be established in the present approach by integrating over the cumulative time averages of the potential energy derivatives

$$\mu_i^{\infty, res} = \lim_{t \rightarrow \infty} \int_{\lambda_1^i}^{\lambda_1^f} d\lambda_1 \sum_{\alpha=1}^k c_{\alpha} \frac{1}{t} \int_0^t dt \frac{\partial U(\vec{\lambda}, t)}{\partial \lambda_{\alpha}} + \mu_j^{\infty, res} \quad (4)$$

where the ensemble average denoted by $\langle \dots \rangle$ in eq 2 is written explicitly as a time average and where the cumulative time averages are taken at intervals of 10 time steps, fitted to a cubic spline, and numerically integrated. The results are shown in Figure 1, and the final values of the integrands are shown in Figure 2. For the water \rightarrow methane conversion, fluctuations on the order of 1 kJ/mol occur out to about 11×100 ps = 1.1 ns, indicating that fairly long simulation times are necessary to obtain $\mu_i^{\infty, res}$ to a precision of a fraction of a kJ/mol. For the water \rightarrow benzene(6) calculations, somewhat longer simulation times up to 2 ns are required to obtain precisions to within 0.5 kJ/mol. The results in Figure 1 also highlight the importance of including the long-ranged corrections to the LJ interactions, particularly for the relatively compact benzene solute, for which the attractive dispersion interactions dominate over the repulsive overlap potential. Here, neglect of these corrections in the

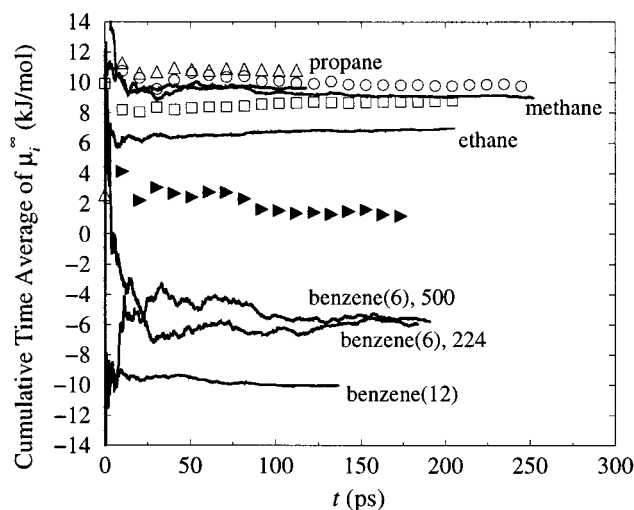


Figure 1. Convergence of the residual chemical potential with simulation time at $T = 298$ K and $P = 0.1$ MPa. Symbols are the results with the omission of the long-ranged corrections to the derivatives with respect to the LJ parameters: \circ , methane; \square , ethane; \triangle , propane; \blacktriangle , benzene with 499 solvent water molecules.

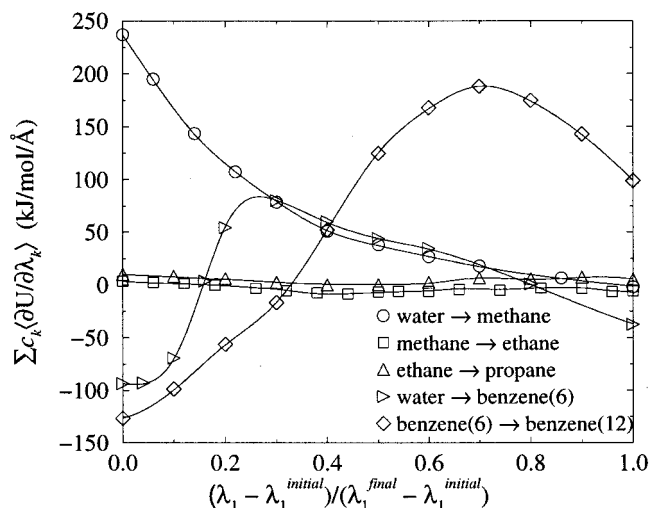


Figure 2. Integrant of eq 2 vs reduced first coupling parameter for the various transformations.

TABLE 2: Pure and Aqueous Mixture Thermodynamic Properties^a at 298.0 K

solute	P (MPa)	ρ (kg/m ³)	U^c (kJ/mol)	$\mu_i^{\infty, res}$ (kJ/mol)
SPC water	7(5)	980(2)	-42.1(1)	-26.2(1)
methane	1(5)	971(2)	-42.1(1)	9.0(3)
ethane	1(5)	973(2)	-42.1(1)	7.0(5)
propane	1(5)	975(2)	-42.1(1)	9.5(7)
benzene(6)	1(5)	978(2)	-42.2(1)	-5.7(5)
benzene(12)	1(4)	978(2)	-42.0(1)	-10.0(6)

^a Value in parentheses is standard uncertainty in the last digit.

potential energy derivatives changes the sign of the chemical potential and results in an overestimate in $\mu_i^{\infty, res}$ of nearly 8 kJ/mol.

The calculated values for the hydrocarbon chemical potentials are given in Table 2 and shown in Figure 3. Overall, very good agreement with experiment is obtained, with the largest errors being those of the propane and benzene(12). In particular, the simulations are able to predict the minimum in $\mu_i^{\infty, res}$ with carbon number n for $n = 2$. Previous calculations for the methane \rightarrow ethane transition in water using all-atom hydrocarbon models have resulted in a *positive* value of between 0.7 kJ/mol to 1.8

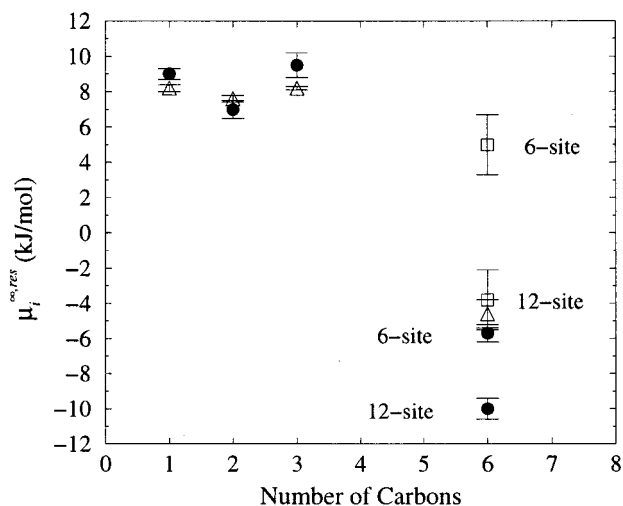


Figure 3. Comparison of calculated (●) with experimental (Δ) results for the residual chemical potential at $T = 298$ K and $P = 0.1$ MPa. The experimental values are averages of results found in references 31, 33, and 34, and their uncertainties are rough estimates based on the spread in the data. The symbols (□) denote Jorgensen and Severance's¹³ calculated values for the united and all-atom benzene models in TIP4P water. The uncertainties in the calculated results are obtained as described in the text.

kJ/mol for the difference $(\mu_{\text{ethane}}^{\infty} - \mu_{\text{methane}}^{\infty})^{\text{res}}$.^{12,30} For the ethane \rightarrow propane transformation, Fleischman and Brooks³¹ obtained a value of -3.5 kJ/mol using the OPLS united atom model and TIP3P water, in contrast to the experimental¹¹ value of 0.6 kJ/mol and the value of 2.5 kJ/mol obtained presently. In all of these previous works, the solute water interactions were cut off at between 7.75 to 8.0 Å. As has been recently pointed out by Mordasini Denti et al.³² in the context of free energy calculations for aromatic compounds in water, the details of the intermolecular cutoff can have a quite significant effect on the final estimates of the free energy. For example, they found a difference of more than 1.6 kJ/mol between the results for the naphthalene \rightarrow benzene transformation under two different cutoff criteria.

Interestingly, the chemical potential of the OPLS 12-site explicit hydrogen model is strongly underpredicted relative to the experimental value^{33,34} by more than 5 kJ/mol. The calculation of $\mu_i^{\infty, \text{res}}$ for both the 6-site and 12-site models of benzene in TIP4P water has been previously made, where values of (5.0 ± 1.7) kJ/mol and (-3.8 ± 1.7) kJ/mol were obtained for the united atom and the all atom models, respectively.¹³ These simulations made use of FEP, and although the system size (265 solvents) was probably adequate, the long-ranged electrostatic interactions were truncated spherically and no mention was made of the inclusion of the long-ranged corrections for the LJ interactions. The present results for the difference in $\mu_i^{\infty, \text{res}}$ between the two models are qualitatively consistent with those of Jorgensen and Severance,¹³ in that the value for the 12-site model is significantly lower than that of the 6-site model. Although some differences in the calculation may be due to the use of different water models, the large discrepancy between the two calculations is most likely due to the neglect of the long-ranged electrostatic interactions and (possibly) long-ranged LJ corrections in the earlier work.

By performing simulations of the LB mixtures, one can also assess the effects of deviations from the LB combining rules on the chemical potential differences by introducing size (η) and energy (ξ) deviation parameters, where $\eta_{\alpha\beta} = 2\sigma_{\alpha\beta}/(\sigma_{\alpha} + \sigma_{\beta})$ and $\xi_{\alpha\beta} = \epsilon_{\alpha\beta}/(\epsilon_{\alpha}\epsilon_{\beta})^{1/2}$. The details of this analysis have

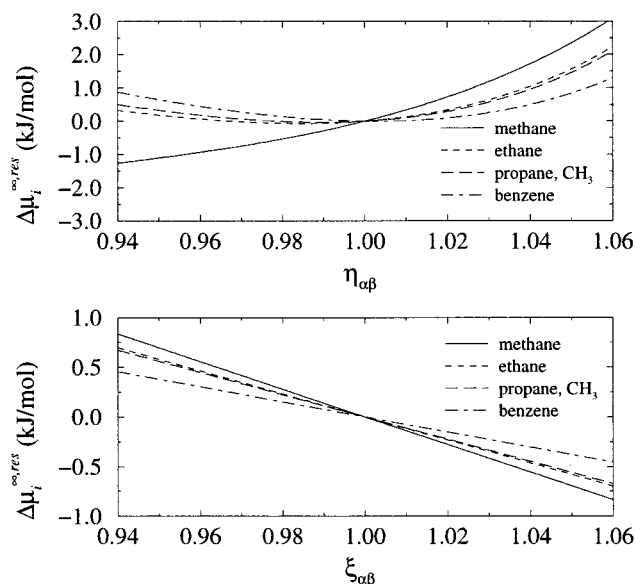


Figure 4. Sensitivity of chemical potentials to deviations from LB combining rules at $T = 298$ K and $P = 0.1$ MPa. (A) deviations from Lorentz rule ($\eta = 1$); (B) deviations from Berthelot rule ($\xi = 1$).

been provided elsewhere,^{4,35} so here we present only the results, shown in Figure 4. These results agree with a similar analysis for the methane/water system by Lin and Wood,¹ who found that the LJ size parameter σ of the water–methane interaction was the most important in terms of sensitivity to the computed methane chemical potential. The present analysis shows that deviations of about 5% in the unlike energy parameters and 2% to 3% in the unlike size parameter are necessary before significant effects (i.e., above the statistical uncertainty) are seen in the estimated values of $\mu_i^{\infty, \text{res}}$.

4. Conclusions

In this work we have demonstrated the use of the single-charging integral method for the calculation of residual thermodynamic properties via molecular dynamics simulation of small multisite united atom hydrocarbons and an all-atom benzene model at infinite dilution in water. The SCI variant of the Kirwood coupling parameter concept utilized herein encounters no numerical difficulties and appears to be a robust, accurate, and efficient route to obtain differences in residual chemical potentials. By subtracting the value of μ for pure SPC water, we obtain estimates for the absolute infinite-dilution chemical potentials of the four hydrocarbons studied which compare very well with the experimental values. The present results, in agreement with recent calculations of Errington et al.,¹⁴ suggest that united atom hydrocarbon models developed from fitting to pure hydrocarbon properties can be used to accurately predict mixture free energies, as long as adequate care is taken to ensure that both sampling problems and cutoff artifacts are alleviated.

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