

## Reversible State Transition in Nanoconfined Aqueous Solutions

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Using molecular dynamics simulations, we find a reversible transition between the dispersion and aggregation states of solute molecules in aqueous solutions confined in nanoscale geometry, which is not observed in macroscopic systems. The nanoscale confinement also leads to a significant increase of the critical aggregation concentration (CAC). A theoretical model based on Gibbs free energy calculation is developed to describe the simulation results. It indicates that the reversible state transition is attributed to the low free energy barrier (of order  $k_B T$ ) in between two energy minima corresponding to the dispersion and aggregation states, and the enhancement of the CAC results from the fact that at lower concentrations the number of solute molecules is not large enough to allow the formation of a stable cluster in the confined systems.

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The association state of solute molecules in aqueous solutions has fundamental importance in a large variety of physical and biological processes [1–7]. For instance, whether solute molecules are in the dissolved or aggregated states can strongly affect the reaction efficiency of chemical catalysis [8–11] and the functions of proteins [12,13]. The technological importance of the solute association state has also drawn extensive attention in the study of the toxicity of nanomaterials in biological cells or tissues [14,15], the fabrication of polymer nanocomposites [16], and the synthetic controlling of oxide nanomaterials [17]. In macroscopic systems, a solute molecule stays in either a stable dispersed phase or a stable aggregated phase, with some exceptions in a critical supersaturation phase [5].

Systems at nanoscales usually demonstrate physical behavior qualitatively different from that of macroscale systems, such as the incomplete local mixing in an alcohol-water mixture [3], the extra-fast flow [18,19] or gating [20,21] through nanochannels, and the surface wetting or dewetting behavior [22–26]. Nanoscale aqueous systems widely exist in biological tissues and other natural materials as well as in modern technological applications, such as the nanoscale spaces confined in between two and more biomolecules [27] and the nanoscale channels in rock gaps [28]. However, the understanding of solute aggregation behavior at nanometer sizes is still poor, although there have been extensive theoretical [29–32] and experimental [33,34] studies of systems at micrometer scales.

In this Letter, we used molecular dynamics (MD) simulations to study the aggregation behavior of aqueous solutions confined in nanoscale geometry. These simulations revealed the existence of a reversible transition

between the dispersion and aggregation states of solute molecules and an enhancement of the critical aggregation concentration (CAC) in the nanoconfined systems. A theoretical model based on Gibbs free energy calculation has been proposed to interpret these distinguishing observations.

Our simulation systems consisted of various numbers of solute molecules, including pentanols ( $N = 8, 13, 15, 17, 19, 21, 25$ ) and hexanols ( $N = 7, 10, 13, 15, 17$ ), which were initially solvated in a cubic box of dimensions  $5.20 \times 5.20 \times 5.20 \text{ nm}^3$  containing  $N_{\text{water}} = 3101$  water molecules, as shown in Fig. 1(a). All MD simulations were performed in the canonical ( $NVT$ ) ensemble using GROMACS 4.5.4 [35]. A constant temperature of  $T = 300 \text{ K}$  was maintained by the  $v$ -rescale method with a coupling time of 0.1 ps. The average pressure in the box was  $\sim 1 \text{ atm}$  (details see PS9 in the Supplemental Material [36]). The confinement boundaries in all six directions were constructed by water walls of about  $5 \text{ \AA}$  thick in which the oxygen atoms were restrained at their lattice sites by harmonic potentials. The time step was 1.0 fs and simulation data were collected every 1 ps. The particle-mesh Ewald method with a real space cutoff of 1.2 nm was used to treat the long-range electrostatic interactions, whereas the van der Waals (vdW) interactions were truncated at a cutoff distance of 1.2 nm. The GROMOS force field [37] and extended simple point charge water model were used. We denoted the  $\text{CH}_3$  or  $\text{CH}_2$  groups by “C” and treated them as the same entity with the Lennard-Jones parameters  $\epsilon_{\text{CC}} = 0.14 \text{ kcal/mol}$  and  $\sigma_{\text{CC}} = 3.97 \text{ \AA}$ .  $\epsilon_{\text{OO}} = 0.17 \text{ kcal/mol}$  and  $\sigma_{\text{OO}} = 3.12 \text{ \AA}$ . We used Stillinger’s criterion [38] to define the aggregation



dispersion state when  $n_{LC} \leq 6$

pentanol or hexanol molecules to the hydrophobic tails, and the fourth term is the free energy of the dispersed molecules [29].  $\gamma_w$  and  $\gamma_{hw}$  are the macroscopic interfacial tension coefficients for the water-vapor and hydrophobic-tail-water [40];  $\delta_{hw}$  and  $\delta_w$  are Tolman lengths [41,42] characterizing the deviations of interfacial tensions from the corresponding macroscopic values;  $v_m$  is the single molecule volume with the width and length of the hydrophobic tail denoted by  $a$  and  $l$ ;  $-\Delta u_{\text{transfer}}$  is the transferring energy of a single hydrophobic tail from the water into the hydrophobic tail of the cluster [40];  $V$  is the volume of the system

Figure 1 presents the solute concentrations at which the reversible state transition occurs with respect to the number of water molecules in the system. We can see that the range of concentration, represented by the length of the vertical lines, shrinks as the size of the system increases. This implies that the reversible state transition is more difficult to be observed in larger confined systems and should disappear at macroscopic scales. When getting the results in Fig. 2 we have used an energy criterion for judging the existence of the reversible state transition: that is, the energy barrier between the dispersion and aggregation states is less than  $5k_B T$ . It is noted that in the cluster is assumed to take a spherical shape, the total number of solute molecules that can be accommodated. For pentanol this upper limit is around 55. That may lead to large error bars for the predictions for the concentration range predicted for  $N_{\text{water}} = 10$  and 20. Their values are lower than the macroscopic CAC value. In summary, we have shown a reversible dispersion-aggregation state transition and an enhancement of the aggregation concentration in aqueous solutions at nanoscale. We note that the reversible state transition has never been reported under nanoconfined conditions despite extensive theoretical, simulation, and experimental works on the association behavior of molecular particles. The importance of this work can be seen from the fact that the confinement of aqueous solutions at nanoscale occurs very frequently in both biological and natural environments. For example, the aggregation of ligand molecules in confined space may prevent the binding between functional hydrophobic groups and proteins. The possible toxicity of SWCNTs also depends on whether

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they are dispersed or aggregated [14]. Oil usually exists in nanoscale space in the underground rock, and the aggregation property of the injected amphiphilic surfactant molecules will reduce the efficiency of oil extraction [43]. In the nanoporous media—soil, the aggregation process of minerals or nanoparticles can initiate the restoration of the carbon element and improves the activity of the soil [44].

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