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Atomistic insight into the role of amine groups in thermoresponsive poly(2-dialkylaminoethyl methacrylate)s

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ABSTRACT

The role of amine groups in the phase separation of thermoresponsive poly(2-dialkylaminoethyl methacrylate)s with dimethyl-, diethyl-, and diisopropylaminoethyl substituents has been studied by atomistic molecular dynamics simulations. The polymer chains present a more compact conformation at higher temperatures, losing contact with the water molecules. In the vicinity of the amine groups, the exclusion of water molecules increases with the increasing hydrophobicity of the amine moieties above the lower critical solution temperature. In particular, the potential of mean force results suggest that the formation of hydrogen bonding between the amine groups and water molecules involves more entropic contributions at higher temperatures in the cases of the diethylaminoethyl and diisopropylaminoethyl groups. These results provide insight for the rational design of side chains of thermoresponsive polymers for smart materials and devices.

1. Introduction

It is well-known that thermoresponsive polymers show conformational transitions in solution around their lower critical solution temperature (LCST), resulting in poor solubility of the polymer chains above that temperature [1,2]. Such changes in solubility have opened up a new horizon for smart materials and devices that respond to changes in the external temperature [3–7]. Over the last decade, molecular dynamics (MD) simulations have provided atomistic information on the conformational transitions, polymer–solvent interactions, and solvent microstructure in thermoresponsive polymer solutions.

Significant research efforts have focused on the LCST behavior of poly(*N*-isopropylacrylamide) (PNIPAM), the most representative thermoresponsive polymer, with single chain systems [8–10], multi-chain systems [11], artificial nanostructures [12,13], drug-delivery applications [14], urea-induced collapse [15,16], co-solvents [17,18], tacticity control [19,20], and copolymerization [21,22] by MD simulation. Most commonly, hydrogen bonding (H-bonding) between the PNIPAM chains and water molecules are weakened, whereas the hydrophobic interactions of isopropyl groups are strengthened in globular conformations of PNIPAM. Such MD calculations have also been extended to a wide range of LCST polymers and polypeptides. As another example of thermoresponsive polymers, the conformational transition of poly(ethylene oxide) (PEO) has been calculated by the Yethiraj group, suggesting that the LCST behavior of PEO in ionic liquids is mainly due to the entropic penalty of the H-bonding between PEO and cations [23–25]. In addition, the Yingling and the Hall group have both demonstrated the LCST behavior of elastin-like polypeptides in aqueous solution and the chain-length dependence on their LCST behavior by atomistic MD simulations [26,27]. Compared to the recent progress on the simulation of LCST behavior, little attention has been paid to the MD simulation of poly(2-dimethylaminoethyl methacrylate), which is responsive to both thermal and pH changes [28].

Fine tuning the temperature- and pH-windows of stimulus-responsive polymers is essential to prepare smart materials and

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devices designed to operate under particular external stimuli in nano- and biotechnologies. Typically, the LCST behavior of thermoresponsive polymers is controlled by copolymerization with other monomers [29–32] or small molecules such as ionic liquids [33]. The side chains of thermoresponsive polymers can also be designed to modulate the hydrophilicity, hydrophobicity, or hydrogen bonding ability. Recently, we have reported that the cloud point of PEO-based functional polymers can be widely tuned through their pendant amine groups in terms of their types and hydrophobicity [34]. In parallel, the Plamper group has also demonstrated that the pH and temperature of which the phase separation occur in poly(2-dialkylaminoethyl methacrylate)s are lowered by increasing the hydrophobicity of the dialkylaminoethyl substituents [35]. In particular, by means of fluorescence spectroscopy, they found that the phase separation of poly(2-dimethylaminoethyl methacrylate) is mainly due to backbone/carbonyl interactions, while the phase separation of poly(2-diethylaminoethyl methacrylate) and poly(2-diisopropylaminoethyl methacrylate) is originated from the less polar dialkylaminoethyl groups. Likewise, the type and hydrophobicity of amine moieties in the side chain influence the phase separation of LCST polymers, but theoretical and fundamental understanding of such substituent effects remains to be developed.

In this study, we have carried out MD simulations of the conformational transitions of a series of poly(2- dialkylaminoethyl methacrylate)s as model polymers for investigating the effect of different amine groups on the LCST behavior. Three poly(2-dialkylaminoethyl methacrylate)s with dimethyl-, diethyl-, and diisopropylaminoethyl substituents were evaluated at two different temperature regimes (below and above the LCST). Since our previous study revealed the exclusion of water molecules in the vicinity of carbonyl groups in the phase separation of poly(2-dimethylaminoethyl methacrylate) [36], we here focused on the role of the carbonyl and amine groups in the phase separation of the poly(2-dialkylaminoethyl methacrylate) series. The structural properties of the specific functional groups and water molecules were investigated. In particular, the hydrogen bonding between the amine groups and water molecules was monitored with the potential of mean force (PMF) calculations.

2. Method

2.1. Polymer modeling

The OPLS-AA force field [37] was applied to single chains of poly(2-dialkylaminoethyl methacrylate)s. Atomistic models with the OPLS-AA force field have been reported to successfully reproduce the LCST behavior of PNIPAM [13,20,22]. We modeled syndiotactic polymers with 30 monomer units, owing to the distinct change in the conformational transition [9]. Poly(2-dimethylaminoethyl methacrylate), poly(2-diethylaminoethyl methacrylate), and poly(2-diisopropylaminoethyl methacrylate) are denoted as PDM, PDE, and PDiP, respectively, as shown in Fig. 1. The fully deprotonated states were only considered in order to compare the roles of the carbonyl and deprotonated dialkylaminoethyl groups in the conformational transitions of the polymer. The TIP4P/2005 model [38] was used for explicit water molecules, because the water model is not only one of the best description of water molecules but it has also been used for PNIPAM solution with the OPLS-AA force field [20,22].

2.2. Simulation details

All of the MD simulation were carried out with GROMACS 5.1.2 package [39]. The polymer topologies were generated by MKTOP script [40] for GROMACS-compatible format. The initial polymer conformation with a fully extended chain was relaxed by a short NVT MD simulation without water molecules. Then, each polymer chain was solvated with 12,000 water molecules in a cubic periodic simulation box of side length 7.2 nm. After an energy minimization of the initial system, the equilibration was performed by a short 100-ps NVT ensemble and 500-ps NPT ensemble with a position restraint potential to the polymer chain. Finally, long NPT MD simulations of 300 ns were calculated at two different temperatures, 290 and 330 K. The target temperature was maintained by using a V-rescale thermostat [41] with a coupling constant of 0.1 ps. A Parrinello–Rahman barostat [42] with a coupling constant of 2.0 ps was used to keep the pressure constant at 1.0 bar. For the short-range nonbonded interactions, the cutoff distance was set to 1.0 nm. For considering the long-range electrostatic interactions, the particle mesh Ewald (PME) method [43,44] was employed. All the bond lengths with hydrogen atoms were constrained with the LINCS algorithm [45]. Thus, a time step of 2 fs was applied.

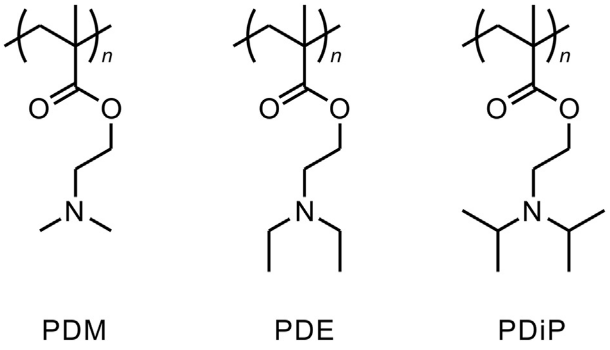

Fig. 1. Molecular structures of poly(2-dimethylaminoethyl methacrylate) (PDM), poly(2-diethylaminoethyl methacrylate) (PDE), and poly(2-diisopropylaminoethyl methacrylate) (PDiP).

The potential of mean force (PMF) was calculated by the umbrella sampling and the weighted histogram analysis method (WHAM) [46]. Each monomer unit was solvated with 3000 explicit water molecules. The distance between the nitrogen atom in the amine group of the monomer and the oxygen atom in a water molecule was restrained by a harmonic potential. Each NPT MD simulation of 10 ns was performed at 25 different distances with 0.05 nm spacing. VMD package [47] was used for the visualization of polymer chains.

3. Results and discussion

Due to the absence of the torsional parameters of the O–C–C–N dihedral in the OPLS-AA force field, we calculated and compared the rotational energy of the torsion angle from *ab initio* [48] and OPLS-AA force field with a 2-dimethylaminoethyl acetate, which is the simplest monomer structure for O–C–C–N dihedral. The molecular structure was scanned with a step size of 15°, based on the O–C–C–N dihedral angle. Fig. 2 shows the overestimated energy barrier of the original OPLS-AA force field (by up to 2 kcal/mol) compared with the *ab initio* calculation at MP2/aug-cc-pVTZ//MP2/cc-pVDZ level. By adding an additional torsional parameter, the energy profile from the fitted OPLS-AA force field was in good agreement with that from the *ab initio* calculation.

Long NPT (*i.e.*, isothermal and isobaric ensemble) MD simulations of 300 ns were performed for single chains of PDM, PDE, and PDiP in water with the fitted torsion parameter at two different temperatures, 290 and 330 K, based on the known LCST of PDM (~40 °C) [49]. Structural analysis was carried out on the