

Origin of the inverse temperature dependence of hydrophobic attraction

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(Received 18 December 2024; accepted 27 May 2025; published 30 June 2025)

Using enhanced sampling techniques, we have precisely characterized the water-mediated interactions between nanometer-sized spherical hydrophobic solutes. The interaction potential is captured with remarkable accuracy by a tailored morphometric theory that distills and integrates essential physical properties of the solvation shell. Notably, our simulations successfully replicate a previously poorly understood phenomenon: the anomalous strengthening of hydrophobic attraction with rising temperature. Our theory pinpoints the origin of this “inverse temperature” effect in the rapid thermal expansion of the solvation shell, a process driven by a critical drying transition. Intriguingly, this effect becomes increasingly pronounced with stronger solute-water van der Waals attraction, i.e., decreasing hydrophobicity—a subtle yet significant feature accounted for by our theory.

DOI: [10.1103/66lz-1yw9](https://doi.org/10.1103/66lz-1yw9)

While many solutes dissolve easily in water, hydrophobic solutes—typically large apolar molecules—tend to separate from water to minimize contact. Amphiphilic molecules, which have both hydrophilic and hydrophobic parts, similarly aggregate to form micelles in aqueous solutions. These behaviors illustrate the so-called “hydrophobic effect,” where hydrophobic entities experience water-mediated attraction [1]. This effect is widely considered essential for the function of various systems, from DNA stability to the dispersion of complex pollutants.

Counterintuitively, the strength of hydrophobic attraction between solutes increases with rising temperature, at least within a specific temperature range [2–4]. In systems such as apolar polymer coils in water, this enhanced attraction can result in phase separation at a lower critical solution temperature [5–7]. This “inverse temperature effect” is typically attributed to water’s unique properties: specifically, an extended hydrophobe is surrounded by a hydration shell composed of water molecules with more extensive hydrogen bonding than in the bulk phase [1,8–12]. As temperature increases, this ordered hydration structure undergoes reorganization [1,8,10,12–14], which—it is argued—increases entropy and drives solute aggregation.

Numerous experimental and computational studies on hydrophobic solutes in water [1,2,12,14–32] have explored various aspects of their interactions and solubility. These studies underscore the significance of solute hydrophobicity, pressure, and temperature. Notably, hydrophobicity presents

differently for very small solutes, which can be accommodated within the water hydrogen bond network, versus larger solutes that disrupt this network, creating a distinct solute-water interface [33–36]. This work concentrates on the latter scenario, where a comprehensive microscopic understanding of the origin of hydrophobic attraction and its dependence on temperature, pressure, solute size, and degree of hydrophobicity has remained elusive.

Using well-tempered metadynamics simulations, we have investigated the temperature (T) dependence of the dimensionless effective potential $\beta W(r)$, where $\beta = 1/k_B T$, for a pair of identical spherical solute particles immersed in the liquid phase of a coarse-grained monatomic water (mW) model [37]. Each solute particle has a radius of $R_s = 10 \text{ \AA}$, and their centers are separated by a distance r . Detailed methods are provided in the Supplemental Material (SM) [38]. The solute particles interact through a purely repulsive potential with each other while exhibiting a weak, van der Waals-like attraction to water molecules with a well depth ε_{sw} . The solutes exhibit hydrophobic behavior for $0 < \varepsilon_{sw} \lesssim 0.7 \text{ kcal/mol}$. Our analysis focuses on $\varepsilon_{sw} = 0.2, 0.4, 0.6 \text{ kcal/mol}$ under a fixed pressure of $p = 0$ atmospheres (atm.), corresponding to liquid-vapor coexistence on the scale where pressure variations influence $\beta W(r)$.

The results, shown in Fig. 1(a)–1(c), demonstrate that for each ε_{sw} , both the range and magnitude of attraction in $\beta W(r)$ increase significantly with rising T . This trend, which qualitatively aligns with previous studies across various models and solute sizes [2–4], mirrors the experimentally observed inverse temperature dependence of the hydrophobic effect.

To explain it, we draw on recent insights into the solvation of isolated hydrophobic solutes, particularly the influence of a surface phase transition known as critical drying. Coe *et al.* [39,40] examined the solvation shell characterized by a region of depleted water density around an extended spherical hydrophobe under ambient conditions (standard temperature and pressure). They demonstrated that its properties are

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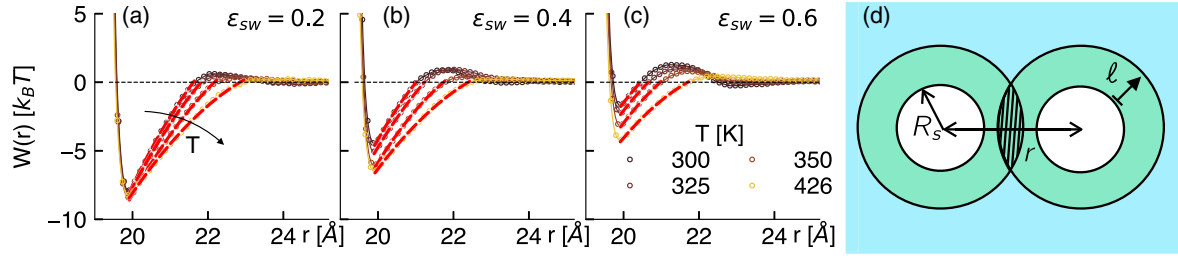


FIG. 1. (a)–(c) Simulation results for the effective potential $W(r)$ for $R_s = 10 \text{ Å}$ at $p = 0 \text{ atm}$ and the temperatures listed in the legend. The solute-water attractive well depth is (a) $\varepsilon_{sw} = 0.2 \text{ kcal/mol}$, (b) $\varepsilon_{sw} = 0.4 \text{ kcal/mol}$, (c) $\varepsilon_{sw} = 0.6 \text{ kcal/mol}$, and models the effect of unavoidable van der Waals attractions between the solute and water. Fits based on Eq. (1) to the attractive part of the potential beyond the solute diameter are shown as dashed lines; fit parameters are listed in Table I. (d) Schematic diagram (not to scale) of a pair of equal extended hydrophobic solutes of radius R_s with solvation shells of width ℓ (typically on the Angstrom scale). The shells intersect in the hatched region.

intrinsically linked to the critical drying transition that occurs when a liquid solvent at liquid-vapor coexistence interacts with a superhydrophobic planar surface [41–43]. A bespoke scaling analysis made predictions for the dependence of the solvation shell’s radial extent (width) and density fluctuations on T , p , and R_s . These predictions were validated through extensive mW simulations and classical density functional theory calculations [39,40,44], down to surprisingly small values of $R_s \approx 10 \text{ Å}$. The study also emphasized that the phenomenology of hydrophobic solvation for extended solutes is a specific instance of a broader class of solvophobic behavior. However, it did not examine the nature of the attraction that occurs between a pair of hydrophobic solutes or its temperature dependence.

The approach of Coe *et al.* emphasizes the central role of the solvation layer width, ℓ , a nontrivial length scale, in a comprehensive description of hydrophobic solvation. Building on this insight, we incorporate ℓ into a morphometric framework for understanding the water-mediated attraction between a pair of spherical hydrophobes. We define the solvation shell as the region of elevated free energy where the fluid’s structure differs from bulk liquid water and assume that the spherical boundary of this region exhibits surface tension. Hydrophobic attraction occurs due to the net reduction in free energy when the solvation shells of two hydrophobic entities overlap, as illustrated schematically in Fig. 1(d). Our model assumes that this arises from two principal contributions.

(i) Reduction in interfacial area: The total surface area of the union of the two overlapping solvation shells is smaller than in their well-separated state.

(ii) Reduction in solvation volume: Overlap reduces the volume within the solvation shells of raised free energy.

Denoting the combined radius of a solute and its solvation shell as $\mathcal{R} = R_s + \ell$, the model attractive potential in the range $2R_s \leq r \leq 2\mathcal{R}$ takes the following form as derived in the Appendix:

$$W_m(r) = -2\pi(2\mathcal{R}^2 - \mathcal{R}r)\tilde{\gamma} - \frac{\pi}{12}(r^3 - 12\mathcal{R}^2r + 16\mathcal{R}^3)\tilde{\delta p}. \quad (1)$$

Here, the first term (the “area” term) captures the linear reduction in surface free energy as r decreases within the given range. Its amplitude, $\tilde{\gamma}$, is the surface tension of the solvation shell. The second term (the “volume” term) accounts for

the corresponding decrease in the grand potential due to the reduction in the total solvation volume. Its amplitude $\tilde{\delta p}$ is the local pressure (p) difference between the solvation shell and bulk water, i.e., the grand free energy density difference. The volume term is cubic in r , and is thus responsible for the curvature of the potential. It is worth noting that the volume term is analogous to the depletion potential observed in mixtures of colloids and ideal polymers [45]. However, the area term in our system is generally dominant in determining the interaction.

Equation (1) is a function of ℓ , $\tilde{\gamma}$, and $\tilde{\delta p}$. These quantities vary with the specific physical conditions of T , p , R_s , ε_{sw} , and are unknown *a priori*. Consequently, we treat them as parameters to be estimated from fits based on Eq. (1) to the measured forms of $\beta W(r)$. The dashed lines in Fig. 1 represent the outcomes of this fitting procedure for the attractive part of the potential beyond the minimum. The assumed form describes the potential shape remarkably well. The fit parameters are tabulated in Table I: they evidence a reduction in $\tilde{\gamma}$ over the temperature range studied of some 20 – 30% similar to that of the bulk liquid-vapor surface tension γ_{lv} of mW [46]. $\tilde{\delta p}$ is also expected to reduce with increasing T and we find a 40% – 50% change [47].

TABLE I. Least squares fits for $\tilde{\gamma}$, $\tilde{\delta p}$, and ℓ based on Eq. (1) for solutes of radii $R_s = 10 \text{ Å}$ at $p = 0 \text{ atm}$ and indicated T and attractive solute-water strength ε_{sw} . Note that at $T = 300 \text{ K}$ $1 \text{ kcal/mol} = 1.677k_B T$ and $\gamma_{lv} = 0.066 \text{ N/m}$ [46].

$\varepsilon_{sw} \text{ (kcal/mol)}$	$T \text{ (K)}$	$\tilde{\delta p} \text{ (atm)}$	$\tilde{\gamma} \text{ (N/m)}$	$\ell \text{ (Å)}$
0.2	300	1713(150)	0.022(1)	0.81(2)
	325	1581(100)	0.021(1)	0.91(2)
	350	1485(200)	0.018(2)	1.09(3)
	426	1181(200)	0.016(1)	1.37(2)
0.4	300	2338(200)	0.020(1)	0.51(2)
	325	1885(150)	0.020(1)	0.62(3)
	350	1727(150)	0.017(2)	0.86(2)
	426	1378(200)	0.015(1)	1.18(3)
0.6	300	3163(400)	0.018(1)	0.23(3)
	325	2022(300)	0.018(1)	0.33(2)
	350	1969(200)	0.017(1)	0.49(2)
	426	1747(200)	0.014(1)	0.85(1)

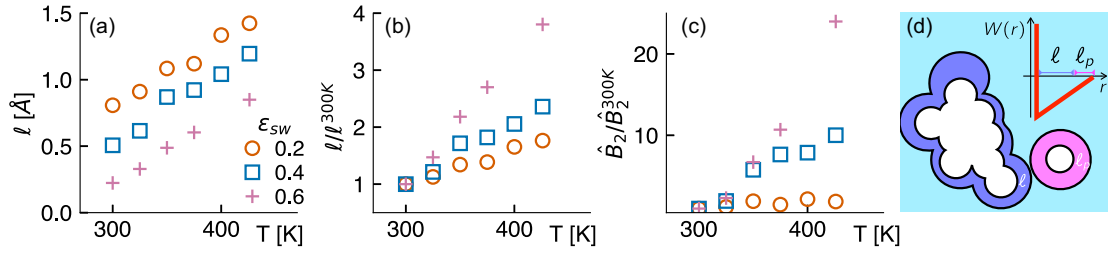


FIG. 2. (a)–(c) Temperature dependence of (a) the solvation shell width $\ell(T)$ as determined from fits to $\beta W(r)$; (b) the relative change ℓ/ℓ_0 with $\ell_0 = \ell(T = 300K)$; (c) the relative change of $\hat{B}_2(T)$, see main text. (d) A probe of solvation width ℓ_p can be used to sample the potential of mean force $W(\vec{r})$ around a larger solute characterized by a spatially varying solvation width ℓ .

A distinctive characteristic of $\beta W(r)$ is a repulsive “hump” at intermediate r , whose height grows with ϵ_{sw} but reduces with increasing T (cf. Fig. 1). This stems from the long-range solute-water attraction, which generates an outer shell of elevated density and lower free energy (relative to bulk water) beyond the hydrophobic solvation shell—overlap between two such regions results in a solute-solute repulsion. The hump, therefore, exemplifies the “accumulation repulsion” effect, well known from colloidal mixtures [48]. As our morphometric model does not explicitly account for this repulsive effect (which is generally relatively minor compared to the attraction), we limit our analysis to the range of r for which $W(r)$ is negative, i.e., $2R_s < r < r^*$ with $\beta W(r^*) = 0$.

Figure 2 presents, for each of the three considered values of ϵ_{sw} , (i) the temperature dependence of ℓ , and (ii) the relative change in ℓ over the temperature range. Additionally, Fig. 2(c) depicts the corresponding relative change in $\hat{B}_2 \equiv -2\pi \int_0^{r^*} r^2 (\exp(-\beta W(r)) - 1) dr$, which represents the contribution of the attractive part of $W(r)$ to the osmotic second virial coefficient.

The data in Fig. 2(a) and Table I reveal the pronounced sensitivity of ℓ to temperature variations. For instance, for $\epsilon_{sw} = 0.4$ kcal/mol, ℓ grows by some 130% over the T range compared to a 25% reduction in $\tilde{\gamma}$ and a 40% reduction in $\delta\tilde{p}$. Figure 2(b) shows that the relative change in ℓ increases with ϵ_{sw} . Likewise, Fig. 2(c) demonstrates that the relative change in $\hat{B}_2$, which quantifies the overall solute-solute attraction, also becomes more pronounced with increasing ϵ_{sw} . These observations demonstrate that the strength of the inverse temperature effect grows with higher ϵ_{sw} , i.e., with greater affinity to water.

The changes in ℓ with T shown in Fig. 2, and those in $\tilde{\gamma}$, and $\delta\tilde{p}$ listed in Table I, collectively explain the inverse temperature dependence of $\beta W(r)$. This occurs because the increase in attractive strength that results from the growth of ℓ with T , outweighs the diminution caused by the reductions in $\tilde{\gamma}$ and $\delta\tilde{p}$. To illustrate the impact of these changes, consider the minimum value of the model potential, $W_m(r)$, at $r = 2R_s$, given by

$$W_m(2R_s) = -2\pi\delta\tilde{p}\left(R_s\ell^2 + \frac{2\ell^3}{3}\right) - 4\pi\tilde{\gamma}(R_s\ell + \ell^2). \quad (2)$$

Substituting the temperature-dependent values of $\delta\tilde{p}$, $\tilde{\gamma}$, and ℓ from Table I into this expression shows that the terms in parentheses on the right-hand side increase far more rapidly with T than their respective prefactors decrease. Consequently,

$\beta W(r)$ becomes more attractive as the temperature rises. In the Appendix, we show that the local density profile surrounding an isolated solute also indicates increasing hydrophobicity with rising temperature and displays characteristics that align with the length scale ℓ obtained from our measurements of $W(r)$.

Our morphometric model and simulations thus identify the pronounced increase of ℓ with T as the central mechanism behind the inverse temperature effect. This raises an important question: why is ℓ so sensitive to temperature changes compared to other competing factors, such as the reduction in $\tilde{\gamma}$ and $\delta\tilde{p}$? A possible explanation lies in the influence of proximity to the drying transition on the properties of the solvation shell, a hypothesis that we now proceed to describe and test.

Under ambient conditions, water in contact with a finite spherical hydrophobe is not at a critical drying transition. However, ambient water is near to coexistence, with a very small supersaturation (the coexistence pressure $p_{coex} \approx 1/20$ atm). A binding potential analysis [39,40] of the free energy associated with the solvation shell surrounding an extended spherical solute, under the assumption of a vaporlike solvation layer, reveals that ℓ scales (up to an additive constant) as

$$\ell \sim -\xi_b \ln(\beta\sigma^3\delta p'), \quad (3)$$

where ξ_b is the bulk vapor phase correlation length, σ is the water molecular diameter, and $\delta p'$ is an effective oversaturation that accounts for curvature effects and the magnitude of the solute-water attractive strength:

$$\delta p' = \delta p + \frac{2\gamma_{lv}}{R_s} + g(\epsilon_{sw}, \ell). \quad (4)$$

Here, $\delta p = p_l - p_v$ represents the oversaturation of the vaporlike (v) solvation layer at the chemical potential corresponding to the bulk liquid with pressure p_l . γ_{lv} denotes the liquid-vapor surface tension at the solvation shell boundary. The “attraction pressure” $g(\epsilon_{sw}, \ell)$ resulting from solute-water interactions is an effective pressure acting on this boundary. The precise form of the ℓ dependence of $g(\epsilon_{sw}, \ell)$ depends on the asymptotic character of the solute-solvent and solvent-solvent interactions, e.g., for long-ranged van der Waals solute-water interactions, one finds $g(\epsilon_{sw}, \ell) = b_0(T)\epsilon_{sw}\ell^{-3}$ with $b(T) = b_0(q_l - q_v)$, a weakly decreasing function of T [40]. For truncated van der Waals interactions, or an exponentially decaying solute-water interaction potential, $g(\epsilon_{sw}, \ell)$ is expected to decay exponentially with ℓ . However,

it will be sufficient for our purposes that $g(\varepsilon_{sw}, \ell)$ is positive and a decreasing function of ℓ and of T [40,49].

Equations (3) and (4) describe how ℓ scales with R_s , T , δp , and ε_{sw} near the critical drying point. This critical point corresponds to the limit of a planar substrate ($R_s^{-1} \rightarrow 0$) that is sufficiently hydrophobic [$g(\varepsilon_{sw}, \ell) \rightarrow 0$], with the pressure approaching its coexistence value ($\delta p \rightarrow 0$). On approaching criticality, ℓ diverges logarithmically [42,43]. We propose that the pronounced sensitivity of ℓ to changes in T is a near-critical phenomenon arising when R_s^{-1} , δp , and g are small but finite and relevant even when the solvation shell is not fully vaporlike.

To elaborate, when the temperature increases, the effective oversaturation $\delta p'$ [Eq. (4)] decreases due to the temperature dependence of three key factors: (i) δp vanishes at coexistence and heating water reduces the deviation from the boiling point; (ii) the surface tension γ_{lv} is a decreasing function of T ; (iii) the attraction pressure $g(\varepsilon_{sw}, \ell)$ decreases with rising T and additionally is a decreasing function of ℓ [40]. Because of these effects, and the overall factor $\beta = 1/k_B T$ in Eq. (3), $\beta \delta p'$ decreases with temperature. For small $\beta \delta p' < 1$, the logarithmic form of Eq. (3) turns this into a strong increase in ℓ and hence, via Eq. (1), the potential depth. In the Appendix, we show that variations in ℓ are consistent with Eqs. (3) and (4).

As to why the inverse temperature effect becomes more significant as ε_{sw} increases [Figs. 1 and 2(c)], this is linked to the role of the attraction pressure $g(\varepsilon_{sw}, \ell)$ in Eq. (4). Increasing ε_{sw} in Eq. (3) leads to a decrease in ℓ , matching observations [Fig. 2(a)]. However, an increase in ε_{sw} also amplifies $g(\varepsilon_{sw}, \ell)$ so that the right-hand side of Eq. (3) is ℓ dependent. This creates a positive feedback loop: as ε_{sw} increases, the relative change in ℓ and $\hat{B}_2$ over a given temperature range also grows.

We conclude with some general remarks on the relationship between our study and prior research and the outlook for future work. Previous theories of the T dependence of the hydrophobic effect have largely focused on the free energy of solvation ΔG^{sol} , which can provide information on solubility. Such works employ coarse-grained thermodynamic frameworks that often presuppose, without clear validation, that the inverse temperature dependence of the hydrophobic effect arises from the reorganization of hydrogen-bonded water structures (see, e.g., [8,9,13,50]). These qualitative approaches cannot make detailed predictions about hydrophobic forces, such as their range, magnitude, and dependence on T and p .

The hydrophobic solvation theory developed by Lum, Chandler, and Weeks (LCW) [16,33,51] offers a seminal microscopic framework, highlighting the emergence of a layer of depleted density around an isolated extended solute, independent of assumptions about specific hydrogen-bonded structures. While it makes no predictions regarding hydrophobic forces, LCW theory has been applied to explore the increase in ΔG^{sol} with rising temperature [51]. However, its approach is heuristic, focusing on changes in the local density profile without explaining their underlying causes.

Our study reveals the key importance of the physical properties of the solvation shell—particularly its width—and the role of critical drying in advancing the understanding of

two-body hydrophobic forces. Combining simulations with a morphometric model and scaling theory that leverages these insights creates a robust, universal, and quantitative framework for describing hydrophobic interactions at the microscale. This approach surpasses traditional thermodynamic methods and LCW theory. Crucially, our framework provides an interaction-based explanation for the inverse temperature effect, one which dispenses with ad hoc assumptions about changes in hydrogen bonding. While our primary analysis employs a computationally efficient coarse-grained (monatomic) water model—albeit one that exhibits a tetrahedral liquid network—the observed effects are also present in SPC/E water, which displays forms for $\beta W(r)$ similar to those found in the mW model (see Appendix), and reinforcing the broad applicability of our findings.

Our approach offers a pathway to a deeper understanding of how temperature, pressure, solute size, and degree of hydrophobicity influence aggregation and phase separation processes. It also paves the way for enhanced characterization of hydrophobic forces in systems containing large apolar molecules, amphiphiles, and proteins. The functional behavior of such systems, driven by the hydrophobic effect, often stems from spatial variations in the degree of hydrophobicity. As schematically illustrated in Fig. 2(d), these variations could be mapped via simulation using a small spherical hydrophobic probe of known $\ell = \ell_p$ to measure the local force profile. This approach could provide a more detailed, spatially resolved quantification of the range and strength of hydrophobic interactions than what is available with current methods [52].

The authors have benefited from helpful conversations with Bob Evans and Jennifer McManus. This work used the Isambard 2 UK National Tier-2 HPC Service [53] operated by GW4 and the UK Met Office and funded by EPSRC (EP/T022078/1). NBW acknowledges the support of the Leverhulme Trust Grant No. RF-2024-173.

The data that support the findings of this article are openly available [55].

Appendix: Derivation of morphometric expression for $W(r)$. We investigate the evolution of the (grand) potential as the spheres move closer together and their solvation shells begin to overlap, as schematically depicted in Fig. 1(d). The width of the hydrophobic solvation shell is denoted by ℓ , and we define the combined radius of the solute and vapor layer as $\mathcal{R} = R_s + \ell$. The effective solute-solute potential, also known as the “potential of mean force,” is expressed as

$$W_m(r) = \Omega_{ex}(r) - \Omega_{ex}(r \rightarrow \infty), \quad (\text{A1})$$

where $\Omega_{ex}(r)$ is the excess grand potential of the system when the solute particles are separated by a linear distance r .

As r is reduced in the range $2R_s \leq r \leq 2\mathcal{R}$ so that the solvation shells progressively overlap, we can identify two contributions to $W(r)$.

(i) *Interfacial area reduction:* As the solvation shells overlap, the interfacial area between the solvation shells and the surrounding liquid decreases. The total external surface area of the body formed by the union of two intersecting spheres

of radius is given by

$$A_u(r) = 4\pi\mathcal{R}^2 + 2\pi\mathcal{R}r. \quad (\text{A2})$$

It follows that the reduction in surface area when the solvation shells overlap compared to their combined surface area at $r = \infty$ is $\delta A(r) = -2\pi(2\mathcal{R}^2 - \mathcal{R}r)$. Since there is a free energy cost arising from the interface between the solvation shell and the liquid, the contribution to $\Omega_{ex}(r)$ varies as $\delta A(r)\tilde{\gamma}$ where $\tilde{\gamma}$ is the solvation shell surface tension which is a positive quantity whose magnitude is expected to reduce with increasing T .

(ii) Increase in bulk volume: As the solvation shells overlap, the total volume available to the more stable bulk liquid phase increases. The increase is the negative of the volume of the lens formed by two intersecting spheres of equal radii $\mathcal{R} = R_s + \ell$, separated by a distance r , for which one finds a cubic dependence on r :

$$V_o(r) = \frac{\pi}{12}(4\mathcal{R} + r)(2\mathcal{R} - r)^2. \quad (\text{A3})$$

The corresponding contribution to $\Omega_{ex}(r)$ is $-V_o\delta\tilde{p}$ where $\delta\tilde{p}$ is the pressure difference between the bulk liquid and the solvation shell at the chemical potential of the bulk liquid.

Inserting these results into Eq. (A1) and setting $\Omega_{ex}(r \rightarrow \infty) = 0$ yields Eq. (1) of the main text:

$$W_m(r) = -2\pi(2\mathcal{R}^2 - \mathcal{R}r)\tilde{\gamma} - \frac{\pi}{12}(r^3 - 12\mathcal{R}^2r + 16\mathcal{R}^3)\delta\tilde{p}.$$

Both terms in this expression approach zero from below as $r \rightarrow 2\mathcal{R}^-$. We note that in principle the value of ℓ appearing in Eq. (1) depends on r , however, we expect this dependence to be weak and neglect it here.

Local density profile and adsorption of water at an isolated solute. It is useful to compare our findings on the temperature dependence of $W(r)$ with those of the local density profile [56] surrounding an isolated sphere. Figure 3 illustrates the temperature dependence of $\rho(r)$ (expressed in units of the bulk number density ρ_b) at the conditions corresponding to the $W(r)$ measurements in Fig. 1(a). The observed increase in hydrophobic attraction with rising temperature correlates with variations in $\rho(r)$. Specifically, compared to the strongly hydrophilic limit, the density near the solute surface decreases significantly as T rises, leading to a reduction in total surface adsorption, $\Gamma = 4\pi \int r^2 dr (\rho(r) - \rho_b)$. This trend reflects an increase in the solute's effective hydrophobicity with rising temperature.

We find that the values of ℓ extracted from our measurements of $W(r)$ and listed in Table I align with a shoulder in the density profile, which evolves into a peak at high T .

Scaling of the solvation shell width. Within the binding potential framework for drying at spherical solutes [39,40], the solvation shell width, ℓ , depends on the choices of T , P , R_s^{-1} , and ε_{sw} , as described by Eq. (3). Our estimates for ℓ —obtained by fitting measurements of $W(r)$ at various ε_{sw} and T —allow us to test the scaling expression of Eq. (3). In Fig. 4, we plot the right-hand side of Eq. (3) against ℓ for several combinations of ε_{sw} and T . Following Coe *et al.* [40], we

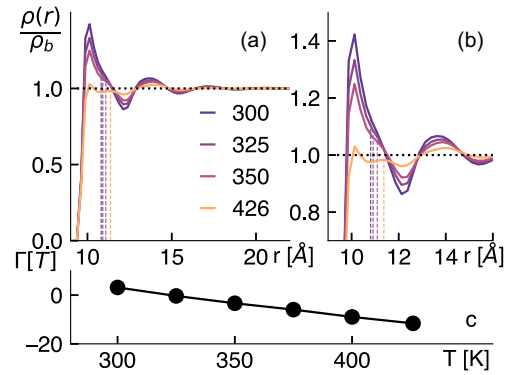


FIG. 3. (a) Temperature dependence of $\rho(r)$ normalized by its bulk value ρ_b for mW water in contact with a solute of radius $R_s = 10 \text{ \AA}$ at $p = 0$ and solute-water affinity $\varepsilon_{sw} = 0.2 \text{ kcal/mol}$. (b) Enlargement of the region close to the solute surface showing the correspondence of values of ℓ from Table I (vertical lines) with a shoulder/peak in the profile. (c) Temperature dependence of the total surface adsorption Γ .

assume that the attraction pressure $g(\varepsilon_{sw}, T) = b(T)\varepsilon_{sw}\ell^{-3}$. If scaling holds, as is anticipated sufficiently close to the critical drying transition [39,40], the data should collapse onto a single linear master curve.

The data approaches the expected linear trend in the limit of high temperature and weak solute-water attraction, where near-critical behavior becomes more pronounced and eventually merges with the scaling found for larger solutes [39,40]. However, in the less hydrophobic regime of lower temperatures and stronger solute-water attractions, one sees clear deviations from the scaling form.

Temperature dependence of $\beta W(r)$ for SPC/E water model. Results similar to those obtained with the mW water model have also been observed using the simple point

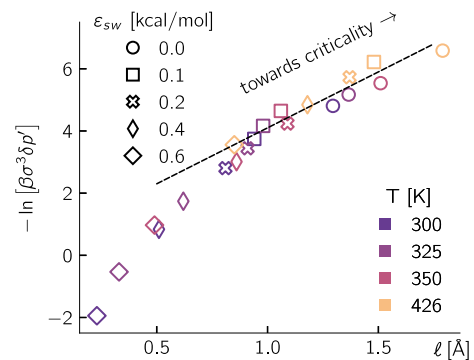


FIG. 4. The scaling expression Eq. (3) plotted versus ℓ for various ε_{sw} and T . Values of ℓ and $\tilde{\gamma}$ are taken from Table I, and σ is assigned the mW value $\sigma = 2.3925 \text{ \AA}$. As the system is close to bulk coexistence at all T , we set $p_l - p_v = 0$. The quantity $b = 2(\rho_l - \rho_v)\rho_b\sigma^6$, with $\rho_l - \rho_v$ the density difference between the bulk liquid and vapor. The latter is only very weakly dependent on T for mW in the range of temperatures studied [46] and we set it constant to minimize the number of unknown T -dependent parameters. The dashed line is a guide for the eye to indicate the approach to the linear regime at high temperatures and low solute-water affinities.

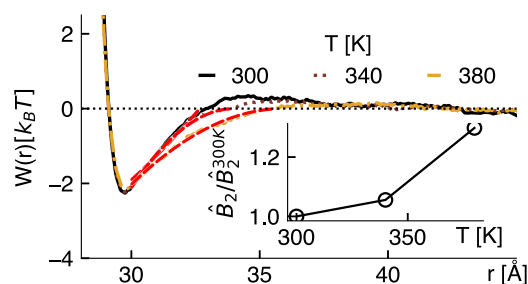


FIG. 5. Effective potential $W(r)$ expressed in units of $k_B T$ between a pair of solutes of radius $R = 15$ Å. The solute-fluid interaction potential takes the form described in the SM and has strength $\varepsilon_{sw} = 0.4$ kcal/mol. The solvent is SPC/E water, and three values of T are considered, as shown in the legend. Dashed red lines are the theoretical model discussed in the main text. Inset: relative change in $\hat{B}_2$ (see main text) as a function of temperature.

charge extended (SPC/E) water model [57]. In the SPC/E model, the hydrogen and oxygen atoms in a water molecule

are represented as distinct point charges at specific relative angles, incorporating an additional polarization correction. This adjustment increases the computational complexity of metadynamics calculations. Analogous to the mW model, we introduce a weak attraction characterized by the energy scale ε_{sf} between the solute and the three-point charges of the water molecule, simulating the effect of van der Waals forces.

Figure 5 displays the effective potential $W(r)/k_B T$ for three different temperatures at $\varepsilon_{sw} = 0.4$ kcal/mol, alongside the fits derived from the model in Eq. (1). Despite the differences in the physical features of the SPC/E and mW models, the overall shape of the potential remains identical, with variations observed in the depth and range of the potential. These variations are well captured by the model fitted to the attractive region. Additionally, the inset shows the relative change in the attractive contribution to the second virial coefficient, reflecting the influence of temperature on the hydrophobic effect and aligning with the findings for the mW model.

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