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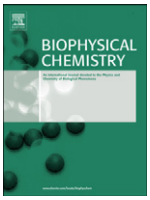

Short communication

Size dependence of cavity volume: A molecular dynamics study

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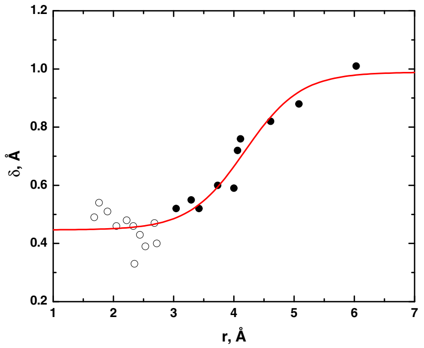
HIGHLIGHTS

- ► We use MD simulations to compute the partial molar volumes for solutes of varying sizes.
- ► We determine the thermal volume, V_T, for each compound.
- ► The thickness of thermal volume increases sigmoidally with the radius of a solute.

GRAPHICAL ABSTRACT



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ABSTRACT

Partial molar volume, V°, has been used as a tool to sample solute hydration for decades. The efficacy of volumetric investigations of hydration depends on our ability to reliably discriminate between the cavity, V_C, and interaction, V_I, contributions to the partial molar volume. The cavity volume, V_C, consists of the intrinsic volume, V_M, of a solute molecule and the thermal volume, V_T, with the latter representing the volume of the effective void created around the solute. In this work, we use molecular dynamics simulations in conjunction with the Kirkwood–Buff theory to compute the partial molar volumes for organic solutes of varying sizes in water. We perform our computations using the Lennard-Jones and Coulombic pair potentials as well as truncated potentials which contain only the Lennard-Jones but not the Coulombic contribution. The partial molar volume computed with the Lennard-Jones potentials in the absence of the Coulombic term nearly coincides with the cavity volume, V_C. We determine the thermal volume, V_T, for each compound by subtracting its van der Waals volume, V_W, from V_C. Finally, we apply the spherical approximation of solute geometry to evaluate the thickness of the thermal volume, δ. Our results reveal an increase in the thickness of thermal volume, δ, with an increase in the size of the solute. This finding may be related to dewetting of large nonpolar solutes and the concomitant increase in the compressibility of water of hydration.

The partial molar volume of a solute in an aqueous solution has been used for decades as a means to characterize solute–solvent interactions [1–7]. The underlying concept is simple. Solvent molecules in the vicinity of a solute are structurally and thermodynamically altered and, therefore, display a packing arrangement which is distinct compared to that of the solvent in the bulk. The differential packing of the solvent affected by a solute and solvent in the bulk, in turn, contributes to the partial molar volume of the solute and, therefore, is reflected in it.

The partial molar volume, V°, of a solute is described by the following expression [6,8]:

$$V^{\circ} = V_C + V_I + \beta_{T0}RT \tag{1}$$

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where V_C is the volume of the cavity in solvent enclosing a solute; V_I is the interaction volume, which is the volume effect of direct solute–solvent interactions; β_{T0} is the coefficient of isothermal compressibility of solvent; R is the universal gas constant; and T is the absolute temperature. The ideal term, $\beta_{T0}RT$, reflects the volume contribution of the translational degrees of freedom of the solute.

Inspection of Eq. (1) reveals that V_I is the only term that samples the hydration properties of a solute. Thus, to study hydration, one needs to extract the contribution V_I to the partial molar volume of a solute. This is not a trivial matter. As is seen from Eq. (1), to determine V_I, one needs to devise a reliable way of estimating the cavity volume, V_C. Stated differently, the usefulness of partial molar volume as a tool for hydration studies depends on our ability to reliably evaluate the cavity volume, V_C. The latter is generally presented as the sum of the intrinsic volume, V_M, of the solute molecule and the thermal volume, V_T, which reflects the effective void around the solute molecule created by mutual vibrational motions of solute and solvent molecules and steric effects:

$$V_C = V_M + V_T. \tag{2}$$

For a small molecule, the intrinsic volume, V_M, can be approximated by its van der Waals volume, V_W. It has been suggested that the thermal volume, V_T, can be computed as the volume of the layer of void around the solute with the thickness of the layer, δ, being constant independent of the chemical type of the solute or its geometry [6,9]. With this assumption, the cavity volume for a spherical solute can be presented as follows [9]:

$$V_C = V_M + V_T \approx (4N_A\pi/3)(r+\delta)^3 \tag{3}$$

where r is the van der Waals radius of the solute; and N_A is Avogadro's number.

There have been various empirical and theoretical estimates of the thickness of the empty layer, δ, reported in the literature [6,9–13]. For small molecules, the different estimates of δ are in good agreement with each other, being within a range of 0.4 to 0.6 Å [6,9,13]. However, the values of δ estimated for proteins diverge significantly, ranging from 0.226 to 1.0 Å [10–12]. Some 15 years ago, we performed a volumetric study of a number of globular proteins in their native states [10]. Our empirical analysis of the volumetric data revealed that, for native globular proteins, the thickness of the thermal volume, δ, is ~1.0 Å, twice as high as that for small molecules [10]. This result has raised a question about the possible dependence of δ on the size of a solute.

In the present work, we tackle this problem by combining molecular dynamics (MD) simulations with the Kirkwood–Buff (KB) theory to compute the partial molar volume for a number of solutes varying in size and to resolve the resulting partial molar volumes into their intrinsic, thermal, and interaction components. The KB approach has proven useful and been applied to volumetric characterizations of a wide variety of biologically relevant solutes [11,14–16]. In an alternative procedure, the partial molar volume of a solute can be directly computed as the difference in the ensemble average volumes between two NPT boxes, one containing solvent and a single solute molecule and the other containing pure solvent at the same temperature and pressure [17,18]. The ensemble average volume, V, for each NPT box can be derived from MD simulations. The two approaches are, generally, in good agreement and produce very similar results as demonstrated in our recent study in which the KB and direct methods have been applied to calculating the partial molar volumes of a large number of organic and inorganic solutes [13].

For our study, we chose solutes of varying sizes, including oligoglycines with neutralized termini, mono-, di-, tri-, and tetrasaccharides, a sugar alcohol, and the cyclic oligosaccharide β-cyclodextrin. We employ MD simulations to compute the solute–solvent radial distribution functions (RDF) which are subsequently used in conjunction with the KB theory to determine the partial molar volumes of the solutes. To compute the RDF and the partial molar volume of each solute, we carry out the MD simulations with the full pair interaction potentials, $U_{ij} = 4\varepsilon_{ij}[(\sigma_{ij}/r)^{12} - (\sigma_{ij}/r)^6] + q_iq_j/(4\pi\varepsilon_0\varepsilon r)$, and with modified pair potentials that are limited to the Lennard-Jones terms, $U_{ij} = 4\varepsilon_{ij}[(\sigma_{ij}/r)^{12} - (\sigma_{ij}/r)^6]$, and do not contain the Coulombic contribution. Comparison of the partial molar volumes obtained with the two different pair potentials enables us to extract and analyze the V_M, V_T, and V_I contributions in Eqs. (1) and (2). Table 1 presents the partial molar volumes of the solutes, studied in this work, computed with (second column) and without (third column) the Coulombic potential along with the experimental partial molar volumes of some of the solutes reported in literature (sixth column). Inspection of the data presented in Table 1 reveals a satisfactory agreement between the computed and experimental partial molar volumes of the saccharides and the sugar alcohol (lactitol). Experimental data on oligoglycines with neutralized termini are not available since, at neutral pH, these molecules predominantly exist as zwitterions.

As shown in our previous work, the partial molar volume of a solute computed with the Lennard-Jones potential in the absence of the Coulombic term, V_{LJ}, nearly coincides with the cavity volume, V_C [13]. Thus, the cavity volume, V_C, corresponds to the partial molar volume of the nonpolar analog of a solute molecule (a hypothetical molecule that has the same geometry as the solute but is devoid of all of the full and partial charges of the latter) minus the translational $\beta_{T0}RT$ terms.

As mentioned above, the thermal volume, V_T, consists of a layer of void volume surrounding the solute. To estimate the thickness of the void layer, δ, we approximated each solute by a sphere. With the spherical approximation, the cavity volume of a solute is given by Eq. (3). We calculated the van der Waals volumes, V_W, required for determining the hard sphere radii, $r = (3V_W/4\pi N_A)^{1/3}$, in Eq. (3) using the group contributions and the additive approach presented by Bondi [19]. The van der Waals volumes, V_W, for the solutes studied here are listed in the fourth column of Table 1.

We used Eq. (3), to compute the value of δ for each solute studied here based on the spherical approximation. For oligoglycines, we used, in addition to spherical, the sphero-cylindrical approximation as described by Kharakoz [6]. The resulting values of δ were virtually identical for the two approximation schemes. By extension, we consider a sphere to be a valid approximation for estimating δ for all solutes studied here.

Our calculated values of the thickness, δ, are presented in the fifth column of Table 1. Fig. 1 plots δ against the van der Waals radii of the

Table 1

The partial molar volumes computed with (V°) and without (V_{LJ}) Coulombic potential, the van der Waals volumes (V_W), the thickness of thermal volume determined from spherical approximation (δ), and the experimental partial molar volumes (exp.) of the solutes.

Solute	V°	V_{LJ}	V_W	δ	exp.
	$cm^3\ mol^{-1}$	$cm^3\ mol^{-1}$	$cm^3\ mol^{-1}$	Å	$cm^3\ mol^{-1}$
Diglycine	96.1 ± 0.9	113.7 ± 1.12	70.5	0.52	
Triglycine	132.3 ± 1.5	153.6 ± 1.1	100.5	0.52	
Tetraglycine	172.0 ± 1.2	204.6 ± 0.6	130.5	0.60	
Pentaglycine	211.5 ± 1.5	242.0 ± 1.1	160.6	0.59	
Galactose	108.7 ± 2.0	141.8 ± 0.7	89.5	0.55	110.3[a]; 111.9[b]
Sucrose	213.0 ± 2.1	274.4 ± 1.1	168.0	0.72	211.9[a]; 210.2[b]
Lactitol	229.8 ± 1.4	290.5 ± 0.8	174.5	0.76	200.1[c]
Maltotriose	307.7 ± 1.3	403.6 ± 1.3	246.8	0.82	309.0[d]; 304.8[b]
Stachyose	418.7 ± 1.3	530.6 ± 1.5	328.9	0.88	401.0[b]
β-Cyclodextrin	722.7 ± 2.5	876.3 ± 1.1	550.6	1.01	710.8[b]

[a] 25 °C, Ref. [46].
[b] 25 °C, Ref. [47].
[c] 20 °C, Ref. [48].
[d] 25 °C, Ref. [49].

solutes, r (closed symbols). Fig. 1 also presents a similar dependence for smaller organic solutes from our previous work calculated by the same method (open symbols) [13]. Inspection of the combined set of data graphically presented in Fig. 1 reveals several important observations. Firstly, for solutes with van der Waals radii less than 4 Å, the values of δ are essentially constant being confined within the 0.4 to 0.6 Å interval. Secondly, as the solute radius increases from 4 to 7 Å, the thickness of thermal volume, δ, increases from ~0.5 to ~1.0 Å. Thirdly, if the sigmoidal trend outlined in Fig. 1 holds, the thickness of thermal volume, δ, should reach a plateau of ~1.0 Å for large solutes with van der Waals radii of ~7 Å and larger.

The observed increase in δ with the solute size agrees with our empirical estimate for globular proteins while being qualitatively consistent with the picture of hydrophobic hydration that can be derived from theoretical and computational studies [10,20–25]. First and foremost, the observed increase in δ with the size of a solute is consistent with the phenomenon of dewetting which gradually takes place as the radius of a cavity increases from ~4 to ~10 Å [20]. Dewetting changes the thermodynamic signature of hydrophobic hydration from being entropy-driven for small solutes to enthalpy-driven for larger ones [20]. With respect to volume, the phenomenon of dewetting should result in an increase in the effective thickness of thermal volume, δ, around a “dewetted” solute in agreement with our results graphically presented in Fig. 1.

The observed increase in δ may also reflect an increase in the compressibility of water of hydrophobic hydration with solute size [22]. According to scaled particle theory (SPT), the thermal volume, V_T, linearly depends on the compressibility of the solvent surrounding a solute [8,26]. By extension, the thickness of the thermal volume, δ, around a solute also should increase as the compressibility of the adjacent solvent increases. It should be noted that the phenomena of dewetting and an increase in the compressibility of water of nonpolar hydration may be interrelated and collectively result in an increase in δ with a rise in solute size.

In conclusion, our results reveal an increase in the thickness of thermal volume, δ, with an increase in the size of a solute. This finding may be related to dewetting of large nonpolar solutes and the concomitant increase in the compressibility of water of hydration. Independent of the veracity of our proposed interpretations, our results provide the first estimate of the δ-versus-solute radius dependence and have practical applications in empirical determinations of the main contributions to the partial molar volume of a solute. In particular, our results will enable one to more rigorously evaluate the cavity, V_C, and interaction, V_I, contributions with the latter representing the volumetric effect of direct solute–solvent interactions.

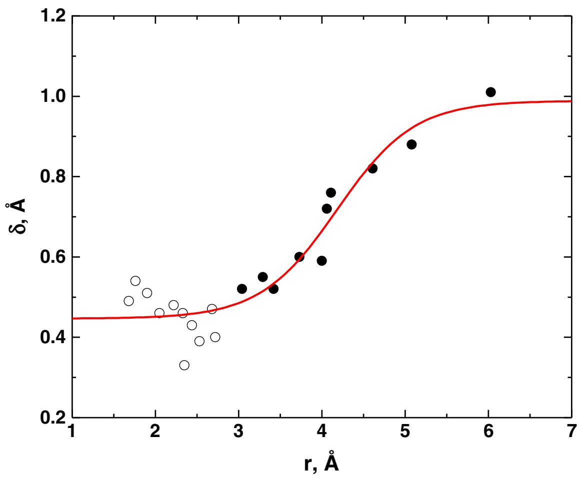

Fig. 1. The dependence of the thickness of thermal volume, δ, on the van der Waals radii, $r = (3V_W/4\pi N_A)^{1/3}$, of solutes from this work (close symbols) and a previous study (open symbols) both computed in an identical manner [13]. The sigmoidal fit of the data (solid line) only serves to guide the eye of the reader rather than conveying any analytical dependence.

1. Methods

1.1. Molecular dynamics simulations

The MD simulations were carried out with the GROMACS software, version 4.0.5 [27]. The solutes were modeled based on the OPLS-AA parameterization [28], while water was modeled using the TIP3P potential [29]. Each simulation box consisted of 2151 to 2173 TIP3P water molecules and one solute molecule in a cubic cell with an edge of 40.0 Å with periodic boundary conditions applied. The Lennard-Jones interactions were evaluated out to a separation of 12 Å and smoothly switched to zero at a cutoff distance of 15 Å. Long-range electrostatic interactions were evaluated using particle mesh Ewald method [30] with a real-space cutoff of 15 Å and a Fourier grid spacing of 1.2 Å.

The MD simulations were carried out in the isothermal–isobaric NPT ensemble for all solutes in water at a temperature of 298 K (Nosé–Hoover thermostat) and a pressure of 1 atm (Parinello–Rahman ensemble) [31–33] using the leap-frog algorithm with a time step of 0.002 ps. All bonds were constrained using LINCS [34]. The steepest descent method was used to perform 500 steps of energy minimization to ensure relaxation of the system. This step was followed by two-phase equilibration runs using the weak coupling technique [35]. Initially, a 100 ps equilibration run was implemented in the canonical NVT ensemble to thermalize the system at 25 °C. This was followed by the second 1 ns run in the isothermal–isobaric NPT ensemble to equilibrate the system at 1 atm and 25 °C. The final production run of 100 ns was performed with configurations saved every 2 ps for analysis. Errors were estimated as the standard deviation of the mean from block averaging over 20 ns for each production run. The resulting MD trajectories were used to compute the solute–solvent RDFs between the center of mass of each solute and the oxygen atoms of water.

1.2. Determination of partial molar volumes via the Kirkwood–Buff integrals

In the limit of infinite dilution, the partial molar volume of a solute is related to the solute–solvent KB integral, G_{12}, via the expression [36,37]:

$$V^{\circ} = -G_{12} + \beta_{T0}RT. \quad (4)$$

The KB integral, G_{ij}, between the species *i* and *j* is given by:

$$G_{ij} = G_{ji} = \int_0^{\infty} \left[g_{ij}^{\mu VT}(r) - 1 \right] 4\pi r^2 dr \quad (5)$$

where $g_{ij}^{\mu VT}(r)$ is the RDF between *i* and *j* in the grand canonical ensemble (μVT) [36–40].

The KB integral reflects the average excess (or deficiency) of *j* particles around the central *i* particle relative to the random distribution in an equivalent volume of the bulk solution. We calculated the KB integrals from our simulated RDFs using the following approximation [41–44]:

$$G_{ij} = \int_0^{\infty} \left[g_{ij}^{\mu VT}(r) - 1 \right] 4\pi r^2 dr \approx \int_0^{R'} \left[g_{ij}^{NPT}(r) - 1 \right] 4\pi r^2 dr \quad (6)$$

where R′ is the extent of the integration beyond which the RDF approaches unity, i.e., the bulk solution value.

The partial molar volumes were computed at the integration cutoff distance, R′, of 12 Å. The choice of this cutoff is justified by our selected cutoff radius for the calculation of Lennard-Jones interactions which, as noted above, is also 12 Å.

In practice, computation of KB integrals is complicated due to the noisiness and long-range oscillations of simulated RDFs which do not converge to unity unless extended simulation boxes (with dimensions exceeding several diameters of the solute molecule) are considered. Although the deviation of RDFs from unity is small (on the order of 1/N in a closed system), the influence of this deviation on the KB integral may be significant due to the factor r^2 in the integrand of Eq. (6) [45]. To enhance the convergence of the KB integrals, we follow the procedure introduced in our previous work [13]. Specifically, we compute the KB integral by averaging the g(r) function beyond the truncation distance of 12 Å and substituting the obtained average as the asymptotic limit in the KB integral in place of unity [see Eq. (6)]. The deviation from unity of the average value of g(r) beyond 12 Å was on the order of ± 0.0001. This procedure enhances the convergence of the KB integral by smoothing the oscillations in the RDFs.

In Eq. (4), the coefficient of isothermal compressibility, β_{T0}, was not computed from MD simulations. Instead, we used the experimental value of β_{T0} which, at 25 °C, equals 45.25×10^{-6} bar^{-1}.

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