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# Single-Molecule Behavior of Asymmetric Thermoresponsive Amphiphilic Copolymers in Dilute Solution

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A bead-and-spring model has been used to simulate the behavior of thermoresponsive asymmetric diblock amphiphilic copolymers with aid of Monte Carlo simulations. The alteration of the thermodynamic conditions was mimicked by using a Lennard-Jones potential, which was related to the measured temperatures by comparison with experimental data for aqueous solutions of two sets of diblock copolymers, namely methoxypoly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide), one with different lengths of the hydrophilic block (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>) and one with varying lengths of the hydrophobic block (MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub>). The influence of the length of both the thermoresponsive and the hydrophilic block on the size and conformation of single molecules at various temperatures was studied by means of simulations. The temperature-induced contraction of the copolymer (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>) entities is only modestly affected by changing the length of the hydrophilic block, whereas for the MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub> copolymer both the transition temperature and the magnitude of the compression of the molecules are strongly influenced by the length of the thermosensitive block. When the MPEG chain fully covers the hydrophobic core, the copolymer moieties are stabilized, whereas poorly covered cores can promote interchain aggregation at elevated temperatures.

## Introduction

In the last decades, thermoresponsive amphiphilic block copolymers have attracted a great deal of attention of the scientific community due to these polymers wide range of interesting and novel properties and applications, such as drug carriers and biomedical usages.<sup>1–5</sup> The composition of these asymmetric copolymers usually consists of a thermosensitive block with stimuli-responsive properties and a block that is less or not sensitive to temperature changes. When the temperature is increased, the thermoresponsive block becomes more hydrophobic and has a tendency to avoid contact with water. One of the most studied features of this kind of system is the tendency to form reversible self-assembly complexes with a core–shell structure in aqueous solution when the temperature is increased. The core contains the hydrophobic segments, and the corona stays hydrophilic. This type of nanoparticles has been found to have a great number of applications in several fields,<sup>5–7</sup> and for a deeper understanding, simulations<sup>8,9</sup> and experiments<sup>10,11</sup> have been conducted. The self-assembly process of many thermoresponsive copolymers often occurs already at temperatures well below the lower critical solution temperature (LCST) if the polymer concentration is sufficiently high, and interchain complexes can be found at temperatures lower than this temperature.<sup>12</sup> As a result of this inclination to form intermolecular associations, the evaluation of the single-molecule features in solution can be difficult to address. The molecular weight of this type of copolymer is usually relatively low ( $\sim 10^4$

g/mol), but to avoid aggregation, the physicochemical characterization of the copolymer must be carried out at low polymer concentrations and this offers experimental problems. This is the main reason the single chain behavior has not been properly established, although it may be a critical aspect to take into account in the design of new copolymers.

A widely used thermoresponsive polymer in aqueous solution is poly(*N*-isopropylacrylamide) (PNIPAAm) due to the large number of applications in fields such as nanotechnology, electronics, and drug delivery found for this polymer and its copolymers.<sup>13,14</sup> Although it is normally argued that PNIPAAm exhibits a LCST value of 32 °C,<sup>7</sup> we have recently reported that this temperature may be altered by the molecular weight and the concentration for low-molecular-weight PNIPAAm polymers.<sup>15</sup> Below the critical temperature, the polymer is soluble in water but above LCST the hydrophobicity of the molecules is increased and the system tends to exhibit a macroscopic phase separation. For high molecular weight PNIPAAm chains in dilute solution, a coil-to-globule transition has been found when the temperature is raised; i.e., this thermoresponsive polymer suffers a collapse at high temperatures but behaves as a hydrophilic polymer at low temperatures.<sup>16</sup> In this paper, we consider dilute solutions of two sets of low-molecular-weight asymmetric diblock copolymers, namely, methoxypoly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide), one with different lengths of the hydrophilic block (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>) and another one with varying length of the hydrophobic block (MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub>). In these copolymers, the PNIPAAm block is the thermosensitive part, while the MPEG block is virtually hydrophilic over the considered temperature region.

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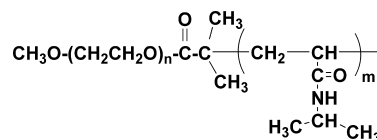
In this investigation, Monte Carlo (MC) simulations have been conducted on thermoresponsive copolymers of the types indicated above at quiescent state and at different temperatures, which allow us to determine the influence of the length of both blocks on the temperature-induced contraction. The copolymer was modeled as a bead-and-spring chain and a multiscale procedure was used to get the values of the chain parameters. Most of the results are compared with the experimental data obtained in a previous publication,<sup>17</sup> but some additional experiments have been carried out. The principal aim of this work is to evaluate the effect of the length of each block on the temperature-induced conformational change of the copolymer to reach a better understanding of this kind of systems, which can lead to design new tailor-made copolymers. The effect of temperature on the end-to-end distance of each block ( $r_i$ ) of the copolymer, on the overall hydrodynamic radius ( $R_h$ ) and on the overall radius of gyration ( $R_g$ ) is evaluated. To the best of our knowledge, this is the first study where the influence of the lengths of both the hydrophobic and hydrophilic block on the temperature-induced collapse and conformational alteration of an amphiphilic diblock copolymer single chain has been addressed.

## Materials and Methods

**Synthesis.** All the chemicals used for the synthesis of the block copolymers were purchased from Aldrich and Fluka. The synthesis of the monomethoxy-capped poly(ethylene glycol) (MPEG) macroinitiators of various lengths was performed in accordance with a published procedure, where the reaction of methoxypoly(ethylene glycol) with 2-bromoisobutryl bromide in the presence of triethylamine was employed.<sup>18</sup> All polymers were synthesized by means of atom transfer radical polymerization (ATRP),<sup>19,20</sup> which was carried out in a water/DMF 40:60 (v/v) mixture solvent at 25 °C via an ATRP system with MPEG-MI/CuCl/Me<sub>6</sub>TREN as the initiator/catalyst system, except for the pure PNIPAAm where ethyl 2-chloropropionate was used as the initiator to conduct the polymerization. The preparation and purification of these copolymers were conducted under similar conditions as described in previous studies.<sup>21</sup> The chemical compositions and structures of the synthesized diblock copolymers were all ascertained by <sup>1</sup>H NMR with a Bruker AVANCE DPX 300 NMR spectrometer, operating at 300.13 MHz at 25 °C by utilizing heavy water as the solvent. The weight-average molecular weights ( $M_w$ ) and polydispersity indexes ( $M_w/M_n$ ) of the copolymers were determined in dilute aqueous solutions by means of asymmetric flow field-flow fractionation (AFFFF) methods,<sup>21,22</sup> which leads to the determination of the number of monomers per block. The experimental procedure and parameters are similar to what was reported previously.<sup>21</sup> It must be noted that all polymer samples have low molecular weights and narrow molecular weight distributions, with values of polydispersity index of approximately 1.1. The chemical structure of the copolymers is depicted in Scheme 1.

**Simulation.** MC simulations were performed with the program MONTEHYDRO,<sup>23</sup> which is freely available at <http://leonardo.inf.um.es/macromol/> and implements the rigid-body treatment to calculate hydrodynamic properties.<sup>24</sup> With this approach, the polymeric chains are treated as having instantaneous rigid conformations to calculate their overall hydrodynamic properties (diffusion coefficient, intrinsic viscosity, hydrodynamic radius, etc.). Thus, a set of conformations of the model chain is generated randomly following certain statistical rules (i.e., a MC procedure), and then the conformational

## SCHEME 1: Chemical Structure of the Thermoresponsive MPEG<sub>n</sub>-*b*-NIPAAm<sub>m</sub> Diblock Copolymer<sup>a</sup>



<sup>a</sup> In one series of copolymers, the values of  $n$  for the investigated samples are 0, 12, 23, and 114 and  $m = 71$ . For the other series of copolymers, the value of  $n = 53$  is constant and  $m$  assumes values of 19, 70, and 114.

properties of each conformation are evaluated using the procedures applicable to rigid particles and the final results are taken just as sample averages. The description of the friction of each element of the model and the computation of the hydrodynamic interaction between them is less complicated when these elements are spherical. Therefore, a simple and convenient way to build the polymeric chain is the usage of beads as elements. Springs with a suitable potential energy have been employed to connect these beads, which gives rise to the so-called bead-and-spring model.<sup>25</sup> The elements of the model must be parametrized to adequately represent the diblock copolymer. Two kinds of beads are required due to the presence of two blocks with monomers of a different nature. For the sake of a better computational efficiency, an optimal number of two monomers per bead can be used without affecting the final result. Hence, we use one type of bead to represent two monomers of the PNIPAAm block and another type for MPEG, and as a consequence, the springs connecting adjacent beads represent a few atoms and are relatively stiff. An adequate potential to represent stiff (hard) springs with finite extensibility and nonlinear elongation (FENE) is the Hard-FENE potential:

$$V^{\text{con}}(l) = -\frac{1}{2}Hl_{\text{max}}^2 \ln\left(\frac{l_{\text{max}}^2 - l^2}{l_{\text{max}}^2 - l_e^2}\right) - \frac{1}{2}Hl_{\text{max}}l_e \ln\left[\frac{(l_{\text{max}} + l)(l_{\text{max}} - l_e)}{(l_{\text{max}} - l)(l_{\text{max}} + l_e)}\right] \quad (1)$$

where  $l_{\text{max}}$  is the maximum elongation of the spring,  $l_e$  is the equilibrium length of the spring,  $l$  is the instantaneous length of the spring, and  $H$  is the spring constant. The potential was devised previously to treat stiff springs with finite extensibility as those used to simulate other semiflexible polymeric structures such as dendrimers.<sup>26</sup> Following a multiscale approach, the parametrization of both the beads and springs of the two blocks was realized from atomistic simulations performed with the commercial program HYPERCHEM distributed by Hypercube, Inc. (<http://www.hyper.com/>). After the atomistic simulation of the two monomers forming a bead, its hydrodynamic radius,  $\sigma$ , is calculated with the program HYDROPRO<sup>27</sup> (freely available at <http://leonardo.inf.um.es/macromol/>). Analogously, regarding the springs we simulated at atomic level the shortest part of the chain that contains a spring to obtain the distribution function of the length of the spring from which the parameters of the eq 1 can be determined. Hence, there are three different springs: the springs that connect the beads in the MPEG block, those for the PNIPAAm block, and a unique spring that connects both blocks. The numerical values found for these parameters are summarized in Table 1.

To address the temperature-induced contraction of these thermosensitive copolymers, the thermodynamical conditions

**TABLE 1: Parameters for the Beads and Spring of the Two Blocks and for the Spring that Connects Both Blocks**

	PNIPAAm block	MPEG block	spring between blocks
$\sigma \times 10^8$ (cm)	4.6	3.18	
$H$ (erg/cm <sup>2</sup> )	84.3	287.9	460.4
$l_e \times 10^8$ (cm)	6.4	4.9	5.9
$l_{\max} \times 10^8$ (cm)	10.5	6.7	13.5

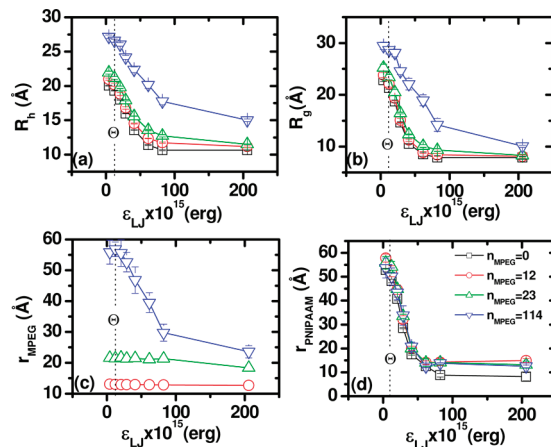
(excluded volume) of the system are simulated using a Lennard-Jones potential:

$$V(r) = 4\epsilon_{\text{LJ}} \left[ \left( \frac{\sigma_{\text{LJ}}}{r} \right)^{12} - \left( \frac{\sigma_{\text{LJ}}}{r} \right)^6 \right] \quad (2)$$

where  $r$  is the distance between two nonbonded elements of the chain. The value of the parameter  $\sigma_{\text{LJ}}$  is calculated as  $0.8l_e$ ,  $l_e$  being the equilibrium spring length, which is a reasonable assumption based on works with Gaussian chains.<sup>28</sup> The energy parameter  $\epsilon_{\text{LJ}}$  is left as an adjustable parameter, although in any case its value will be of the order of  $k_B T$ , where  $k_B$  is the Boltzmann constant and  $T$  is the absolute temperature (e.g., values between  $0.1 k_B T$  and  $k_B T$  are adequate to describe the full range of solvent quality in Gaussian chains).<sup>28</sup> Three different types of excluded volume interactions are taken into account in this study. The first one is the interaction between the elements of the MPEG block, where good solvent conditions are considered for all the studied temperatures because of the hydrophilic character of MPEG. In this case, the parameters of the Lennard-Jones potential were set to the fixed value of  $\sigma_{\text{LJ}} = 1.27 \times 10^{-7}$  cm and  $\epsilon_{\text{LJ}} = 4.1 \times 10^{-15}$  erg. In contrast, PNIPAAm is a thermoresponsive polymer for which the solvent conditions change with temperature and, therefore, the Lennard-Jones potential for elements within this block should be modulated to take this aspect into account. The parameter  $\sigma_{\text{LJ}}$  is kept constant with a value of  $1.84 \times 10^{-7}$  cm, whereas  $\epsilon_{\text{LJ}}$  is changed with temperature, and it assumes higher values (more hydrophobic or worse solvent conditions) as the temperature is increased. In this study, different solvent conditions are simulated when the value of  $\epsilon_{\text{LJ}}$  is increased from  $4.1 \times 10^{-15}$  to  $2 \times 10^{-13}$  erg. Values up to  $1.23 \times 10^{-14}$  erg correspond to good solvent conditions, the value  $1.23 \times 10^{-14}$  erg represents  $\Theta$  solvent conditions and higher values correspond to a poor solvent. We assume that a change of the hydrophobicity of PNIPAAm also affects the thermodynamic conditions of the hydrophilic block.<sup>29,30</sup> To take this aspect into account, we have introduced a third type of excluded volume interaction between two elements belonging to different blocks: the  $\epsilon_{\text{LJ}}$  values for the potential between MPEG and PNIPAAm are the geometric average of the values of each block, whereas the  $\sigma_{\text{LJ}}$  values are the arithmetic average, according with the combining rule of Lorentz–Berthelot.<sup>31</sup> This is a crude approximation, which may not give us the results with a high accuracy and some deviations from reality may be expected, although qualitatively the trend will give us a better understanding of the system. All the results are presented as a function of the  $\epsilon_{\text{LJ}}$  values of the thermoresponsive block.

## Results and Discussion

We have simulated the behavior of different diblock copolymers in dilute aqueous solutions. The copolymers are composed of a hydrophilic block (MPEG) and a thermoresponsive block of PNIPAAm, which possesses a hydrophobicity that increases



**Figure 1.** Temperature dependences of  $R_h$  (a),  $R_g$  (b), end-to-end distance of the MPEG block (c) and end-to-end distance for the PNIPAAm block (d) for dilute solutions MPEG $_n$ -b-PNIPAAm $_{71}$ . The symbols have the same meaning in all the panels. The dotted lines mark the  $\Theta$  conditions.

with increasing temperature; a higher temperature yields a higher value of  $\epsilon_{\text{LJ}}$ . Two different series of these copolymers have been studied. In the first case, the length of the PNIPAAm block was set to a constant number of 71 monomers to establish the effect of the hydrophilic block on the global behavior of the copolymer. This group will be labeled as MPEG $_n$ -b-PNIPAAm $_{71}$ , with  $n = 0, 12, 23$ , and 114. In the second case, copolymers of the type MPEG $_{53}$ -b-PNIPAAm $_m$ , with  $m = 19, 70$ , and 114 are studied and the number of monomers of PNIPAAm in the copolymer is varied while the MPEG block has a constant length of 53 units. The idea is to study the influence of the length of the hydrophobic block on the temperature-induced self-assembly of the copolymer.

One of the advantages in the simulation is that both the global size of the copolymer and the dimensions of a subunit can be evaluated separately. In general terms, the dimensions of all the copolymers have a clear trend, namely, a decrease with increasing temperature, i.e., with increasing  $\epsilon_{\text{LJ}}$  for both the whole polymer and each block. In Figure 1 (corresponding to MPEG $_n$ -b-PNIPAAm $_{71}$ ) and Figure 3 (corresponding to MPEG $_{53}$ -b-PNIPAAm $_m$ ), we show the  $\epsilon_{\text{LJ}}$  dependence of the overall radius of gyration ( $R_g$ ), the overall hydrodynamic radius ( $R_h$ ), and the block end-to-end distances for every case studied in this work. The calculation of  $R_h$  is not a simple task. We compute the single-chain translational diffusion tensor for each generated conformation. For that purpose, we consider the hydrodynamic interaction between the beads of the chain by using the modification of the Rotner–Prager–Yamakawa tensor proposed by Bloomfield and García de la Torre<sup>32</sup> that takes into account beads with different sizes,

$$\mathbf{T}_{ij} = (8\pi\eta_0 R_{ij})^{-1} \left( \mathbf{I} + \frac{R_{ij} R_{ij}}{R_{ij}^2} + \frac{\sigma_i^2 + \sigma_j^2}{R_{ij}^2} \left( \frac{1}{3} \mathbf{I} - \frac{R_{ij} R_{ij}}{R_{ij}^2} \right) \right) \quad (3)$$

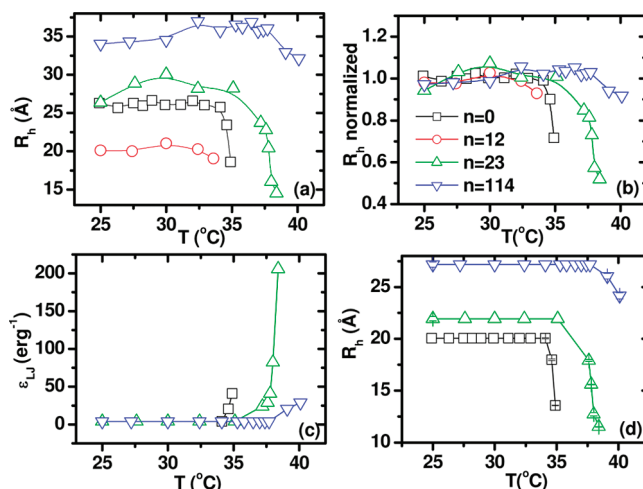
where  $\sigma_i$  is the hydrodynamic radius of bead  $i$ ,  $R_{ij}$  is the distance between beads  $i$  and  $j$ , and  $\eta_0$  is the viscosity of the solvent. The diffusion tensor is then  $\mathbf{D}_{ij} = k_B T \cdot [\delta_{ij} \mathbf{I} + (1 - \delta_{ij}) \zeta_i \mathbf{T}_{ij}]$ ,  $\delta_{ij}$  being the Kronecker delta and  $\zeta_i$  the Stokes friction coefficient of the bead  $i$ . From those individual diffusion tensors we calculate the corresponding diffusion coefficients and make the average over all the conformations. Thus, the hydrodynamic



radius of the polymer is computed from that average diffusion coefficient using the Einstein formula.

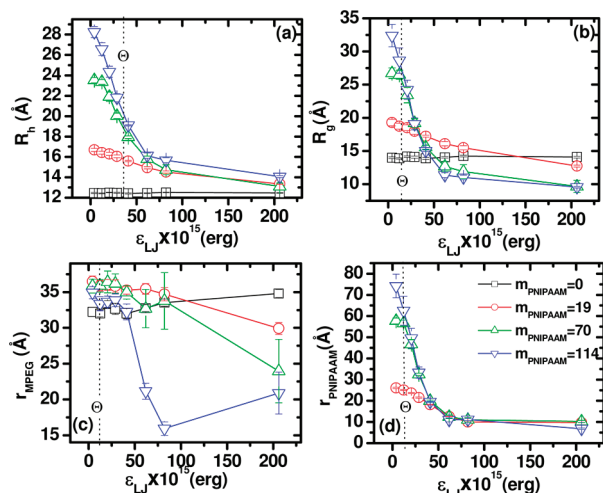
The general observed behavior is that both blocks (PNIPAAm and MPEG) shrink when the temperature is increased and consequently the global dimensions ( $R_g$ ,  $R_h$ ) of the copolymers decrease. As expected, the PNIPAAm block contracts at lower temperatures than the more hydrophilic MPEG block, and a decrease of the size can be observed for the PNIPAAm block even at  $\Theta$  solvent conditions ( $\epsilon_{LJ} = 1.23 \times 10^{-14}$  erg), whereas no change is detected for the hydrophilic block (see dotted lines in Figures 1 and 3 that mark the  $\Theta$  conditions). For the global dimensions, it is observed that the size of the copolymers is nearly the same for  $n_{\text{MPEG}} = 0, 12$ , and 23, but for the longest MPEG block the values of  $R_h$  and  $R_g$  are significantly higher, as seen in Figure 1a,b. This finding indicates that the attachment of short MPEG blocks to the PNIPAAm chain has only a modest effect on the dimensions of the chain. If we look at the local dimensions of the blocks separately through the end-to-end distance of each block,  $r_i$  (Figure 1c,d), it can be noticed that the PNIPAAm block seems to behave independently of the length of MPEG, but at the highest value of  $\epsilon_{LJ}$  a difference between the copolymer with  $n_{\text{MPEG}} = 0$  and the others can be traced. The end-to-end distance of pure PNIPAAm is approximately 6 Å, but in the case of the copolymers it is ca. 10–12 Å, even though the molecular weight of the PNIPAAm blocks is the same in all cases. This may reflect that the MPEG block serves as a protection of the PNIPAAm block, whereby reducing the contact of the PNIPAAm segments with the aqueous surroundings. The PNIPAAm block contracts when the temperature is raised (worse solvent conditions), while the MPEG block is still at good solvent conditions. However, when the hydrophobicity of PNIPAAm is high enough, the MPEG block covers the inner core because of the interaction between these two blocks. In the absence of this protective corona, the hydrophobic core is forced to adopt a much more compact conformation. Hence, as expected, it can be argued that an increment of the contents of MPEG in the composition of the copolymer should lead to a lower hydrophobicity of the whole copolymer, and this is an aspect that must be taken into account in the design of new copolymers. Interestingly, the end-to-end distance of the MPEG block (Figure 1c) decreases when the temperature is raised even though MPEG itself is not thermosensitive and stays hydrophilic at all temperatures. This effect is particularly evident for long MPEG chains, indicating that at elevated temperatures MPEG will curl around the hydrophobic PNIPAAm core to protect it from the aqueous environment. In nondilute solutions, the copolymers with a shorter MPEG block will tend to aggregate at lower temperatures because of the absence of an outer protection, or in other words the steric hindrance effect stabilize the species.<sup>17</sup>

One of the most challenging tasks in this study is to relate the values of  $\epsilon_{LJ}$  to actual temperatures. To face this problem, we need to compare our simulation results with experimental data. A systematic study with the aid of dynamic light scattering (DLS) has been performed on both series of copolymers.<sup>17</sup> For the series with a constant thermoresponsive block, we have determined the values of the apparent hydrodynamic radii at several temperatures for copolymer concentrations of 1 and 0.5 wt %, because at lower concentrations the intensity of the signal was not high enough to obtain reliable correlation function data. At both concentrations for all three copolymers, a population of species with sizes between 20 and 35 Å is present and is related to the unimers, as it is shown in Figure 2a. As expected, both experiments and simulations at good solvent conditions



**Figure 2.** (a) Magnification of the hydrodynamic radii results displayed in Figure 5 in ref 17, which are the experimental data obtained from DLS measurements on aqueous solutions of MPEG<sub>n</sub>-b-PNIPAAm<sub>71</sub>. The  $R_h$  values have been normalized (b) and related to  $\epsilon_{LJ}$  values (c).  $R_h$  obtained from MC simulations versus temperature for dilute solutions of MPEG<sub>n</sub>-b-PNIPAAm<sub>71</sub>, with  $n = 0, 23$ , and 114 (d).

show that the larger the  $n_{\text{MPEG}}$  value, the greater the chain size; however, the  $R_h$  values measured in experiments are higher than those found with simulations, with a difference of about 5 Å. This difference between the experimental and simulated values of  $R_h$  is attributed to difficulties in the determination of  $R_h$  values from the DLS experiments in solutions containing both molecularly dispersed molecules and some large clusters. It should be pointed out that neither polydispersity effects nor interchain associations are taken into account in the simulation, but they might affect the experimental values. To avoid this discrepancy between the absolute values of our experimental and simulation results, our strategy is to normalize the experimental and the simulations values of  $R_h$ , dividing them by their respective values at good solvent conditions. The features are shown in Figure 2b, where the temperature dependences of these ratios are depicted. We can relate the experimental values to the ones determined from MC simulations carried out for every polymer using a suitable range of  $\epsilon_{LJ}$ . In that way, a correlation between a given experimental value of temperature to a value of  $\epsilon_{LJ}$  for each polymer system is made for the polymers with  $n_{\text{MPEG}} = 0, 23$ , and 114 (Figure 2c). The sudden increase observed in the  $\epsilon_{LJ}$  value indicates the onset of copolymer bad solvent conditions. Unfortunately, the comparison is not possible for MPEG<sub>12</sub>-b-PNIPAAm<sub>71</sub> due to the poor experimental data obtained, although it can be assumed that temperatures below 34 °C are good solvent conditions for this polymer. In all cases, it is evident that the conditions corresponding to transition to poorer solvent power (sudden increase of  $\epsilon_{LJ}$ ) occurs at a higher temperature as the length of the MPEG block increases, because of a more efficient stabilization effect of the hydrophobic core of the block copolymer. After converting the  $\epsilon_{LJ}$  values used in the simulations to the corresponding temperature by means of the plots in Figure 2c, Figure 2a gives rise to Figure 2d, where the parameter  $\epsilon_{LJ}$  representing the X-axis in Figure 2a is transformed to the measured temperatures to present the simulation results as a function of an observable parameter. It can be seen that there is a qualitative agreement between the experimental and the simulation results, although the shape of the curves and the  $R_h$  values are not exactly the same. As mentioned above, the polymer entities shrink when the tem-

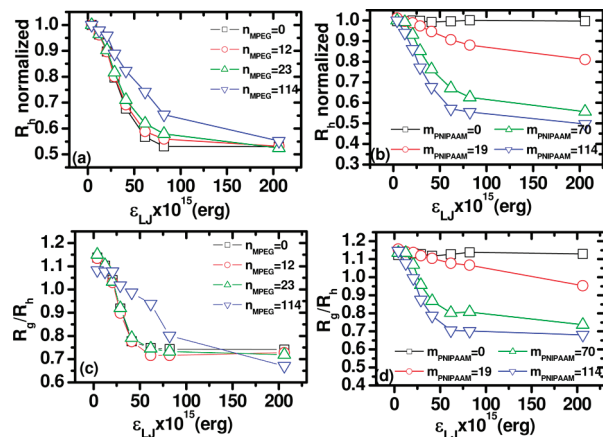


**Figure 3.** Variations on the values of the hydrodynamic radius,  $R_h$  (a), the radius of gyration,  $R_g$  (b), the end-to-end distance of the MPEG block,  $r_{\text{MPEG}}$  (c), and the end-to-end distance of the PNIPAAm block,  $r_{\text{PNIPAAm}}$  (d) of MPEG<sub>53</sub>-*b*-PNIPAAm<sub>*m*</sub>, with temperature. The legend is common for all graphs. The data are calculated from MC simulations. The dotted lines mark the  $\Theta$  conditions for the thermoresponsive block.

perature is raised, and a longer MPEG block shifts the temperature to higher values at which the compression zone appears.

Regarding the series of copolymers with a constant length of the MPEG block and various lengths of the PNIPAAm block (MPEG<sub>53</sub>-*b*-PNIPAAm<sub>*m*</sub>), the temperature dependence of their size is displayed in Figure 3. In this case, the effects of temperature (i.e.,  $\epsilon_L$ ) on the global dimension of the copolymers are sharper than those found for the previous series of copolymers. It is obvious that the contraction of the entities in dilute solution increases with increasing the length of the PNIPAAm block, because the density of NIPAAm elements in the core of the copolymer rises and this promotes a stronger temperature-induced compression. Hence, the dimensions of the copolymers can be easily tuned with the molecular weight of the thermoresponsive block, because that is the block with a stronger contribution to the global size. As expected, the end-to-end distance of pure MPEG ( $m_{\text{PNIPAAm}} = 0$ ) is independent of temperature. However, for the copolymers MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>, the end-to-end distance of the MPEG groups shrinks at elevated temperatures, probably because of the formation of a protective corona around the hydrophobic PNIPAAm core. This aspect plays an important role in the association behavior of these copolymers in solution. When the PNIPAAm core is sufficiently large, it will only partially be covered by hydrophilic MPEG chains, and this affects the stability of the copolymer moieties at elevated temperatures. If the hydrophobic core is not totally protected by the hydrophilic corona, intermolecular associations can evolve, and this may lead to the formation of larger intermicellar structures, which is actually reported from the experimental results. The end-to-end distance of the thermosensitive PNIPAAm block decreases strongly with increasing temperature; this tendency becomes more pronounced with increasing length of the PNIPAAm block (see Figure 3d). For dilute solutions of copolymers with large PNIPAAm blocks, the size becomes about 7 times smaller than at good solvent conditions, showing an enormous compression of the species, which suggests a close-packing of the hydrophobic segments in the core.

We have performed an experimental study for the MPEG<sub>53</sub>-*b*-PNIPAAm<sub>*m*</sub> series by means of DLS to determine the  $R_h$  at



**Figure 4.** Normalized values of  $R_h$  for dilute solutions of MPEG<sub>*n*</sub>-PNIPAAm<sub>71</sub> (a) and MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub> (b). Evaluation of the conformation of the copolymers MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub> (c) and MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub> (d) through the ratio  $R_g/R_h$ .

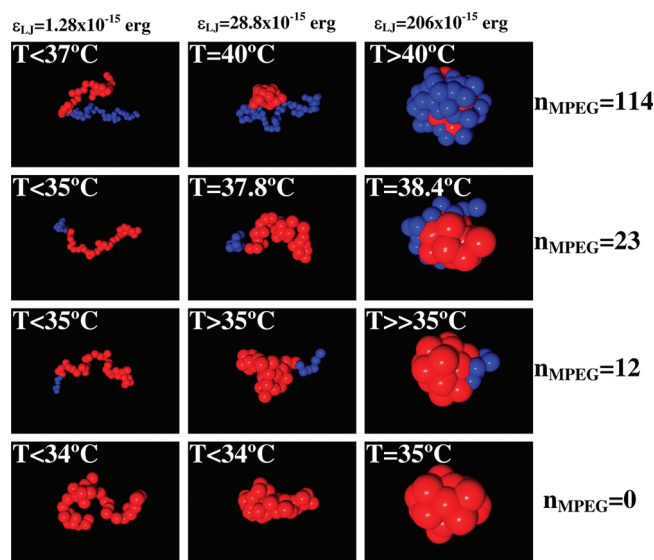
different temperatures for solutions with concentrations 1 and 0.5 wt %. Lower concentrations have been attempted, but the scattered intensities at low temperatures were not high enough to make a reliable analysis of the data. Details for the setup, experimental procedure, and analysis methods can be found in our previous works.<sup>15,17</sup> Unfortunately, for this series of copolymers with a constant length of the MPEG block, the experimental data were not suitable for a parametrization of the temperatures because contraction of the single molecules could not be observed. For the solution of MPEG<sub>53</sub>-*b*-PNIPAAm<sub>19</sub>, only one relaxation mode was detected from DLS, but it cannot be related to the diffusion of unimers because this relaxation mode yields too large values of  $R_h$  ( $R_h \approx 1000$  Å). For MPEG<sub>53</sub>-*b*-PNIPAAm<sub>70</sub>, we have calculated the dimensions of the copolymer with the aid of Monte Carlo simulations at good solvent conditions, and the results yield a value of  $R_h$  equal to 23 Å, which is close to the values of 27–30 Å found from the DLS data. Furthermore, dilute solutions of the copolymer MPEG<sub>53</sub>-*b*-PNIPAAm<sub>114</sub> produce  $R_h$  values in the range 30–35 Å at temperatures in the region from 15 to 37 °C, which is in good agreement with the simulation data at good solvent conditions (28 Å). Once again, the values obtained from the MC simulations are slightly lower than the experimental results.

In accordance with the analysis of the compression of species with increasing temperature or poorer solvent conditions, the normalized hydrodynamic radii of the copolymers (the values of  $R_h$  at good solvent conditions are used as reference) are depicted in Figure 4a,b. For solutions of the copolymer with a fixed length of the PNIPAAm block (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>) it is apparent that the simulation results suggest compaction of the copolymer moieties with increasing temperature, but the length of the hydrophilic block has only a moderate impact on the contraction, which indicates that most of the compression effect originates from the size of the hydrophobic core. In the case of the copolymers with a constant length of the MPEG block and different lengths of the PNIPAAm block (MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub>), a different picture emerges. For these copolymers it is obvious that the temperature-induced compression of the molecules is stronger as the length of the PNIPAAm block increases. Therefore, the number density of segments within the core increases and in addition the large hydrophobic core is only partially covered by the MPEG chains, and this leads to a stronger shrinking of the entities to avoid water contact. This is attributed to a longer length of PNIPAAm segments in the core, and this facilitates a stronger temperature-induced compac-

tion of the particles; i.e., a larger PNIPAAm block can contract more than a smaller one. In addition, if the PNIPAAm block is too large compared to the MPEG group, the MPEG block cannot cover the whole surface of the hydrophobic core. Another consequence of incomplete coverage of the hydrophobic core with MPEG chains is that interchain aggregation is promoted at higher temperatures in solutions of finite polymer concentrations. It is expected and has also been observed experimentally that for the MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub> copolymer with a short length of the MPEG block and the MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub> copolymer with a long PNIPAAm block, the tendency to form interchain complexes at elevated temperatures is enhanced. Furthermore, the simulation results show that the transition temperature is shifted to lower values as the length of the PNIPAAm block is increased (Figure 4b). These results clearly reveal that the size of the PNIPAAm block is decisive for the magnitude of the compression of the particles.

A temperature-induced conformational change of single copolymer molecules is frequently viewed in terms of the ratio  $R_g/R_h$  as shown in Figure 4c,d. A lower value of this ratio indicates a more spherical conformation. It is known that for a random coil chain in a good solvent  $R_g/R_h \approx 1.5$ , while for a uniform hard sphere,  $R_g/R_h \approx 0.77$ .<sup>33–35</sup> The general trend for the MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>*m*</sub> copolymers is a decrease of  $R_g/R_h$  from  $\sim 1.15$  to  $\sim 0.7$  (Figure 4c,d), and this confirms the transition of individual copolymer chains from an expanded conformation to a globular one. We have employed a Hard-FENE model to simulate the stiffness of these short copolymers, and a rigidity of the single chains is intrinsically implemented so they do not behave as a Gaussian coil. This is supported by the high values of  $H$  calculated for both blocks (Table 1). It has been reported that nanofibers with an extended thin-nanorod conformation<sup>36</sup> and worm-like structures,<sup>37</sup> both at good solvent conditions, have values of  $R_g/R_h \approx 1.2$ . Our hypothesis is that these copolymers have a behavior similar to that of the rigid structures mentioned above and this is the reason for the value of 1.15 at low temperatures. Because the association process always coexists with either the single polymer chains or the micelles,<sup>38</sup> it is difficult to determine  $R_g$  values, and we do not have experimental data to support this conjecture. We observe that the copolymer evolves to a more spherical conformation when the temperature is raised, i.e., when the quality of the solvent is decreased. As the length of the PNIPAAm block is increased, the ratio  $R_g/R_h$  becomes smaller and more temperature dependent. A short and rigid chain in an expanded conformation might avoid the interaction between the elements. The value of  $\epsilon_{LJ}$  (or temperatures) must be higher to provoke a contraction for a short PNIPAAm block in comparison with a longer one. The sharp temperature-induced transition can be explained within this framework. When the solvent conditions are sufficiently poor to cause an interaction between the nonbonded units in the chain, the elements that cannot interact are brought together. Hence, these two elements that were slightly or not affected by each other suddenly have a pronounced interaction (due to the high value of  $\epsilon_{LJ}$ ) and a rapid contraction of the thermoresponsive block may occur. Therefore, for the polymers that are short enough, a molecular weight dependence of the temperature of transition is expected.<sup>15</sup>

In Figure 5, snapshots of the conformations of the copolymers of the first series (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>) are shown at different values of  $\epsilon_{LJ}$ , together with the corresponding approximate temperature. The red and bigger beads represent the thermoresponsive units and the blue and smaller beads represent the MPEG block. For each value of  $n_{\text{MPEG}}$ , we have chosen a



**Figure 5.** Pictures extracted from the MC simulations for the series of copolymers with a constant thermoresponsive block length (MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub>).

conformation at a small enough  $\epsilon_{LJ}$  value to be at good solvent conditions, one conformation at an intermediate  $\epsilon_{LJ}$  value, and another one at a high enough  $\epsilon_{LJ}$  value to be at poor solvent conditions. At good solvent conditions, we can see that the polymers do not have an actual coil conformation, as discussed previously, but the chains are quite stretched. In the case of PNIPAAm without the MPEG block, the transition from good to poor solvent conditions is very sharp and it is located at  $T = 34^\circ\text{C}$ . The polymer is initially in an expanded conformation and it contracts when the temperature is increased to form a globular conformation. For the three copolymers ( $n_{\text{MPEG}} \neq 0$ ), we observe a similar behavior; but in this case the contracted hydrophobic core at elevated temperatures is more or less covered by hydrophilic MPEG chains, depending on the length of the hydrophilic block. For the copolymer with  $n_{\text{MPEG}} = 23$ , the collapsed conformation appears at  $T = 38.4^\circ\text{C}$ , and at a temperature higher than  $40^\circ\text{C}$  for the copolymer with the longest hydrophilic block. In the first case, the MPEG subchain is only able to partially cover the hydrophobic core, whereas in the other case it is more efficiently covered. Moreover, this series of snapshots is instructive to understand interchain aggregation of this type of copolymers. Regarding the behavior of these copolymers in nondilute solution, a polymer with a MPEG block that is not able to completely cover the PNIPAAm block has a more pronounced tendency to aggregate than the copolymers with a longer MPEG block (or shorter PNIPAAm block). Therefore, the ratio MPEG/PNIPAAm is also decisive in the formation of aggregates.

## Conclusions

We have shown with this work that the bead-and-spring model using a Hard-FENE spring is suitable for the simulation of low-molecular-weight amphiphilic copolymers. The conformational changes induced by temperature in thermoresponsive polymers can be simulated using appropriate values for the parameters of the Lennard-Jones potential employed to mimic the solvent quality; thus a higher value of  $\epsilon_{LJ}$  is related to higher temperatures, implying poor solvent conditions for PNIPAAm. In this investigation, copolymers of the types MPEG<sub>*n*</sub>-*b*-PNIPAAm<sub>71</sub> and MPEG<sub>57</sub>-*b*-PNIPAAm<sub>*m*</sub> have been studied by Monte Carlo simulations. Our results show good agreement with



experimental data, although they are limited and not always available. These simulations have demonstrated how a single chain of a thermosensitive block copolymer undergoes a transition from a stretched to a globular conformation. A larger portion of the PNIPAAm block in the copolymer gives rise to a more pronounced compression of the copolymer moieties, and the ratio  $R_g/R_h$  reveals a temperature-induced contraction. Due to simulation, we can study the hydrophilic and hydrophobic blocks independently, and this allows for a better understanding of the contraction process. Thus, it can be rationalized how an increment in temperature can lead to a contraction of the thermoresponsive block, which is followed by a total or partial coverage of the hydrophobic block by the hydrophilic one. The change of the length of the hydrophilic block has only a moderate influence on the temperature-induced compression of the species, whereas longer sequences of the PNIPAAm block alter the transition temperature and a significantly stronger temperature-induced collapse is observed. It is shown by simulation that for a given length of the PNIPAAm block, a short sequence of the MPEG block leads to a partially covered hydrophobic core and this situation promotes the formation of interchain complexes at elevated temperatures in solutions of finite polymer concentrations.

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