Hydrophobic Polymer Chain in Water That Undergoes a Coil-to-Globule Transition Near Room Temperature

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ABSTRACT: A simple model of a hydrophobic polymer in water is studied. The model polymer, a chain of Lennard-Jones particles with a fixed bond length, is designed in such a way that it undergoes a coil-to-globule conformational change near room temperature upon heating in liquid water. At low temperatures (\(\leq 270\) K), the polymer chain under vacuum takes a globular conformation, whereas in water, it adopts an extended form. At higher temperatures (\(\geq 320\) K), the polymer has a more compact conformation in water than under vacuum. The same polymer chain in a nonpolar solvent is always extended and shows no sign of a coil-to-globule transformation up to 360 K. The heat-induced collapse of the polymer uniquely observed in water is not attributed to the hydrophobic effect alone. Instead, the solvent attractive interaction is stronger than methane in the sense that the monomer solvent LJ energy parameter is \(\alpha_{\text{solvent}} \approx 0.6\) for water, whereas it is \(\approx 0.2\) for methane. The similarity in temperature-dependent behavior between aqueous solutions of polymers and those of hydrophobes implies that the hydrophobic effect plays a crucial role in the coil-globule transition of thermoresponsive polymers, but how it actually works is still unanswered. The similarity in temperature-dependent behavior between aqueous solutions of polymers and those of hydrophobes implies that the hydrophobic effect plays a crucial role in the coil-globule transition of thermoresponsive polymers, but how it actually works is still unanswered.

INTRODUCTION

Some water-soluble polymers in aqueous solutions undergo a coil–globule transition, or gradual conformational change, in response to temperature variation. Characteristically, they collapse upon heating, which is in contrast to polymers in organic solvents.\(^1\) Examples of those water-soluble polymers are poly(N-isopropylacrylamide), poly(N,N-diethylacrylamide),\(^4\) and poly(N-vinylcaprolactam).\(^5\) Also, many water + polymer solutions exhibit a lower critical solution temperature, above which the solubility of the polymer in water decreases with increasing temperature. These features seen for water-soluble polymers are in accord with what is known as the hydrophobic effect: as temperature increases, the solubility of hydrophobes in water decreases and the effective attraction between such molecules in water becomes stronger.\(^6\)\(^–\)\(^10\) The similarity in temperature-dependent behavior between aqueous solutions of polymers and those of hydrophobes implies that the hydrophobic effect plays a crucial role in the coil–globule transition of thermoresponsive polymers, but how it actually works is still an unanswered question. For example, the hydrophobic effect manifests itself in different ways: in the solubility of individual monomers, in the pair interaction between monomers, in the multibody interaction among monomers, and in the interaction between large hydrophobic objects in water. It remains to be seen which aspect of the hydrophobic effect plays a more important role in the temperature-induced coil-to-globule transition of thermoresponsive polymers.

The hydrophobic effect may not be the only driving force for the coil-to-globule transition of water-soluble polymers; it is possible that hydrophilic groups in such polymers also play some important role, and also that structural details give rise to mechanisms specific to individual polymers. In fact, earlier experimental and theoretical studies have derived several conjectures with varying degrees of complexity as to how the coil-to-globule transition occurs in water.\(^1,4,11–17\) Still, it is of fundamental importance to study simple models of water-soluble polymers: one can then examine whether or not the hydrophobic effect alone is sufficient to account for generic features of the coil-to-globule transition, and if so, one can proceed to elucidate which aspect of the hydrophobic effect is essential. Simulation studies of simple hydrophobic chains in explicit water, water-like solvents, and implicit solvents have revealed important features of the hydrophobic effect relevant to the coil–globule transition.\(^18–26\) Furthermore, the use of such simple models has a significant advantage in performing extended molecular simulations and thus obtaining equilibrium properties for a wide range of thermodynamic states.

In this article, we devise and study a model polymer chain that undergoes a heat-induced coil-to-globule transformation in water near room temperature. The model polymer is a flexible chain of methane-like Lennard-Jones (LJ) particles with a fixed bond length. The monomer–solvent LJ energy parameter is optimized so that the polymer is in an intermediate state near room temperature. The monomer with this LJ parameter is less hydrophobic, or more "hydrophilic," than methane in the sense that the monomer–solvent attractive interaction is stronger than the monomer–monomer one. But we consider the monomer hydrophobic with emphasis on the fact that typical hydrophobic solutes cannot participate in hydrogen bonding of...
water and the solubility in water is low and decreases with increasing temperature.

To clarify the role of water in the coil-to-globule transformation, we performed molecular dynamics (MD) simulations of a polymer chain in explicit water, in a nonpolar solvent, and under vacuum at temperatures varying from 240 to 360 K. It will be seen that temperature dependences of the equilibrium polymer conformation in the three environments are characteristically different. With numerical results of the solvation free energy of individual monomers and the potential of mean force between two monomers, we will discuss which aspect of the hydrophobic effect is more relevant to the heat-induced coil-to-globule transformation uniquely observed in water.

## MODEL AND COMPUTATIONAL METHOD

The model system consists of a single chain of LJ particles and solvent molecules. The solvent is either the TIP4P/2005 model of water\(^27\) or an LJ liquid; here, we call the latter the nonpolar solvent. The number \(n\) of monomers (LJ particles) in the polymer chain is chosen to be 30 for most of the calculations reported below; additional calculations are also performed for shorter and longer chains \((n = 15 \text{ and } 60)\). The number of solvent molecules is 2000 for each solvent. The LJ energy and size parameters of the nonpolar solvent are chosen to be \(\varepsilon_0 = 0.7749 \text{ kJ mol}^{-1}\) and \(\sigma_0 = 0.31589 \text{ nm}\), the oxygen LJ energy parameter of the polymer chain is chosen to be \(\varepsilon_0 = 0.373 \text{ nm}\), the oxygen LJ size parameter, respectively. Then, when the number density and temperature of the nonpolar solvent are the same as those of liquid water, the first peak of the radial distribution function, \(g(r)\), appears at nearly the same distance as the first peak of the oxygen–oxygen \(g(r)\) of water.\(^28\)

The model polymer is a flexible chain of 15 monomers with a fixed bond length \(l = 0.345 \text{ nm}\). The only intrachain potentials are LJ pair potentials between monomers (except bonded pairs), with \(\varepsilon_m = 1.2301 \text{ kJ mol}^{-1}\) and \(\sigma_m = 0.373 \text{ nm}\), the standard parameter set for methane.\(^29\)

The polymer–solvent interaction is a sum of the LJ pair potentials between monomer and solvent particles (or an oxygen atom for water), with LJ parameters \(\sigma_{ms} \text{ and } \varepsilon_{ms}\) common for water and the nonpolar solvent: \(\sigma_{ms} = (\sigma_o + \sigma_m)/2 = 0.344445 \text{ nm}\) and \(\varepsilon_{ms} = \varepsilon_0\) will be determined so that the polymer chain undergoes the coil–globule transformation in water near room temperature. It will be seen that an optimized value is \(\varepsilon_{ms} = 1.35597 \text{ kJ mol}^{-1}\), which is larger than \(\sqrt{\varepsilon_m\varepsilon_o} = 0.9763 \text{ kJ mol}^{-1}\).

MD simulations are performed for the model systems using GROMACS 4.6.1.\(^{30,31}\) The temperature \((T)\) and pressure \((p)\) are controlled by the Nose–Hoover thermostat and the Parrinello–Rahman barostat, respectively. The periodic boundary conditions are applied to a cubic simulation cell except for the polymer in vacuum. For all of the intermolecular pair potentials, the LJ part is truncated at 1.1 nm and the long-range Coulomb interaction is calculated by the Ewald sum with the potentials, the LJ part is truncated at 1.1 nm and the long-range boundary conditions are applied to a cubic simulation cell except for those of the aqueous solution. Earlier studies have shown that the solvation thermodynamics of simple solutes in a nonpolar liquid can be qualitatively similar to that in water if the density variation of the nonpolar liquid with temperature resembles that of water;\(^{21,32}\) we will see whether or not, under such a condition, the polymer chain in the nonpolar solvent exhibits a heat-induced coil-to-globule conformational change as in water.

For purposes of further analysis, the NPT and NVT MD simulations are performed for individual monomer particles dissolved in water and in the nonpolar solvent, respectively. The simulation conditions are the same as those for the polymer solutions, except that simulations at 280 K are not performed. The number of solvent molecules is 2000 and that of the monomers 30. The pair potentials between monomers, between solvent molecules, and between monomer and solvent molecules are all identical to those for the corresponding polymer solutions. The \(g(r)\) between monomers in the limit of infinite dilution is evaluated with the finite number of monomers accurately using a technique employed earlier for obtaining \(g(r)\) between methane molecules in water,\(^9\) and then the corresponding potential of mean force \(W(r) = –kT \ln g(r)\), with \(k\) the Boltzmann constant, is obtained.

The excess chemical potential \(\mu^*\) of the monomer in the infinitely dilute solutions is evaluated using the test-particle insertion method. For this purpose, MD simulations are performed for the two solvents consisting of 700 molecules. The temperature is varied from 270 to 360 K; the pressure is fixed at 1 bar for water, whereas the density of the nonpolar solvent is fixed at that of water at each temperature. The number of insertion per frame is \(10^4\), the number of frames is \(8 \times 10^5\), and the time interval between frames is 0.05 ps.

The solvation enthalpy \(h^*\) and solvation entropy \(s^*\) for a general solvation process are given by temperature derivatives of \(\mu^*\):

\[
h^* = \left[ \frac{\partial (\mu^*/T)}{\partial (1/T)} \right] + kT \alpha
\]

and

\[
s^* = -(\partial \mu^*/\partial T) + kT \alpha
\]

with a general coefficient of thermal expansion \(\alpha = V^{-1}(dV/dT)\). For water, \(\alpha = \alpha^w\) the coefficient of thermal expansion of the model water at 1 bar, which is very close to the experimental data; for the nonpolar solvent, again, \(\alpha = \alpha^w\) because the density variation with temperature was chosen so. (The solvation process of the monomer in water is the one at a fixed pressure, with the system’s volume change \(v\) being the partial molecular volume of the monomer; the corresponding solvation process in the nonpolar solvent is the one accompanied by a particular volume change:\(^{32}\) \(v = v_p^*\)) with \(v_p^*\) the partial molecular volume of the monomer in the...
nonpolar solvent and $\alpha_p$ the coefficient of thermal expansion of that solvent at a fixed pressure of the system.) The temperature derivatives of $\mu^*$ are obtained by fitting numerical results of $\mu^*$ to a quadratic function of $T$, and then $h^*$ and $s^*$ from the thermodynamic identities above.

The free energies of cavity formation in the pure solvents and at the immediate neighborhood of an existing monomer particle in the solvents are evaluated by Bennet’s acceptance ratio (BAR) method. Here, the cavity formation means that the process of forming a purely repulsive particle in solvent, where the particle interacts with solvent molecules via the Weeks–Chandler–Andersen (WCA) repulsive part of the LJ monomer–solvent potential. In the BAR calculation, the number of solvent molecules is 700, and MD simulations of 6 ns each are performed at 18 intermediate and 2 terminal states.

Statistical errors in the numerical results are estimated as follows. Error bars of data points for the radius of gyration $R_g$ of the polymer chain are those defined by the maximum and minimum block averages of 10 ns each. Error bars of other quantities given in the figures are standard deviations of block averages of 10 ns each (1 ns each in the BAR calculation).

### RESULTS AND DISCUSSION

To study the coil–globule conformational change of the hydrophobic polymer chain near room temperature under ambient pressure, first of all, we wish to determine an optimal value of the LJ energy parameter $\epsilon_{ms}$ for the monomer–solvent interaction. As a reference value we choose $\epsilon_{mo} = 1.04305$ kJ mol$^{-1}$, the methane–water’s oxygen LJ energy parameter developed by Docherty et al. and then optimize the factor $\lambda$ in $\epsilon_{ms} = \lambda \epsilon_{mo}$. Figure 1a shows the radius of gyration $R_g$ of the model polymer in water at 298 K and 1 bar for $\lambda = 1, 1.1, 1.25, 1.3, 1.5, 2$, and $3$. Here and below, we plot $R_g$ as a dimensionless quantity $R_g/R_g^{\text{ideal}}$ with $R_g^{\text{ideal}} = (n \ell^2/6)^{1/2}$, the radius of gyration of the corresponding freely jointed chain (the formula for $R_g^{\text{ideal}}$ is asymptotic in $n$ but sufficiently accurate even for $n = 30$).

When the monomer–water LJ potential is that of methane–water ($\lambda = 1$), the polymer chain is in a globule state or more compact than the ideal freely jointed chain, that is, $R_g/R_g^{\text{ideal}} < 1$; when $\lambda \geq 2$, it is in a swollen state; and when $\lambda$ is in a small range between 1.25 and 1.5, $R_g$ varies sharply with $\lambda$. Thus, we have chosen $\lambda = 1.3$ as an optimal value for studying the conformation change of the hydrophobic chain near room temperature, although any value around 1.3 could well be a suitable choice. With the optimal value of $\lambda = 1.3$, and also with $\lambda = 1$ for comparison, equilibrium polymer conformations in

\[\text{Figure 1. Variations in the radius of gyration } R_g \text{ of the polymer chain in water at 298 K and 1 bar. (a) } R_g \text{ vs } \lambda(\equiv \epsilon_{ms}/\epsilon_{mo}) \text{ the ratio of the monomer–solvent LJ energy parameter } \epsilon_{ms} \text{ to the methane–water one } \epsilon_{mo} \text{ in ref 33. The arrow indicates the data point at } \lambda = 1.3, \text{ a value chosen as optimal; (b) } R_g \text{ vs temperature for } \lambda = 1 \text{ and } 1.3. R_g^{\text{ideal}} \text{ is } R_g \text{ for the corresponding freely jointed chain.}
\]

\[\text{Figure 2. Conformational change of the polymer chain in water, the nonpolar solvent, and vacuum with temperature. (a) } R_g \text{ vs temperature. (b–d) Instantaneous conformations at 270 K (left) and 360 K (right) in (b) water, (c) the nonpolar solvent, and (d) vacuum.}
\]
The polymer chain with $\lambda = 1.3$ is indeed the optimal value that makes the model polymer chain in water at 270 K. Remember that the LJ potential for the monomer species vs temperature: $\mu^* / kT$, $h^* / kT$, and $s^* / k$ in (a) water and (b) the nonpolar solvent.

A crucial difference between water and the nonpolar solvent begins to appear as the temperature rises from 270 K. In the nonpolar solvent the polymer’s $R_g$ changes very little over the whole range of temperature: it decreases only slightly, but the polymer chain remains in the extended state at 360 K. The $R_g$ in water, on the other hand, decreases with increasing $T$ from 240 to 360 K and does so most rapidly between 270 and 320 K. The coil-to-globule conformational change is also clearly seen in the snapshots in Figure 2b. The change is not as sharp as what may be called the “transition” due to the shortness of the polymer chain. We performed additional MD simulations of the polymer chains consisting of 15 and 60 monomers and confirmed that the longer the chain the sharper the conformational change.

Now we consider the model polymer chain in three different environments: water, the nonpolar liquid, and vacuum; and we see how the conformation of the polymer varies with temperature in each environment. Figure 2 shows three characteristic variations of $R_g$ with temperature and the corresponding three sets of polymer conformations at low and high temperatures. The polymer chain under vacuum takes compact globule conformations at low temperatures (e.g., $R_g / R_g^{\text{ideal}} = 0.96$ at 240 K) whereas the same chain in water at those temperatures has extended conformations (e.g., $R_g / R_g^{\text{ideal}} = 1.91$ at 240 K). Compare a typical instantaneous conformation in water with that in vacuum both at 270 K as displayed in Figure 2b,d (left for both images), respectively. These results demonstrate that water has the effect of weakening the direct (van der Waals) monomer—monomer interaction at these low temperatures. This observation is seemingly opposite to the concept of the hydrophobic attraction, but it is perfectly consistent with recent experimental and theoretical results indicating that the solvent-mediated interaction between hydrophobic molecules or groups is less attractive than the direct interaction at low temperatures or even near room temperature. The same polymer in the nonpolar solvent at low temperatures is also extended with its $R_g$ as large as that in water at 270 K. Remember that the LJ potential for the monomer—solvent interaction as well as the number densities of the solution has been chosen to be identical to those in water. With this condition and at low temperatures, both water and the nonpolar solvent drive the hydrophobic monomers in the polymer chain apart from each other.

The key question now is what makes the significant difference between thermal responses of the polymer conformation in water and in the nonpolar solvent. A first step is to examine solvation thermodynamics quantities of individual monomers in the two solvents. Figure 3 shows $\mu^*/kT$, the excess chemical potential divided by $kT$, of the monomer at infinite dilution as a function of $T$. Note that at ambient pressures $\mu^*/kT$ is essentially equal to minus the logarithm of the Ostwald absorption coefficient (a measure of the solubility of gases). In water $\mu^*/kT$ is positive (the solubility is small) and increases with $T$ (the solubility decreases upon heating) as expected for hydrophobic hydration.
temperatures. Both in water and in the nonpolar solvent the with it. Figure 4 shows the curves magnitudes than in water and in the nonpolar solvent. The structure of water is determined by the directional intermolecular interactions, whereas that of the nonpolar solvent is determined by the packing of spheres; so, their structures should change differently with T. Nevertheless, as we observed, the temperature dependences of μ* /kT, h*/kT, and s*/k, the solvation thermodynamic quantities of a single monomer, are essentially the same for the two solvents if their densities vary with T in the same manner. Under the same conditions, however, the temperature dependences of W(r)/kT, the property concerning a pair of monomers, are significantly different. This means that the way the structure of water varies with temperature manifests itself in the effective attraction between monomers, but it does not do so in the solvation quantities of individual monomers.

Next, we consider temperature-dependent properties associated with a pair of monomers: the potential of mean force W(r) between two monomers and the quantities associated with it. Figure 4 shows the curves W(r)/kT at varying temperatures. Both in water and in the nonpolar solvent the first minima of W(r)/kT are located at a common distance r1 = 0.39 nm, but there are notable differences in W(r). First, the potential curve W(r)/kT in water changes with temperature significantly, whereas that in the nonpolar solvent is insensitive to T. In water, the first minimum W(r1)/kT becomes lower (more negative) with increasing T, whereas the second minimum at a solvent-separated distance becomes lower negative (Figure 4a). In the nonpolar solvent, the only notable change in W(r)/kT with T is that the barrier between the first and second minima becomes lower with increasing temperature (Figure 4b). Variations of W(r1)/kT at the first minimum with temperature are plotted in Figure 5a. It is seen that W(r1)/kT decreases significantly with increasing T in water (−0.54 at 270 K; −1.01 at 360 K), whereas it is nearly constant in the nonpolar solvent (−0.69 at 270 K; −0.74 at 360 K).

The results displayed in Figure 5a—the effective pair attraction between monomers becomes stronger with T in water, but not in the nonpolar solvent—is consistent with the observation that the polymer undergoes a coil-to-globule transformation upon heating in water but not in the nonpolar solvent. Also, the magnitude relationship between W(r1)/kT’s in water and the nonpolar solvent is reversed at around 290 K, whereas the relationship between Rg’s in the two solvents is also

![Figure 4](image1.png) Potential of mean force between monomer particles in solutions of the monomer: (a) water and (b) the nonpolar liquid.

![Figure 5](image2.png) Potential of mean force at contact distance vs temperature: (a) the total effective potential W(r)/kT; (b) the cavity term W_cav(r)/kT; (c) the attractive potential term W_attr(r)/kT.

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reversed at around 280 K. Thus, it is clear that there exists a
definite correlation between $R_g$ and $W(r_1)/kT$.

One may look at the difference between water and the
nonpolar solvent displayed in Figure 5a through an
alternative expression. The potential of mean force $W(r)$
between a pair of monomers may be expressed as

$$W(r) = \mu^*(r) - \mu^*$$

(1)

where $\mu^*(r)$ is the excess chemical potential of a monomer at
distance $r$ from another one already present in a solution,
whereas $\mu^*$ is the excess chemical potential of a monomer in
the uniform solution. In both water and the nonpolar solvent,
at $r = r_0$, both $\mu^*(r_1)/kT$ and $\mu^*/kT$ increase with $T$. The
important difference is

- water: $\frac{d[\mu^*(r_1)/kT]}{dT} < \frac{d[\mu^*/kT]}{dT}$
- nonpolar solvent: $\frac{d[\mu^*(r_1)/kT]}{dT} \approx \frac{d[\mu^*/kT]}{dT}$

(2)

That is, the local solubility of the monomer at $r_1$ away from
another monomer present in the solvent decreases with $T$ more
slowly than the solubility in water whereas in the nonpolar
solvent, the local and bulk solubilities decrease with $T$ at nearly
the same rate.

The excess chemical potential $\mu^*$ may be considered as a
sum of the two terms, the free energy $\mu^*_{\text{cav}}$ of cavity formation
and the attractive part $\phi_{\text{att}}$ of the solute-solvent interaction energy

$$\mu^* = \mu^*_{\text{cav}} + \phi_{\text{att}}$$

(3)

Likewise, the local excess chemical potential is

$$\mu^*(r_1) = \mu^*_{\text{cav}}(r_1) + \phi_{\text{att}}(r_1)$$

(4)

This idea of separating contributions from strong repulsions at
short distances and weak attractions at long distances is a basis of
the modern molecular theory of liquids. In the present
study, $\mu^*_{\text{cav}}$ is evaluated as the excess chemical potential of a
particle interacting with solvent molecules via the WCA
repulsive part of the LJ potential and $\phi_{\text{att}}$ is taken to be all
the other contributions to $\mu^*$. Note that the local $\mu^*_{\text{cav}}(r_1)$
in eq 4 is the excess chemical potential of a cavity (the WCA purely
repulsive particle defined as above) at distance $r_1$ away from an
LJ monomer already present in the solution. The local $\phi_{\text{att}}(r_1)$
is defined as the rest of the contributions to $\mu^*(r_1)$.

The difference between water and the nonpolar solvent as
expressed in eq 2, or equivalently in Figure 5a, is due to the
difference concerning the free energy of cavity formation. This
can be seen by expressing $W(r_1)$ as a sum of the cavity
contribution and the rest. From eqs 1, 3, and 4 with $r = r_1$

$$W(r_1) = W_{\text{cav}}(r_1) + W_{\text{att}}(r_1)$$

(5)

where $W_{\text{cav}}(r_1) = \mu^*_{\text{cav}}(r_1) - \mu^*_{\text{cav}}$ an effective potential the
“cavity” (the WCA particle) would feel at $r_1$ away from the
monomer present in the solvent; $W_{\text{att}}(r_1) = \phi_{\text{att}}(r_1) - \phi_{\text{att}}$ may
be considered as the contribution from all the attractive interactions
between the two monomers and between the monomer and solvent
molecules. The $W_{\text{cav}}(r_1)/kT$ as a
function of temperature exhibits a striking contrast between
water and the nonpolar solvent, as shown in Figure 5b: the one
in water monotonically decreases with $T$, whereas the other in
the nonpolar solvent increases with $T$. That is, in water, the
solvent-induced attraction between the monomer and the cavity becomes stronger upon heating, whereas it becomes weaker upon heating in the nonpolar solvent. The $W_{\text{cav}}(r_1)/kT$’s in the two solvents exhibit similar temperature dependences as shown in Figure 5c: they decrease with increasing temperature with nearly the same rate.

The full potential of mean force $W(r_1)$ between two
monomers may also be expressed as a sum of the potential
mean force between two cavities $W_{\text{cav-cav}}(r_1)$ and the rest
arising from monomer—monomer and monomer—solvent
attractive interactions $W_{\text{att-att}}(r_1)$

$$W(r_1) = W_{\text{cav-cav}}(r_1) + W_{\text{att-att}}(r_1)$$

(6)

Temperature dependences of $W_{\text{cav-cav}}(r_1)/kT$ for water and the
nonpolar solvent are again qualitatively different (see Figure
S1b): the former (in water) decreases with increasing $T$
whereas the latter (in the nonpolar solvent) monotonically
increases with $T$. Temperature dependences of $W_{\text{att-att}}(r_1)/kT$
for the two solvents are qualitatively the same: both decrease
with increasing $T$ as shown in Figure S1c.

Thus, one can conclude that the fact that the monomer–
monomer attraction, as measured by $W(r_1)/kT$, becomes
stronger upon heating in water, whereas it is nearly constant in
the nonpolar solvent (Figure 5a) results from the contrasting
temperature dependences of $W_{\text{cav}}(r_1)/kT$ in eq 5 or of
$W_{\text{cav-cav}}(r_1)/kT$ in eq 6.

We have seen that qualitative differences between water and
the nonpolar solvent first appear at a level of the effective pair
attraction between monomers—not at a level of the solvation
of a single monomer—and then consistently manifest
themselves in the contrasting thermal responses of the polymer
chain. Why do these differences appear? Although some aspects
of the hydrophobic effect can be understood primarily in terms
of the solvent density, the differences in question should result from solvent properties other than the density and its variation with temperature because now they are chosen to be the same for water and the nonpolar solvent.

One thing to note regarding the question above is that
$W_{\text{cav-cav}}(r_1)$ is the difference $\mu^*_{\text{cav-cav}} - 2\mu^*_{\text{cav}}$ where $\mu^*_{\text{cav-cav}}$
is the excess chemical potential of a pair of cavities that are a fixed
distance $r_1$ apart and $2\mu^*_{\text{cav}}$ is twice the excess chemical potential of
a single cavity. As shown in Figure S2, $\mu^*_{\text{cav-cav}}/kT$ and $2\mu^*_{\text{cav}}/
kT$ monotonically decrease with increasing $T$ in both water and
the nonpolar solvent. This trend is reasonable: $\mu^*_{\text{cav}}/kT$ and
$\mu^*_{\text{cav-cav}}/kT$ are essentially $-\ln P_{\text{cav}}$ and $-\ln P_{\text{cav-cav}}$ with the probabilities of finding a single cavity and a pair of cavities in a solvent, and those probabilities increase with increasing $T$ as the solvent density is decreasing with $T$ (above 4 °C). Thus, there is no qualitative difference between water and the nonpolar solvent, in temperature dependence of the free energy of cavity formation, either $\mu^*_{\text{cav}}$ or $\mu^*_{\text{cav-cav}}$. The qualitative difference between water and the nonpolar solvent appears when we look at the temperature dependence of the difference $W_{\text{cav-cav}}(r_1) \equiv \mu^*_{\text{cav-cav}} - 2\mu^*_{\text{cav}}$. Therefore, the origin of the difference may be to do with the structures of water and the nonpolar liquids.

In fact, the solvent–solvent pair distribution function $g(r)$
of water changes with $T$ much more significantly than that of
the nonpolar solvent under the condition that the number densities
of the two solvents vary with $T$ exactly in the same way (Figure
S3). Consistently, the monomer–solvent pair distribution
function in water also changes pronouncedly compared with
that in the nonpolar solvent. Thus, the contrasting behaviors of
the effective pair potential $W(r)/kT$ between monomers in the
two solvents are associated with variations in the microscopic solvent structure with temperature.

## SUMMARY
To summarize, a model of the hydrophobic polymer chain that undergoes a coil-to-globule transformation in water near room temperature is devised and examined. The polymer chain is swollen by water around the freezing point of water, whereas in vacuum it takes compact conformations, indicating that water as a solvent actually weakens the attractive interactions among monomers at those temperatures. This is consistent with recent theoretical and experimental results on the hydrophobic interaction. As the temperature increases the radius of gyration $R_g$ decreases, with the largest rate around room temperature, and becomes smaller than that under vacuum around 320 K.

To elucidate the role of water on the heat-induced coil-to-globule transformation, the same model polymer in a nonpolar solvent was studied under the condition that the monomer–solvent interaction is the same as that in water and the number density of the solvent is the same as that of water at each temperature. The polymer chain is extended in the nonpolar solvent as much as that in water at temperatures around 280 K and below, but it does not exhibit any conformational change to the compact globule state upon heating, unlike in water. The hydrophobic effect on a single monomer alone, that is, the temperature dependence of the solubility of a monomer species in water, cannot explain why the polymer collapses upon heating in water but not in the nonpolar solvent. But the temperature-dependent solvent effect on a pair of monomers, as measured by $W(r_1)/kT$ the potential of mean force between monomers at a contact distance divided by $kT$, can account for the different thermal responses of the polymer. The strength of attraction is enhanced in water upon heating, but it remains more or less the same in the nonpolar liquid. This important difference between water and the nonpolar solvent is found to be due to the qualitatively different temperature dependences of $W_{cav}(r_1)/kT$, the cavity contribution to the potential of mean force.

We have shown that the heat-induced coil-to-globule transformation of the simple polymer chain can be traced to the temperature-dependent hydrophobic attraction between a pair of individual monomers. In reality, thermoresponsive water-soluble polymers have more complex chemical structures with both hydrophobic and hydrophilic groups, and so the mechanism of their coil-to-globule transition may be a combination of several different factors. Important issues to be examined for more realistic polymers then include: (1) whether or not the temperature-dependent pair attraction between hydrophobic groups still plays a major role in the coil–globule transition; (2) how the mechanism of transition changes with the size of the hydrophobic groups; and (3) how hydrogen bonding among hydrophilic groups or between those groups and solvent molecules contributes to the heat-induced transition.

## ASSOCIATED CONTENT

### Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcb.6b08347.

Temperature dependences of $W(r_1)/kT$, $W_{cav}(r_1)/kT$, and $W_{at-cav}(r_1)/kT$ in eq 6 (Figure S1); temperature dependences of excess chemical potentials of a pair of cavities $2\mu_{cav}^{\ast}/kT$ and $\mu_{at-cav}^{\ast}/kT$ (Figure S2); solvent–solvent pair distribution functions at varying temperatures (Figure S3); monomer–solvent pair distribution functions at varying temperatures (Figure S4) (PDF).


