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New Poly(phenyleneethynylene)s with Cationic, Facially Amphiphilic Structures

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Received April 19, 2002

Hydrophilic and hydrophobic patterning has been suggested as an important property in guiding secondary and tertiary folds of proteins.[1] Amphiphilic protein secondary structures are common and include β-sheets which fold with alternating polar (P) and nonpolar (NP) amino acids and α-helices that have a seven amino-acid repeat with a sequence of NP-P-P-NP-NP-P-NP.[2] This results in amphiphilic 2-D planes and cylinders, respectively. In addition, the overwhelming majority of P side chains found in these systems are charged residues so that the structures are polyelectrolytes. As a result, these objects are markedly different from most traditional amphiphilic polymers based on block or random copolymers. We have recently reported on a class of facially amphiphilic polymers based on arylamides which mimic the physical and biological properties of natural surface active antimicrobial host defense peptides.[3] These polymers were designed to be amphiphilic along the backbone as opposed to block or random copolymers. Using poly(phenyleneethynylene) (PPE) as a molecular scaffold, we now have designed cationic, amphiphilic polymers containing primary amines and NP alkyl groups. These polymers are *m*-PPEs patterned with P cationic and NP groups to favor an extended all trans conformation. As a result, they should have some rigid rod-type character.

The study of nonionic amphiphilic PPEs has attracted much attention recently. Swager and co-workers examined a series of para substituted PPEs at the air−water interface in which the orientation of the aromatic ring to the water surface depended on both the substitution pattern of the P and NP groups and the pressure of the compressed film.[4] As a result, the effect on absorption and emission spectra due to interchain association was investigated in detail. Moore and co-workers patterned meta substituted derivatives to favor a helical conformation in a nonsolvent and showed a transition between random coil and helical conformations as the nonsolvent composition was increased.[5] A few other polymers have been reported with architectures that make them facially amphiphilic including polythiophenes and polyphenylenes.[6,7]

The synthesis of a cationic, amphiphilic monomer for PPE materials began with Mitsunobu conditions for alkylation of starting material, 3,5-diiodo-4-hydroxy-benzonitrile, followed by nitrile reduction with borane−THF to yield the benzylamine which was protected as the *tert*-butyl carbamate (Boc). This produced diiodo monomers as stable, crystalline solids. Subsequent polymerization of these monomers is outlined in Figure 1 and gave the desired Boc protected polymer after precipitation.[8] Molecular weight determination was performed on protected polymers which are freely soluble in common organic solvents and is reported in Table 1. Deprotection of the Boc group was accomplished with 4 M HCl/dioxane. ^{1}H and ^{13}C NMR confirm quantitative removal of the Boc groups with no subsequent side reaction.

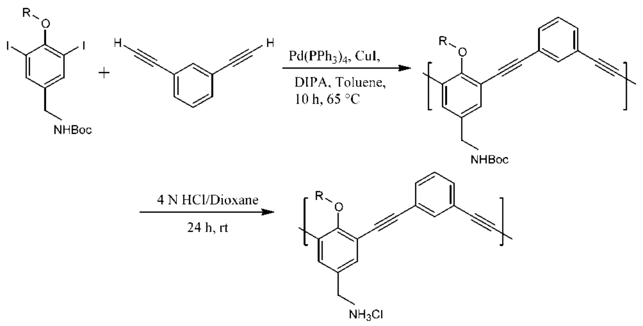

Figure 1. Synthesis of cationic, amphiphilic PPE polymers via Sonogashira conditions.

Table 1. Polymer Number, Alkyl Side Chain, Molecular Weight, and Polydispersity Are Reported for a Series of PPE Materials

polymer number	alkyl group	M_n (Da)	PDI
1	C_5H_{11}	1.78×10^4	2.2
2	(S)−2-methylbutyl	1.15×10^4	1.3
3	$C_{12}H_{25}$	1.01×10^4	1.4

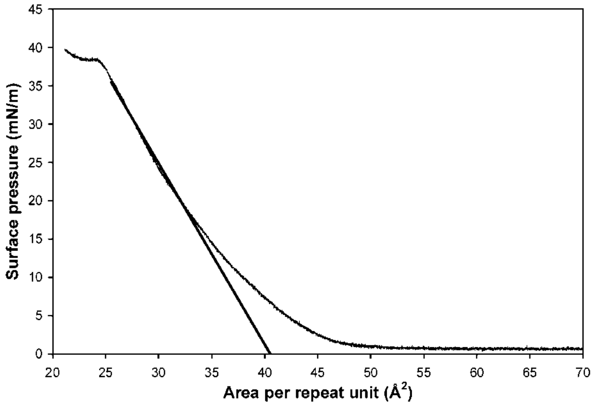

Figure 2. Pressure−area isotherm for **1** indicates monolayer formation. Extrapolation to zero pressure gives a repeat unit of 41 Å^2.

The ability of these materials to adopt amphiphilic conformations was investigated at the air−water interface using Langmuir techniques. Dilute solutions of **1** were spread onto the water surface and compressed to give an isotherm as shown in Figure 2. The polymer sample produces stable monolayer films with an area per repeat unit of ∼41 Å^2 which is in good agreement with molecular models that predict 44 Å^2 per repeat unit. This area was calculated using an extended molecular length of 11.0 Å and a $\pi-\pi$ stacking distance of 4.0 Å. In addition, molecular dynamics calculations of

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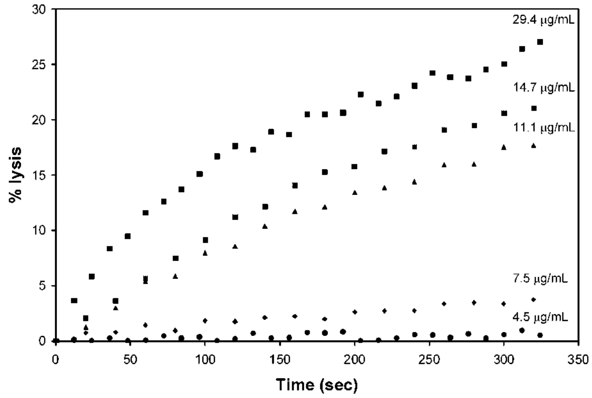

Figure 3. Graph showing the percentage of lysed vesicles over time as the concentration of **1** is increased. 100% lysis was determined by the addition of 50 μL of 0.2% Triton X-100.

two extended oligomers were performed in Materials Studio and gave an area of 44.7 Å^2. The modeled orientation assumes the polymer molecules are standing up with their aromatic rings perpendicular to the water surface. In this configuration, the polar cationic amine salts are immersed in the water layer and the hydrophobic alkyl chains completely removed from the aqueous surface.

Langmuir experiments indicate that this polymer is highly amphiphilic and prefers to form monolayers at the air−water interface. The surface activity of this cationic polymer was explored further by monitoring the disruption of phospholipid vesicles.[3] Large unilamellar vesicles (LUV) with 10 mol % excess negative charge were prepared by reverse phase evaporation of a SOPS: SOPC (1:9) solution.[9] Leakage of calcein was monitored at 515 nm as a function of polymer concentration and is shown in Figure 3. The rate and percentage of lysed LUVs as measured by calcein leakage increases as the concentration of **1** is increased. Initially the rate of leakage is fast but slows down as less free polymer is left in solution. The ability of these polymers to induce calcein leakage from anionic LUV confirms their surface active nature. Higher polymer concentration experiments suffered from polymer aggregation.

On the basis of the design of **1**, we also expected that the polymer could self-assemble in aqueous solution.[7] In fact, it appears from the LUV leakage experiments that this is true. To investigate if **1** is aggregated in aqueous solution, we monitored the emission spectra as a function of water composition starting with neat DMSO. The emission spectra shown in Figure 4 were obtained as a function of water composition. The concentration of the sample was kept constant to directly observe the effect on quantum yield. It can be seen from Figure 4 that the intensity of emission decreases with increasing water concentration and the band is broadened and slightly red-shifted. The insert in Figure 4 shows the emission spectra taken at concentrations from the leakage experiments and are very similar to the 90% water spectrum. These observations are in agreement with intermolecular aggregation of polymer chains in an extended conformation as the water content is increased.[4,10] The slight red-shift indicates tight packing of the chromophores does not occur in the aggregate. Spectra taken in $CHCl_3$ or THF as solvent give emission maxima close to that observed for DMSO (±2 nm), indicating that the observed change with water addition is not related simply to solvent polarity. The formation of an extended, or all trans, backbone is favored over other conformations because of the substitution pattern of P and NP groups. A helical conformation in which the NP groups fold in the interior while P side chains are exposed to the solvated exterior cannot be ruled out at this time; however, the observed emission spectra are different from those reported for helical PPEs.[11]

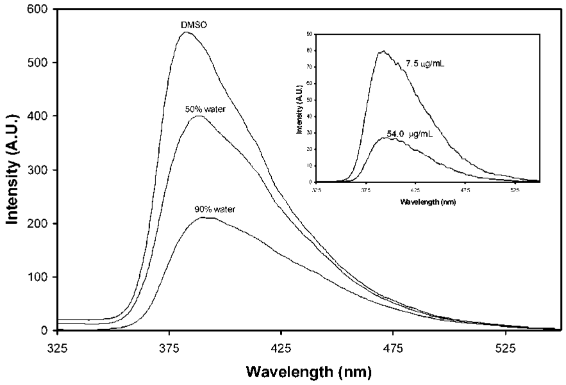

Figure 4. Emission spectra of **1** as water is added to the solution. The concentration of each spectrum is identical. The inset shows emission of **1** near the upper and lower limit concentrations of leakage experiments.

We report the synthesis of new PPE derivatives containing polar cationic and nonpolar alkyl groups. These groups are patterned to favor an extended conformation and produce facially amphiphilic polymers. Langmuir and emission experiments are in agreement with an extended amphiphilic structure. Vesicle leakage experiments indicate that these polymers are membrane active. From these preliminary observations and others in the literature,[5,7] it can be expected that polymers with facially ionic amphiphilicity will organize into interesting supramolecular structures.

Acknowledgment. Financial support for this work is gratefully acknowledged from the National Science Foundation through MRSEC at UMass. We thank Professor Hsu for use of the Langmuir trough and Daniel J. Duffy.

Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA026607S