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Identifying trends in hydration behavior for modifications to the hydrophobicity of poly(n-isopropylacrylamide)

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ABSTRACT

Poly(n-isopropylacrylamide), PNIPAM, is a thermo-responsive polymer that has been thoroughly studied for its many applications, such as drug delivery and actuators. Below the lower critical solution temperature (LCST), PNIPAM is well hydrated in the elongated conformation. The transition occuring at the LCST results in a less hydrated collapsed state above the LCST. This volume phase transition is dependent upon the hydration of the polymer and its hydrophobicity. Some research has been done on potential modifications of PNIPAM for applications, but until now there has not been a study of the hydration properties as a function of hydrophobicity. The work presented in this paper applies a Voronoi analysis of the hydration of PNIPAM, as well as PNIPAM with other alkyl substituents. We show from classical MD simulations that increasing hydrophobicity can increase the volume phase change, but there is a lower limit to this trend. Additionally, replica exchange molecular dynamics were conducted on PNIPAM showing a fluctuation between elongated and collapsed states near the LCST.

1. Introduction

Thermo-responsive polymers are a subclass of stimuli-responsive polymers responding to environmental temperature changes. This class of polymers exhibits a lower critical solution temperature (LCST) at which a phase transition occurs [1,2]. One such polymer in this subclass is poly(n-isopropylacrylamide), or PNIPAM, which exhibits an LCST due to entropic effects [3,4]. The interactions resulting in the phase transition also cause a volume change at the transition temperature [5]. An LCST of about 32 °C (305 K), near body temperature, has driven the study of PNIPAM for biomedical applications (such as tissue engineering and drug delivery) [6–10]. Additional studies have also been done for the use of PNIPAM in the area of self-driven motors [11,12].

The roles of hydration and polymer–polymer interactions in the volume phase transition of PNIPAM have been highly studied [5,13–18,6,19–21]. Below the LCST, enthalpic contributions from amide-water hydrogen bonds stabilize PNIPAM in the hydrated, elongated state by dominating the entropic contributions of the hydrophobic isopropyl groups which are surrounded by a stable water clathrate structure [6,19–21]. The water clathrate destabilizes above the LCST, and the entropic contributions from the hydrophobic interactions between water and the isopropyl groups overwhelm the enthalpic contributions from polymer-water hydrogen bonding, stabilizing the collapsed conformation [6,21]. Additionally, waters are expelled from the center of the polymer as it transitions from elongated to collapsed, with the trapped waters contributing to stabilization [6,22,23]. The process of volume phase transition is dependent upon hydration of the polymer, and therefore upon the polymer–polymer and polymer–water interactions [24–26,14]. The hydration of PNIPAM was predicted to follow a scheme such that the forming of a single amide-water hydrogen bond leads to further formation of polymer-water hydrogen bonds [18,24]. Additionally, the tacticity of PNIPAM affects the LCST and whether it will even be soluble in water [27]. Further, changing molecular composition by increasing or decreasing the hydrophobicity of the polymer has been shown to decrease and increase the LCST, respectively [28,13,29]. To our knowledge, there has not been a comparative study of the hydration behavior responsible for the volume phase transition at varying levels of hydrophobicity, nor has there been a study of the behavior of PNIPAM at the LCST. Since these studies are needed to fully understand the trend, we present here a study in which the isopropyl groups of PNIPAM have been substituted with methyl, ethyl, or t-butyl groups.

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2. Methods

2.1. Building PNIPAM

The molecular operating environment (MOE) was used to build a 30-mer of PNIPAM in the elongated conformation [30]. An atactic 30-mer was created with the RS scheme (RRRSSSSRRRRSSSSRRRRSSSSRRRRSSS). The system was energy minimized using gradient descent with a cutoff of 0.0001 [30]. PNIPAM was then solvated in a box of 10,347 TIP3P waters to ensure the proper density and that the polymer would not interact with its periodic image once periodic boundary conditions were applied [31]. The TIP3P water model was chosen because it properly identifies the solvent-solute interactions when using the OPLS-AA force fields [31–33]. The system was again energy minimized with the gradient descent algorithm in MOE to ensure no steric clashes and provide a starting point for simulations [30]. Simulations for methy-, ethyl-, and t-butyl-substituted PNIPAM were constructed as follows (see Fig. 1 for monomer units of PNIPAM and alkyl-substituted PNIPAM). PNIPAM with methyl substituents was created by taking the previously constructed box (including the 10,347 waters) and substituting the isopropyl groups on PNIPAM with methyl groups. The box of solvated methyl-substituted PNIPAM was then energy minimized with the gradient descent algorithm to ensure no steric clashes or excess spaces [30]. The same procedure was followed with ethyl and t-butyl substituents.

2.2. Molecular dynamics simulations

The four systems (methyl-substituted PNIPAM, ethyl-substituted PNIPAM, PNIPAM, and t-butyl-substituted PNIPAM) were simulated with molecular dynamics to identify differences between elongated and collapsed conformations of each polymer and identify trends in hydration properties associated with changing hydrophobicity. The NPT ensemble was used to run molecular dynamics simulations using NAMD with the OPLS-AA forcefield, Particle Mesh Ewald summation, and Langevin thermostat [34,33,35]. A 2 fs timestep and periodic boundary conditions were used. Molecular dynamics simulations were run at atmospheric pressure and temperatures bracketing the experimental LCST of PNIPAM (250 K, 270 K, 290 K, 300 K, and 310 K) for 50 ns with samples taken every 1 ps until the radius of gyration (R_g), potential energy, and volume converged. Each MD simulation had the same initial configuration with temperature being the only difference. Subsequent molecular dynamics simulations were run for methyl-substituted PNIPAM (270 K, 290 K, 310 K, 330 K, 350 K), ethyl-substituted PNIPAM (250 K, 265 K, 273 K, 280 K, 310 K), and t-butyl-substituted PNIPAM (230 K, 270 K, 290 K, 310 K). The simulation temperatures for alkyl-substituted PNIPAM started at 310 K, with additional temperatures chosen above or below this temperature, based on the R_g, to obtain results for both elongated and collapsed states.

2.3. Replica exchange molecular dynamics

PNIPAM was also simulated using replica exchange molecular dynamics implemented in NAMD to better isolate the LCST and identify how the hydration properties are changing with temperature [36]. A choice of 12 replicas was chosen with temperatures ranging from ±50 of the experimental LCST, resulting in a range of 250–350 K. Each replica was run with the NPT ensemble, Particle Mesh Ewald summation, and Langevin thermostat [35]. The initial configuration of each replica was the final configuration of PNIPAM from the 270 K classical MD simulation.

2.4. Voronoi implementation

The MDAnalysis library in Python was used to parse the trajectory and configuration (psf) files [37]. The Voronoi polygons (VP) were constructed using pyvoro, a wrapper class around Voro++ [38]. The coordinates input to Voro++ were wrapped into a periodic cube. Radical Voronoi Polyhedra tesselations were used with weights corresponding to the Lennard-Jones σ parameter of the OPLS-AA forcefield and periodic boundary conditions were applied [39]. Each polymer molecule, including hydrogens, had its own VP, and every water molecule was placed in a VP centered at the oxygen [40]. The VP were reconstructed every iteration (i.e. every 50 ps).

For each iteration, the hydration shells were determined with the following scheme [41]: The water is in the first hydration shell if the VP of the water shares a face with at least one VP of a polymer atom. The water is in the second hydration shell if the VP of the water shares a face with at least one VP in the first hydration shell, and is not in the first hydration shell. Otherwise, the water is considered to be bulk.

The average number of waters in the first hydration shell (HS1) and the second hydration shell (HS2) were calculated by finding the total number of waters in the shell and dividing by the number of monomer units. Also, the number of waters associated with each monomer unit were found by determining the nearest neighbor of the water molecule in the first hydration shell and marking that water as belonging to the monomer unit containing its nearest neighbor. Additionally, the volume of the entire first and second hydration shells were calculated and tracked throughout the simulations.

The partial molar volume of the system can be approximated by the apparent volume (V_{app}), where Voloshin et al. define the apparent volume to be $V_{app} = V_{\text{int}} + V_{hyd,N} - \frac{N_{hyd}}{\rho_0}$ [42,43]. The instrinsic volume (V_{int}) was given by the Voronoi volume of the polymer; similarly the hydration volume ($V_{hyd,N}$) was given by the first hydration shell Voronoi volume [39]. The bulk density for the same number of atoms in the first hydration shell ($\frac{N_{hyd}}{\rho_0}$) was calculated by finding the average bulk water volume and multiplying by the number of atoms in the first shell. The Voronoi volume of the polymer ($V_{VP,int}$) was calculated by summing the Voronoi volumes for each VP of the polymer. Similarly, the Voronoi volume of the first hydration shell ($V_{VP,hyd,N}$) and average bulk water volume ($V_{VP,b,N}$) were calculated by summing or averaging, respectively, over the VP volumes of those respective waters.

3. Results

3.1. Classical MD

From classical MD simulations, the LCST of PNIPAM was determined to be between 290 K and 300 K, comparable to the experimental LCST of 305 K (see Fig. 2 and Figs. S1–S4). The difference between the experimental and simulated LCST values for PNIPAM may be attributed to the water model, suggesting the exact values we calculate may be shifted but the trends are reliable. The LCST of methyl-substituted PNIPAM increased in comparison to unsubstituted PNIPAM (to about 305 K), and the LCST of t-butyl-substituted PNIPAM decreased (to about 270 K), as expected. However, the LCST of ethyl-substituted PNIPAM decreased to about 280 K. Additionally, the radius of gyration (R_g) tended to be larger for t-butyl-substituted PNIPAM and smaller for methyl-substituted PNIPAM as compared to the R_g of PNIPAM, but ethyl-substituted PNIPAM had a similar range to PNIPAM. Noting the hydration properties, the molecular volume and partial molar volume were greater above the LCST than below. Additionally, a decrease in number of hydrating waters and volume of hydration shells was also observed,