Hydrogen Bonding and the Conformations of Poly(alkyl acrylamides)

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Abstract: The conformations of poly(alkyl acrylamide) oligomers in nonpolar solvents were studied using molecular dynamics techniques. Poly(methyl acrylamide) was found to collapse to a globule-like conformation at low temperatures; however, excluded volume effects inhibited the collapse of poly(octadecyl acrylamide). A high density of structured units, characterized by a trans-gauche-trans-trans-gauche-trans torsional sequence along the backbone, was noted in all simulations. Such units were found to create a particularly stable set of intramolecular hydrogen bonds. An oligomer constructed with these stable units was found to have significantly lower minimized energy than both the all-trans and the helical backbone conformations. The constructed conformation had lower Coulomb energy (more hydrogen bonds) than the all-trans conformation and lower dihedral energy (less backbone distortion) than the helical conformation. The propensity for poly(octadecyl acrylamide) to form hydrogen bonds introduced significant disorder into the orientation of the alkyl side chains. This disorder would inhibit crystallization and restrict the ability of such polymers to form epitaxial seeds for nucleating paraffin crystals.

Introduction

Poly(alkyl acrylamides) (PAAms) are reversibly soluble polymers that have a variety of interesting properties and a wide range of potential technological applications. In aqueous solutions PAAms exhibit a lower critical solution temperature (LCST) below which the polymer has an extended conformation with hydrogen bonding between the water and the functional groups of the polymer.[1] Above the LCST the polymer collapses to form a globule with the formation of intrachain and interchain hydrogen bonds. The thermoshrinking properties are responsible for many potential applications such as enzyme immobilization,[2] drug delivery,[3] and the concentration of dilute solutions.[4] The hydrophilic backbone and the hydrophobic side chains of PAAms combine to enable the production of well-ordered Langmuir Blodgett films.[5,6] PAAms have also been shown to modify the properties of paraffin crystals grown from solution.[7]

PAAms have been studied extensively experimentally,[8,9] but molecular modeling studies of these polymers are rare.[10] In this

paper we present the results of a molecular dynamics study of the conformations of two polymer types, poly(methyl acrylamide) (PAAm-1) and poly(octadecyl acrylamide) (PAAm-18), at a range of temperatures. We use interatomic potentials that simulate the presence of a nonpolar solvent such as heptane. Many of the interesting properties of PAAms, particularly the thermoshrinking, are exhibited in aqueous solution. It is therefore likely that they are determined, in part, by the competition between intrapolymer hydrogen bonding and polymer−water hydrogen bonding. To begin to understand this competition, it would be useful to characterize the intrapolymer hydrogen bonding motifs and how they influence the conformation of the polymer. Thus in this paper we have chosen to study the conformational behavior of PAAms in alkane solvents: in alkane solvents there is no scope for polymer−solvent hydrogen bonding, and attractions between side chains within the polymer are also minimized, so that intrapolymer hydrogen bonding motifs will be the major influence on the polymer's conformational behavior. We note that PAAms are also beginning to find applications in organic solvents. For example, PAAm-18 has been shown to modify the properties of paraffin crystals formed in oil; thus the study of the conformations in organic solvents should give useful insights into this inhibitor mechanism.

In the next section of this paper we describe the simulation protocol and the derivation of the effective solvent potentials used for the model. In the following two sections we describe the results of MD simulations of PAAm-1 and PAAm-18 for a range of temperatures and we compare the energies of three low-temperature conformations. The conclusions are summarized in the final section.

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Method and Potentials

The simulations were performed on oligomers with 65 C atoms on the backbone and 32 side groups, using the general purpose MD program DL-POLY.[11] A schematic representation of the oligomers is shown in Figure 1. A 2 fs time step, a Nosé Hoover thermostat with relaxation time of 0.01 ps, and a direct Coulomb sum with a cutoff of 100 Å were used for all calculations. The Coulomb cutoff is larger than the size of the molecule, therefore all the charge interactions are included explicitly.

A united atom model was employed for the CH, CH_2, and CH_3 groups of the backbone and side groups and the interaction potentials for these groups were a modified form of those presented by Moller et al.[12] and discussed in an earlier publication.[13] The interatomic potential parameters for the atoms of the functional group were taken from the CHARMM force fields. The electrostatic potential charges for a monomer unit (methyl acrylamide), calculated with Gaussian 92 (6-31G**), were used for the effective atomic charges of the oligomer. The calculated charges are summarized in Table 1.

The choice of nonbonded interaction potentials for the simulations was more problematic. We aimed to derive a potential that simulates the presence of a solvent without the need to include the solvent molecules explicitly in the calculation. Without such a device, the computer time required to simulate polymers of the size considered here would be prohibitive. Three different methods for modifying the standard Lennard-Jones potentials (LJ) to derive an effective solvent potential were investigated. The first involved reducing the LJ energy parameter (ϵ), which resulted in an overall reduction in the potential energy and a shallower well. In the second method we transformed the LJ potential to a $12-6$ potential ($V(r) = A/r^{12} - B/r^6$) and reduced the attractive (B) term of the transformed potential while leaving the repulsive (A) term unchanged. Reducing B by a factor b results in a reduction in the potential well depth of b^2, but also increases the effective size of the site by a factor $b^{1/6}$. This is more realistic than the first method as it is the long-range behavior that is affected by the presence of a solvent. In the third method we reduced the potential cutoff and employed a shifted force potential to ensure that the force was continuous at the cutoff point, thereby avoiding large force discontinuities that cause significant energy drift in MD simulations. The third method is similar to that commonly employed by polymer modelers to simulate the presence of a good solvent where a potential cutoff equal to the position of the well minimum is used, giving a purely repulsive interaction.[14] In our case the cutoff is taken at a distance slightly larger than the position of the well minimum, with the result that there is a small attractive term and a shallow minimum in the potential energy. This allowed us to incorporate the variations in attraction between the different functional groups present—a factor that might be expected to influence the conformational behavior of the polymer.

A fourth method of incorporating an effective solvent was also considered: using the potential of mean force calculated from the radial distribution function for methyl/methylene groups in hydrocarbon liquids. However, this method proved to be inappropriate. There is substantial correlation in the distribution of solvent about neighboring methyl or methylene groups in a hydrocarbon, and this cannot properly be represented as a sum of pairwise distribution (hence not as a sum of pair potentials, as would be required to use potentials of mean force). The net result was that all polymers showed globular conformations with this method, even at high temperatures. The method was therefore rejected without further analysis.

To test the different types of modified potential we performed a 2 ns, 300 K, MD simulation on a $C_{36}H_{74}$ molecule immersed in a heptane

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Table 1. The Calculated Atomic Charges Used in the Simulations (see Figure 1 for the molecular structure)

group	$(CH_3)_b$	CH_2	CH	C	O	N	H	$(CH_n)_s$
charge/e	0.0	0.0	0.029	0.680	−0.620	−0.718	0.371	0.258

[a] $(CH_3)_b$ refers to the CH_3 group on the backbone and $(CH_n)_s$ refers to the CH_3 group on the side chain of PAAm-1 and the CH_2 group nearest the backbone of the side chain in PAAm-18.
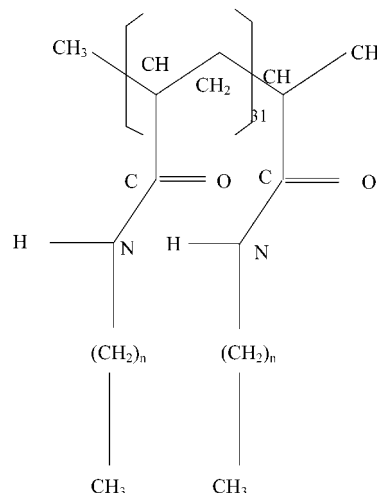

Figure 1. A schematic representation of the molecular structure of the PAAm-1 and PAAm-18 oligomers. *n* denotes the number of CH_2 groups in the side chains. $n = 0$ for PAAm-1 and $n = 17$ for PAAm-18.

solvent. Heptane was modeled explicitly using the same united atom model used for the polymer side chains. Equivalent simulations were performed on the polymer molecule in a vacuum but with the modified nonbonded potentials. A comparison was made between the properties (specifically the mean radius of gyration and the mean density of gauche defects) of the molecule in the effective solvent and those for the molecule in the explicit solvent. The results are summarized in Table 2. The shifted force potential with a cutoff of 5 Å gives results that are in reasonable agreement with the explicit solvent calculation and we have therefore chosen this form of the nonbonded potential to simulate the organic solvent.

Discussion

PAAm-1 Simulations. The conformations of the PAAm-1 oligomer were examined by performing 10 ns simulations at four different temperatures and calculating the mean radius of gyration and mean number of gauche defects for the final 6 ns. The results are plotted in Figure 2. There is a monotonic increase in the number of gauche defects with increasing temperature but the radius of gyration displays a minimum at 350 K. A visual inspection of the polymer conformations reveals that the polymer folds to a hairpin conformation after about 3 ns of the 300 K simulation and remains in the folded conformation for the remaining 7 ns. In the 350 K simulation the oligomer collapses to a globule after about 1 ns and the globule is stable for the remainder of the simulation. Snapshots of typical configurations of the 300 and 350 K simulations are shown in Figure 3. A similar collapse is observed during the 400 K simulation but in this case the transition is reversible and the oligomer opens to the extended conformation after 2 ns. The globule does not persist for any significant period of time during the 450 K simulation. The time dependence of the radius of gyration at three different temperatures is shown in Figure 4.

The distribution of gauche bonds on the oligomer backbone was analyzed for each simulation. We present this analysis in

Table 2. *a*The Mean Radius of Gyration (R_G/Å) and the Mean Number of Gauche Defects (n_G) for a $C_{36}H_{74}$ Molecule during a 2 ns 300 K MD Simulation with Various Effective−Solvent Nonbonded Lennard-Jones Potentials*a*

	re-scaled ϵ			re-scaled B			shifted force		
case	scale factor	R_G/Å	n_g	scale factor	R_G/Å	n_g	r_{cut}/Å	R_G/Å	n_g
1	0.1	8.6	9.9	$B/\sqrt{10}$	9.4	7.8	4.5	9.4	8.0
2	0.2	8.4	10.2	$B/\sqrt{5}$	9.0	8.4	4.8	9.4	8.3
3	0.4	7.5	10.5	$B/\sqrt{4}$	8.9	8.7	5.0	9.3	8.6
explicit solvent								9.7	8.6

a In these potentials the solvent is considered to reduce the effective well-depth (re-scaled ϵ), attraction (re-scaled B), or range (shifted force truncation) of the PAAm interactions
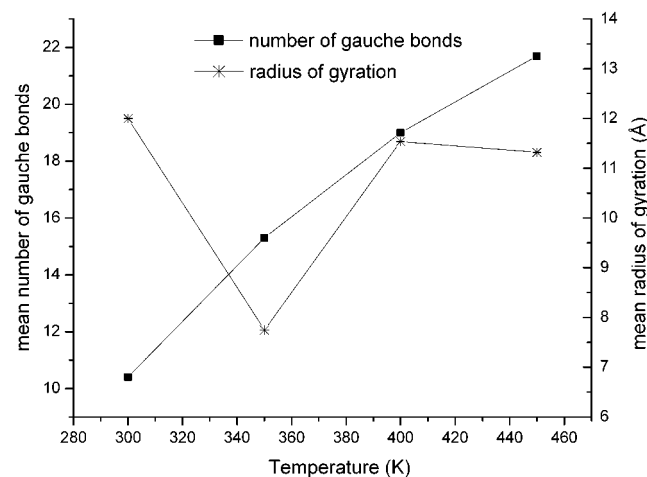

Figure 2. The backbone radius of gyration and number of gauche defects, averaged over the final 6 ns of a 10 ns simulation, of the PAAm-1 oligomer and plotted against the simulation temperature.

terms of the frequency with which an all-trans segment of length *N* is found along the oligomer backbone. No attempt has been made to distinguish between gauche ± conformers as adjacent gauche defects were extremely rare, and it was clear from the analysis that the distribution of all-trans segments is a good descriptor for the PAAm conformational behavior. Results were averaged over the final 6 ns and are presented in Figure 5. For each simulation temperature there is a distinct peak for a segment size of 2 trans bonds. The presence of the peak is indicative of a nonrandom distribution of gauche bonds along the backbone and it suggests that the tgttgt motif (where t represents a trans bond and g represents a gauche bond) is particularly stable. Indeed an inspection of the simulation snapshots reveals that many such motifs do occur spontaneously along the backbone connecting four consecutive side groups. The tgttgt configuration orients the bonds in such a way that 4 hydrogen bonds are formed between the C=O and NH groups of the 4 side groups of the motif.

The stability of the tgttgt motif was investigated by constructing an oligomer with such motifs and comparing the energy with other low-energy conformations. Three syndiotactic conformations were considered (see Figure 6). Conformation 1 (C1, Figure 6a) has an all-trans backbone with the side groups oriented to produce hydrogen bonds across the backbone. Conformation 2 (C2) has the side groups oriented to create hydrogen bonds along the direction of the backbone. Relaxation of this conformation produces a helical structure (Figure 6b) as the backbone distorts to reduce the length of the hydrogen bonds. The third conformation was constructed from the tgttgt motifs linked with trans bonds and the relaxed configuration is shown in Figure 6c. The hydrogen bonding structure of the motifs
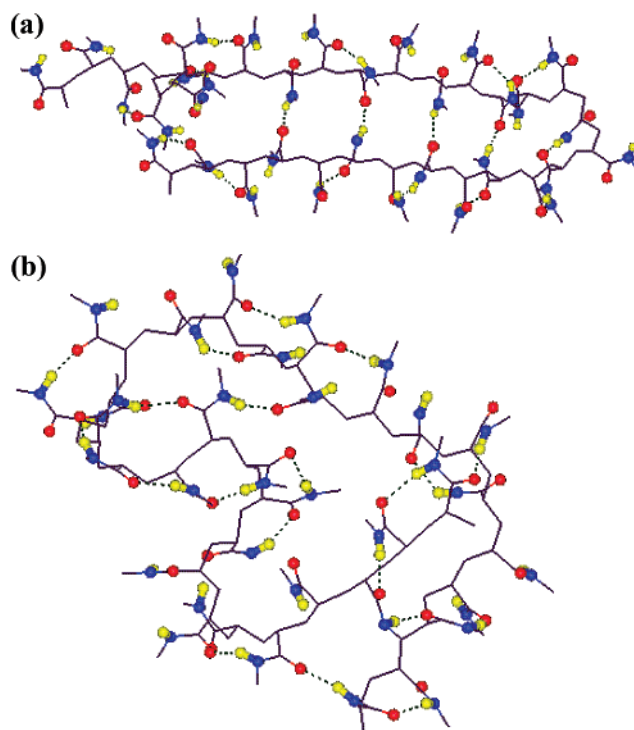
Figure 3. Snapshots of (a) the 300 K simulation of PAAm-1 showing the folded, hairpin conformation and (b) the 350 K simulation of PAAm-1 showing the globule conformation. The O atoms are shown in red, the N atoms are shown in blue, and the H atoms are shown in yellow. The C−C bonds are shown as black lines and the hydrogen bonds are shown as broken lines.

involves closed hydrogen bonding cycles between the four side chains, and as such requires the tgttgt units to be separated by at least two backbone bonds: an extended tgttgttgttg... conformation is not possible. Minimized energies for these three structures were calculated by using very low temperature MD simulations (100 ps, 2 K) and the energy components, averaged over the final 6 ps, are summarized in Table 3. Note that with the potentials used in this study, the hydrogen bonding energy is incorporated into the Coulomb energy term. C2, the helical structure, has the highest energy as the gain in the Coulomb energy is more than offset by the high dihedral angle energy introduced by the distorted backbone. It is interesting to note that the helical conformation has been shown experimentally to be stable for a similar polymer (poly(*N*-propargylamide)).[15] One significant difference between poly(*N*-propargylamide) and PAAm-1 is that the O atom is further from the backbone in poly(*N*-propargylamide) therefore the torsional strain caused by hydrogen bonding between C=O and NH groups on adjacent side chains would be reduced; the tacticity may also have an

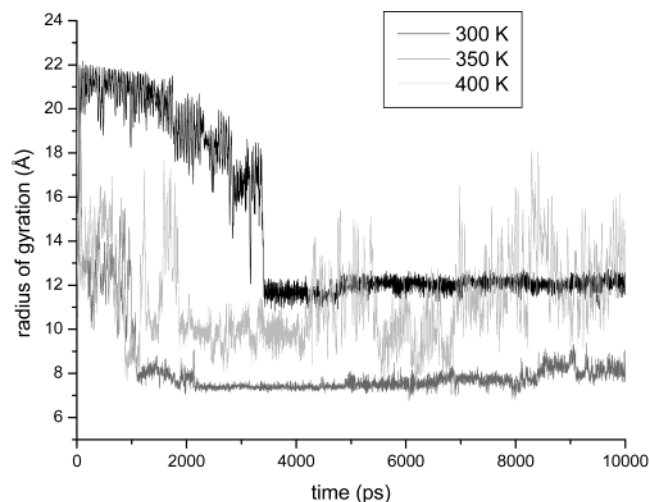(15) Nomura, R.; Tabei, J.; Masuda, T. *J. Am. Chem. Soc.* **2001**, *123*, 8430.

Figure 4. The variation in the radius of gyration of the backbone of the PAAm-1 oligomer during the course of the 300, 350, and 400 K simulations. The results for the 450 K have been omitted for clarity.
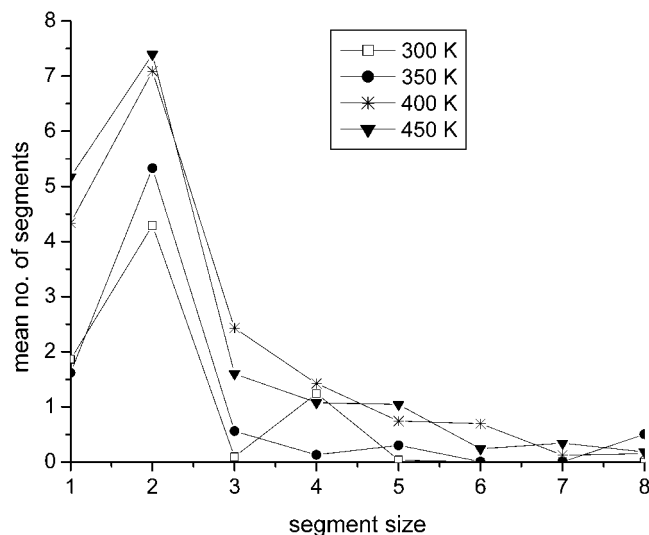

Figure 5. The number of all-trans segments of a given length, averaged over the final 6 ns of the 300, 350, 400, and 450 K simulations of PAAm-1.

Table 3. Minimized Energies for Five Typical Conformations of a PAAm-1 Oligomer, Calculated Using Very Low Temperature MD (average for the final 60 ps of a 100 ps, 2 K simulation)[a]

	energy components (kJ mol^{-1})					
conformation	E_{conf}	E_{vdw}	E_{coul}	E_{bond}	E_{angle}	E_{dihed}
all-trans (C1)	−804.1	38.8	−976.2	5.3	28.1	99.5
helical (C2)	−714.4	43.3	−1545.5	12.6	65.4	709.3
motif (C3)	−987.4	3.8	−1464.5	10.6	63.5	399.0
hairpin	−940.4	30.0	−1248.8	8.2	63.5	206.8
globular	−1003.8	49.3	−1415.5	9.5	71.8	281.1

[a] E_{conf}, E_{vdw}, E_{coul}, E_{bond}, E_{angle}, and E_{dihed} refer to the total configuration energy, the van der Waals energy, the Coulomb energy, the bond stretching energy, the bond bending energy, and the dihedral angle energy, respectively.

influence as there is evidence that helical conformations form more easily in isotactic poly(acrylamides).[16] The lowest energy conformation we found for PAAm-1 was C3, the conformation with a high density of tgttgt motifs. In this case the energy

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gained from the increase in the number of hydrogen bonds more than compensates for the dihedral energy penalty caused by the backbone distortion. The minimized energies for a typical hairpin conformation and a globular conformation are also included in Table 3 for comparison. The initial configurations for these calculations were chosen at random from the 300 K simulations and other choices gave different energies. However, we note that the globular conformation has a comparable, but marginally lower, configuration energy than the motif conformation but the hairpin conformation has a higher configuration energy. The problems associated with finding the global minimum energy conformation for polymers are well established; however, we have identified a conformation with a configuration energy significantly lower than the all-trans conformation and comparable to the globular conformation and that forms rapidly and spontaneously at room temperature.

The C2 and C3 conformations were used as starting configurations for additional 10 ns simulations, equivalent to those discussed for C1 earlier in this section. If such simulations had attained equilibrium during the initial 4 ns equilibration period we would expect the results to be independent of the initial configuration. This was the case at 450 K. There was some variation between the 400 K simulations in that the metastable globule noted earlier for C1 did not appear in the C2 or C3 simulation, resulting in a slightly higher mean radius of gyration (11.3 Å). This is consistent with high energy barriers associated with breaking the hydrogen bond patterns for these two conformers in a hydrophobic solvent. More significant dependence on the initial configuration was found for the lower temperature simulations. At both 300 and 350 K the folded or globule transition occurred for C1 and C2 initial conformations but not for the lower energy C3 configuration. The results imply that it is easier to make the transition to the more stable globular conformation from the higher energy helical and all-trans conformations than from the lower energy tgttgt motif conformation.

These simulations indicate that both the globular conformation and the extended motif conformation are stable at low temperatures (below 400 K) but extended conformations are stabilized by a larger entropy contribution at higher temperature. This is the reverse of what is observed in aqueous solution, where the collapse to the globular conformation occurs at high temperatures. In a nonpolar solvent there is competition between entropy effects and energy gain from intrachain hydrogen bonding whereas in an aqueous solution the competition is between solution−polymer hydrogen bonding and intrachain hydrogen bonding.

PAAm-18 Simulations. The effect of increasing the length of the alkyl side chains was examined by carrying out equivalent MD simulations on PAAm-18 oligomers. Initially very low temperature (2 K) simulations were performed to give a comparison between the minimized energies of the three conformations. The results are summarized in Table 4 and as before C3 had the lowest energy and the helical conformation had the highest energy. The relaxed conformations are illustrated in Figure 7. In all cases the alkyl side chains were oriented in a number of distinct directions, in contrast to comb-shaped polymers studied in previous work where the side chains tend to form well-ordered layers.[17] The spread in the side-chain

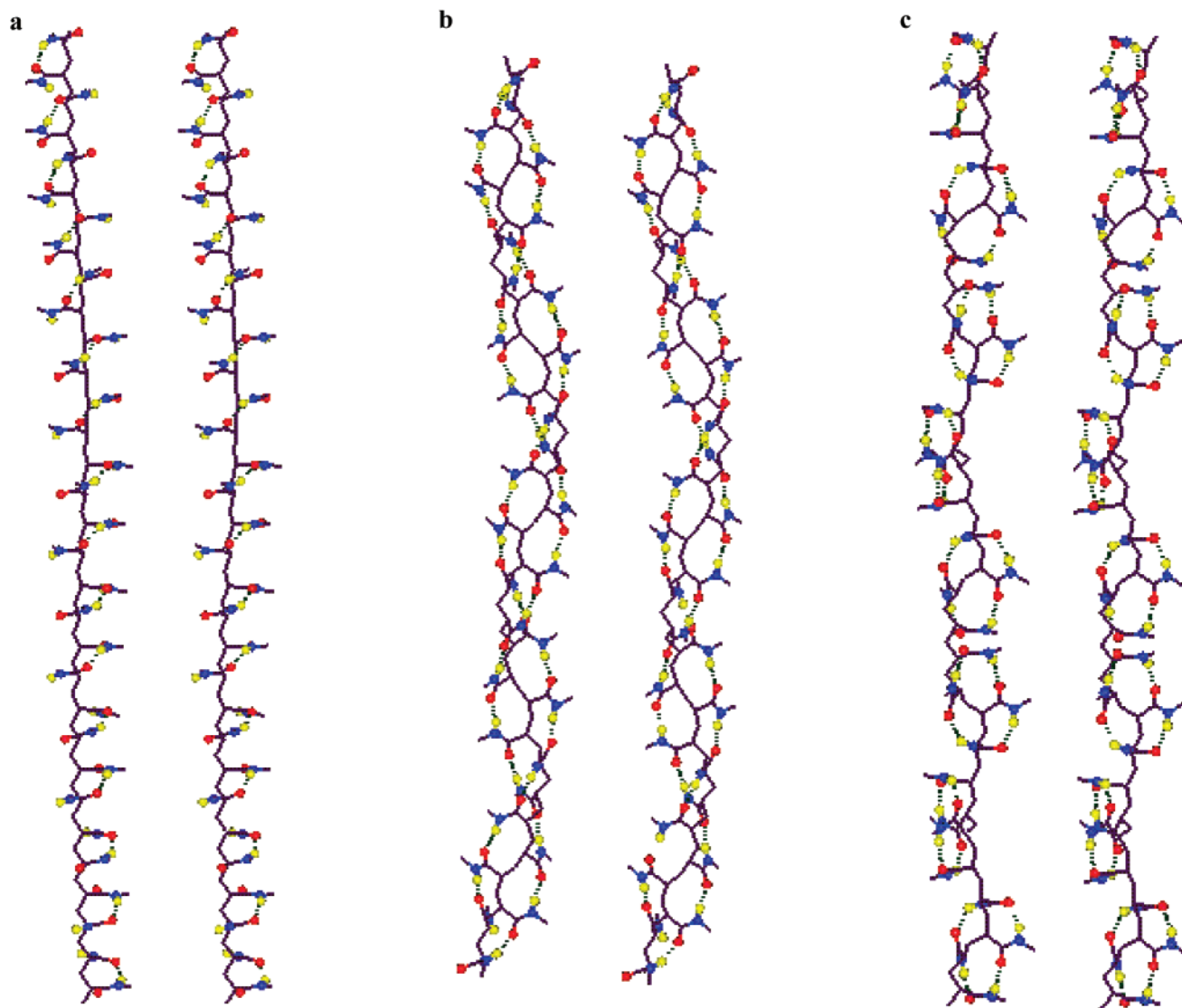(17) Duffy, D. M.; Rodger, P. M. *Phys. Chem. Chem. Phys.* **2002**, *4*, 328.

Figure 6. Stereo images of (a) the all-trans backbone, (b) the helical, and (c) the tgttgt motif conformations (2 K) of PAAm-1. The O atoms are shown in red, the N atoms are shown in blue, and the H atoms are shown in yellow. The C−C bonds are shown as black lines and the hydrogen bonds are shown as broken lines.

Table 4. Minimized Energies of Three Typical Conformations of a PAAm-18 Oligomer, Calculated from the Final 60 ps of a 100 ps, 2 K MD Simulation[a]

conformation	energy components/(kJ mol^{-1})					
	E_{conf}	E_{vdw}	E_{coul}	E_{bond}	E_{angle}	E_{dihed}
C1	−803.1	27.2	−977.6	5.3	30.9	111.0
C2	−691.2	−26.1	−1549.8	11.5	79.5	793.8
C3	−940.8	−97.2	−1450.2	11.6	91.5	503.2

[a] E_{conf}, E_{vdw}, E_{coul}, E_{bond}, E_{angle}, and E_{dihed} refer to the total configuration energy, the van der Waals energy, the Coulomb energy, the bond stretching energy, the bond bending energy, and the dihedral angle energy, respectively.

orientation will have a significant inhibiting effect on the crystallization of such polymers and on their ability to act as nucleation seeds for paraffin crystals.

The dynamic properties of PAAm-18 oligomers were studied by performing 80 ns MD simulations for a range of temperatures, starting from the all-trans configuration. The conformations were captured every 10 ps for analysis. The radii of gyration and number of gauche defects of the polymer backbone, averaged over the final 60 ns of the simulations, are summarized

in Figure 8. The variation of both parameters with temperature is weak and there is no evidence of a collapse to the globular configuration. An inspection of the radii of gyration plots showed no evidence of even transient globular conformations.

The number of all-trans segments is correlated with the segment length in Figure 9. There are pronounced peaks for trans segment sizes of 2 and 4 bonds for the two lower temperatures, corresponding to a high density of tgttgt motifs separated by 2 trans bonds (i.e. a tgttgt-tt-tgttgt motif), as in the C3 conformation. Thus it would appear that the C3 conformation is particularly favorable for PAAm's with long alkyl side chains because the excluded volume effects inhibit the backbone collapse. There is less structure in the 450 K plot, indicating that entropy effects are beginning to become important in the high-temperature simulation. Even so, the 450 K simulation still shows a strong peak at $n = 2$, but a substantial reduction in the frequency of $n = 4$ in favor of $n = 1$. This is consistent with a destabilization of the tgttgt dimers identified above, but without destabilizing the underlying tgttgt motif.
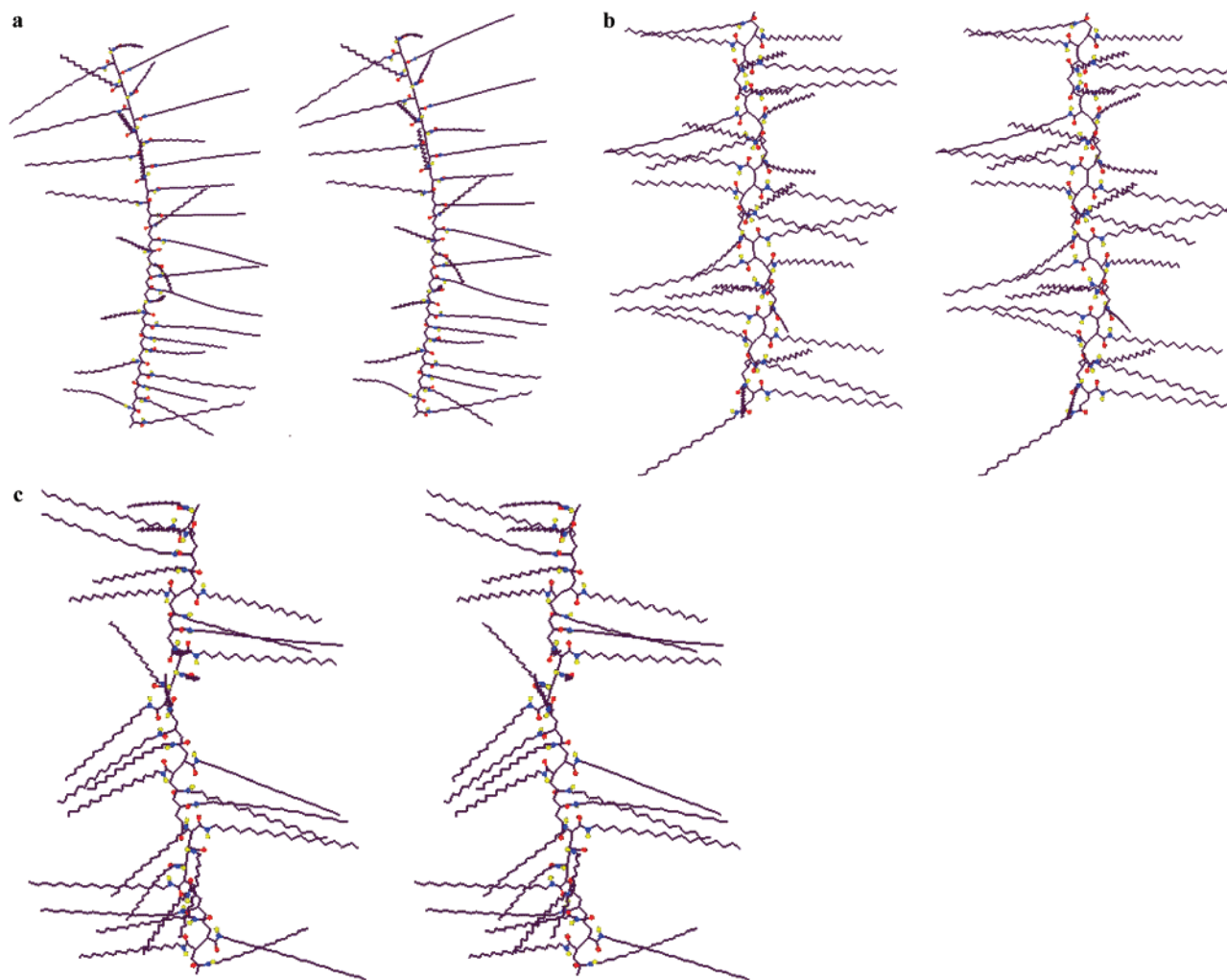
Figure 7. Stereo images of (a) the all-trans backbone, (b) the helical, and (c) the tgttgt motif conformations (2 K) of PAAm-18. The O atoms are shown in red, the N atoms are shown in blue ,and the H atoms are shown in yellow. The C—C bonds are shown as black lines.
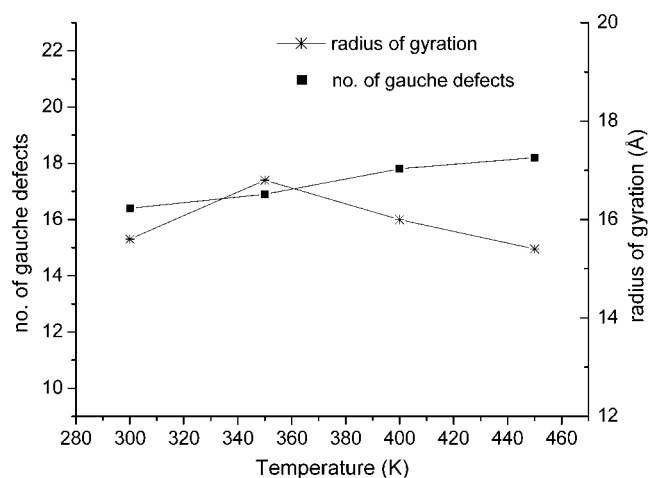

Figure 8. The backbone radius of gyration and number of gauche defects, averaged over the final 60 ns of an 80 ns simulation of the PAAm-18 oligomer, plotted against the simulation temperature.

Figure 9. The number of all-trans segments of a given length, averaged over the final 60 ns of the 300, 350, 400, and 450 K simulations of PAAm-18.

Conclusions

We have studied the properties of oligomers of poly(alkyl acrylamides), PAAm's, in an effective organic solvent and found that intrachain hydrogen bonding had a significant effect on the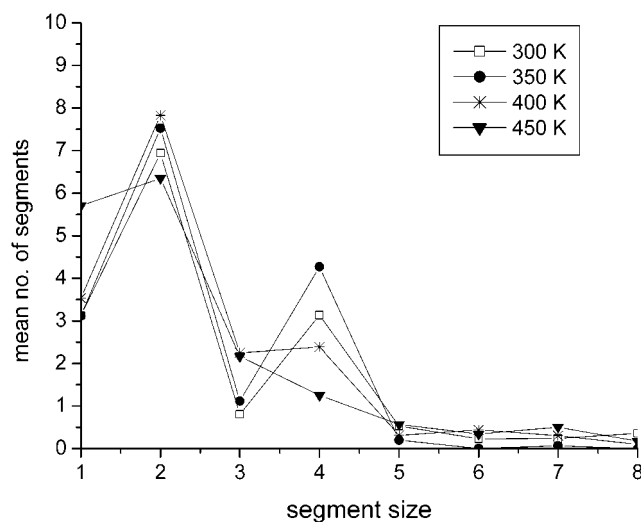 backbone conformations at all temperatures. Analysis of the conformations from high-temperature MD simulations revealed the predominance of a trans-gauche-trans-trans-gauche-trans motif connecting four side groups along the backbone. The construction of an oligomer with a high density of such motifs

confirmed that this conformation had indeed significantly lower configuration energy than the all-trans backbone conformation.

The irreversible collapse from the initial extended conformation to a globule conformation was observed in the lower temperature (300 and 350 K) simulations on PAAm-1, but occurred reversibly on a simulation time scale in the higher temperature (400 and 450 K) simulations. The reverse effect is observed for similar polymers in aqueous solutions, where the coil globule transition is observed at high temperatures. The addition of octadecyl side chains (PAAm-18) led to a significant change in this behavior, such that the collapse to a globular conformation was not observed in any of the simulations. The excluded volume effects associated with the side chains prevented the backbone collapse.

Energy minimization calculations revealed disorder in the orientation of the alkyl side chains of PAAm-18. The disorder arose from the reorientation of the bonds connecting the side groups to the backbone in such a way as to maximize the formation of hydrogen bonds between the C=O and NH groups.

The side-chain disorder will reduce the crystallization rate of the polymer and also inhibit the ability for the side -chains to act as epitaxial seeds for paraffin crystal nucleation. Thus the alkyl chains would attract long chain alkanes in solution but the random orientation would not favor crystallization.

In summary, we have carried out a preliminary molecular modeling study of the PAAm-type polymers and have demonstrated that the intrachain hydrogen bonds have a strong influence on the conformations and properties of these materials, even in organic solvents. Similar calculations in aqueous solutions, perhaps using inverse Monte Carlo methods to develop effective solvent potentials for such a structured solvent,[18] will lead to further insight into the many interesting properties of these materials.

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