Hydrated Nonpolar Solute Volumes: Interplay between Size, Attractiveness, and Molecular Structure

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A solute's partial molar volume determines its response to pressure, which can result in changes in molecular conformation or assembly state. Computing speed advances have made accurate partial molar volume evaluation in water routine, allowing for the dissection of the molecular factors underlying this significant thermodynamic variable. A recent simulation analysis of the volumes of nonpolar molecular solutes in water reported that the apparent solvent-free border thickness enshrouding these solutes grows with increasing solute size, based on the assumption the solute can be treated as an individual sphere [Biophys. Chem. 161 (2012) 46]. This suggests the solvent dewets these solutes as they grow in size. Via simulations of dewetted repulsive spherical solutes, we show that the border thicknesses of the largest non-polar molecular solutes tend towards that of a repulsive sphere. When attractive interactions are accounted for, however, the spherical solute border thicknesses fall below that of the largest molecular solutes. We demonstrate that if the molecular solutes are treated with atomic detail rather than approximated as an individual sphere, the border thickness variation is minimal. A geometric model is put forward that reproduces the inferred border thickening, indicating the implied dewetting results from a breakdown in the spherical volume approximation.

Under the assumption that the hydrated volume of a nonpolar solute can be approximately treated as the packing of water about a sphere, the phenomenological expression

$$V_{\text{hyd}} \approx 4\pi(r_{\text{vdW}}^{\text{eff}} + \delta_{\text{sph}})^3/3 \quad (1)$$

has proven useful to correlate partial molar volume results [1-3]. The hydrated volume, V_{hyd} , is determined as the solute's partial molar volume less that of an ideal gas particle in solution (i.e.,

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$V_{\text{hyd}} = \bar{V}_{\text{solute}} - RT\kappa_0$ where RT is the product of the ideal gas constant and the temperature and κ_0 is the pure solvent compressibility). The effective van der Waals radius in eq. (1) is determined as $r_{\text{vdW}}^{\text{eff}} = (3V_{\text{vdW}}/4\pi)^{1/3}$, where the solute's entire van der Waals volume (V_{vdW}) is collapsed onto a single sphere. The remaining term in this expression, δ_{sph} , is the solute's spherical border thickness, which approximates water packing about the solute as an empty layer devoid of water surrounding the solute sphere. Border thicknesses for small solutes typically range from 0.4 Å to 0.6 Å, although values up to 1.0 Å have been observed for proteins [4]. Recent simulations performed by Chalikian and coworkers [2, 5] of a series of solutes composed of atomic Lennard-Jones (LJ) sites with their partial charges turned off to make them nonpolar found that the spherical border thickness grew with increasing solute size. This observation was interpreted as water pulling away from the solute and dewetting the solute/solvent interface as predicted by scaled-particle [6-8] and Lum-Chandler-Weeks [9] theories. Here we analyze this surprising, and potentially important, result by comparing the measured border thicknesses against simulations of spherical solutes of varying size in water and a simple geometric model to account, in part, for the solute shape.

Figure 1 compares the border thicknesses of repulsive, spherical solutes (modeled as shifted Weeks-Chandler-Andersen (WCA) particles [10]) evaluated from simulations in TIP4P/2005 water [11] at 25°C and 1 atm (see **Methods**) as a function of their size against those determined by Chalikian and co-workers [2, 5] for molecularly detailed non-polar solutes (Table 1). For the repulsive spheres we find that the border thickness is an increasing function of the solute size, consistent with solute dewetting [12]. Dewetting is marked by depression of the water density in the first hydration shell with increasing solute size [6-9] resulting from an imbalance of forces for solvent molecules partially stripped of their full solvation shell next to a repulsive, low

curvature interface[13, 14]. It has previously been demonstrated in simulations of hard-sphere solutes in water [12] and Lennard-Jonesium[8] that depression of the solvent density next to solutes larger than the solvent is accompanied by net solvent desorption. This solvent desorption in turn is directly tied to excess growth in the solute's partial molar volume greater than would be anticipated with the change of the solute's van der Waals radius [8]. The spherical border thickness of the molecular solutes with effective radii up to ~ 4 Å is approximately constant with $\delta_{\text{sph}} \approx 0.5$ Å, in agreement with experimental correlations for the border thickness (Figure 1). The border thickness is an increasing function of size for molecular solutes with effective radii greater than ~ 4 Å, however, falling just below that of similarly sized repulsive spheres for the largest solutes simulated here.

A shortcoming of the comparison made above is that we neglected attractive solute/water interactions while dispersive interactions were included in the molecular solute simulations composed of LJ sites. The attractive volume increment can be evaluated by a series expansion about the repulsive solute reference system[15]. Truncating this expansion after the first order term, the attractive contribution to the volume is given by the integral

$$\Delta V_{\text{att}} \approx (RT)^{-1} \int \varphi_{\text{att}}(r - r_{\text{shift}}) \chi(r) 4\pi r^2 dr, \quad (2)$$

where $\varphi_{\text{att}}(r - r_{\text{shift}})$ is the shifted WCA attractive interaction (see **Methods**), while the solute volume's interaction susceptibility, $\chi(r)$, is determined by the cross fluctuation between the system volume and water density as a function of distance from the solute, i.e., $\chi(r) = \langle V \rangle \langle \rho_{\text{sw}}(r) \rangle - \langle V \rho_{\text{sw}}(r) \rangle$ [15]. The interaction susceptibilities for three solutes of increasing size determined from the repulsive spheres in water are reported in Figure 2. This plot shows the susceptibility is largest for waters in the first hydration shell of the solute. This growth of the

susceptibility in the hydration shell results from the increasing compressibility of the dewetting layer making the proximal water density increasingly sensitive to attractive perturbations[16].

The border thicknesses of the spherical solutes with ΔV_{att} added to the repulsive solute volumes drop significantly (Figure 1), indicating attractions counter dewetting and draw water backtowards the solute. The comparison between δ_{sph} for the attractive spheres and molecular solutes with radii less than 4 Å is excellent. For solutes larger than 4 Å, however, δ_{sph} for the molecular solutes depart from those of the attractive spheres and begin to rise towards that of the repulsive spheres. This suggests that water gradually pulls away from the molecular LJ solutes beyond a critical solute size, despite the fact that attractions draw water closer to spherical solutes for all sizes.

The inference that molecular nonpolar solutes dewet is surprising and stands in difference to successful partial molar volume group contribution correlations, which assume the solute's hydrated volume is the sum of its constituent group volumes without regard to the number of groups making up the solute[17-19]. Indeed, the group volumes largely depend only on local correlations between the group and neighboring water molecules[20]. The growth of the border thickness, however, rests on the assumption that molecular solutes can be approximated as a sphere. Expanding eq. (1) to its leading order in δ_{sph} , i.e., $V_{\text{hyd}} \approx 4\pi r_{\text{vdW}}^3/3 + 4\pi r_{\text{vdW}}^2 \delta_{\text{sph}} + \dots$, the hydrated volume is dominated by the solute's van der Waals volume plus a solvent contribution proportional the sphere's area. Since spheres exhibit the smallest area for a given volume it may be anticipated that eq. (1) will breakdown for molecularly detailed solutes, which necessarily have larger exposed surface areas. Moreover, since the surface area-to-volume ratio is a decreasing function of a sphere's radius we may expect unphysical growth of the calculated border thickness with increasing solute size. Indeed alternate volume correlations utilizing the

phenomenological border thickness apply it to the solute’s actual van der Waals area. A more realistic correlation for the hydrated solute volume may be obtained by considering the solute’s molecular topology explicitly to calculate the border thickness. In this case we evaluate the hydrated volume by adding the border thickness (referred to below as δ_{mol}) to the van der Waals radii of the constituent atoms that make up the solute (**Methods**). Figure 3 and Table 1 compare δ_{sph} and δ_{mol} as a function of the solute effective van der Waals radii. In difference to δ_{sph} , δ_{mol} is well behaved over the range of sizes considered, adopting values between 0.32 Å and 0.55 Å that are more in line with expectations. The question remains, why does δ_{sph} grow unexpectedly with increasing molecular solute size?

A simple model to illustrate how a solute’s border thickness can be significantly overestimated is to consider the geometry of spherocylinders. The van der Waals volume of a spherocylinder with a molecular radius R and end cap-to-cap length L is

$$V_{\text{vdW}}^{\text{cyl}} = 4\pi R^3/3 + \pi R^2 L, \quad (3a)$$

while it’s hydrated volume for a fixed border thickness δ_{mol} is

$$V_{\text{hyd}}^{\text{cyl}} = 4\pi(R + \delta_{\text{mol}})^3/3 + \pi(R + \delta_{\text{mol}})^2 L. \quad (3b)$$

The effective spherical border thickness of the spherocylinder subsequently is $\delta_{\text{sph}} = (3V_{\text{hyd}}^{\text{cyl}}/4\pi)^{1/3} - (3V_{\text{vdW}}^{\text{cyl}}/4\pi)^{1/3}$. We plot δ_{sph} for spherocylinders as a function of $r_{\text{vdW}}^{\text{eff}} (= (3V_{\text{vdW}}^{\text{cyl}}/4\pi)^{1/3})$ in Figure 3 assuming $R = 1.9$ Å, comparable to the effective van der Waals radius of methane, and $\delta_{\text{mol}} = 0.44$ Å, which falls in the middle of the values reported in Table 1, while allowing L to vary from zero on up. The spherical border thickness for spherocylinders grows by more than a factor of two over the range of solute sizes plotted. More interestingly, the spherocylinder model predictions closely follow the δ_{sph} ’s for the molecular solutes reported

in Table 1. Clearly the growth of δ_{sph} for the spherocylinder model is not a result of dewetting since δ_{mol} is held fixed in this calculation. Rather this indicates a breakdown in the pseudo-spherical description of the solute volume. Indeed, the spherocylinder model predicts δ_{sph} grows in proportion to $r_{\text{vdW}}^{\text{eff}}$ and does not plateau as might be anticipated for dewetting of a large spherical nonpolar surface[2, 8].

The accuracy of the spherocylinder model should *not* be taken as validation that these solutes are cylindrical, which is geometrically unreasonable given the range of molecular structures reported in Table 1 and simplicity of the description embodied by eq. [3]. Instead we believe the spherocylinder model's success results from the qualitatively improved balance between growth of the solute van der Waals area relative to its volume as captured by the ratio $A_{\text{vdW}}/V_{\text{vdW}}$. The area-to-volume ratio for the molecular solutes is a weakly decreasing function of the solute size (Figure 4 with A_{vdW} reported in Table 1), appearing to plateau for large solutes. For a sphere the ratio $A_{\text{vdW}}/V_{\text{vdW}} = 3/r_{\text{vdW}}$ falls well below that over the molecular solutes, dropping to zero in the limit of an infinite sphere (Figure 4). For a spherocylinder, with a van der Waals area of $A_{\text{vdW}}^{\text{cyl}} = 4\pi R^2 + 2\pi RL$, the area to volume ratio only falls slightly with increasing solute size and plateaus at $1.05 \text{ \AA}^{-1}$ ($= 2/R$ with $R = 1.9 \text{ \AA}$) in the infinite solute limit (Figure 4). While $A_{\text{vdW}}/V_{\text{vdW}}$ for molecular solutes is typically greater than that for similarly sized spherocylinders, the difference is small compared to that for the sphere and the predicted plateau is reasonable. While the spherocylinder model underestimates the molecular solute van der Waals area for a given solute size, the fact that the area-to-volume ratio for both the molecular and spherocylinder descriptions plateau over a similar size scale indicates that the differences can be accommodated by the spherocylinder model by utilizing a slightly larger

empirical values of δ_{mol} . The spherical model for the solute volume, on the other hand, would be unable to overcome its deficiencies with a simple constant border thickness.

In summary, while purely repulsive spherical solutes in water do show indications of dewetting with increasing solute radius manifest as solute/solvent border thickening, attractive interactions suppress dewetting. The apparent dewetting of molecularly detailed nonpolar solutes with increasing size, however, is not real. Rather, the growth of the phenomenological spherical border thickness results from a breakdown of the spherical solute approximation applied to molecular solutes. If the solute's molecular structure is taken into account when evaluating the hydrated solute volume the border thickness varies significantly less from solute to solute with values ranging from 0.32 Å to 0.55 Å. Beyond the van der Waals volume then, our observations demonstrate that an improved accounting of water packing against the solute's area improves the phenomenological description of the hydrated volume.

Methods

Simulations of individual repulsive, spherical solutes in aqueous solution were performed in the isothermal-isobaric ensemble using the GROMACS 5.0 simulation package[21]. The temperature and pressure were fixed at 25°C and 1 bar using the Nosé-Hoover thermostat[22, 23] and Parrinello-Rahman barostat[24], respectively. Water was modeled using the TIP4P/2005 model[11], while solute/water interactions for the repulsive spherical solute was determined by the shifted WCA potential[10], $\varphi_{\text{WCA}}(r - r_{\text{shift}})$, where the position at which the solute/water interaction diverges to infinity has been shifted from the origin to r_{shift} . The WCA potential represents the repulsive portion of the shifted LJ potential following the standard WCA perturbation theory division between attractive and repulsive forces, i.e., $\varphi_{\text{LJ}}(r - r_{\text{shift}}) =$

$\varphi_{\text{WCA}}(r - r_{\text{shift}}) + \varphi_{\text{att}}(r - r_{\text{shift}})$. The LJ well-depth and diameter used here are 3.444 Å and 0.9765 kJ/mole, respectively, corresponding to the cross interactions between water and methane modeled as a united-atom site[25] obtained using Lorentz-Berthelot combining rules[26]. Simulated values of r_{shift} ran from 0 Å to 7 Å in 0.5 Å increments. Simulations were conducted of one solute in a bath of anywhere between 648 and 2307 water molecules depending on the solute size. An additional simulation of 1000 water molecules and no added solute was performed to characterize pure solvent properties. Short range van der Waals interactions were truncated beyond 12 Å with no long-range correction, while electrostatic interactions were evaluated using particle-mesh Ewald summation[27]. Water's internal constraints were held fixed using the SETTLE algorithm[28]. Simulations were conducted for 100 ns following at least 1 ns for equilibration using a time step of 2 fs. Partial molar volumes for the solutes were determined as the difference in the average simulation volume for the system with and without the solute added, i.e., $\bar{V}_{\text{solute}} = \langle V \rangle_{\text{water+solute}} - \langle V \rangle_{\text{water}}$ with the pure water simulation volume scaled to match the number of waters in the mixture. The ideal gas contribution to the partial molar volume was determined from pure solvent simulation fluctuations to be $RT\kappa_0 = 2.02 \text{ Å}^3$.

The van der Waals radius of the shifted WCA solutes can be determined from their effective solvent excluded volume. This volume is determined here by the integral

$$(r_{\text{vdW}} + \sigma_{\text{wat}}/2)^3 = 3 \int_0^\infty \{1 - \exp[-\varphi_{\text{WCA}}(r - r_{\text{shift}})/RT]\} r^2 dr \quad [4]$$

where $\sigma_{\text{wat}} = 2.8 \text{ Å}$ is the effective hard-sphere diameter of water.

The van der Waals areas and volumes reported in Table 1 were determined using Monte Carlo integration. The atomic van der Waals radii of the carbon, hydrogen, nitrogen, and oxygen atoms used were 1.7 Å, 1.2 Å, 1.55 Å, and 1.55 Å. To determine the volume of each molecule they were placed in a bounding box and choosing 2.5×10^8 random points. The molecular

volume (either van der Waals or hydrated volume) was determined as the volume of the box times the number of points found to lie within a specified radius (either the van der Waals radius of each atom or the van der Waals radius plus the molecular border thickness δ_{mol}) of any atomic site of the molecule divided by the number of points inserted into the box. The molecular border thicknesses reported in Table 1 were obtained by fitting the volumes obtained by Monte Carlo integration to the hydrated volumes reported by Chalikian and coworkers by adjusting δ_{mol} . The error in the volumes was found to be $\pm 0.02 \text{ \AA}^3$ or less. To determine the van der Waals surface area of each molecule, 2.5×10^8 random points were chosen on the van der Waals sphere about each atom of the molecule. The van der Waals area of an atom was determined as the fraction of random points found to be outside the van der Waals radii of all the other atoms of the molecule times the area of the sphere with the van der Waals radius of that atom. The total van der Waals area was subsequently determined as the sum of a molecule's constituent atomic van der Waals areas. The error in the areas was found to be $\pm 0.02 \text{ \AA}^3$ or less.

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Figure 1. Dependence of the volumetric border thickness on the effective van der Waals radius. Results are reported for shifted WCA solutes in water without and with (via eq. [1]) added attractions as well as for the molecular solute simulation results reported in Table 1. Symbols are defined in the figure legend. The straight lines through the WCA simulation results serve only as a guide for the eye.

Figure 2. Shifted WCA solute volume attraction response function determined from molecular simulations. Results are reported for three different WCA shifts, with the x -axis shifted by r_{shift} to facilitate comparison. Lines indicating different values of r_{shift} are defined in the figure legend.

Figure 3. Comparison between the effective border thicknesses determined based on the spherical versus molecular approximations as a function for the van der Waals radius for the solutes reported in Table 1.

Figure 4. Ratio of the van der Waals area to volume as a function the van der Waals radius. Results are reported for the spherocylinder and spherical models as well as for the solutes reported in Table 1.

Table of Contents Figure

Highlights

- The partial molar volumes of molecular nonpolar solutes in water are shown to vary between that of an attractive spherical solute to a repulsive spherical solute with increasing solute size, suggesting systematic dewetting of the molecular solutes.
- When the topology of the molecular solute is taken into account, the dewetting inferred from growth of the phenomenological spherical border thickness is found to disappear.
- A simple geometrical model based on spherocylinder geometry is shown to account for the effective growth of spherical border thickness.

Table 1. Volumetric properties of the nonpolar molecular solutes in TIP3P water at 25°C and 1 atm reported by Chalikian and coworkers. All partial charges were turned off for these solutes with only Lennard-Jones interactions between the solute sites and water. The hydration volume was determined from the simulation partial molar volumes as $V_{\text{hyd}} = \bar{V}_{\text{solute}} - RT\kappa_0$ (errors reported in parentheses). The van der Waals volumes and areas were determined by Monte Carlo integration as described in the **Methods** section. The spherical border thicknesses were determined as $\delta_{\text{sph}} = (3V_{\text{hyd}}/4\pi)^{1/3} - (3V_{\text{vdW}}/4\pi)^{1/3}$, while the δ_{mol} were fitted to V_{hyd} by Monte Carlo integration as described in the **Methods** section.

<i>solute</i>	$V_{\text{hyd}} (\text{\AA}^3)$	$V_{\text{vdW}} (\text{\AA}^3)$	$A_{\text{vdW}} (\text{\AA}^2)$	$\delta_{\text{sph}} (\text{\AA})$	$\delta_{\text{mol}} (\text{\AA})$
methane	63.1(1.2)	28.3	48.0	0.58	0.55
ethane	87.8(1.3)	45.1	70.3	0.55	0.49
benzene	140.3(1.7)	83.5	109.5	0.51	0.44
methanol	71.4(1.5)	37.2	59.9	0.50	0.46
ethanol	98.1(1.0)	53.9	81.5	0.52	0.45
1,2-ethanediol	105.1(2.8)	62.7	91.7	0.46	0.40
urea	84.0(2.0)	54.3	82.7	0.37	0.32
alanine	131.3(1.5)	85.4	120.7	0.42	0.34
glycine	104.2(1.2)	68.6	99.3	0.38	0.32
diglycine	186.8(1.9)	117.1	160.7	0.51	0.39
triglycine	253.0(1.8)	165.6	222.3	0.52	0.36
tetraglycine	337.7(1.0)	214.1	284.3	0.61	0.40
pentaglycine	399.8(1.8)	262.7	346.1	0.60	0.37
galactose	233.4(1.2)	153.8	194.3	0.50	0.38
sucrose	453.6(1.8)	287.1	349.6	0.67	0.45
lactitol	480.4(1.3)	297.8	365.4	0.72	0.48
maltotriose	668.2(2.2)	422.2	510.9	0.77	0.46
stachyose	879.1(2.5)	555.2	663.2	0.84	0.48
β -cyclodextrin	1453.1(1.8)	927.9	1042.6	0.98	0.50

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