CONFORMATIONAL ANALYSIS OF ALTERNATING COPOLYMERS AND THEIR ASSOCIATION INTO NANOARCHITECTURES

A.S.W. Chan, M. Groves and C. Malardier-Jugroot[*]

[*] Department of Chemistry & Chemical Engineering,
Royal Military College of Canada, Kingston, ON, Canada,
anita.chan@rmc.ca, cecile.malardier-jugroot@rmc.ca

ABSTRACT

Our research focuses on the characterization of the association and the properties in aqueous solution of nano-structures, particularly on nanotubes composed of amphiphilic alternating copolymers. These copolymers constitute a pH sensitive hydrophilic group (maleic anhydride) alternating with a hydrophobic group. To investigate the role of the nature of the hydrophobic groups on the association, the self-assembly of two different polymers are compared: poly(isobutylene-alt-maleic anhydride) (IMA) and poly(styrene-alt-maleic anhydride) (SMA). It has been well reported that, at pH7, SMA forms stable nanotubes by association through a linear conformation due to H-bonding and pi-cation interactions. A theoretical approach was chosen to investigate and characterize the behavior of IMA chains at different pH values. To optimize IMA at different pH values, a complete conformational method was applied using both semi-empirical and *ab initio* molecular modeling methods. The present paper will describe in detail the conformational analysis of IMA, the association among IMA chains to form nanotubes and discuss the influence of the nature of the hydrophobic group on the association. The theoretical prediction will also be compared to experiment (dynamic light scattering)

Keywords: amphiphilic, copolymer, computational, characterization, IMA.

1 INTRODUCTION

Copolymers are macromolecules that result from the chemical integration of two or more monomer units into random, alternating, block or graft architecture chains. The self-assembly of block copolymers has been extensively studied showing very ordered and defect-free structures at the nanometer scale [1]. On the other hand, the association between alternating copolymer chains is still not well understood. This particular association is expected to show significant advantages over self-assembled structures due to uniform interactions along the polymer chains [2]. Alternating copolymers are repetitive copolymers, and the global behavior of the association can be modeled using few repetitive conformational units [3]. Therefore, computational chemistry serves as an excellent tool to study alternating copolymers and characterize precisely the different interactions among the chains.

Nanoscale structures formed by alternating copolymers have proven very efficient for the solubilization of small hydrophobic molecules in water for applications in storage, delivery and nanoelectronics [4]. The solubilization process is dependent on the interactions among the polymer chains it is therefore crucial to understand the self-assembly process.

To develop new nanomaterials tailored to specific applications, it was proposed to base our approach on a model carefully investigated and illustrated by poly(styrene-*alt*-maleic acid) (SMA) in water [5]. It has been well observed that SMA forms stable nanotubes by the association of 8 poly(styrene-*alt*-maleic anhydride) (SMA) chains into a nanotube [6] in aqueous solution at pH7. The association results from a linear conformation due to H-bonding, π-π and π-cation interactions [7]. The characterization of SMA has been obtained using molecular modeling simulations and Small Angle Neutron Scattering (SANS). The combined characterizations of the nanotube revealed that the interior of the tube is hydrophobic while the exterior is hydrophilic (Figure 1). With this property in mind, a method for solubilizing small hydrophobic molecules [5] was developed.
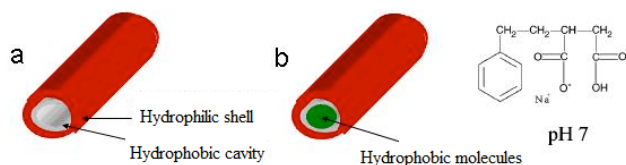

Figure 1: Pictorial representation of a) SMA nanotube in water, and b) hydrophobic molecules within the SMA nanotube.

However, the solubilization of small organic molecules containing a benzene group disrupts the π-π interactions within the tubes and therefore breaks the tubular structure. In order to generalize a method to small organic molecules containing a benzene group, we choose a new alternating copolymer poly(isobutylene-alt-maleic anhydride) (IMA) in water (Figure 2). IMA is also a water-soluble polymer and has the same properties as SMA: indeed, its structure is pH-dependent due to the maleic anhydride ring [8]. The main difference between the two compounds lies in the hydrophobic group of the copolymer; SMA contains a

benzene ring. The π-cation interactions are well-known stabilization interactions for protein-ligand complexes [9-10]. With the absence of the π-orbitals on the isobutylene group, the association mechanism would be significantly altered due to the loss of this interaction.
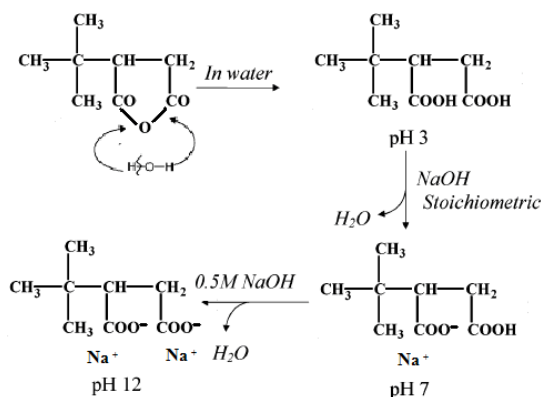

Figure 2: Structure of isobutlylene-maleic anhydride at different pH values.

A theoretical approach was chosen to investigate and characterize the behavior of IMA chains at different pH values (3, 7 and 12). To optimize IMA at different pH values, a complete conformational method was applied using both semi-empirical (PM3) and *ab initio* (Restricted Hartree-Fock (RHF) and Density Functional Theory (DFT)) molecular modeling methods.

2 METHODS

2.1 Conformational Analysis Using Theoretical Methods

The computations were performed using Gaussian 03 [11]. A geometric optimization was performed on the monomers at the RHF/6-31G(d,p) level of theory followed by precise scans of dihedral angles around the molecule. The scans are performed one by one at 5° increments of the dihedral angle, and the most stable structure obtained within one scan is used as a starting structure for the next scan [12-15]. For cost efficiency, the scans were performed at the PM3 level of theory of pH 3 [16-17] and the RHF/3-21G level for pH7 and pH12. Since the parameters for the sodium atom are not implemented at PM3 level in Gaussian, a higher level of theory was required for computation. The minima were then re-optimized and a frequency scan was performed at the DFT/6-31++G(d,p) levels of theory.

2.2 Synthesis of Copolymer Nanotubes

The polymers were purchased from Aldrich Co. and have molecular weights of 6,000 and 350,000 for IMA (~85% purity) and SMA (~85-90% purity) respectively.

Low concentrated (0.05% wt in deionized water) amphiphilic copolymer nanotube solutions of IMA and SMA were prepared and then sonicated for a few hours (2-3 hours for SMA and 6 hours to 1 day for IMA). The pH of the solution was adjusted to 7 by stoichiometric addition of sodium hydroxide.

2.3 Dynamic Light Scattering Characterization

The radius of gyration of the copolymer nanotubes templates was measured in water using DLS (Brookhaven model 9025) equipped with 632.8nm He-Ne laser. The measurements were taken at a 90° angle. The samples were filtered using filters with a pore size of 0.4-0.5µm.

3 RESULTS AND DISCUSSION

3.1 Conformational Analysis Using Theoretical Methods

Since a geometric optimization does not always produce the most stable structure for a molecule with conformational flexibility, a precise series of scans in energy was applied to find the most favorable conformation for each dihedral angle. The main advantage of this technique is that the energy of different conformations of a molecule can be obtained for each chirality. In addition, the intra and intermolecular interactions can be precisely characterized.

To optimize IMA at different pH values, a complete conformational method was applied. This involved a geometric optimization of structure followed by precise scans of dihedral angles around the molecule. The most stable structure obtained within one scan was used as a starting structure for the next scan. Finally, another geometric optimization and a frequency calculation were performed. The optimization method was applied to the monomer, the dimer and the trimer for all three pH values. This optimization method analyzes the conformation of the first and second monomeric segments that are repeated throughout the entire polymer chain. All the possible chiralities of the polymer chain were considered.

In an aqueous solution of poly(isobutylene-*alt*-maleic anhydride) at pH 3, the maleic anhydride ring is hydrolyzed to give two acid groups similar to poly(styrene-maleic anhydride). With the increase of pH, free hydrogen atoms are less likely to bond to the acid groups whereas the sodium counterions stabilize the site. The fully optimized structures are illustrated on Figure 4.

At pH 7, two conformations of the monomer can be obtained corresponding to the hydrolysis site of the two acid groups (Figures 4c, 4d). The two structures have very similar energies; therefore both structures were kept for the study of the dimer at neutral pH.

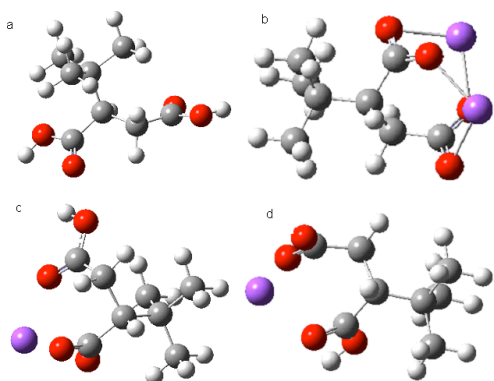From these figures, it is possible to observe an electrostatic interaction between the acid groups and the

Figure 4: Conformations of the monomer IMA after optimization, energy scans and re-optimization at pH 3 (a), pH 12 (b), and pH 7: hydrolysis on the first acid group (c) and on the second acid group (d).

sodium atom. This was not observed on the conformation of the monomer at pH 12. The presence of the single sodium ion seems to induce a stable hydrogen-like bond, which will alter the backbone of the polymer chain as observed upon further investigation. This is similar to the behavior of SMA [3].

The dimers were obtained by attaching the monomer at a specific binding site. The dimer structure of IMA has one chiral center that affects the conformation of the polymer chain; this is the chiral carbon attached to the terminal carboxylic group. The structures were optimized at the RHF/6-31G level for all pHs. The obtained structures at pH 3 and pH 12 are on Figure 5.
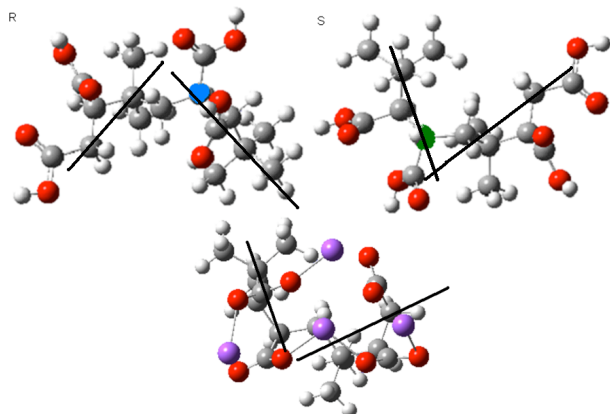

Figure 5: (top) Two different conformations of the dimer of IMA at pH 3 corresponding to the two chiralities. Painted atoms represent the chiral center; (bottom) IMA dimers in the R conformation at pH 12. Black lines represent the bent backbone of each monomeric segment.

Since most of the conformers have yet to be optimized successfully, it is difficult to form a general conclusion from the structure at the different pH values. However, from the optimized structures (R and S for pH 3 and R for

pH 7 and 12), there is a linear backbone formation at pH 7 that is absent at pH 3 and 12. The conformations of the dimer at pH 7 are linear although slightly twisted, and at pH 3 and 12, the dimer is clearly bent.

For the pH 7 conformations (Figure 6), it appears that a hydrogen bond forms within the acidic group of each monomer whereas the sodium ion interacts with the anions to stabilize the whole structure. This stabilization would, in theory, produce a strong backbone for the polymer. This linear behavior and strong backbone is similar to that of SMA. This linearity is crucial to the self-assembly of amphiphilic copolymer nanotubes since the linear conformation favours the association of the chains by decreasing the entropic cost [3]. However, for SMA, the backbone is mainly due to H-bonding and the sodium ion stabilizing the hydrophobic group: the benzene ring. Since the cation-π interaction is missing for IMA, the sodium stabilizes the anion of the acid group and forms ion-ion interaction. This will be confirmed by the complete conformational and orbital analysis.
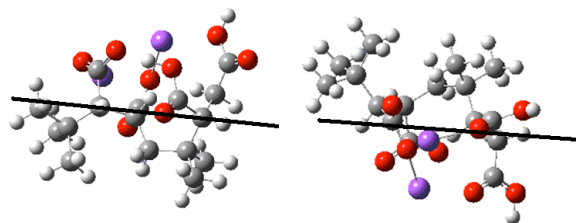

Figure 6: IMA dimers in the R conformation at pH 7: hydrolysis on the first acid group (left) and on the second acid group (right). The black line shows the linear backbone of the entire dimmer.

Each trimer possesses two chiral centers connecting each monomer of the molecule. The different chiralities of the trimer give 4 possible structures. A full optimization of the trimer structure was performed at pH 3. Figure 7 illustrates the amount of bending in the trimer. This confirms the non-linearity of one conformation at pH 3. This bending behavior was expected since there are no observable stable inter-monomer H-bond interactions at low pH. SMA showed similar behavior.

3.2 Dynamic Light Scattering Characterization

The hydrodynamic radius was also quantified on all nanotube samples using DLS. The results are displayed on Figure 8. The limitation of the instrument was between ~20 nm to a few hundreds of nm. The values for pH 3 and pH 7 are not zero, but they are simply below the limitation of the instrument. The results confirm the similarity in the association mechanism for both IMA and SMA polymer chains. An association occurs at neutral pH and allows the polymer chain to form stable structures. At low or high pH
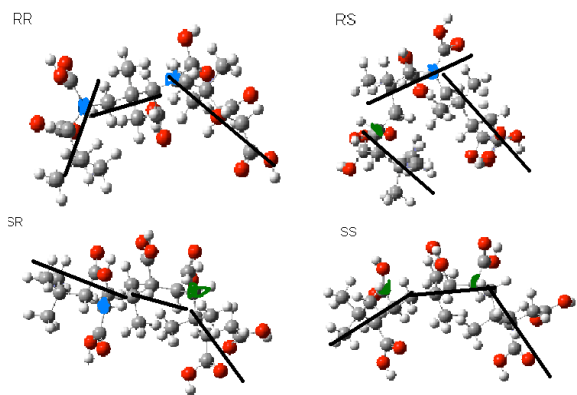
Figure 7: Four different conformations of the trimer of IMA at pH 3 corresponding to all four possible conformations of the four chiralities. The painted atoms represent the chiral centers of the trimer. The black lines representing the backbone of the trimer show the degree of bending for each conformer.

values, the polymer chain is unable to form a structure large enough to be detected by DLS. It can be concluded that the linear association that would from nanotubes can only occur at neutral pH.
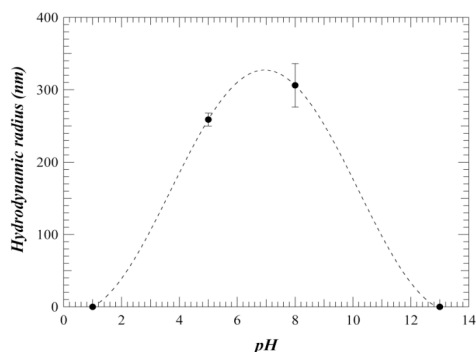

Figure 8: The points represent R_h values of 0.05 wt%. IMA at varying pH obtained from DLS. Values at pH1 and pH13 are below the resolution of the instrument. N.B., the dotted line is an eye guide and not an actual fit.

4 CONCLUSION

The conformation of oligomers of IMA at different pH values was investigated using computational chemistry to compare them with a similar compound, SMA, which showed polymer chains associating only at intermediate pH. The conformational analysis of the monomers showed that they behave consistently with SMA monomers.

Poly(styrene-*alt*-maleic anhydride) is a known polymer used in the synthesis of nanotubes [11]. Since the R conformations at pH 7 did show indications of a stronger backbone (through H-bonds and electrostatic interactions through sodium), it might be possible to produce a more rigid alternating copolymer nanotubes using poly(isobutylene-*alt*-maleic anhydride).

Applications of these tubes range from the solubilization of small hydrophobic organic compound in aqueaous solution to templating nanowires. Understanding these mechanisms would have great implications in the field of nanotechnology.

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