A new insight into the understanding of the collapsed form of poly(N-isopropylacrylamide) molecules

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Abstract

Possible collapsed forms of poly(N-isopropylacrylamide) molecules are reviewed on the basis of first principle calculations. Various configurations and associated conformations are detailed. The calculated optimized structures exhibit different possibilities of creating networks of intra-molecular bonds of the hydrogen type. We show that the most remarkable one is able to form a local, self-saturated and well ordered helix. We also indicate in which direction the synthesis of the molecule should be oriented to improve its global behavior in term of hydrophobic/hydrophilic behavior.

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1. Introduction

The poly(N-isopropylacrylamide) (P-NIPAM) molecules are of major interest for NanoBioTechnology applications [1]. They have been widely studied due to their sensitivity to temperature and their subsequent ability to undergo a phase transition at their lower critical solution temperature (LCST) [2–5]. Furthermore, the associated P-NIPAM chain has its phase transition accompanied with a volume change: below the LCST, the molecule is hydrated and swelled while it is dehydrated and collapses beyond this critical temperature [2–7]. The transition is also found to be reversible and narrow: it is referred to as the coil to globule transition. The P-NIPAM chains are hydrophilic in the coil state while they become water repellent (hydrophobic) in the globule-like conformation [1,8–11].

These two aspects of the P-NIPAM molecules make it a good candidate for many applications, in particular in the field of micro or nano-systems for biological applications. The actuation of a fluid may be activated and/or monitored by the breathing of a “Soft” surface functionalized by P-NIPAM thin brushes [12]. On the other hand, the hydrophobic/hydrophilic transition of the modified surfaces may also be used to adsorb and release biological material such as proteins [1,13].

Surprisingly, from a modeling viewpoint, only few attempts have been dedicated to the P-NIPAM molecules and their fundamentals [6,14]. Consequently, the major intrinsic issues remain unknown: hydrophobic/hydrophilic nature, phase transition, reversibility, etc. This lack of information is often associated with the intrinsic difficulty to describe certain complex microscopic mechanisms such as hydrogen bonds, governing the macroscopic properties partly via conformational entropy considerations.

In this view, the aim of this paper is to establish some preliminary milestones by giving the most precise atomistic picture of the collapsed form of this molecule, i.e. in its dehydrated phase. The density functional theory (DFT) is used all along this work. Due to its intrinsic limitations,
the investigation will cover the possible formation of intramolecular interactions of the unfolded molecule. After a brief presentation of the computational method and a description of the P-NIPAM molecule, we will turn to the interaction between isolated molecule fragments. We will then examine the effect of the molecule backbone on these interactions, particularly its rigidity. Finally, the system size is increased as much as possible with regard of the quantum cluster approach in view to get preliminary insight into the global structuring of the polymer.

2. Theoretical basis

The structural properties as well as energetics of the P-NIPAM molecules with increasing sizes are calculated within the density functional theory (DFT) [15] using the Becke’s three parameters exchange functional and the gradient-corrected functional of Lee et al. [16,17]. The calculations are done with integral option (Grid = ultrafine). Several basis sets have been employed from 6-31G to 6-31++G** depending on the system size. Obviously, hydrogen bonds are better resolved with the addition of both polarization and diffuse functions; the 6-31++G** has been used for the two monomer P-NIPAM model. Despite this fact, from 4 to 6 monomers along the P-NIPAM backbone, the 6-31G basis set has been used due to the number of structures being investigated (all of them are not reported here). These basis sets have been demonstrated to reproduce accurately the energetic and structural properties of a number of similar systems [6,18]. Concerning the hydrogen bonding which is central to this study, it is well known that the DFT predicts it reasonably well, especially in the cases of moderate and stronger interactions [19–22]. All calculations have been performed by means of the Gaussian98 package [23].

3. Results and discussion

The P-NIPAM molecule is a sequence of the following basic element: [−CH₂−CH−CO−NH−CH−(CH₃)₂] that can be repeated \( n \) times (see Fig. 1 with \( n = 2 \)). We will refer to several subsystems of this basic element, using the subsequent denominations.

The molecule is composed of a repeated sequence of CH₂−CHFr groups. In each group, the fragment Fr is connected on the backbone carbon chain. In practice, the length of the sequence depends on the state of polymerization (typically ranging from ~80 to 4500 units). In this paper, we will limit ourselves to sequences of six groups (hexamers), due to limitations in DFT calculations. This length is shown to be sufficient to find the folded configurations and conformations of dehydrated P-NIPAM.

The fragment Fr is a limited chain which contains two ionic parts, C=O and N–H, and an umbrella termination (see Fig. 1).

The umbrella is situated on the top termination of the fragment. It is composed of the non polar –CH−(CH₃)₂ group.

We first consider isolated fragments in order to well establish different types of possible hydrogen bondings between the smallest structures. The fragment part of the molecule includes the polar region which is the expected core of further interactions, particularly of the hydrogen type, with the medium: other fragments, water molecules, biological molecules, surfaces, etc. Two conformations can be derived for an isolated fragment: (i) the oxygen atom of the C=O part and the hydrogen atom of the N–H part are situated on both sides of the fragment axis (see Fig. 1), and (ii) these atoms are in the same side of the fragment axis. We have calculated that the conformation (i) is 0.11 eV more stable than (ii). At the same time, the activation barrier for the transition between these two conformations, a 180° rotation of the O=C–N–H dihedral angle, has been calculated to be 0.84 eV. Therefore, at room temperature, the most stable conformation represents about 99% of all conformations and the equilibrium is reached within a second (when considering an attempt frequency of the order of \( 10^{14} \) s⁻¹). These values do not take into account the possible backbone effects and the fact that the rotation will be influenced by the possibility of having hydrogen bonds between adjacent fragments. These effects, the later in particular, would reinforce the stable conformation because of repulsive electrostatic interactions. Therefore, in the following, only the most stable fragment conformation will be considered. We have already mentioned the fact that from a rough chemical
examination of the molecule, it is clear that the polar region of the fragment is susceptible to generate bonds of the hydrogen type either by creating an intra-molecular N–H···O=C bond, or by establishing bonds with the surrounding water molecules of the type N–H···OH$_2$ or C=O···HOH. In view to determine these aspects precisely and quantitatively, we consider now two backbone-unconnected fragments. In this way, all other contributions such as the constraint induced by the backbone rigidity, are avoided when expressing the interaction energy. The structure of the optimized complex is shown in Fig. 2. First, this calculation indicates a gain in energy of 0.26 eV which can be attributed quasi-exclusively to the hydrogen bond. This energy, as well as the O···H bond length (2.02 Å) and the 180° value of the N–H···O angle, is a clear indication of a moderate hydrogen type of bonding, in good agreement with literature data [18–21]. We also learn, from the optimized structure, that these two fragments prefer to have their axes perpendicular to each other probably due to a steric repulsion imposed by the umbrellas. The respective C–N bonds of the two isolated fragments are actually at 79° of each other.

We now consider a complete P-NIPAM including its fragments and backbone. The bonds emanating from the interacting fragments, forcing the backbone to bend, are expected to be weakened. The resulting structure and its configurational and conformational properties will also become more complex. As indicated in a previous work by Katsumoto et al. [6], we can distinguish two main configuration groups: an isotactic P-NIPAM group where the fragments are in the same side of the backbone axis and a syndiotactic P-NIPAM group where the fragments are alternatively on the opposite sides of this axis (Fig. 3). Then, in each group, several conformations may arise due to the fact that the backbone flexibility authorizes several arrangements. A total number of seven configurations have been reported by Katsumoto et al. [6]. They have calculated the optimized structures and the corresponding energies for all configurations and have made a comparison between them. In our calculations, we find all these configurations but also new ones, not reported by Katsumoto et al. because of the large number of secondary minima present in this polymer and the small number of fragments (diads) considered by these authors. In the following, we will discuss some of the new configurations of both isotactic and syndiotactic groups for the molecules containing from two to six fragments along the backbone axis. Table 1 summarizes the main results.

When considering diads only, according to [6], one of the racemo diad structure exhibits the most stable conformation of all cases. Actually, the optimized structure shows that the hydrogen bond may form without deformation of the backbone axis (Fig. 3 on the left). We have also observed that, in this particular case, the angle between the fragment axes (68.5°) tends to reach the nominal value of 79° thus reducing the constraint imposed on the hydrogen bond (2.09 Å) as well as the inter-umbrella interaction.

The energy of this conformation is considered as the reference for all calculated diad molecules. The next conformations reported in [6] are at 0.13 and 0.14 eV above the reference and correspond, respectively to a racemo and to a meso diad conformation. Our calculations however, show that a meso diad conformation does exist at only 0.06 eV above the reference. This conformation which can be considered as being the second more stable configuration, contains a hydrogen bond between the two fragments. The absence of hydrogen bonds in all meso conformations reported in [6] explains why this particular conformation may have been missed. The presence of our new conformation close to the reference indicates that, although the racemo conformation seems to be slightly more stable than the meso one, the situation is not clearly established when considering only two fragments in the polymer.

Going up to four fragments, the situation changes radically and contradicts the general conclusion given in Katsumoto et al. [6] on the stability of racemo conformations. Here, we try, in the building procedure of our four fragment molecule, to maximize the number of hydrogen bonds and to create a bond network in order to stabilize the system, in both isotactic and syndiotactic cases. In the isotactic case, the hydrogen bonding is straightforward between successive fragments, leading to a network of hydrogen bonds (data not shown). The resulting conformation is the most stable structure within all calculated four fragment molecules and will be considered as the reference. In this conformation, we observe a slight bending of the
This bending is needed to adapt the fragment axes between each other. An identical procedure is much more complicated to achieve in the syndiotactic case because the active parts of the fragments are far apart. We have tried two options. In the first one, we start with a highly distorted backbone in order to bring the active ionic groups of the fragments close to each other. This first option leads us to a conformation where a complete network of three hydrogen bonds does exist. But this conformation is at 0.66 eV above the previous isotactic conformation taken as the reference. The second option consists in omitting to establish such a hydrogen bond network thus leaving unsaturated active parts in some fragments. In this second option, the molecule exhibits two hydrogen bonds instead of three. The energy is only 0.03 eV above the reference, lying therefore well below the saturated structure obtained with the first option. The strain energy to bend the backbone is much more important than the gain due to a supplementary hydrogen bond.

Few intermediate conclusions can be drawn. First, there is a crossing over of stability between the isotactic and syndiotactic conformations when we increase the number of considered fragments. Second, contrary to the syndiotactic conformations, the deformation imposed on the backbone in the isotactic conformations is compatible with the gain in energy resulting from the formation of hydrogen bonds. Third, the best syndiotactic conformation has a propensity to be unsaturated. Transposed on the real material, containing a large number of fragments, the associated hydrogen bond network should be broken every two fragments, leaving locally unsaturated polar regions. Therefore, it is expected that the global behavior of the system will be dramatically affected. The presence of these unsaturated active regions will cause severe modifications of the hydrophobic/hydrophilic nature of the film. For instance, any water molecule will stick around these unsaturated sites lowering the hydrophobicity beyond the LCST temperature. This effect could possibly be moderated by the fact that it is still possible to form inter-P-NIPAM bonds to go towards the self-saturation of these sites. At this stage, it becomes clear that a key point in designing P-NIPAM molecules with specific properties is the synthesis part of the process as it is impossible, once the molecule polymerized, to induce transitions from syndiotactic to isotactic conformations.

To reach the limits of the DFT calculation possibilities in terms of the number of atoms considered, we have tried to increase the number of fragments up to six in view to examine the ability of the molecule to remain self-stabilized by the hydrogen bond network despite the constraint imposed on the backbone. Again, it is still possible to form the hydrogen network for both iso and syndiotactic cases. The stability of the isotactic conformation is confirmed, and even increased, with 0.92 eV difference with regard of the syndiotactic conformations having also reached its self-saturation. This isotactic structure is shown in Fig. 4, where we can observe five hydrogen bonds along the backbone between successive fragments. The optimized molecule shows its backbone well structured into a pentagonal helix with a 9.55 Å pitch. The fragments are positioned around the helix and connected to each other by hydrogen bonds. Looking the molecule through the helix axis of the distorted backbone, the sixth fragment is just superimposed on the first one.

Table 1
Summary of the characteristics of the main calculated conformations of P-NIPAM

<table>
<thead>
<tr>
<th>Conformation type</th>
<th>Number of fragments</th>
<th>Energy (eV)</th>
<th>Other characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racemo*</td>
<td>0.00</td>
<td>H bond, linear backbone</td>
<td></td>
</tr>
<tr>
<td>Racemo</td>
<td>0.22</td>
<td>No H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Racemo 2</td>
<td>0.26</td>
<td>H bond, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Meso</td>
<td>0.06</td>
<td>H bond, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Meso</td>
<td>0.14</td>
<td>No H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Isotactic</td>
<td>0.00</td>
<td>3 H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Isotactic 4</td>
<td>0.39</td>
<td>2 H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Syndiotactic</td>
<td>0.03</td>
<td>2 H bonds, linear backbone</td>
<td></td>
</tr>
<tr>
<td>Syndiotactic 6</td>
<td>0.66</td>
<td>3 H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Isotactic 6</td>
<td>0.00</td>
<td>5 H bonds, distorted backbone</td>
<td></td>
</tr>
<tr>
<td>Syndiotactic 6</td>
<td>0.92</td>
<td>5 H bonds, distorted backbone</td>
<td></td>
</tr>
</tbody>
</table>

The most stable structure of each molecule size is taken as reference.
* This calculated structure corresponds to the one also calculated by Katsumoto et al. and corresponds to Ref. [6].

Fig. 4. View in the direction of the backbone axis of the self-saturated isotactic conformation having six fragments and a self-saturation via hydrogen bonds. The dashed lines represent the hydrogen bond network.
4. Conclusions

The properties of the collapsed form of P-NIPAM molecules, as a result of their ability to form networks of intramolecular hydrogen bonds between adjacent fragments, are reviewed using quantum chemistry calculations. The calculations reveal that the global properties of the film will dramatically be affected by the P-NIPAM synthesis process, i.e. the fragment positioning with respect to the molecular backbone axis (tacticity). The isotactic conformation is more stable than the syndiotactic conformations beyond molecules composed of two fragment units. The syndiotactic conformations will have their stability greatly increased with the breaking of some hydrogen bonds, leaving active parts in the fragments unsaturated. Following this idea, the ratio of syndiotactic conformations along the polymer chain should lower the hydrophobicity while the isotactic conformations should increase it. With six fragment units along the backbone, the isotactic conformation, while being far more stable than the self-saturated syndiotactic conformation, is able to form a well structured helix. Furthermore, this last conformation is self-saturated, having all its polar groups neutralized via hydrogen bonds. This result opens exciting emerging questions: the flexibility of this spring-like structure, in terms of stretching and bending, interaction between helixes, stability of the helix, impact of this type of structure on the entropy of the global system. This last question may shed light on the reversibility of the phase transition induced by temperature variations. To answer such open questions also imply to consider large size molecules and use more adequate potentials, such as classical potentials, for treating the problem. In this view, the present work is of great interest to motivate the choice of force field interaction potentials. We believe that the presented calculations open new research axis to address the fundamental questions raised by these molecules. The effect of water molecules in these structures is the subject of current research to get insight into the swelled form of P-NIPAM below the LCST temperature.

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References