

## Self-Organization of *n*-Alkane Chains in Water: Length Dependent Crossover from Helix and Toroid to Molten Globule

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We demonstrate a chain length dependent crossover in the structural properties of linear hydrocarbon (*n*-alkane) chains using detailed atomistic simulations in explicit water. We identify a number of exotic structures of the polymer chain through energy minimization of representative snapshots collected from molecular dynamics trajectory. While the collapsed state is ring-like (circular) for small chains ( $C_nH_{2n+2}$ ;  $n \leq 20$ ) and spherical for very long ones ( $n = 100$ ), we find the emergence of ordered helical structures at intermediate lengths ( $n \sim 40$ ). We find different types of disordered helices and toroid-like structures at  $n = 60$ . We also report a sharp transition in the stability of the collapsed state as a function of the chain length through relevant free energy calculations. While the collapsed state is only marginally metastable for  $C_{20}H_{42}$ , a clear bistable free energy surface emerges only when the chain is about 30 monomers long. For  $n = 30$ , the polymer exhibits an intermittent oscillation between the collapsed and the coil structures, characteristic of two stable states separated by a small barrier.

### Introduction

Linear polymer chains constitute an important class of systems that are of direct relevance not only to experimental systems but are also of great merit as theoretical models of many complex phenomena such as protein folding. In addition, they provide sufficiently simple framework to allow detailed study. As a result, a lot of effort has been devoted toward understanding the structure and collapse dynamics of linear homopolymers.<sup>1–5</sup> Many of the earlier computer simulation studies can be divided into two groups. In the first class, one uses different types of implicit solvent models. This approach has been particularly popular in the study of polymer collapse and protein folding. In the second class, one uses solvent (mostly water) explicitly. The study of explicit solvent model is gaining popularity as it is becoming clear that many properties are not modeled effectively by the implicit solvent models,<sup>5</sup> and only explicit solvent can properly capture the role of hydrodynamic interactions in the collapse dynamics.<sup>6</sup>

In the implicit solvent models, analytical theoretical studies range from extensions of Flory–Huggins type mean-field approach to sophisticated field theoretic techniques. The quality or nature of the solvent enters implicitly through interaction between the atoms of the polymer chain. Here the attention has been focused largely on the statistical properties of the polymer and also on the collapse transition from extended chain in good solvents to collapsed state in poor solvents. Computer simulations in this class of implicit solvent models have primarily employed Brownian and Langevin dynamics. The simulations serve not only to understand statistical properties of interacting polymer chains (even in the single chain limit), but also to understand the formation/selection of a wide range of spatial structures like rod, toroid, and helix. Theoretical investigations

of the formation and relative stability of such ordered structures have proven difficult.

Previously Brownian dynamics simulations of a bead–spring model of polymer chain with implicit solvent have found formation of interesting collapsed structures in long polymer chains with length ranging from 60-mers to 200-mers.<sup>1,2</sup> The structures include rods, helices, and toroid-like depending on the rigidity of the chain. However, fully atomistic simulations with explicit solvent (water) have not yet observed such well-defined ordered structures. A statistical mechanical analysis of free energy of various structures was reported by Miller et al., which considered semiflexible chains with emphasis on DNA, although the conclusions appear to be quite general.<sup>7</sup> This work predicts a crossover from toroid to molten globule form at large chain lengths.

Mountain and Thirumalai have studied small hydrocarbon chains in explicit SPC/E water very systematically and found that the small alkanes (until *n*-octane) do not perturb the hydrogen-bonded network of water to a large extent and hence they do not exist in any collapsed form.<sup>8</sup> In a subsequent molecular dynamics study on *n*-eicosane ( $C_{20}$ ) in water, the same group has found much higher stability for U-shaped collapsed structures as compared to the unfolded conformations.<sup>9</sup> Sun et al. have studied the structure of *n*-octadecane in water using configuration biased Monte Carlo method, where the hydrocarbon chains are found to exist in predominantly extended, but not all-trans conformations.<sup>10</sup> But their results did not support any clear two state picture between the folded and unfolded states. Very recently, in a detailed study of solubility and molecular conformations of *n*-alkane chains in water Ferguson et al. have confirmed the absence of any hydrophobic collapse for chains shorter than  $C_{20}$  and suggested that the primary effect of the solvent is to introduce a barrier of the order of  $k_B T$  between the collapsed and extended conformations.<sup>11</sup>

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As known widely and recently demonstrated quantitatively by Chang and Yethiraj, the structural properties of the collapsed state can be fundamentally different in the presence of explicit solvent from what is obtained with implicit solvent models.<sup>5</sup> They have found sausage-like structures for a freely jointed chain model in the presence of water. Note that many of the simulation studies invoke a simplistic model potential to be able to be comparable to existing theoretical models, but that restricts the possibility of these classes of models to reproduce the more diverse structural features of a realistic system.

In view of the above, one would like to formulate the following questions:

1. What are the possible structures of collapsed hydrocarbon chains in explicit solvent model? Is the structure at room temperature a random coil (molten globule) or it can sustain ordered structures like rods, helices, and toroids? We must reiterate that such structures have been observed earlier by Brownian dynamics simulations of a bead-spring model of a chain consisting of 60 monomers.<sup>1</sup>
2. Is there a critical length of the polymer chain above which the collapsed state is stabilized? What is the nature of the equilibrium between the extended (coil) and collapsed states?

In the present work, we carry out detailed atomistic simulations of unbranched hydrocarbon (*n*-alkane) chains in explicit water, by varying the chain length systematically, in an attempt to answer the above questions. The rest of the paper is organized as follows. In the next section, we describe our simulation methodologies in brief. Section III contains the results and discussion on the chain length dependence of the coil-globule equilibrium along with relevant free energy calculations. Here we have also presented the representative energy minimized structures as obtained from respective trajectories. Finally, we summarize our findings in Section IV and conclude.

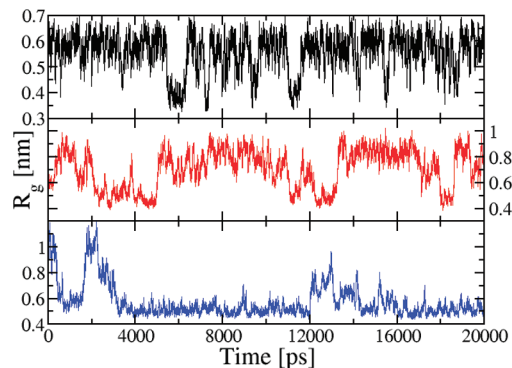
### Simulation Details

All of our calculations involve a single molecule of *n*-alkane chain solvated in a simple cubic box containing SPC/E model of water at ambient conditions of 300 K temperature and 1 bar pressure. We have retained full atomistic details except for hydrogen atoms bound to the carbon atoms, which are treated as united atoms within GROMOS96 43a2 force field. To perform the molecular dynamics simulations, we have chosen GROMACS<sup>12</sup> (version 4.0.4), which is a highly efficient and scalable molecular simulation engine. The bonds have been kept constrained to their equilibrium length because that allows for use of larger timesteps. All simulations were started from the all-trans conformation of the polymer and the radius of gyration has been computed over a trajectory of 20 ns to observe the equilibrium between extended and collapsed states.

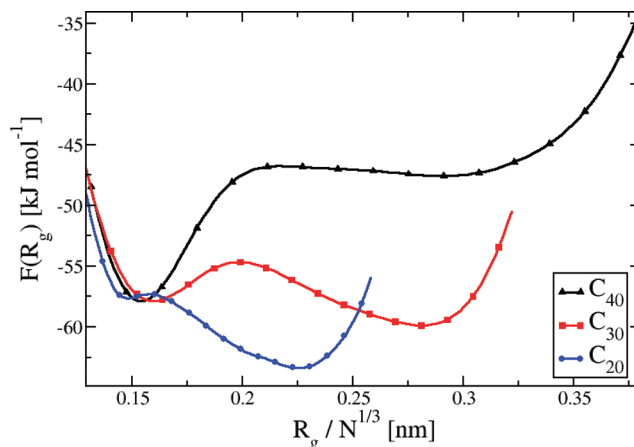
We have also computed the free energy surface as a function of the radius of gyration of the polymer using the well-tempered Metadynamics algorithm<sup>13</sup> implemented within PLUMED<sup>14</sup> (version 1.0.0), which is a plugin that can be seamlessly incorporated within GROMACS.

### Results and Discussion

In Figure 1, we follow the time evolution of the radius of gyration ( $R_g$ ) of the polymer chain for three different lengths of 20, 30, and 40. From the MD trajectory, we find that there is clear evidence of fluctuations between two distinct states with large difference in  $R_g$ . While the collapsed state appears only intermittently for  $C_{20}$ , it starts to overcome the extended coil state only when the chain length is about 30. At this particular



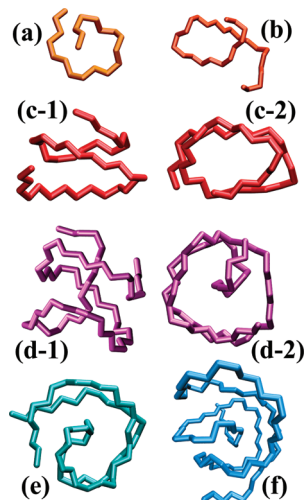
**Figure 1.** Time evolution of the radius of gyration ( $R_g$ ) for  $C_{20}$  (top),  $C_{30}$  (middle), and  $C_{40}$  (bottom). While a two state picture starts to emerge at  $C_{20}$ , we observe large intermittent fluctuations between the two states at  $C_{30}$ .



**Figure 2.** The free energy surfaces as a function of the radius of gyration for three different alkane chain lengths 20, 30, and 40. The  $X$ -axis has been rescaled to  $R_g/N^{1/3}$  (where  $N$  is the number of monomers in the polymer) so that the collapsed state appears at the same value for all different lengths.

length the two states are almost equally stable as confirmed by the free energy surface shown in Figure 2 as well. As the length of the chain increases, the collapsed state starts to dominate very rapidly and the coil state becomes only marginally metastable at  $C_{40}$ . It is interesting to note that at these intermediate length scales there exist large scale intermittent fluctuations between the two states characterized by a rather large difference between both radius of gyration and solvent accessible surface area of the polymer.

In Figure 3, we show the representative structures of the collapsed state at different lengths. We find that for  $C_{20}$  the collapsed state is almost like a ring with two ends close to each other. Evidently such a conformation has large entropic cost, which is not compensated by the number of contacts formed. Hence this state is observed as a “shoulder” in the free energy surface. But at the length of 40, we find the collapsed state has distinct helical characteristics. We must note at this point that this system lacks any specific interaction like hydrogen bonding at regular interval that promotes helical order in proteins. Only simple competition between rigidity of the chain, number of intrachain contacts, solvent accessible surface area, and entropic cost could produce such beautiful ordered structure at these intermediate length scales. But of course when one moves to higher sizes, the system cannot sustain any long-range helical order and it collapses into semiordered globular shape as shown in case of  $C_{100}$  (structure (f) in Figure 3). Even though the collapsed form has a globular shape, close inspection shows an



**Figure 3.** Representative energy minimized structures observed depending on the length of the polymer chain: (a) 20-mer, (b) 30-mer, (c) 40-mer (c-1 and c-2 correspond to sideview and topview, respectively, of the same helical structure), (d–e) 60-mer (d-1 and d-2 correspond to sideview and topview, respectively, of the same disordered helical structure), and (f) 100-mer.

ordering in the alignment of the polymer segments. The driving force to maximize the number of intramolecular contacts leads to a core–shell-like structure, where the shell is often characterized by a bent rod-like shape consisting of two segments running in parallel.

We have been able to identify at least two interesting ordered structures through energy minimization of representative snapshots collected from the trajectory of  $C_{60}$ , which exists in predominantly disordered form in the collapsed state. They are (1) disordered helix (Figure 3, structure d) and (2) double strand toroid (Figure 3, structure e). It is interesting to note how one end of the chain resides inside the helix in order to maximize the nonbonded interaction energy.

## Conclusion

To the best of our knowledge, this is the first systematic study of the coil–globule equilibrium for  $n$ -alkane chains in explicit water that explores the critical length of the polymer required to stabilize the collapsed state. Both the molecular dynamics trajectory and the free energy surfaces confirm that the extended and collapsed states are equally stable for the chains of length 30, above which the collapsed state is stabilized very rapidly, but below which the collapsed state is mostly unstable. This is in agreement with several earlier studies that report the absence of collapsed state in chains of length below 20. Interestingly, for  $n = 30$  the two states are separated by a barrier of the order of  $k_B T$  that leads to a large scale fluctuation between the two states that resembles fluctuations observed for a first order phase transition near a critical point.

We also demonstrate that despite having no specific interaction to promote long-range helical order, the collapsed state develops a distinct helical structure for chains of intermediate lengths around  $C_{40}$ . It is clear that the helical structure provides the optimum balance between maximum intramolecular contact formation, minimum solvent accessible surface area and entropy at this particular length scale. Of course with longer chains such long-range helical order becomes difficult to sustain. At  $n = 60$ , we find a curious modification of the helical form, where one end of the polymer resides inside the helix to maximize the number of contacts even further.  $C_{60}$  exhibits another

minimum energy structure with a toroid-like shape consisting of parallel double-strand segments.

The present study is primarily focused on chains of lengths of intermediate size. We find interesting the crossover of chain configurations from rods/coils (for  $n < 20$ ) to circular ( $n = 20–30$ ), largely helix ( $n \sim 40$ ), and ultimately largely globular state at length about 60. We believe this is the first atomistic simulation study to observe the formation of such exotic structures for a simple system like alkanes in water.

A novel aspect of the present study is the use of metadynamics to calculate the free energy of different chain configurations in explicit water. This is a formidable task not only because of the presence of large number of water molecules, but also because the structures themselves are often separated by small energy barrier to prevent accurate characterization. However, we do observe excellent agreement between the structures identified in MD simulations and the minima calculated by metadynamics.

We must note here that the conformational equilibrium would be sensitive to the choice of the force field used for both hydrocarbon and water. There seems to be a quantitative inconsistency between earlier studies regarding the relative stability of the collapsed state around  $C_{20}$ .<sup>9–11</sup> The equilibrium should primarily be governed by the bending and torsional potential parameters that would dictate the flexibility of the polymer chain. Thus it can be expected that the TraPPE force field with softer torsional potential would exhibit higher stability<sup>10,11</sup> for collapsed structures as compared to the GROMOS96 force field used in this study. Moreover, our preliminary results indicate that water models that provide stronger hydrogen-bonded network would shift the equilibrium toward the collapsed state even further. A comprehensive analysis of such sensitivity on the force field will be discussed elsewhere. Future work shall also focus on identifying the structures in larger chains and also the mechanism of collapse and the role of water in such a process.

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