

# Computer Modeling Of Star Polymer Molecules With Diblock Arms

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## ABSTRACT

Three different star polymer molecules in an aqueous environment were studied using molecular dynamics simulations and an explicit representation of the water solvent. The simulations for each system were performed at four different temperatures and thermally induced conformational changes were observed. Each of the three star polymers consisted of 16 diblock arms bound to a small adamantane core. The diblock arms in each case consisted of a hydrophobic region (either polylactic acid (PLA), polyvalerolactone (PVL) or polyethylene (PE)) and a PEO hydrophilic region, offering a range of conformational flexibility and different relative amounts of ester vs. aliphatic chain content. The study shows the cores to be strongly phase separated and solid-like. The ester-based systems are glassy (solid but disordered), but the polyethylene system exhibits highly ordered structure. Results suggest drug association with ester-based star polymers to be at the water-hydrophobic core interface.

**Keywords:** molecular dynamics, simulation, star polymer, diblock star copolymer

## 1 INTRODUCTION

Star polymers are molecules with a topology of three or more arms bound to a common junction. This junction might be as small as a single atomic site, or a single functional group, or as large as a dendrimeric system or even a nanogel [1,2]. Of interest here are star polymers with identical arms where each is a diblock copolymer consisting of a hydrophobic region close to the junction site, and a hydrophilic region farther away from it. In an aqueous environment, the hydrophobic components of these molecules collapse into a “molten globule” and the hydrophilic region either coats the hydrophobic region, thereby shielding it from water, or otherwise extends into the water. The point is that the hydrophilic material, in addition to making the whole molecular system more soluble through its favorable interactions with water, will also offer protection to the hydrophobic core and thereby slow or prevent its degradation and also prevent aggregation with other star polymer molecules, a process driven by hydrophobic interaction that would certainly occur otherwise.

Diblock star copolymers of this type have been proposed as potential vehicles for the delivery of hydrophobic drug molecules [1,2] in physiological environments. That is, hydrophobic drug molecules will

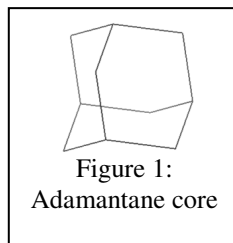
enter into the hydrophobic interior of the star polymers, which can then be delivered easily due to the overall solubility of such moieties.

A very attractive feature of such delivery vehicles is that there are a variety of aspects [1, 2] available to the polymer chemist that could allow tuning of the star for selective uptake, drug release rates, and degradation profiles. These include the number of arms and their overall length, the choice of hydrophobic and hydrophilic component for each arm, as well as their relative amounts within each arm.

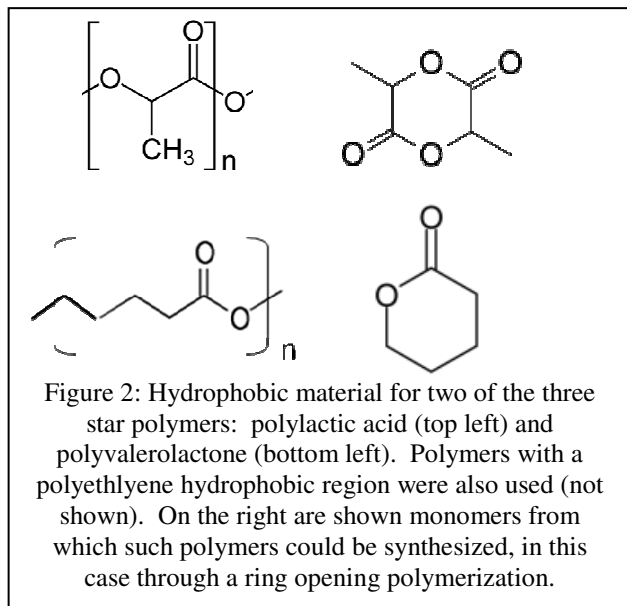
Although there have been significant advances in the ability to synthesize such molecules, there are basic physical properties, both structural and kinetic, that are still relatively unknown, or, at least, are poorly understood. For example, from a structural perspective, what is the shape of such molecular systems; what is the concentration of the various components (water, hydrophobic and hydrophilic material) in each of the various regions of a solvated star polymer; how structured or disordered is each component; what is the thermal dependence of these structures and behaviors? From a kinetic perspective, how rapidly do the various components diffuse between the various regions, and within each region, of the star polymer; are the regions better characterized as liquids, glassy solids or a crystalline solids? Finally, since a star polymer differs from a polymer blend of similar composition because of topological constraints, how similar are the various environments within the star polymer to bulk phases of the same composition? And, of course, how might arm length, arm number and arm chemical composition affect any of these properties? Answers to these kinds of simple physical chemistry questions would go a long way to advancing the art of designing star polymers for specific applications such as drug delivery.

## 2 MOLECULAR SIMULATIONS

Three different star polymer molecules in an aqueous environment were modeled and studied using molecular dynamics simulations. Each consisted of 16 diblock arms bound to a small adamantane core (Figure 1). Adamantane offers a diamond-like structure of 10 carbon atoms onto which up to 16 arms may be connected. This offers a simple model for experimental star polymer systems that are actually much larger. The diblock arms in each case consisted of a hydrophobic region and a (PEO) hydrophilic region. The



three molecular systems studied were identical except for the composition and length of the hydrophobic component (Figure 2), which was either polylactic acid (PLA), polyvalerolactone (PVL) or polyethylene (PE). These choices offered a range of conformational flexibility, as well as different relative amounts of ester versus aliphatic chain content.



The star polymers arms were constructed by connecting some number of hydrophobic repeat units (Table 1) to a hydrophilic chain of six PEO units to make diblock copolymer strands, then 16 of these were attached, hydrophobic part first, to the adamantane. Force field parameters were assigned mainly from the OPLS-AA parameter set [3,4], and simulations were performed using the LAMMPS simulation package [5] and BlueGene/L supercomputers at the IBM Almaden Research computing facility. The molecular models were built in an extended conformation and simulations of the isolated molecules were run until partially collapsed structures were obtained.

Name	Star Polymer Formula	Arm Length
PLA	A[LA <sub>16</sub> -CH <sub>2</sub> -EO <sub>6</sub> -H] <sub>16</sub>	67
PVL	A[VL <sub>8</sub> -EO <sub>6</sub> -H] <sub>16</sub>	78
PE	A[E <sub>12</sub> -EO <sub>6</sub> -H] <sub>16</sub>	50

Table 1: Star polymer systems of this study, along with the extended arm length of each of the 16 arms, in Angstroms. A=adamantane; LA=lactic acid; VL=valerolactone; E=ethylene; EO=ethylene oxide.

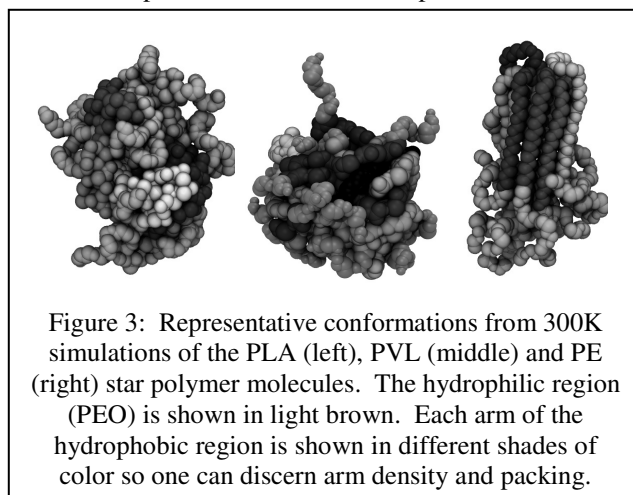
Since the influence of aqueous solvent is critical to the thermodynamic and kinetic behavior of solutes, an explicit representation of the water solvent was used for this study. The model chosen, TIP4P-Ew [6], has been shown to reproduce very accurately the bulk properties, structural, thermodynamic and kinetic, of liquid water. The partially collapsed structures of each star polymer were thus combined with sufficient water to fill at liquid water

densities a cubic simulation cell of approximately 11 nanometers on an edge.

The simulations for each system were performed at four different temperatures: 300K, 350K, 400K and 450K. This allowed for the observation of thermally induced conformational changes. Given that the range of physiological temperatures is really quite small (approx 290K-310K), performing simulations over such a wide range of temperatures may seem like wasted effort. However, there are several reasons for doing so: (1) today's state of the art force fields still lack sufficient accuracy to predict temperatures of structural transitions (even for protein folding studies for which force fields are rather mature), but one may be able to relate the results of force fields used in simulations at one temperature with experimental results at some another, allowing a mapping between the simulations and experiments. (2) It is important to establish whether and how the thermal behavior of structural or kinetic properties relates to chemical and structural composition. (3) It is not known a priori what the relevant equilibration/relaxation and correlation/sampling times these materials exhibit, nor even if simulations of feasible length can characterize them. By performing simulations over a range to temperatures, one can judge, as the temperature is lowered, at what point these times begin to exceed computational feasibility and thereby provide grounds for whether sufficient sampling can and has been performed.

### 3 RESULTS

Simulations for each of the three molecular systems involved extensive equilibration followed by at least 50 nanoseconds of production at each temperature. Conformations were saved at 10 picosecond intervals and these were subjected to several types of analysis. Structural metrics, such as radius of gyration and shape anisotropy were measured, and averages, standard deviations and time correlation functions were measured for each. Kinetic properties such as the correlation times for reorientation of unit vectors placed on the various repeat units were also



measured. Of particular interest were Voronoi analyses [7,8] performed on each conformation. Voronoi polyhedra around each particle partition space into regions closer to each particle than to any other (Figure 4). This allows one to measure the volume and interfacial surface area associated with any partitioning of material, such as the

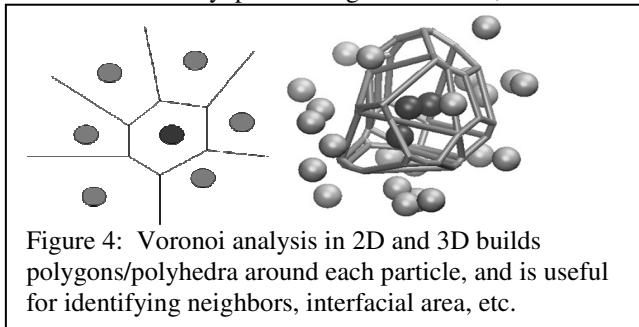


Figure 4: Voronoi analysis in 2D and 3D builds polygons/polyhedra around each particle, and is useful for identifying neighbors, interfacial area, etc.

volume of the hydrophobic core and the water-hydrophobic core interfacial area (i.e., solvent-accessible area). We also used it to identify when a water molecule was “interior” to the polymer.

At even the highest temperatures, all three of these star polymer systems have hydrophobic cores with a dense, compact structure (Figure 3). The most striking observation was that the hydrophobic part of the PE star polymer formed a highly ordered and rigid tubular structure that was stable at the two lower temperatures, and went through a cylindrical to globular structural transition between 350K and 400K.

The orientationally averaged density as a function of distance from the adamantane core is shown in Figure 5 for the PLA star polymer. (The other temperatures and other polymers show similar features). Here one can see what appears to be deep penetration of water into the hydrophobic core region. However, this is actually an artifact of orientationally averaging over a deeply pitted and grooved irregular surface rather than an indication that water resides within the hydrophobic region. A better indication of the amount of water in this region is provided

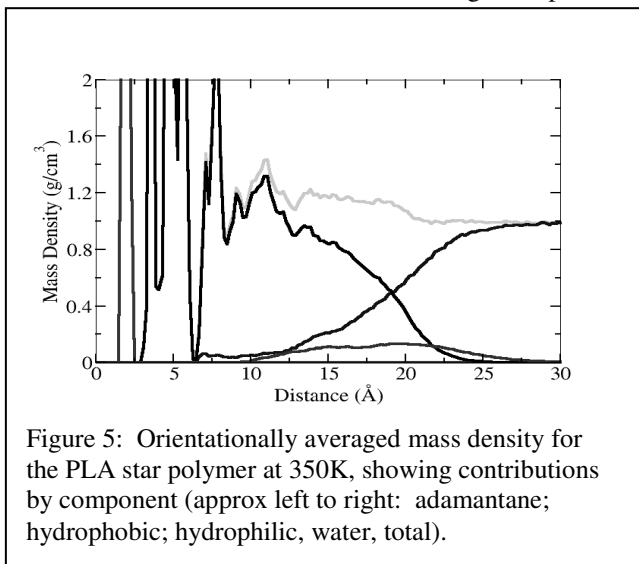


Figure 5: Orientationally averaged mass density for the PLA star polymer at 350K, showing contributions by component (approx left to right: adamantane; hydrophobic; hydrophilic, water, total).

by the Voronoi analysis where one can identify a water molecule as being *interior* to the core if all of its Voronoi neighbors are hydrophobic material. The results of this analysis (Figure 6) show, contrary to what is implied in Figure 5, that the presence of interior water molecules is rather rare, especially at lower temperatures where, for polymers of the size studied here, is it less than half a water

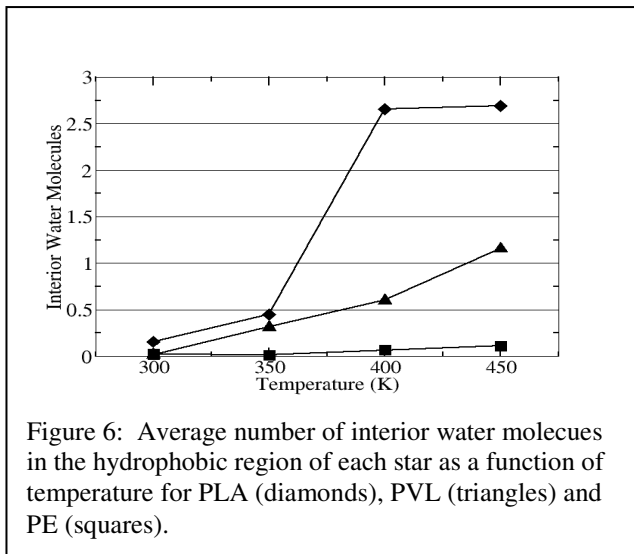


Figure 6: Average number of interior water molecules in the hydrophobic region of each star as a function of temperature for PLA (diamonds), PVL (triangles) and PE (squares).

molecule on average. Notably, between 350K and 400K, the water content in the PLA star shows a large increase, but even at high temperatures it is only holding about 2.5 molecules.

Another important metric that was monitored was the orientational correlation function. For this, *directional* unit vectors were placed on each repeat unit and followed as a function of time during the simulation. These vectors were projected onto a molecule-fixed coordinate system determined by the relatively rigid adamantane core. The

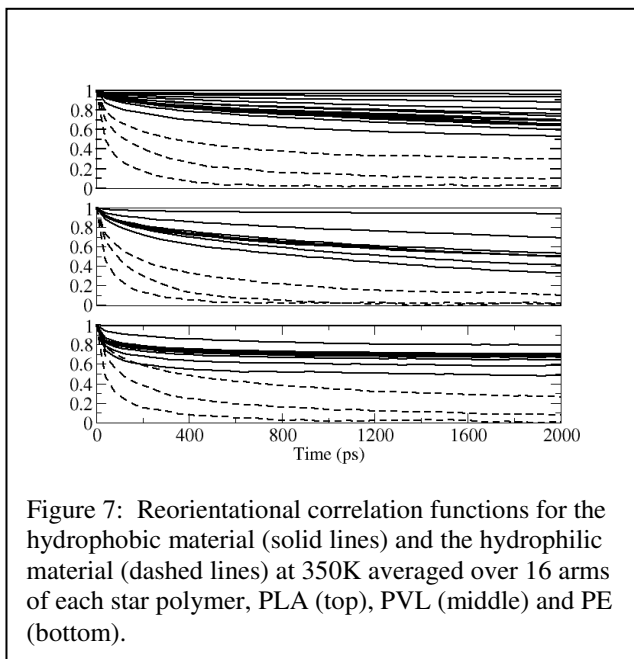


Figure 7: Reorientational correlation functions for the hydrophobic material (solid lines) and the hydrophilic material (dashed lines) at 350K averaged over 16 arms of each star polymer, PLA (top), PVL (middle) and PE (bottom).

correlation functions were computed for each repeat unit on each arm of the star and then correlation functions corresponding to the same distance along the length of each of the 16 arms were averaged. The result, shown in Figure 7, shows that correlation functions for the PEO (dashed lines) decay rapidly, with the PEO units at the ends of each star polymer arm having the shortest orientational memories. These are behaving as one might expect for a molecule in the liquid phase. In contrast, the correlation functions for the hydrophobic material show much slower decay, and are more representative of a solid or a very viscous liquid. Figure 7 shows that the correlation functions for the hydrophobic material in the PE star are not decaying at all at 350K; the PVL shows the fastest decay, but even this decay is not representative of what one might consider to be a liquid.

#### 4 CONCLUSIONS

Analysis of the orientationally averaged mass density curves and the results of the Voronoi analysis of this study shows that for these star polymers, the hydrophobic cores are very strongly phase separated both from water and from the hydrophilic material (PEO), forming a sharply defined interface with water. The concentration of water inside the hydrophobic region is extremely small, and water penetration events are very shallow and short lived (<40 picoseconds). Moreover, reorientational correlation functions for vectors attached to repeat units of the hydrophobic region indicate that the core is relatively solid. For both ester-based systems (PLA, PVL) the hydrophobic regions are glassy (solid, but disordered), but the polyethylene system exhibits a highly organized (solid and ordered) structure that persists up to relatively high temperatures, showing a structural “melting” transition.

We remark that the extreme dryness of the hydrophobic interior can come about for different reasons that are illustrated with these example star polymers. In one case, operative for nonpolar cores as exist in the PE star, the aliphatic chains have no attraction to water, and the water avoids the core region so that it can form hydrogen bonds with other water molecules in the solvent. In other words, the driving force for phase separation of the core is hydrophobic interaction, as is seen for small nonpolar solutes in water. However, a different mechanism seems to be operative for the ester-based polymers. Unlike with aliphatic chains, these have a high concentration of polar carbonyl groups, and the water and ester groups are, in fact, mutually attracted, as evidenced by the aqueous solubility of small molecule esters. However, the ester-ester interactions seem to be stronger than water-ester interactions, so water is expelled from the core in this case so as not to interfere with the formation of favorable interactions among the ester groups. I.e., the hydrophobic material appears to be phase separating from water because of its cohesive nature.

We speculate that due to the rigidity and cohesive nature of ester-based hydrophobic regions, hydrophobic cargo (drug) molecules may associate with these types of star polymers at the water-hydrophobic interface, i.e., in a surface adsorption process rather than by being solvated into the interior of the core. This is in contrast to the common view that such molecules are *dissolved*, or *encapsulated*, into the interiors of the hydrophobic regions of star polymer systems.

We remark that many of these results are consistent with and further supported by the work of Huynh, et al., in Prof. Christine Allen’s group at the University of Toronto. Their group reported on [9] similar molecular systems, six arm star polymers with a variety of arm lengths, each with polycaprolactone (PCL) as the hydrophobic material and PEO as the hydrophilic material. (PCL has one more methylene unit between ester groups than PVL.) A more comprehensive discussion and many further details and conclusions concerning these star polymers will be available in an upcoming publication [10].

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