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THE INFLUENCE OF THE STARTING STRUCTURE AND WATER MODEL ON THE CONFORMATION TRANSITION OF POLY(N-ISOPROPYLACRYLAMIDE) THERMORESPONSIVE POLYMER - IN SILICO STUDIES

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Abstract. Molecular dynamics (MD) simulations are intensively used to obtain information on the microscopic behavior of a system and to evaluate certain properties which they determine at macroscopic level. But, as well as setting up an experiment in a "wet" laboratory, also setting up a simulation in a virtual enviroment implies many variables that influence the results. Two of the variables are the starting structure of the system and the water model in which it is solvated.

The present work aims to identify an optimal combination of this two variables able to reveal best the transition from an extended to a collapsed conformation for poly(n-isopropylacrylamide) (PNIPAM) thermoresponsive polymer.

Keywords: molecular dynamics simulation, thermoresponsive polymer, state transition.

1. Introduction

Molecular Dynamics (MD) simulations relies on the concept of force fields, determining the way is which the atoms interact. The first step in setting up a MD simulation is to build the structure of the system, in order to determine the charges and the coordinates of the atoms, informations needed as inputs in MD simulations. After running the simulations, the resulted trajectories of atoms are analyzed by tracking their time-dependent positions, leading to information on the microscopic structures and of the interactions within, further used in the evaluation of certain system properties such as solubility, diffusion coefficient, state transition temperature.

We studied poly(n-isopropylacrylamide), PNIPAM, one thermoresponsive polymer that exhibits a state transition from a extended conformation to globular one (Fig. 1).

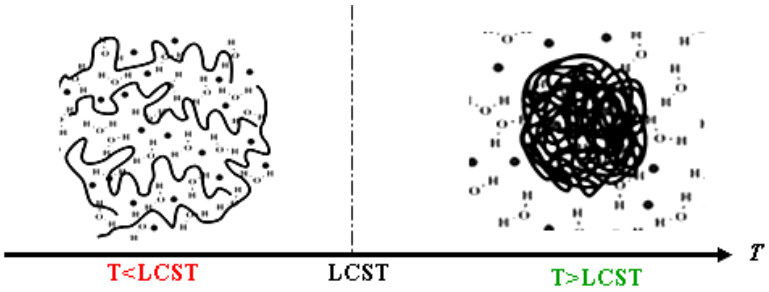


Fig. 1. Ilustration of structural conformation transition

The polymer behaviour in water, at 300K, for five different starting structures, was analyzed and the radius of gyration was evaluated as a measure of the polymer's collapsed state.

2. Molecular Dynamics Simulations

2.1. Starting structure

Three saturated structures of NIPAM monomer capped with (H-, -CH3), (CH3-, -CH3), (CH3-, -H) for head, middle and tail residues were build in Avogadro software [1]. For each structure ab initio MD simulations were performed to find the lowest energy structure in gas phase with Gaussian 09, PM6 semi-empirical method [2] (Fig. 2).

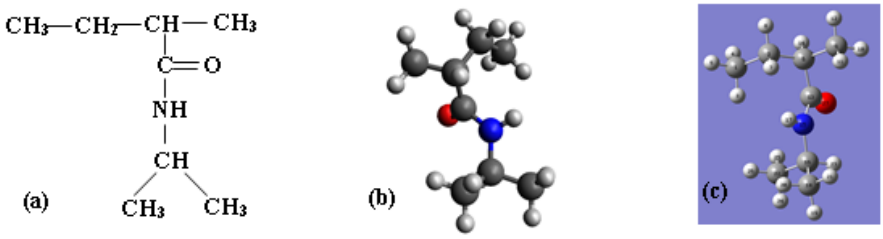


Fig. 2. NIPAM middle monomer: chemical structure (a), Avogadro structure (b) and energy minimized structure (c); for easy observation, atoms are differently colored: C atoms - dark gray, N atom - blue, O atom- red, H atom - light gray

The 30-mer polymer was obtain by "merging" the head, the 28 middle and the tail residues, in LEaP module of AMBER program [3], using *gaff* force field (Fig. 3) and visualized with VMD software [4].

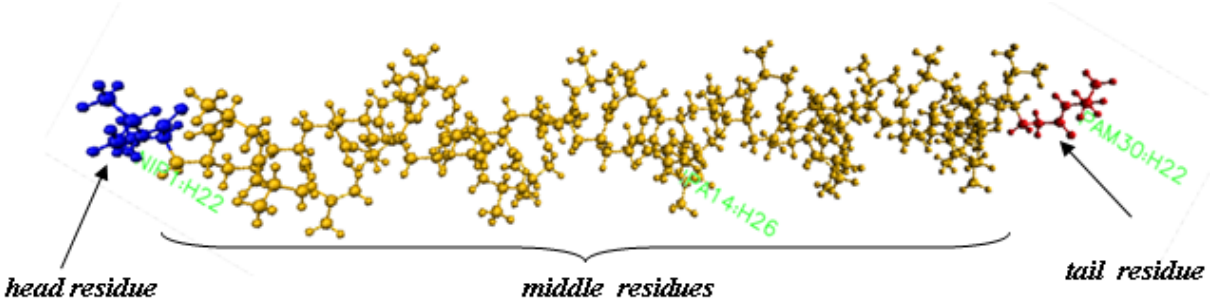


Fig. 3. The starting structure of 30-mer PNIPAM

This starting structure was solvated in a cubic box of 80Å, with three different water models, *i.e.* TIP3P, TIP4PEW and SPC/E, using Packmol software [5] (Fig. 4).

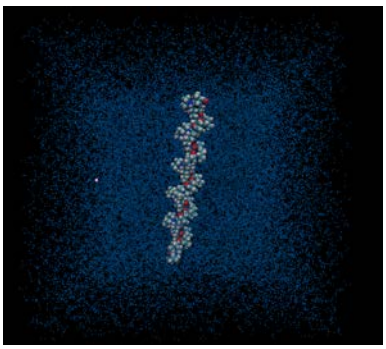


Fig. 4. Solvated 30-mer PNIPAM in TIP3P water model

2.2. Simulation details

The starting structure was energy minimized in constant volume periodic boundaries, in two stages: (i) in the first one, the polymer atoms are kept fixed through position restraints, while the

energy of the water molecules is minimized, in 1.000 steps; (ii) in the second stage, the polymer atoms are free, so that the entire system is minimized, in 2500 steps.

The system was heated up to 290K, 300K, 310K, 320K and 330K, imposing constrained hydrogen bonds by SHAKE algorithm and a collision frequency of 1ps in Langevin dynamics. The heating was performed also in two stages: first, the system was heated from 0K to the final temperature by keeping the polymer fixed, for 20ps, in constant volume periodic boundaries; secondly, the polymer atoms are free and the entire system is equilibrated, at constant temperature, in constant pressure periodic boundary for a total time 100 ps.

In all cases, a cutoff distance of 10.0Å, was considered.

In the end, the stability and equilibrium of the structures were evaluated by monitoring the time evolution of potential, kinetic, total energies and temperature (Fig. 5).

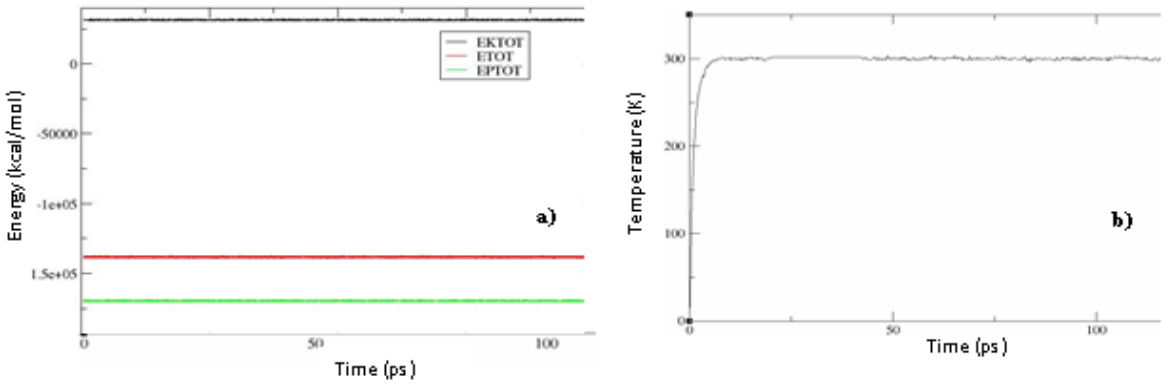


Fig. 5. The time evolution of potential, kinetic, total energies (a) and temperature (b), at 300K, for TIP3P water model

Each of the final structure resulted after equilibration (Fig. 6), having different starting extension degree (SS1 - 19.23Å, SS2 - 18.92Å, SS3 - 18.44Å, SS4 - 18.45Å, SS5 - 17.58Å), was considered as starting structure in the molecular dynamics simulations.

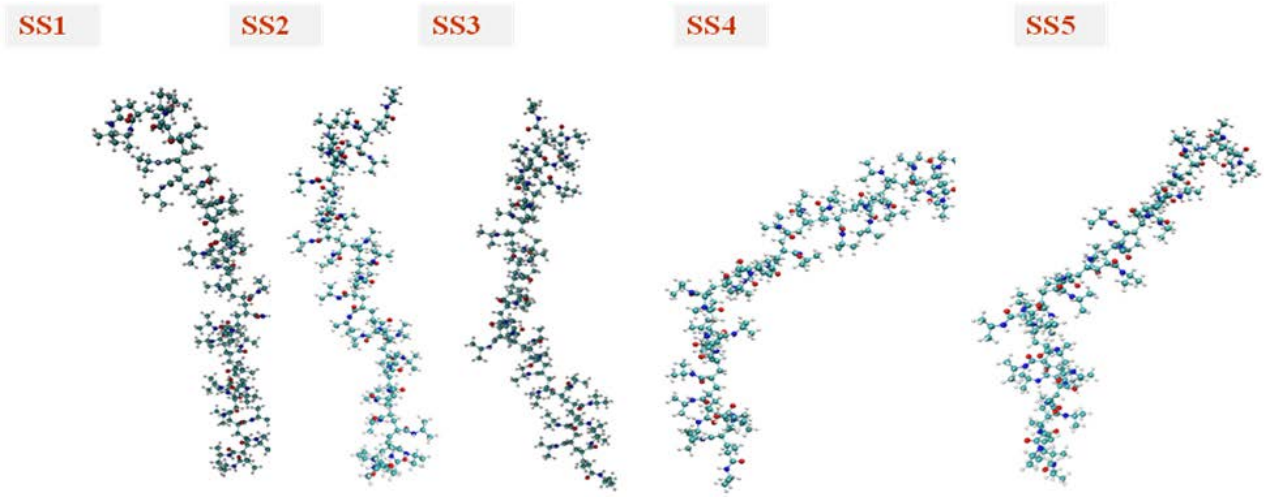


Fig. 6. The starting structures, resulted after heating at
290K (SS1), 300K (SS2), 310K (SS3), 320K (SS4), 330K (SS5)

NPT (*N=const., p=const., T=const.*) MD simulations at $p = 1\,atm$ were performed using Amber18 pmemd.cuda module with a 10Å cutoff for non-bonded interactions. The length of the bonds involving hydrogen atoms were constrained through the SHAKE protocol. The Langevin algorithm was used to control the temperature, with a collision frequency of $3ps^{-1}$. The lenght of the simulation was 200ns. All simulations were performed at 300K, very close to the experimental transition temperature.

2.3. Analysis of Molecular Dynamics Trajectories

The radius of gyration was calculated with the cpptraj algorithm of AMBER and its time evolution is represented in Fig. 7.

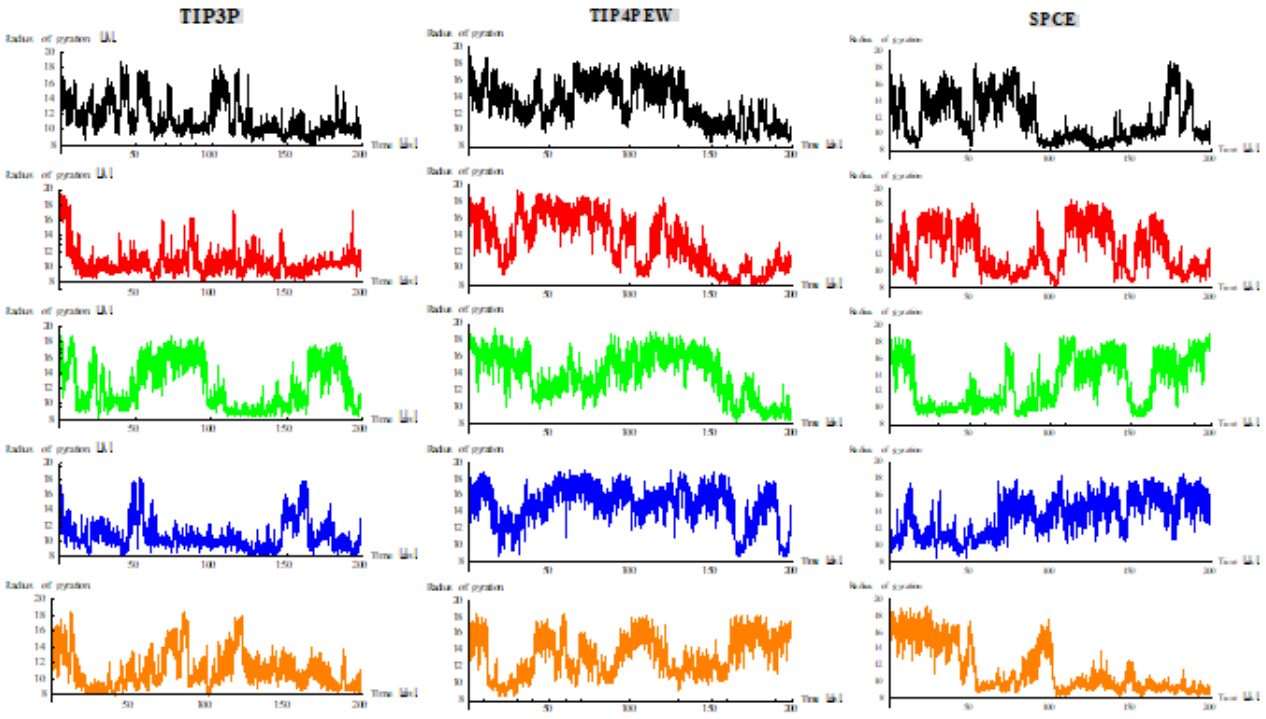


Fig. 7. Radius of gyration time evolution for the five starting structures
(SS1 - first line, SS2 - second line, SS3 - third line, SS4 - fourth line, SS5 - fifth line)

For all three water models, fluctuations between the extended and the collapsed conformations are observed for most of the starting structures, according to the results of Galbraith [6] which states that strong instabilities appear near the transition point.

The distribution of radius of gyration values (Fig. 8) offer us information on how long "stays" the polymer in the collapsed state at 300K.

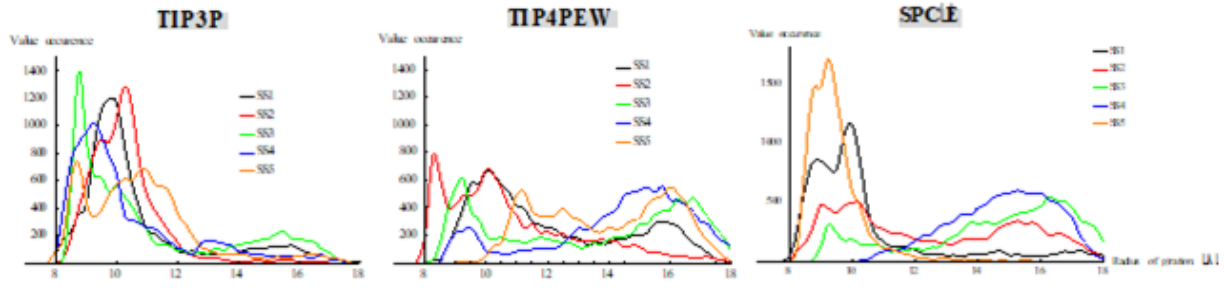


Fig. 8. Values distribution for radius of gyration

The analysis of the above plots reveals that, for the TIP3P water model, the most stable system is the one with SS3 as starting structure, while for the SPC/E water model, the one with SS5. The TIP4PEW water model does not allow the collapse for none of the studied starting structure.

Further, comparing the amplitude of values occurrence for TIP3P and SPC/E water models, we can conclude that by combining the SS5 starting structure and SPC/E water model, is created the optimal MD simulation set-up in order to observe the transition of the structure conformation from the extended one to the collapsed one.

3. Conclusions

The influence of the starting structure and of the water model on the structural conformation of poly(n-isopropylacrylamide) PNIPAM thermoresponsive polymer during molecular dynamics simulations was studied.

It was concluded that the transition from the extended to the collapsed conformation is best observed for the starting structure with the smaller end-to-end polymer length solvated in SPC/E water model.

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