

Molecular dynamics simulation of a model oligomer for poly(*N*-isopropylamide) in water

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Received 2 December 2003; in final form 10 January 2004

Published online: 4 February 2004

Abstract

Molecular dynamics (MD) has been used to simulate a dilute aqueous solution of a 50-units oligomer model for the thermoresponsive polymer poly(*N*-isopropylacrylamide) at 300 and 310 K, i.e., below and above its lower critical solution temperature (LCST) in water. Statistical analyses of the system trajectories show that at 310 K the oligomer exhibits a more compact conformation than at 300 K, in qualitative agreement with experiments, and that it is surrounded by a smaller number of first-hydration-shell water molecules.

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1. Introduction

The linear poly(*N*-isopropylacrylamide) (pNIPAAm, Fig. 1a) is a thermoresponsive polymer whose aqueous solutions exhibit a reversible transition with a lower critical solution temperature (LCST) of 32 °C [1,2]. The LCST, which marks the separation between solubility and insolubility [3,4], can be modulated by copolymerization of NIPAAm with different comonomers [5,6] yielding potentially useful materials responsive to a variety of stimuli, such as temperature, pH, light or electric field [7,8]. At LCST, pNIPAAm-based systems undergo a collapse resulting from structural changes of the whole intermolecular network: a coil-to-globule transition of the single polymer chains [4,9,10] is followed by aggregation. The intramolecular collapse has been extensively studied especially in connection with fundamental problems, such as the protein folding [11]. In this context, recent circular dichroism experiments indicate that few degrees below the LCST a copolymer based on NIPAAm and the optically active comonomer *N*-methacryloyl-L-leucine (10/1) possibly exhibits single-chain intramolecular rearrangements resembling a coil-

to-globule transition [12]. Similar conclusions have been previously reached using dynamic light scattering on either dilute aqueous solution of high molecular weight pNIPAAm [13] or pNIPAAm aqueous solutions with added surfactants [14]. On the other hand, a transition temperature slightly higher (33.7 °C) is indicated by calorimetric measurements [15].

Aiming to investigate microscopic details of the pNIPAAm–water interaction related to single chain conformational changes occurring across the LCST, we undertook the present work on a system consisting of a 50-units oligomer surrounded by more than 20 000 water molecules, to mimic as far as possible the experimental conditions necessary to study the coil-to-globule transition. Moreover, the all-atom Amber force field [16,17] was used to describe inter- and intra-molecular interactions. Previous simulations [18,19] were mainly focused on water structuring properties and were performed on concentrated aqueous solutions in a wide range of temperatures using the united-atom Amber force field.

2. Computational methods

Ab initio calculations on a ‘monomer’ of pNIPAAm (Fig. 1b) were done at RHF/6-31G* level with

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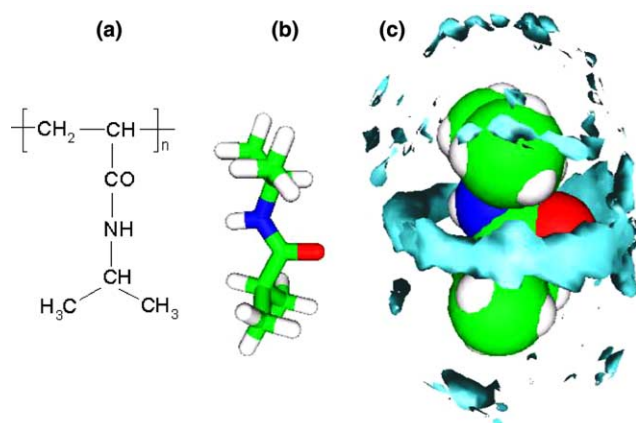


Fig. 1. (a) pNIPAAm chemical formula; (b) NIPAAm unit ('monomer') terminated with one hydrogen and one methyl group; (c) spatial distribution function of the water oxygen atoms surrounding the monomer. The isosurface corresponds to $g(r) = 3$.

GAUSSIAN 98 [20], and the atomic charges were evaluated according to the RESP protocol [21]. The 50-units oligomer of pNIPAAm was 'synthesized' by random addition of *d*- and *l*-structures, mimicking the atacticity of the whole chain. NPT MD simulations at $P = 0.1$ MPa were performed using the Amber6 SANDER module [22]. A 9-Å cutoff and Ewald sums were used for non-bonded interactions and the TIP3P water model was assumed [23]. SHAKE algorithm [24] kept constrained the bond-lengths involving hydrogen atoms. The integration step was set to 1 fs. Graphic visualization was done with gOpenMol [25].

3. Results and discussion

In Fig. 1b, we report the structure of the NIPAAm 'monomer' which has been fully optimized by ab initio quantum mechanical calculations. To this purpose, a hydrogen atom and a methyl group were added to the alkyl side of the NIPAAm unit involved in the polymeric backbone.

In order to explore the monomer hydration characteristics below and above the LCST, we performed two 1-ns NPT MD simulations at $T = 300$ K and $T = 310$ K of a system consisting of one monomer and 518 water molecules. Results of statistical analyses of the trajectories, reported in Table 1, show that at 300 K, 23.5 waters reside within the first hydration shell of the monomer (i.e., within 3.5 Å from the monomer atoms), 2.1 of which are hydrogen-bonded to it. An overall picture of the monomer hydration is shown in Fig. 1c by the spatial distribution function (SDF), $g(r)$, providing a three-dimensional representation of the density of the water oxygen atoms around the monomer. The SDF is calculated as follows [26]:

$$g(\mathbf{r}) = \rho(\mathbf{r})/\rho_0,$$

where $\rho(\mathbf{r})$ indicates the number density of the water oxygen atoms at the position \mathbf{r} and ρ_0 its average within the simulation box. The position vector \mathbf{r} is defined in a coordinate system attached to the solute molecule. This SDF shows that the first-hydration-shell waters are mainly localized in the hydrophilic region of the monomer, as expected.

We also report in Table 1 the translational self-diffusion coefficient of the first-shell waters, D , which is evaluated according to the Einstein equation [24]

$$\langle |r_i(t) - r_i(0)|^2 \rangle = 6Dt,$$

whose left-hand side represents the mean square displacement of the first-shell waters as a function of time, being $r_i(t)$ and $r_i(0)$ the positions of their centers of mass at time t and at the start of each of the segments in which the trajectories are subdivided, respectively. A 1.5-ps segment duration was found a reasonable compromise between the contrasting requirements of being short enough to monitor the mobility of waters within the first-shell space region, and long enough to make applicable the Einstein equation [27]. Table 1 shows that at 300 K the D coefficient of the waters surrounding the monomer is ca. 19% smaller than that of TIP3P water. A similar value ($D = 4.5 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$) has been recently found using the same water model and algorithmic approach for the

Table 1
Hydration and diffusion data for pNIPAAm 'monomer' (1), 50-units oligomer (50) and TIP3P water (wt) at 300 and 310 K

	<i>fs</i>	<i>hbfs</i>	<i>hblfs</i>	<i>wwh</i>	<i>wsh</i>	<i>ssh</i>	<i>D</i>
1 (300 K)	23.5	22.9	2.27	53.6	2.1		4.8
1 (310 K)	23.1 (-1.7)	22.4 (-2.2)	2.20 (-3.1)	50.8 (-5.2)	2.0 (-4.8)		5.5 (14.6)
50 (300 K)	435.0	425.9	2.46	672.5	85.9	2.8	3.8
50 (310 K)	407.4 (-6.3)	397.1 (-6.8)	2.39 (-2.8)	609.0 (-9.4)	82.4 (-4.1)	2.7 (-3.6)	4.3 (13.2)
wt (300 K)	7.3	7.1	2.03				5.9
wt (310 K)	7.2 (-1.4)	6.9 (-2.8)	1.97 (-3.0)				6.6 (11.9)

The column headings indicate the average numbers of first-shell water molecules (i.e., residing within 3.5 Å from the atoms of the solute) (*fs*), *hbfs* of which are involved in hydrogen bonding*, their self-diffusion coefficient, D (in $10^{-5} \text{ cm}^2 \text{ s}^{-1}$), the number of water–water (*wwh*), water–solute (*wsh*) and solute–solute (*ssh*) HBs and the average number of HBs per first-shell water (*hblfs*). The percentage changes of 310-K data with respect to 300-K data are shown within parentheses.

* Hydrogen bond definition: distance $r_{\text{OO}} \leq 3.5$ Å; angle $\theta_{\text{OHO}} \geq 150^\circ$ [34].

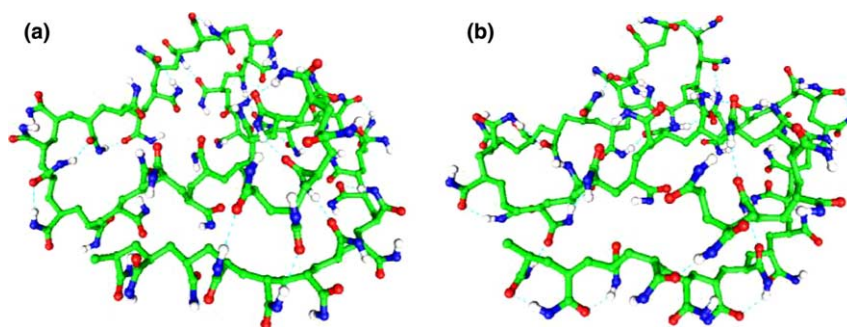


Fig. 2. Final configurations of MD simulations in vacuo of the 50-U oligomer at 300 K (a) and at 310 K (b): for clarity, only backbone, O and NH are shown. Dashed lines represent hydrogen bonds.

first-hydration of the osmolyte TMAO [28], which has been shown to strongly interact with water [29].

To understand the effect of water on the pNIPAAm structure, we first performed 1-ns MD simulation of the 50-units oligomer in vacuo at 300 and 310 K. The statistically representative configurations reported in Fig. 2 show that there is no remarkable difference between the system configurations equilibrated at either temperature and that the prevailing interaction in vacuo is an extensive intra-chain hydrogen bonding, which induces rather compact structures. Therefore, one can expect that relevant structural changes can occur when the oligomer is surrounded by water, due to the presence of water–solute hydrogen bonds (HBs) competing with intra-chain HBs.

We then conducted two 4.4-ns NPT MD simulations at 300 and 310 K of a system consisting of one 50-units oligomer and 20 211 water molecules. These simulations were preceded by a 30-ps simulation at 500 K to randomize the initial system configuration. The last configuration of the 500-K simulation was taken as initial configuration of 50-ps equilibration phases of both 300- and 310-K simulations.

Oligomer structural changes occurring along these simulations were monitored through the solute gyration

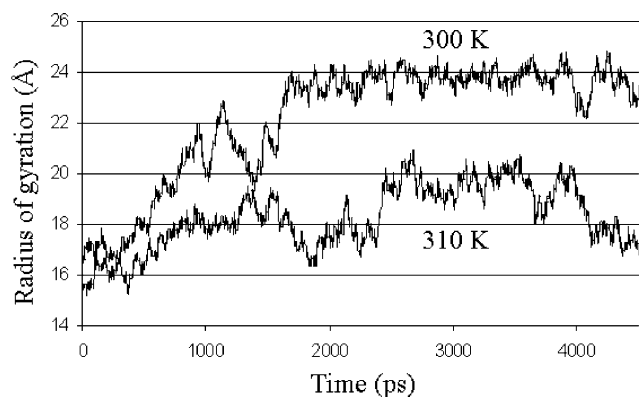


Fig. 3. Time evolution of the solute radius of gyration along the MD simulations of a system involving one 50-units oligomer and 20 211 TIP3P [23] water molecules at 300 and 310 K.

radius, whose time evolutions are reported in Fig. 3. In Fig. 4 we show the start configuration (inset a) and the end configurations of the 310-K (inset b) and 300-K (inset c) simulations. We observe that the solute attains a more compact configuration at 310 K than at 300 K, in qualitative agreement with experiments [13,14], and that rather larger fluctuations in the solute gyration radius occur at 310 K. Moreover, a ‘hairpin’ region (marked by a square in Fig. 4) is present in both the final oligomer configurations, which appears as remarkably persistent, being already present at the end of the

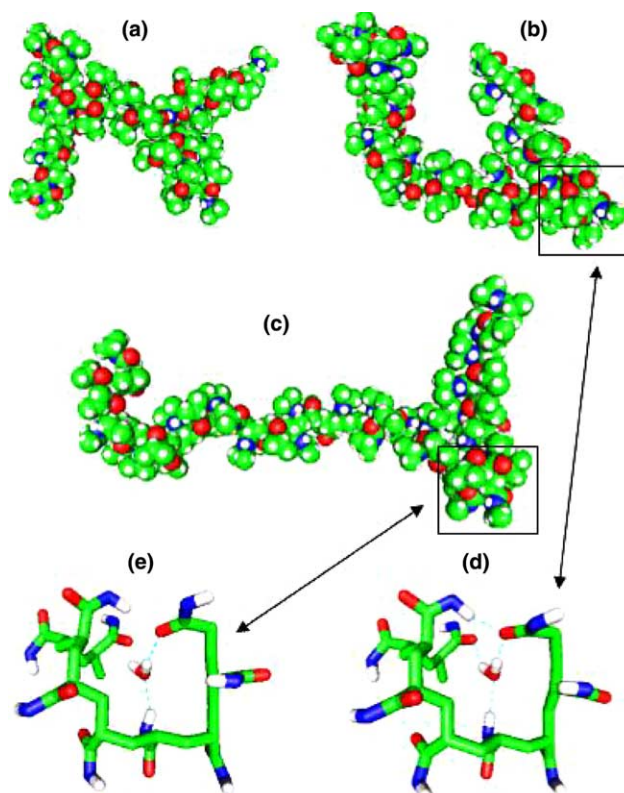


Fig. 4. Initial (a) and final configurations of 4.4-ns MD simulations of the oligomer aqueous solution at 310 K (b) and at 300 K (c). (d) and (e) represent the backbone views of the oligomer segments labeled by squares. Dashed lines indicate hydrogen bonds.

preceding 500-K simulation. Statistical analysis and direct graphical inspection show that it is related to intra-chain HBs and to the presence along the whole simulations of the same water molecule, which often forms three HBs with non-adjacent hydrophilic groups of that oligomer segment (insets d and e of Fig. 4). A signature of rather strong interactions stabilizing the hairpin region is present in the atomic fluctuations data reported in Fig. 5a which evidences a peculiar behavior of the oligomer units included in that region, namely from 30 to 45 units. One may observe that quite low atomic fluctuations occur for 34 and 40 units, which are

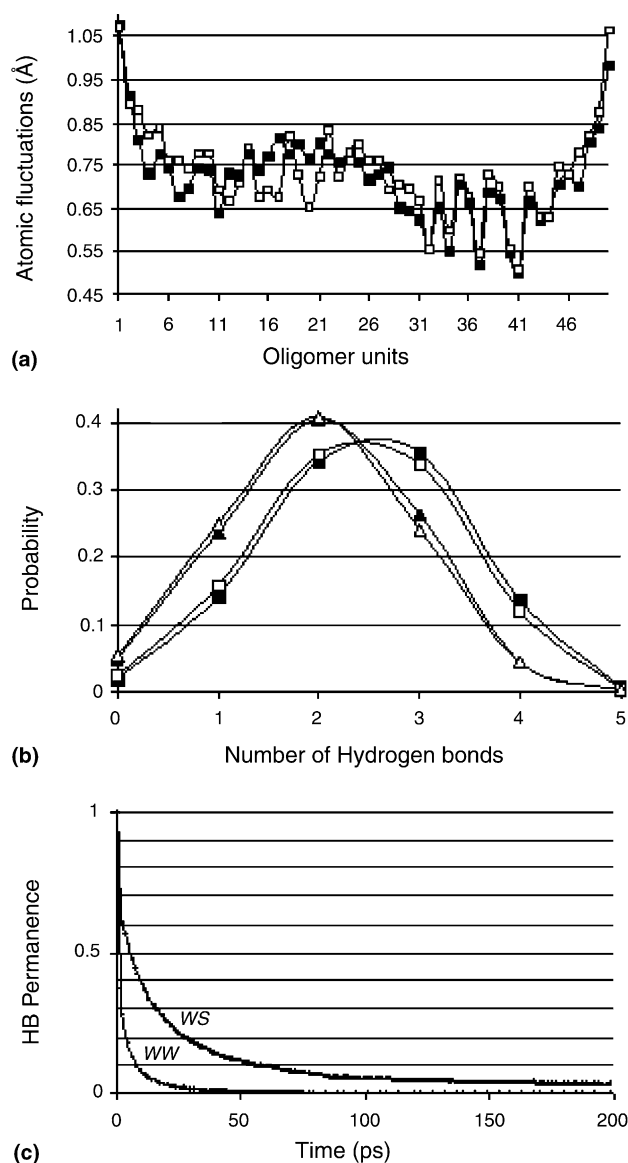


Fig. 5. (a) Average atomic fluctuations of the oligomer units at 300 K (full squares) and 310 K (open squares). (b) Distributions of the hydrogen bonds per first-shell water molecule for pure TIP3P water (triangles) and the 50-units oligomer (squares) at 310 K (open symbols) and 300 K (full symbols). (c) Permanence of water–water (*ww*) and water–solute (*ws*) HBs. Lines are eye-guides.

involved in the most persisting intra-chain HB, and for 32 and 37 units, which together with unit 40 are linked to the above mentioned water molecule.

Table 1 data, which for the oligomer have been obtained by averaging over the last 1-ns part of its trajectories, help to examine connections between structural changes and hydration properties. Thus, one sees that for the oligomer the number of the first-shell waters, *fs*, is at 310 K 6.3% smaller than at 300 K, while the analogous value for the monomer is 1.7%, i.e., similar to that for the TIP3P test case. The corresponding decrease in the numbers of the first-shell waters involved in hydrogen bonding, *hbfs*, is 6.8% for the oligomer and 2.2% for the monomer. These data indicate that as the temperature increases, a decrease is induced in the number of the first-shell waters around the oligomer remarkably larger than around the monomer, speaking for a reduction of the oligomer surface exposed to the solvent at 310 K, in agreement with the above presented evidence for a more compact structure at 310 K. However, this reduction appears larger for hydrophobic groups than for the hydrophilic ones. Indeed, Table 1 shows that the numbers of the water–water (*wwh*) and water–solute (*wsh*) hydrogen-bonds decrease for the oligomer by 9.4% and 4.1%, respectively, and by 5.2% and 4.8% for the monomer, suggesting that the *wwh*-bond promoters (namely, the solute hydrophobic groups) become hidden from the solvent more effectively than the hydrophilic groups, which favor the *wsh* bonds.

In Fig. 5b we report HB distributions for the first-shell waters. They show that: (i) for both pure water and water surrounding the oligomer the HB distributions are slightly but clearly shifted toward smaller HB numbers at the higher temperature; (ii) there is a remarkable difference between the HB distributions for pure water and for the oligomer solution, the latter being shifted toward larger HB values. The monomer HB distributions (not shown) practically superimpose to those for the oligomer. These features are well represented by the values of mean number of HBs per water molecule, *hbfs*, reported in Table 1.

We also examined the persistence of the water–water and water–solute HBs. In Fig. 5c, we report the permanence of HBs vs. time, evaluated by an autocorrelation procedure conceptually similar to the ‘intermittent’ algorithm [33] used in [18]. From these data one sees that 10% of the water–water (*ww*) and water–solute (*ws*) HBs still survive after ca. 7 ps and 60 ps, respectively, indicating that, while the HBs network around the solute appears as continuously reshuffling, it is rather steadily anchored to it.

From Table 1 one also sees that the average number of intra-chain HBs, *ssh*, slightly decreases going from 300 to 310 K. Direct inspection and statistical analysis show that in the more extended conformation at 300 K

the solute–solute HBs occur mainly between adjacent oligomer units, while HBs linking non-adjacent units appear somewhat longer-lasting at 310 K, thus participating more effectively to the oligomer coiling. This effect would be probably more evident for longer chains.

An overall view suggested by the above observations is that the action of water on the oligomer is equivalent to a tension due to the presence of multiply bonded water molecules, which strives to elongate the chain as much as permitted by intra-chain HBs and water molecules buried within the solute. Such tension can be viewed as a solvent-induced force on the solute [30], some cases of which have been previously simulated [31,32]. By raising the temperature, the water hydrogen bonding deteriorates to some degree, thus conceivably affecting its action on the oligomer structure.

Finally, since the present approach has proved to reproduce, at least qualitatively, the pNIPAAm behavior across the LCST region, we expect that its use can be extended to investigate microscopic aspects related to the insertion of comonomers.

4. Conclusions

The present Letter reports on 4.4-ns MD simulations at 300 and 310 K (namely, below and above the LCST) of a dilute aqueous solution consisting of a reasonably long (50 units) oligomer model of pNIPAAm and over 20 000 water molecules, to mimic as far as possible experimental conditions suitable to investigate single-chain configurational changes. Statistical analyses of the trajectories show that the equilibrated oligomer configurations are more compact at 310 than at 300 K, in qualitative agreement with experiments. Correspondingly, the number of water molecules residing in the first coordination shell is at 310 K ca. 6% lower than at 300 K. Comparison with results of MD simulations of an aqueous solution of a NIPAAm monomer suggests that this hydration change is mainly due to hiding of hydrophobic groups from the solvent at the higher temperature. Moreover, the statistical analysis indicates that isolated water molecules buried inside the polymer contribute to stabilize the conformation of chain segments affecting the overall evolution of pNIPAAm structural changes.

Acknowledgements

We thank Davide Rebecani, Gian Paolo Ghilardi and Massimo Fierro for their technical assistance with our Linux cluster.

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