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Determination of Partial Molar Volumes from Free Energy Perturbation Theory

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ABSTRACT

Partial molar volume is an important thermodynamic property that gives insights into molecular size and intermolecular interactions in solution. Theoretical frameworks for determining the partial molar volume ($V°$) of a solvated molecule generally apply Scaled Particle Theory or Kirkwood-Buff theory. With the current abilities to perform long molecular dynamics and Monte Carlo simulations, more direct methods are gaining popularity, such as computing $V°$ directly as the difference in computed volume from two simulations, one with a solute present and another without. Thermodynamically, $V°$ can also be determined as the pressure derivative of the free energy of solvation in the limit of infinite dilution. Both approaches are considered herein with the use of free energy perturbation (FEP) calculations to compute the necessary free energies of solvation at elevated pressures. Absolute and relative partial molar volumes are computed for benzene and benzene derivatives using the OPLS-AA force field. The mean unsigned error for all molecules is 2.8 cm^3/mol. The present methodology should find use in many contexts such as the development and testing of force fields for use in computer simulations of organic and biomolecular systems, as a complement to related experimental studies, and to develop a deeper understanding of solute-solvent interactions.

INTRODUCTION

The partial molar volume of a substance, V_i, in a solution depends on the temperature, pressure, and concentrations of all components. A particularly fundamental quantity is the partial molar volume of a substance in a pure solvent in the limit of infinite dilution, V^o, which reflects the change in volume upon addition of a single solute molecule. Similarly, the free energy of solvation of the substance (ΔG_{solv}) corresponds to the change in free energy associated with its transfer from the gas phase into the solvent at infinite dilution. The two quantities are interrelated through the fundamental relationship, $dG = VdP - SdT$, such that at constant temperature, the pressure derivative of the free energy of solvation is equal to V^o (eq 1).[1,2] From a computational standpoint, one can then envision computation of V^o via either

$$\left(\frac{d\Delta G_{solv}}{dP}\right)_T = V^\circ \qquad (1)$$

a direct calculation of the change in volume of a pure liquid upon adding the solute or by computing the free energy of solvation as a function of pressure. Such direct calculations were first performed when it became possible to carry out Monte Carlo statistical mechanics simulations in the NPT ensemble, e.g., for methane in water and sodium and methoxide ions in methanol.[3] However, given the computer resources *ca.* 1980, the computed V^o values could not be adequately converged.

The situation has evolved, and today precise results can be obtained for both ΔG_{solv} and V^o. In particular, free energies of hydration have become increasingly used to evaluate the performance of molecular mechanic force fields, such as OPLS, AMBER, CHARMM, and AMEOBA.[4-14] Systematic studies of small molecule solvation are viewed as important tests for force-field parameters prior to their utilization in simulations of biological systems. However, computations of partial molar volumes and pressure and temperature effects on solution properties have not been regularly incorporated into force-field parameterization; rather they are sometimes investigated after the parameterization is complete.[15-20] This report focuses on the calculation of partial molar volumes V^o by both the direct and derivative (eq 1) methods to establish optimal protocols and test some results for the OPLS-AA force field.[4,5]

For additional background, it should be noted that theoretical frameworks that have been used to compute partial molar volumes of small molecules including Scaled Particle Theory (SPT),[21] Kirkwood-Buff theory (KBT),[22] and more direct techniques.[16,23-29] Each method has its advantages.[30] SPT yields an expression for the work of cavitation in hard sphere and real fluids,[31] and KBT can probe the local environment around a solute, giving insight into preferential solvation and solute-solvent interactions.[32] However, with the advancement of computational capabilities, more straightforward ways of estimating partial molar volumes are becoming popular. Floris in 2004 and Moghaddam and Chan in 2007 reinvestigated the direct method (DM) and showed that it could be used to obtain reliable results for hard-sphere cavities in water.[24,25] The direct method computes $V°$ as the difference between the total volume of N solvent plus one solute (A) molecules and the total volume of N solvent molecules alone. This can be done in two approaches. First, the position of the solute can be fixed (N, A) and the solute's $V°$ can be determined from eq 2. The brackets $\langle V \rangle$ indicate total ensemble averages of volume; κ_T represents the computed isothermal compressibility of the pure liquid; and, the last term in eq 2 accounts for the contribution of translational motion of the solute, which amounts to 1.1 cm^3/mol in water at 25 °C.[32,33] Alternatively, the solute can be allowed to freely translate and rotate through the solvent (N+A) and the solute's $V°$ can be determined from eq 3. Since 2007, Weinberg and coworkers have similarly applied this methodology using molecular dynamics to analyze partial molar volumes of hydrocarbon solutes in a variety of solvents and volumes of activation for three reactions.[17,18] Additionaly, Ashbaugh and co-workers recently used the direct method in conjunction with other techniques to compute $V°$ values for amino acid side chains and volumes of micellization.[16] Others have employed this method to study thermodynamic properties of small proteins.[26,29]

$$V° = \langle V_{N,A} \rangle - \langle V_N \rangle + k_B T \kappa_T \qquad (2)$$

$$V° = \langle V_{N+A} \rangle - \langle V_N \rangle \qquad (3)$$

Alternatively, $V°$ can be determined by computing free energies of solvation at several pressures and fitting the data to a line (eq 1). In this report, this approach is referred to as the slope method, since V° is given by the slope of the linear fit. Although most experimental partial molar volumes are determined via densitometric analyses,[34-37] the slope method has been applied experimentally to study very insoluble molecules in water.[38] Computationally, this approach has been less well explored than the direct methods. Moghaddam and Chan termed it the indirect method and used particle insertion to calculate methane's free energy of hydration as a function of pressure, and thus methane's $V°$ via the slope of the linear fit.[24] Mohori and co-workers applied particle insertion methods and a thermodynamic perturbation theory with a hard-sphere reference to examine several thermodynamic properties of a 3D-Mercedes-Benz water model, including pressure and temperature derivative properties. They observed an "almost linear" relationship between transfer free energies and pressure.[15] Additionally, Dahlgren and co-workers have investigated several derivative properties of Na^+ and Cl^- solvation free energies via thermodynamic integration.[39] However, in the present case free energy perturbation theory (FEP) based upon the Zwanzig equation[40] is applied to compute the requisite free energies of solvation.

With FEP theory, the free energy difference between an initial and final state of a system is computed as an ensemble average of the potential energy difference between those states, sampled at the initial state (eq 4). In Monte Carlo (MC) or molecular dynamics (MD) statistical mechanic simulations, FEP theory can be applied to study chemical equilibria via a thermodynamic cycle (Scheme 1).[11,40-44] In this way, FEP theory has been used successfully to compute relative or absolute free energies of solvation for many small organic molecules.[9-11,43] In conjunction with the thermodynamic cycle in Scheme 1, a relative free energy of solvation ($\Delta\Delta G_{\mathrm{solv}}$) between two molecules can be calculated by transforming molecule (A) into a different molecule (B) in the gas phase and solution (eq 5).[11,40-44] An absolute free energy of solvation is computed in a similar manner, except that the final state of the perturbation (B) is a "null" or non-existent molecule; in this case $\Delta G_{\mathrm{B}} = 0$ and eq 6 applies. These calculations are often referred to as molecular annihilations and effectively make a molecule "disappear" from the gas phase and solution in separate calculations.[9] Computationally, the gas phase is treated as an ideal gas at a temperature of 25 °C and a pressure of 1 atm using a single molecule in isolation.

$$\Delta G(\mathrm{A} \rightarrow \mathrm{B}) = G_{\mathrm{B}} - G_{\mathrm{A}} = -k_b T ln\langle \exp[-(E_{\mathrm{B}} - E_{\mathrm{A}})/k_b T]\rangle_{\mathrm{A}} \quad (4)$$

$$\Delta\Delta G_{solv} = \Delta G_B - \Delta G_A = \Delta G_{Soln} - \Delta G_{Gas} \qquad (5)$$

$$\Delta G_A = -(\Delta G_{Soln} - \Delta G_{Gas}) \qquad \text{for B null} \qquad (6)$$

The slope method can be applied with FEP theory to determine a molecule's partial molar volume by combining eqs 1 and 6 with $\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{A}}$ and noting that $\left(\frac{d\Delta G_{Gas}}{dP}\right)_T = 0$ in the ideal gas phase, thus yielding eq 7. Operationally, one needs to perform the annihilations of the solute in the solvent as a function of external pressure in the NPT ensemble and fit the free energy results to a line. In a similar manner, differences in partial molar volumes ($\Delta V°$) for two solutes A and B can be obtained from relative FEP calculations using eqs 1 and 5.

$$\left(\frac{d\Delta G_{solv}}{dP}\right)_T = -\frac{d}{dP}(\Delta G_{Soln})_T = V° \qquad (7)$$

Scheme 1

$$\begin{tikzcd}
\mathrm{A} \arrow[r, "\Delta \mathrm{G}_{\mathrm{Gas}}"] \arrow[d, "\Delta \mathrm{G}_{\mathrm{A}}"'] & \mathrm{B} \arrow[d, "\Delta \mathrm{G}_{\mathrm{B}}"] & \text{Gas} \\
\mathrm{A} \arrow[r, "\Delta \mathrm{G}_{\mathrm{Soln}}"'] & \mathrm{B} & \text{Solution}
\end{tikzcd}$$

In this report, the slope method is used to evaluate the precision of FEP theory for computing partial molar volumes in explicit-solvent condensed phase simulations. This work uses much of the same methodology that has been reported previously for computing free energies of hydration at 25 °C,[9-11,43] except that simulations are also run at several pressures above 1 atm. Partial molar volumes computed via FEP theory are compared with results from the direct methods.

COMPUTATIONAL DETAILS

All Monte Carlo simulations and free energy perturbation calculations were carried out with the *BOSS* program using the isothermal-isobaric ensemble at 25 °C.[45] Water was represented using the TIP4P water model.[46] All other solvents and solute molecules were represented with the OPLS-AA force field.[4,5,47,48] Prior to computing ΔG_{solv} values at elevated pressures, pure liquid simulations of water, carbon tetrachloride, and benzene solvents were conducted to equilibrate all solvent boxes at elevated pressures. Direct method and FEP calculations ensued.

Pure Liquid Simulations. Metropolis MC simulations[49] were performed at increasing pressures for pure water, carbon tetrachloride (CCl_4), and benzene. Pressures in water ranged from 1 to 8000 atm in increments of 1000 atm. Pressures in carbon tetrachloride and benzene were performed up to 1000 atm and 650 atm, respectively, in increments of 150–250 atm. Reduced pressures for non-aqueous solvents were used to conform to experimental freezing pressures. At 25 °C, water freezes at *ca*. 9500 atm;[50-52] CCl_4 freezes at 1314 atm;[53] and benzene freezes at 703 – 725 atm.[53,54] These limits for CCl_4 and benzene have been generally well observed in several thermophysical studies.[55-58] Computed densities at elevated pressures show excellent agreement when compared to experiment (Tables S1–S3, Figures S1–S3).[50,55,56,59,60] With the TIP4P model, the maximum percent error is 1.6%; the density of water is slightly overestimated at all pressures. For carbon tetrachloride and benzene the computed densities fall below the experimental values at all pressures and show maximum percent errors of 4.3% and 1.8%, respectively. This data suggests that TIP4P and OPLS-AA models are reasonably well-suited for volumetric studies at elevated pressures.

Simulations were carried out using cubic cells of 267 or 512 solvent molecules with periodic boundary conditions; the larger box was used for TIP4P water. Solvent molecules freely translated and rotated, but their intramolecular degrees of freedom were not sampled. Attempted changes in the volumes of the system were automatically adjusted by the program to achieve acceptance rates of *ca.* 40%, and the ranges for translations and rotations were set to yield acceptance rates of 40-50%. Solvent-solvent cutoff distances of 10Å were used for water and CCl_4, and a cutoff distance of 12 Å was used for benzene. Nonbonded cutoff distances are based on center-of-mass separations or the O-O distance for water and include quadratic smoothing to zero over the last 0.5Å.[4,9] For non-aqueous solvents, the *BOSS* program automatically includes an energy correction to account for long-range Lennard-Jones interactions neglected beyond cutoff distances.[45] To ensure proper convergence at higher pressures, all simulations were equilibrated for 100 million (M) configurations, after which the averaging was continued for another 120 million configurations (100M/120M).[61] Simulations of water and CCl_4 began from stored solvent boxes in *BOSS*; neat benzene was generated as a custom solvent. Equilibrated solvent boxes for each pressure were subsequently used in the FEP calculations.

Direct Method. Due to the ease and general success of estimating partial molar volumes directly from total simulation volumes,[16-19,24,25,33] the direct method was used to compute the partial molar volume of benzene in water, carbon tetrachloride, and benzene. To test convergence, calculations were performed using 20M/20M, 50M/50M, 100M/100M, 250M/250M, 500M/500M, 800M/800M and 1000M/1000M configurations. Cubic cells of 500 water, 264 CCl_4, and 266 benzene solvent molecules were used with periodic boundary conditions. For simulations involving a benzene solute, solute-solvent cutoff distances were set to 10 Å and quadratic smoothing was performed over the last 0.5Å of the cutoff. Solute moves were attempted every 100 steps and solute translations and rotation ranges were set to ±0.06Å and ±6.0°. Internal degrees of freedom of the solute were fully sampled. All other simulation conditions are identical to those used in the pure liquid simulations, except that these simulations were performed only at 1 atm. For each solvent, three calculations were performed: solvent with no solute (V_N), solvent with a fixed-position solute ($V_{N,A}$), and solvent with an unrestrained solute (V_{N+A}), corresponding to eqs 2 and 3.[24] Statistical uncertainties (± 1σ) were calculated from the batch means procedure using batch sizes of 1 – 5M configurations.[11,62]

Monte Carlo/Free Energy Perturbations. Relative and absolute free energies of hydration were computed with the *BOSS* program using MC/FEP calculations, as described previously.[9-11,42,43] Alchemical transformations were performed in gas and solution according to the thermodynamic cycle in Scheme 1 to compute relative or absolute free energies. First, absolute ΔG_{solv} values for water, CCl_4, and benzene were computed in their respective neat liquid via complete annihilation. ΔG_{solv} values for benzene in water and carbon tetrachloride were also determined in the same manner. Second, relative values, $\Delta\Delta G_{solv}$, were computed by alchemically transforming benzene derivatives into benzene in the gas phase and in water. The pressure dependence of ΔG_{solv} or $\Delta\Delta G_{solv}$ was then analyzed to derive partial molar volumes of all solutes.

Absolute ΔG_{solv} values were determined in the three solvents at all pressures as described in the above Pure Liquid section. Benzene was selected for study in all three solvents due to its hydrophobic nature, the availability of experimental data,[34,35,38,63-65] and its inclusion in previous studies.[11,17,18,38,48,66-68] Water and CCl_4 were also examined in their pure liquids to help validate the methodology. To annihilate a molecule, all force field intermolecular interactions for the solute must be scaled to zero. This is best accomplished in two separate steps. First, all partial atomic charges are scaled to zero to remove the electrostatic contribution. Second, in a separate calculation, all Lennard-Jones parameters are scaled to zero while simultaneously shrinking the molecule. In the second step, solute shrinking is accomplished over the course of the simulation by perturbing all atom types to idealized sp^2 or sp^3 dummy atoms with equilibrium bond lengths of 0.3Å. Each step of the annihilation was performed using twenty-one λ windows of simple overlap sampling (21-SOS)[11,69] with 8M/8M configurations in the gas phase and 30M/75M configurations in solution.[9] To avoid endpoint problems in the final window, SOS sampling was performed up to $\lambda = 0.99$ and double-wide sample (DWS) was used to complete the transformation (λ

= 0.99 → 1.00). Statistical uncertainties (± 1σ) were calculated using batch sizes of 1M configurations.[11,62] For individual computed ΔG_{solv} values, the maximum uncertainty is below 0.25 kcal/mol, which is comparable to typical experimental uncertainties of 0.3 kcal/mol near ambient conditions.[70,71]

For each ΔG_{solv}, a single solute molecule was placed in a box of 500 water, 264 CCl_4, or 266 benzene solvent molecules to enable consistent comparison with results obtained from the direct method. Equilibrated solvent boxes from the above pure liquid simulations provided the initial solvent coordinates. All solvent and solute simulation conditions mirror those described above in the Pure Liquid and Direct Method sections. Again, all internal degrees of freedom of the solute were fully sampled, and all solvent molecules were internally rigid. Once absolute free energies of solvation were obtained for all solutes at all pressures, $V°$ was determined from the slope of the best fit line (eq 1). Units of kcal/mol·atm were converted to cm^3/mol, the normal experimental units.

Relative $\Delta\Delta G_{\mathrm{solv}}$ for several benzene derivatives were computed in water up to 4000 atm in increments of 500 atm. These calculations used 21-SOS sampling with no end-point modifications and 8M/8M configuration in the gas phase and 15M/30M configurations in solution. Decoupling of the electrostatic and Lennard-Jones perturbations is not needed. All other simulation details in were identical as described above. Linear fits of the data were used to determine $\Delta V°$ for the perturbations.

RESULTS

Direct Method Comparison. In this work, benzene was modeled in three solvents and the total average volumes from the simulations were used for in eqs 2 and 3. Because the total volume fluctuates during the simulations and the difference between two large numbers is being taken, high standard uncertainties are expected, if enough statistical sampling is not performed.[3] The convergence of the results was investigated by increasing the lengths of the MC runs as summarized in Table 1.

Table 1. Computed Partial Molar Volumes (cm^3/mol) of Benzene From the Direct Methods at 25°C and 1 atm.

Number of Configurations	Average Total Volume[a] V_N	$V_{N,A}$	V_{N+A}	$10^6\kappa_T$[b]	V°(eq 2)	V°(eq 3)
Water						
20M/20M	14917.3	15040.3	15006.0	38.7	74.1 ± 21.0	53.4 ± 19.2
50M/50M	14910.9	15019.1	15077.2	54.8	65.2 ± 16.3	100.1 ± 17.3
100M/100M	14895.9	15053.7	15053.1	53.6	95.0 ± 14.3	94.7 ± 14.5
250M/250M	14937.2	15057.1	15062.7	48.9	72.2 ± 8.5	75.6 ± 8.9
500M/500M	14925.9	15064.0	15038.5	46.9	83.2 ± 6.1	67.8 ± 6.1
800M/800M	14918.6	15061.8	15056.6	51.5	86.3 ± 5.8	83.1 ± 5.7
1000M/1000M	14918.4	15064.0	15053.2	50.7	87.7 ± 5.2	81.2 ± 5.1
Expt.[c]				45.8	83.1	83.1
Carbon Tetrachloride						
20M/20M	43323.0	43419.7	43411.3	108.6	58.2 ± 36.7	53.2 ± 28.8
50M/50M	43220.5	43424.3	43412.3	116.2	122.7 ± 21.6	115.5 ± 21.8
100M/100M	43277.5	43396.2	43391.4	116.8	71.5 ± 17.1	68.6 ± 17.0
250M/250M	43257.1	43386.5	43408.3	120.6	77.9 ± 12.0	91.1 ± 11.8
500M/500M	43259.8	43409.2	43411.0	118.7	90.0 ± 7.6	91.0 ± 7.5
800M/800M	43273.6	43422.1	43400.0	121.5	89.4 ± 6.4	76.1 ± 6.4
1000M/1000M	43260.3	43403.1	43410.2	119.7	86.0 ± 6.2	90.2 ± 5.9
Expt.[d]				108.9	90.5	90.5
Benzene						
20M/20M	39641.5	39766.3	39838.3	107.3	75.1 ± 43.1	118.5 ± 40.1
50M/50M	39789.2	39888.7	39875.4	101.2	59.9 ± 23.9	51.9 ± 24.1
100M/100M	39720.1	39833.7	39876.1	109.4	68.4 ± 21.3	93.9 ± 20.3
250M/250M	39704.8	39854.1	39840.0	98.4	89.9 ± 12.2	81.4 ± 12.0
500M/500M	39727.1	39818.5	39843.9	103.9	55.1 ± 9.4	70.4 ± 9.8
800M/800M	39700.5	39858.6	39859.3	102.7	95.2 ± 7.8	95.6 ± 7.8
1000M/1000M	39700.1	39851.3	39844.3	103.6	91.0 ± 7.1	86.9 ± 7.1
Expt.[e]				98.2	89.5	89.5

[a] Volume in Å^3. [b] κ_T in atm^{-1} [c] Refs. 34 and 35. [d] Ref. 63. [e] Refs. 34 and 64.

To obtain converged properties such as the density and heat of vaporization of a pure liquid via MC methods, 20M/20M configurations are generally considered sufficient for simulations run at 1 atm.[4,72] However, the uncertainties for *V*° are seen to be 20 – 40 cm^3/mol with this sampling. Increasing the sampling up to 1 billion configurations (1000M) appears to be necessary to reduce the uncertainties to a few cm^3/mol. Even between 500M and 800M configurations, the results from eq 3 change by 15.3

cm^3/mol in water, 14.9 cm^3/mol in CCl_4, and 25.2 cm^3/mol in benzene. There is no striking difference in convergence using eq 2 or eq 3, though in general allowing the solute to translate and rotate in MC simulations is advantageous for convergence of solute-solvent properties such as radial distribution functions. Altogether, the results suggest that at least 1000M configurations should be used with the present system sizes for determining partial molar volumes via the direct methods. Statistical uncertainties of ±6 cm^3/mol are suggested by the results in Table 1 at this length. The results for $V°$ also have good accuracy with average discrepancies of 3 cm^3/mol with the experimental data, which is consistent with the small errors (*ca.* 2 %) that are normally obtained for pure liquids with the OPLS-AA force field.[4] Longer simulations were not pursued here. In research by others, up to 10 billion MC configurations have been used for averaging,[3,24] while MD simulations of 40 – 500 ns have been used to compute $V°$ values.[16-18] In both cases, the statistical uncertainties remain near 3 cm^3/mol. For comparing direct method results with those from the MC/FEP calculations, the $V°$ values computed with 1000M configurations will be used.

Absolute Free Energies of Solvation. Absolute free energies of solvation were determined for water in water, CCl_4 in CCl_4, and benzene in the three solvents as a function of pressure (Table 2). The computed free energies of hydration at 1 atm show errors of 0.2 – 1.6 kcal/mol. These errors are consistent with previous results with OPLS force fields, although the error for benzene in water is somewhat higher than previously reported.[10,14] For the present simulations, long-range Lennard-Jones corrections for benzene in water amount to 0.59 kcal/mol.[41,73] This correction would lower benzene's free energy of hydration to 0.16 kcal/mol, which is in statistical agreement with previous calculations. Unfortunately, few experimental free energies of solvation are available at high pressures. The results for water in water and benzene in water are also plotted in Figure 1. There is no clear curvature, which implies that $V°$ is relatively constant over this pressure range (eq 1). Assuming this constancy, estimates of experimental free energies of solvation at elevated pressure can then be made from the observed $V°$ and ΔG_{solv} at 1 atm. Table S4 lists such estimated results for ΔG_{solv} for all present solutes and solvents at high

Table 2. Computed Free Energies of Solvation (kcal/mol) in Three Solvents with Increasing External Pressure (atm) at 25°C[a]

Water			**Carbon Tetrachloride**			**Benzene**	
Pressure	**ΔG_{solv} (H_2O)**	**ΔG_{solv} (C_6H_6)**	**Pressure**	**ΔG_{solv} (CCl_4)**	**ΔG_{solv} (C_6H_6)**	**Pressure**	**ΔG_{solv} (C_6H_6)**
1	-6.13[b]	0.75[c]	1	-3.58[d]	-3.40[e]	1	-3.59[f]
1000	-5.77	2.89	250	-3.01	-2.78	50	-3.30
2000	-5.32	4.73	500	-2.46	-2.30	200	-3.08
3000	-5.03	6.71	750	-1.83	-1.80	350	-2.66
4000	-4.52	8.40	1000	-1.14	-1.29	500	-2.36
5000	-4.33	10.49				650	-2.26
6000	-3.87	12.17					
7000	-3.57	13.47					
8000	-3.15	16.02					

[a] Computed uncertainties are less than 0.25 kcal/mol. [b] Expt. ΔG_{solv} = -6.33; Ref. 70. [c] Expt. ΔG_{solv} = -0.86; Ref. 70. [d] Expt. ΔG_{solv} = -4.40; Ref. 78. [e] Expt. ΔG_{solv} = -4.50; Ref. 71. [f] Expt. ΔG_{solv} = -4.56; Ref. 78.

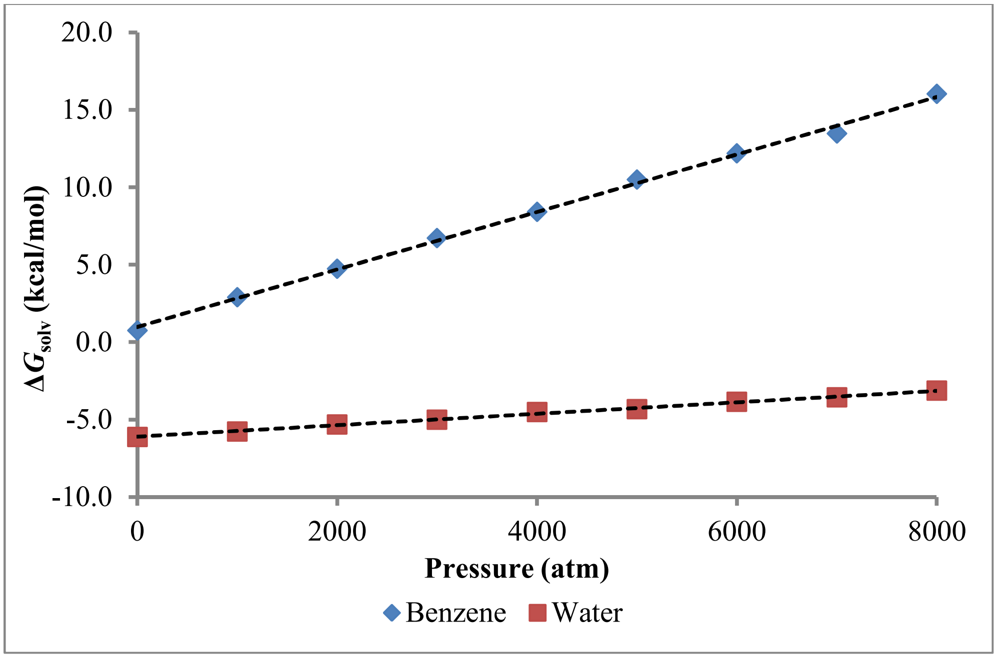

Figure 1. Computed free energies of solvation (kcal/mol) for water in water (red) and benzene in water (blue) vs external pressure (atm); dashed lines represent best fit lines; R^2 = 0.997 (water) and 0.998 (benzene) .

pressure. The unsigned errors between the computed and the estimated experimental ΔG_{solv} values are well maintained as pressure increases.

Partial Molar Volumes. The relationship between free energy and pressure is expected to deviate from linearity at high pressures, especially in organic solvents which are more compressible than water. However, the effect is not obvious in the present results (Figure 1), and the data can be modelled well with linear equations ($R^2 > 0.90$). Quadratic fits of the data (Table 2), which account for solvent compressibility, were also performed. However, high error estimates were observed for the quadratic coefficients. The magnitude of the predicted uncertainty was generally greater than or equal to the intrinsic value of the coefficient, indicating that this parameter is not well described by the data.[74] Similar difficulties have been described previously.[39] Thus linear fits were chosen for data analysis; the slope yields $V°$. This analysis is similar to that performed for reactions under high pressure, where the volume change corresponds to the volume of activation.[2,75,76] In computing volumes of activation, Eckbert suggested using data below a limit of 10% compression of the solvent.[75] For TIP4P water, 10% compression is reached around 4000 atm, and thus linear fits to determine $V°$ in water were restricted to data in the range of 1 – 4000 atm. The pressure ranges were smaller for carbon tetrachloride and benzene with compressions less than 10%, so all computed data were used.

Because the molecular annihilations decouple electrostatic and van der Waals interactions of the solute in two separate calculations, the effects of pressure on both components were obtained. Using benzene in water as an example, Figure S4 shows that the linear increase of ΔG_{solv} is dominated by the van der Waals (Lennard-Jones) component, while the free energy change for neutralizing all atoms of the solute is essentially constant at -1.9 kcal/mol (Table S5). Thus, the computed $V°$ values are highly dependent on the Lennard-Jones parameters used to model a solute and the linear increase of ΔG_{solv} with pressure is a volume effect. It becomes increasingly difficult to create a cavity for the solute with increasing pressure.

Table 3. Calculated Partial Molar Volumes (cm^3/mol) of Water, CCl_4, and Benzene in Solution from the Slope Method (eq 1) and Pure Liquid Simulations at 25 °C

Solute	**Solvent**	$V°$	V_{Total}/N^a	**Expt.** $V°$
water	water	16.3	18.0	18.1^b
CCl_4	CCl_4	100.1	101.4	97.0^c
benzene	benzene	84.8	91.0	89.5^d
benzene	water	79.0	--	83.1^e
benzene	CCl_4	86.1	--	90.5^f

[a] Determined from pure liquid simulations at 1 atm. [b] Refs. 50 and 59; from the density of water at 1 atm. [c] Ref. 56; from the density of carbon tetrachloride at 1 atm. [d] Refs. 34, 48, and 64. [e] Refs. 34 and 35. [f] Ref. 63.

To investigate the precision of obtaining $V°$ from the slope method, single molecules were first annihilated in their pure liquids. $V°$ values were determined from the slopes of the data in Table 2 and compared to the molar volume of a single solvent molecule from the respective pure liquid simulations (Table 3). The molar volume of a single solvent molecule from a pure liquid simulation is determined by dividing the average total volume of the pure solvent box by the number of solvent molecules in the box (V_{Total}/N). $V°$ should equal V_{Total}/N within the statistical uncertainty. For both TIP4P water and CCl_4, $V°$ is *ca.* 1.5 cm^3/mol less than V_{Total}/N. The uncertainty for $V°$ can be approximated from the standard error of the estimate that is obtained from the linear fit.[74] For $V°$ determined in water or carbon tetrachloride solvents, the estimated uncertainty is *ca.* 1.8 cm^3/mol; for benzene in benzene the uncertainty increases to 8.0 cm^3/mol. Thus, the accord between the computed $V°$ and V_{Total}/N values is reasonable, and the statistical uncertainties are similar to those from the longest direct method results in Table 1. It is also pleasing that the computed $V°$ values for benzene in water (79.0), benzene (84.8), and carbon tetrachloride (86.1) are in the same order as observed experimentally; the computed values are uniformly 4-5 cm^3/mol too low. The $V°$ values for carbon tetrachloride and benzene in carbon tetrachloride are also in the right order. In view of the statistical uncertainties, this may all be serendipitous, though it does encourage further study and application of the slope method. Similarly, if one averages the results from the 1000M/1000M direct calculations, the computed $V°$ values for benzene in water, benzene, and carbon tetrachloride are 84.5, 89.0, and 88.1 cm^3/mol, which has the order of the last two values switched. In both cases, an important qualitative prediction is correct, i.e., that the partial molar volume of benzene in water is smaller than in the other solvents. This can be interpreted as reflecting a hydrophobic effect that aims to reduce the surface area of water molecules in contact with benzene and/or a solvent size effect whereby smaller molecules can form more compact arrangements about an object than larger molecules, like peas vs. oranges.

Relative Partial Molar Volumes. In addition to computing partial molar volumes by annihilating entire molecules in solution, relative FEP calculations provide a means to estimate differences in partial molar volumes ($\Delta V°$). By computing $\Delta\Delta G_{\mathrm{hyd}}$ at increasing pressures, $\Delta V°$ can be estimated from the slope of the fit. This is illustrated here for derivatives of benzene in water. As shown in Table 4, computed relative free energies of hydration for benzene derivatives at 1 atm with the OPLS-AA force field are in excellent agreement with experimental results.[11,70] The mean unsigned error is 0.44 kcal/mol, and the largest error (1.08 kcal/mol) is for nitrobenzene relative to benzene. Computed $\Delta\Delta G_{\mathrm{hyd}}$ values were then obtained at increasing pressures up to 4000 atm, as reported in Table S6.

The resultant computed $\Delta V°$ values are also in good agreement with experiment (Table 4). The mean unsigned error is 2.7 cm^3/mol, and the statistical uncertainties are 1.0 – 2.0 cm^3/mol. In all cases, the R^2 values for the linear fits are above 0.84, with half greater than 0.95. The linear fits for phenol and aniline have R^2 values less than 0.50 and are discussed below. Experimental $\Delta V°$ values are derived from the $V°$ of benzene in water determined by Masterson[34] and the values for benzene derivatives from Shahidi.[65] Although Shahidi reports the $V°$ of benzene as 81.3 cm^3/mol,[65] a variety of literature sources suggest it is closer to the value reported by Masterson;[35,38,66,77] thus 83.1 cm^3/mol was used for the $V°$ of benzene in water.

The calculations in best agreement with experiment generally involve the appearance or disappearance of a methyl group. For example, Δ*V*° results for perturbing toluene to benzene, anisole to phenol, *N*-methylaniline to aniline, and *N,N*-dimethylaniline to *N*-methylaniline all show errors of 1.4 cm^3/mol or less. Errors are somewhat higher for the benzamide series. Perturbing *N,N*-dimethylbenzamide to *N*-methylbenzamide or *N*-methylbenzamide into benzamide gives errors of 3.0 – 4.0 cm^3/mol. For both cases, there are no significant differences in the Lennard-Jones parameters between the initial and final molecules, aside from the CH_3 to H mutation, and the data are all well fit by linear models ($R^2 > 0.930$). For all H to CH_3 conversions, the average Δ*V*° for methylation is 17.7 cm^3/mol, which is in excellent agreement with experiment, 17.3 cm^3/mol.[65]

Table 4. Computed Relative Partial Molar Volumes (cm^3/mol) in Water From the Slope Method[a]

			$\Delta\Delta G_{hyd}$ (kcal/mol)[b]		$\Delta V°$ (cm^3/mol)	
Ph–X	**→**	**Ph–Y**	**Computed**	**Expt.[c]**	**Computed**	**Expt.[d]**
CH_3		H	0.31 ± 0.03	0.03	-15.2	-13.9
F		H	-0.27 ± 0.02	-0.06	-2.9	-8.4
Cl		H	-0.44 ± 0.03	0.26	-11.7	
OH		H	5.14 ± 0.05	5.76	-2.0	-1.8
NH_2		H	4.40 ± 0.04	4.63	+1.6	-6.4
OCH_3		H	0.65 ± 0.06	1.60	-22.0	-22.5
CHO		H	3.12 ± 0.08	3.16	-13.0	-13.7
$COCH_3$		H	3.08 ± 0.10	3.72	-26.0	-29.9
NO_2		H	2.18 ± 0.07	3.26	-11.9	-13.0
OCH_3		OH	-4.50 ± 0.07	-4.16	-21.3	-20.7
NHMe		NH_2	-0.90 ± 0.06	-0.80	-19.1	-17.7
NMe_2		NHMe	-0.91 ± 0.06	-1.24	-15.3	-16.5
$COCH_3$		$CONH_2$	-6.68 ± 0.06	-6.43	-16.9	-10.6
CONHMe		$CONH_2$	-2.99 ± 0.07		-21.0	-17.8
$CONMe_2$		CONHMe	-2.80 ± 0.07		-21.0	-17.0
Mean Unsigned Error			**0.44**		**2.7**	

[a] computed uncertainties are less than 0.15 kcal/mol. [b] at 1 atm. [c] Ref. 70. [d] 83.1 cm^3/mol is used for benzene's reference PMV in water (Ref. 34); all other PMVs from Ref. 65.

Other computed results which show close accord with experiment include anisole to phenol and anisole to benzene with errors of *ca.* 0.5cm^3/mol, and benzaldehyde to benzene, where the error is 0.7 cm^3/mol. For acetophenone to benzene and nitrobenzene to benzene, larger transformations that simultaneously mutate three non-hydrogen atoms, the errors are 3.9 and 1.1 cm^3/mol, respectively. Altogether these results indicate that the MC/FEP calculations are robust for determining $\Delta V°$, even when several non-hydrogen atom are mutated simultaneously.

A peculiarity of the current data is the results for phenol and aniline (Table 4). Although the error for phenol to benzene is only 0.2 cm^3/mol, the error for aniline to benzene is 8.0 cm^3/mol. A significant amount of scatter is present in the data, as represented by low correlation coefficients for the linear fits of the pressure results ($R^2 < 0.50$). Such transformations have a large impact on the solute – water interactions since a strongly hydrogen bonding group is being fully deleted. Convergence for the solvent structure and $\Delta V°$ is expected to be more difficult in such cases. Thus, it is possible that the small error for phenol to benzene is coincidental. Notably, when an absolute $V°$ for phenol in water is determined via molecular annihilation, similar to benzene above, a $V°$ of 78.3 cm^3/mol is obtained ($R^2 = 0.996$). From phenol's and benzene's independently calculated $V°$ values, $\Delta V°$ for phenol to benzene is then +0.7 cm^3/mol, which gives an error of 2.5 cm^3/mol. This is likely a better estimate of the error due to the improved linear fit of the absolute calculations. In order to obtain more precise results in cases where there is a large change in hydrogen bonding, it is advisable to perform longer runs or to perform the perturbations in smaller steps, e.g., OH to F to H.

CONCLUSIONS

The results presented here show that estimates of a molecule's partial molar volume may be readily obtained using MC simulations and either the direct methods (eqs 2 and 3) or the slope method (eq 1) to a precision of a few cm^3/mol. Direct method calculations are more straightforward and require only one simulation per solute once the volume of the solvent system has been determined. Calculations performed on an Intel Core2 3.3 GHz processor with the *BOSS* program required *ca.* 7.5 hours for 1000M configurations of averaging. The additional 1000M configurations of equilibration that was used is excessive; *ca.* 200M would suffice. Thus, using 4 processors with independent runs, one could obtain results for 4000M configurations of averaging in about 8 hours or 12 billion configurations in a day. It is of historical interest to note that for the earliest calculations of this type, only 0.7M and 2M configurations of averaging were executed for systems with 100 or 127 solvent molecules.[3]

To determine V^o for a single solute with the slope method, the current protocol used at least twelve calculations: two gas phase calculations at 1 atm, and two condensed phase calculations for each of five pressure increments. On the same Intel processor, one FEP window for the liquid phase takes about 70 minutes; and, the full 21-SOS annihilation requires *ca.* 30.2 hours when all windows are run sequentially on one processor. Thus, on one processor the current slope calculations took about 12 days per molecule, i.e., 30-40 times longer than the direct calculations for similar precision. This could be sped up by only using three pressures rather than five, and the FEP calculations are readily parallelizable by running different windows on different processors. However, the slope method is competitive for computation of differences in V^o values since the full annihilations are replaced by small perturbations. This was illustrated for the substituted benzenes where the unsigned errors compared to experimental data averaged only 2.7 cm^3/mol. In view of the shorter runs and lack of electrostatic decoupling, the relative FEP calculations needed only about 35 minutes per FEP window or *ca*. 10 hours for a complete calculation. If three pressures were used, the total calculation time would be 30 hours, which is likely shorter than the direct calculations that would be required to yield a similar level of precision for the difference in V^o values for the two molecules. Operationally, it is easy to parallelize both types of calculations, so many molecules could be processed in one day with reasonable resources.

Concerning accuracy, the present results supported the quality of the TIP4P and OPLS-AA models for problems associated with liquid densities. For benzene in the three solvents, the average error in V^o from the direct calculations is 3.0% (Table 1) and it is 5.0% for the slope calculations (Table 3), which are similar to the statistical uncertainties in the results. Further calculations of partial molar volumes should find use in force field development and in developing an enhanced understanding of solute-solvent interactions.

SUPPLMENTARY INFORMATION

Supplementary Tables and Figures have been provided containing detailed thermodynamic results for liquid densities as a function of pressure and partial molar volumes (8 pages).

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