Water-Soluble *meta*-Poly(phenylene ethynylene) Oligomers with Stable Helical Secondary Structure

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ABSTRACT: Two novel water-soluble *meta*-poly(phenylene ethynylene) (mPPE) copolymers were synthesized and characterized, each contained ester and amine functional groups attached to *exohelix* positions on the phenylene rings and one contained methoxy *endohelix* functional groups. Secondary structure formation was investigated for these materials in aqueous solutions using ultraviolet and fluorescence spectroscopy. Additionally, the folding behaviors are reported for the mPPEs and their protected amine precursors in other protic and aprotic solvents. Results indicate that both mPPEs are able to form stable helical structures in water, while only the non-methoxylated polymer exhibited a helical structure in acetonitrile and several alcohols. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 50: 2019–2028, 2012

KEYWORDS: amine; ester; foldamer; helical polymer; *meta*-poly (phenylene ethynylene); poly(phenyl acetylene); Sonogashira coupling; water soluble

INTRODUCTION *meta*-Poly(phenylene ethynylene)s (mPPEs) are a class of macromolecules that are able to fold into stable helical conformations under suitable conditions.[1–14] This biomimetic property makes them ideal for a variety of applications, including self-assembled nanostructures for sensor, drug delivery, and other biological applications.

The ability of an mPPE to form stable helical structures is influenced by a number of tunable factors. Among them, the effects of altering functional groups on the mPPE's aromatic rings, resulting in a so-called functionalized mPPE, are often the first factors to be considered in mPPE structural design. Those functional groups can stabilize the helical conformation through interactions with the solvent,[2] by strengthening π-stacking effects,[15,16] or by introducing specific intramolecular hydrogen bonds.[17,18] Other important factors affecting helix formation in solution include the chain length of the mPPE[2,19,20] and the type of solvent(s) used.[21] Several studies have been conducted to elucidate the relationship between the factors mentioned and the folding behaviors of functionalized mPPEs.[2,15,19–21]

A considerable limitation of many functionalized and unfunctionalized mPPEs is that they are insoluble in water, which precludes their use in biological applications. Further, for the few mPPEs that are reported to be soluble in water or water-rich solutions, not all of them are observed to fold into a helical conformation once solvated. For example, Arnt and Tew[22,23] synthesized an mPPE that is soluble in a mixture of dimethyl sulfoxide (DMSO) and water, but there was no evidence that the polymer formed a stable helical conformation in that solution. Li et al.[24] reported an mPPE with acid functional groups that exhibits a gel-like property in water solutions. To date, examples of mPPEs that are both water soluble and folding biased are quite rare. Stone et al.[25] reported the synthesis of a helical mPPE having long ether pendants, which stabilize the helical conformation and make the polymer soluble in water, and, finally, Tan et al.[26] reported the formation of an ionic mPPE-containing sulfate groups, which folded into a helical structure in water.

In an effort to expand the number of known water-soluble mPPEs, we report the synthesis of two new mPPE structures that are both highly soluble in water and able to form stable helical structures in aqueous solutions. The polymer repeat units and a conceptual representation of the mPPE helical structure are shown in Figure 1. It is also significant that these polymers contain readily accessible amine functional groups, which may prove useful for biological applications that require specific and directed interactions with enzymes or proteins. Additionally, we report the folding behaviors of these two mPPEs and their precursors in several other protic and aprotic solvent systems.

For the mPPE oligomers synthesized in this study (see Fig. 1). R and R' denote the customizable functional groups on the polymer backbone. For an mPPE exhibiting a helical secondary structure, the *endohelix* functional groups R are

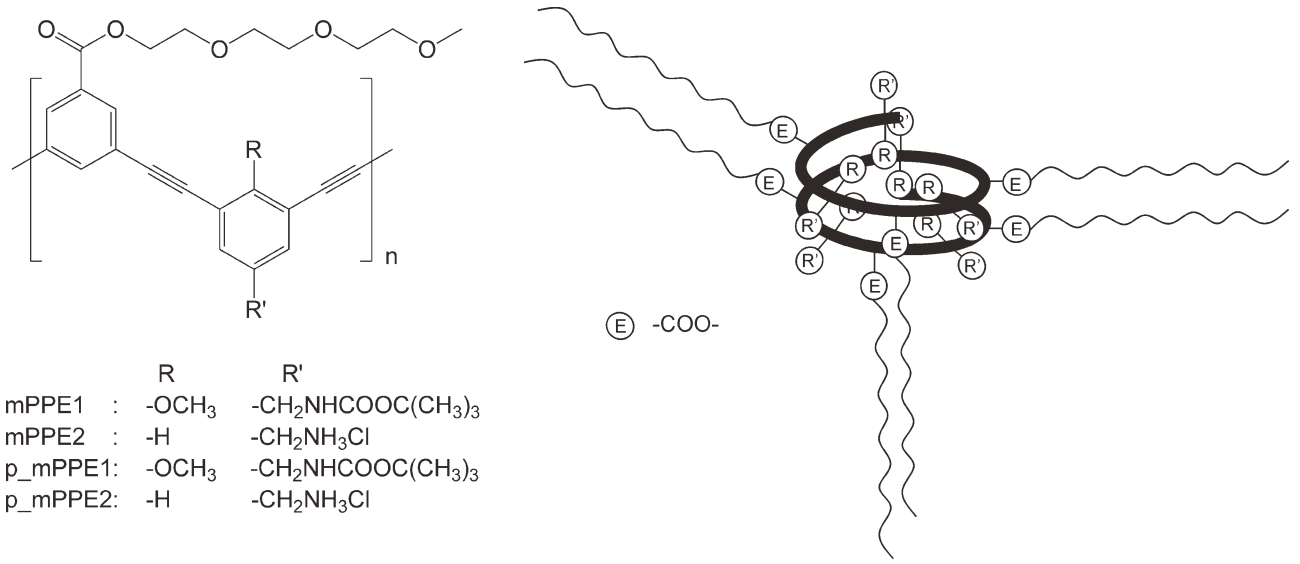

FIGURE 1 *meta*-Poly(phenylene ethynylene) (mPPE) oligomers synthesized in this study (left) and a conceptual representation of the mPPE helical secondary structure (right). *R* and *R*′ denote the customizable functional groups on the polymer backbone. For an mPPE exhibiting a helical secondary structure, the endohelix functional groups *R* are located inside the helical cavity, whereas the exohelix functional groups *R*′ are positioned at the outer wall of the helical structure.

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RESULTS AND DISCUSSION

Molecular weight analyses were performed for the mPPEs before the deprotection step, using gel permeation chromatography (GPC) calibrated with narrow molecular weight distribution polystyrene standards and short mPPEs of known molecular weight.[16,27,28] Two samples of the mPPE2 variation (R═H) were isolated via fractionation using flash column chromatography, and we denote these polymers as mPPE2L (long chain length polymer) and mPPE2S (short chain length polymer). This allowed us to examine the chain length dependence of secondary structure formation by the polymer, which has previously been shown to be significant.[19,20] A single sample of mPPE1 (R═OCH_3) was obtained. The folding behaviors of the protected amine precursors of the amine functionalized mPPE samples (denoted as p_mPPE1, p_mPPE2S and p_mPPE2L) were also examined.

The number and weight–average molecular weights (M_n and M_w, respectively) calculated from GPC results for the protected mPPEs are reported in Table 1. We note that small amounts (less than 5%) of very high-molecular weight polymer were present in the p_mPPE2 and p_mPPE2L samples, but were not included in molecular weight averages, because they were beyond the range of the GPC calibration standards. We also note that the values in daltons reported in Table 1 do not reflect the true molecular weight distributions of the mPPE samples because of the size and structural differences between mPPEs and the polystyrene calibration standards. For a qualitative evaluation of chain length dependence of mPPE folding behavior, the number of aromatic rings in the mPPE samples were initially estimated with the assumption that the GPC results using polystyrene standards overestimate the real molecular weight of the mPPE samples by a factor of two, based on the observations for *para*-PPEs by Huang and Tour and by Bunz.[27,28] From that, the chain length of the synthesized mPPEs could be estimated using the following equation:

$$\text{Estimated number of aromatic rings} = 2 \cdot \left(\frac{M_p}{F \cdot M_{\text{repeatunit}}} \right) \quad (1)$$

TABLE 1 Estimated Number of Aromatic Rings in Polymer Samples as Derived from GPC Data for p_mPPE1, p_mPPE2L, and p_mPPE2S

Calculated values	p_mPPE1	p_mPPE2L	p_mPPE2S
M_w[a]	21,735	12,591	8,376
M_n[a]	9,622	6,822	3,818
M_p[a]	9,481	8,661	3,812
Number of aromatic rings per chain[b]	18	16	8
Number of aromatic rings per chain[c]	26	24	10

[a] Calculated from GPC data using mono disperse polystyrene standards.
[b] Estimated using eq 1 with $F = 2$, rounded to the nearest even number.[27,28]
[c] Estimated using eq 1 with $F = 1.4$, rounded to the nearest even number.[16]

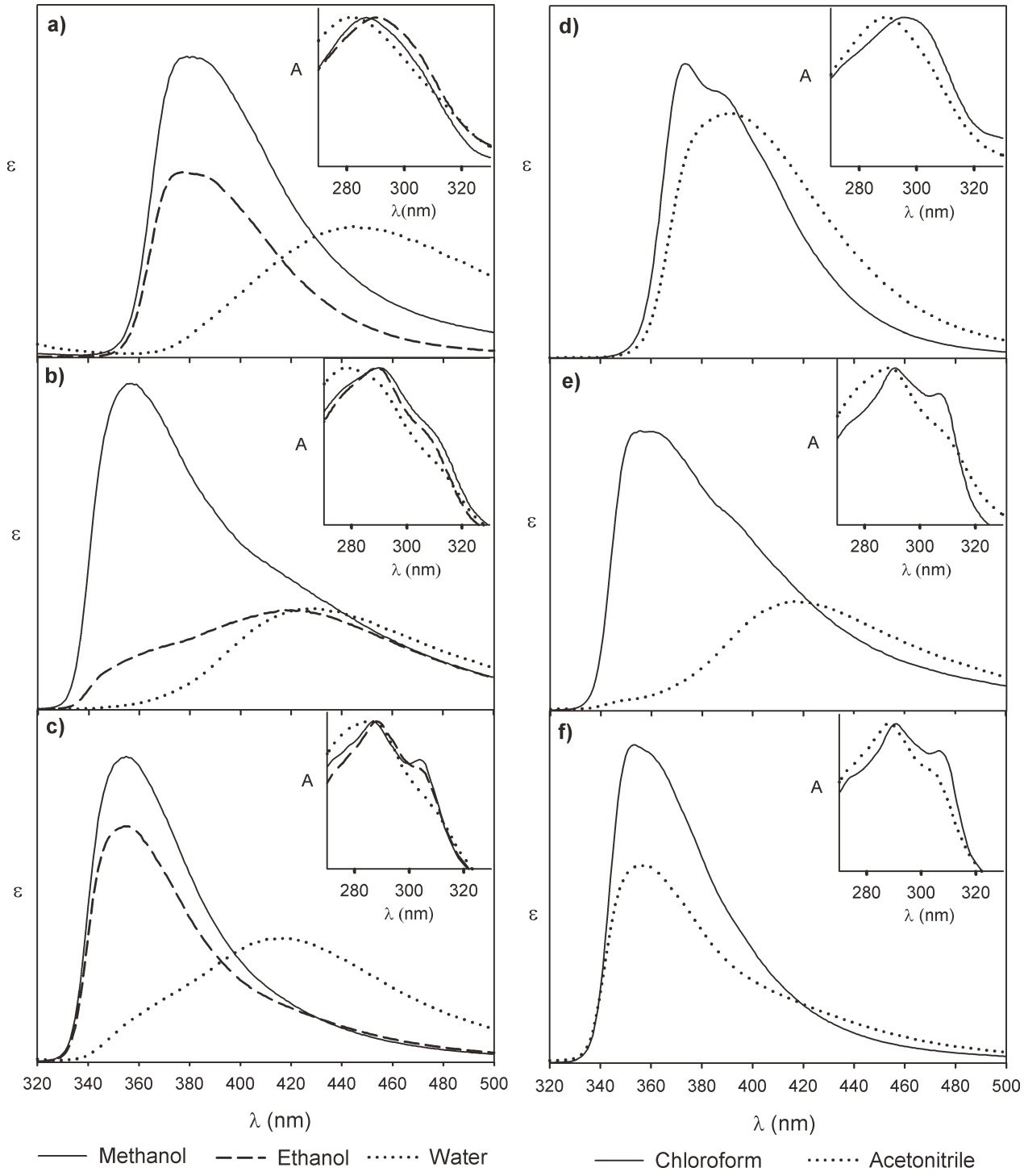

FIGURE 2 Fluorescence emission and UV absorbance (normalized, inset) spectra of the studied mPPE systems: (a) mPPE1, (b) mPPE2L, and (c) mPPE2S in methanol, ethanol, and water and (d) p_mPPE1, (e) p_mPPE2L, and (f) p_mPPE2S in chloroform and acetonitrile.

where M_p is the mean peak molecular weight of the studied polymer from GPC, $M_{repeatunit}$ is the calculated molecular weight of its repeated unit, and F is the overestimation factor from using monodisperse polystyrene as the standard.

Because mPPEs are able to fold into significantly more compact conformations than linear *para*-PPEs, this estimation should be considered as the lower limit for the mPPE chain length. These lower bounds are listed in Table 1, showing that the mPPE samples were estimated to be longer than the

TABLE 2 Secondary Structure Formation by mPPE Samples in Different Solvents as Determined by Fluorescence Emission Ratio and UV Absorbance Ratio

	Fluorescence emission ratio[a]			UV absorbance ratio[b]		
Solvent	p_mPPE1	p_mPPE2L	p_mPPE2S	p_mPPE1	P_mPPE2L	p_mPPE2S
Chloroform	0.14	0.39	0.16	0.96	0.85	0.83
Acetonitrile	0.34	9.7	0.29	0.74	0.71	0.74
Methanol	0.34	11.29	0.54	0.74	0.69	0.73
	mPPE1	mPPE2L	mPPE2S	mPPE1	mPPE2L	mPPE2S
Methanol	0.23	0.73	0.17	0.86	0.87	0.82
Water	5.9	7.73	4.3	0.69	0.68	0.62
Ethanol	0.16	2.61	0.2	0.85	0.72	0.74
1-Propanol	0.15	3.21	0.17	0.77	0.70	0.77
2-Propanol	0.12	1.83	0.59	0.86	0.80	0.86

A fluorescence emission ratio greater than unity indicates that the mPPE has folded into a helical conformation.

[a] Reported emission ratios for mPPE1 and p_mPPE1 are I_{450}/I_{380}; for all other samples, the values are for I_{425}/I_{350}.

[b] Reported absorbance ratios for mPPE1 and p_mPPE1 are A_{305}/A_{289}; for all other samples, the values are for A_{305}/A_{290}.

seven repeat units needed for folding.[2,20] The upper limits listed in Table 1 for mPPE samples are calculated using an F factor of 1.4, based on GPC results for a trimer mPPE, mPPEa, using the same polystyrene standards as reported earlier.[16] A more accurate estimation of mPPE molecular weight distribution using viscometry and/or light-scattering methods in combination with simulation data will be addressed in our future studies, and an excellent discussion of these methods, as they are applied to related helical polymer structures, can be found in the publications by Percec et al.[29,30]

The folding behavior of each mPPE sample was evaluated using ultraviolet (UV) and fluorescence spectroscopy, spanning a range of three independent variables: solvent type, mPPE chain length, and mPPE chemical functionality (as determined by the functional groups R and R' listed in Fig. 1).[2,15,16,21] Previous studies have established that each of these factors can influence the stability of the mPPE helical conformation,[2,15,16,20,21] and, in general, because of the complex interrelationship among those factors, no simple trend can be precisely anticipated with respect to them without the use of advanced molecular simulations.[16] Therefore, a combinatorial approach was used in this work, the results of which are presented in Figure 2 and summarized in Table 2. Specifically, we determined the folding behavior of each protected amine polymer (p_mPPE1, p_mPPE2L, and p_mPPE2S) in acetonitrile, chloroform, and ethanol and used five hydrogen-bonding solvents of varying polarity (ethanol, methanol, 1-propanol, 2-propanol, and water) to examine the extent of helical secondary structure formation with the water-soluble mPPEs (mPPE1, mPPE2L, and mPPE2S).

For mPPE1 and the protected amine precursor p_mPPE1 samples, the UV absorbance ratio A_{305}/A_{289} and the fluorescence emission ratio I_{450}/I_{380} were examined (subscripts denote wavelengths in nm). However, for mPPE2L, mPPE2S, and their protected amine precursors, p_mPPE2L, and p_mPPE2S, slightly different absorbance (A_{305}/A_{290}) and emission (I_{425}/I_{350}) ratios were used to evaluate secondary structure formation. As noted in previous studies,[2,15,16,21] fluorescence emission ratios greater than unity indicate a hypochromic effect, brought on by compact arrangements of phenylene rings as found in the mPPE helical structure. Further, a shift in the UV absorbance in favor of the shorter wavelength indicates an abundance of *cisoid* conformations in the chain and confirms the presence of a helical secondary structure. Conversely, if the fluorescence emission ratio is less than unity, and the UV absorbance is shifted to higher wavelengths, the sample would be categorized as unable to fold in the solvent.

Several features of the UV spectra made this method less effective in determining the folding behaviors of our mPPE samples when compared with those reported in previous studies.[2,15] For example, the spectra for mPPE1 and p_mPPE1, shown in the insets of Figure 2(a,d), are generally broad and lack the characteristic shoulder in the vicinity of 305 cm^{-1}, preventing a reliable assessment of the amount of *cisoid* conformations present in the mPPEs. Further, when examining the deprotected mPPEs, the shift of the maximum absorbance wavelength in water makes it difficult to compare the amount of *cisoid* conformations relative to the other solvents based on absorbance at fixed wavelengths (i.e., using the A_{305}/A_{289} ratio). Because of these features, we used the emission ratios from fluorescence emission spectra as our primary tool for characterizing the folding behavior of each mPPE system, with the absorbance ratio from UV absorbance spectra playing a supplementary role. In what follows, we note the effects of each independent variable in our combinatorial study on the folding of the mPPE samples.

Solvent Effects on Folding

The amine (deprotected) mPPE samples synthesized in this study were soluble in water and other protic solvents. Both the mPPE variations (mPPE1 and mPPE2) were found to form a helical secondary structure in aqueous solution, making them viable candidates for biological applications. Additionally, the mPPE2L sample exhibited a stable helical structure in ethanol, 1-propanol, and 2-propanol, although the other deprotected samples did not show evidence of folding in solvents other than water. Finally, the folding behavior of all the mPPE samples dissolved in methanol was characterized, but the protected polymer p_mPPE2L was the only one to exhibit an ability to fold into helical conformations.

Although some solvents are known to have a strong effect on the folding behavior of mPPEs, others are rather unpredictable in this respect. For example, chloroform largely inhibits helix formation by mPPEs, while some mPPEs in acetonitrile fold into a helix and others do not.[16] Thus, in addition to the protic solvents considered in this study, several other solvents were used, which have previously been shown to promote or hinder mPPE folding. We found that chloroform inhibits helix formation by the protected mPPE samples (p_mPPE1 and p_mPPE2), which is consistent with the solvent's known propensity to denature the helical conformation of mPPEs. Similarly, no ordered folding was observed for any of the reported samples in acetonitrile solution, except for the long-chain length protected polymer sample p_mPPE2L.

Chain Length Effects on Folding

The experimental results indicate a significant effect of the polymer chain length on the stability of the mPPE2 helical structures. Although both mPPE2L and mPPE2S folded into an ordered helical conformation in water, only the long-chain length mPPE variants (mPPE2L and p_mPPE2L) were found to form stable, helical secondary conformations in several other solvents, including acetonitrile, methanol, ethanol, and propanol. Based on this data, we speculate that there exists a minimum chain length for mPPE2, below which a given oligomer will not fold into a helical conformation even in favorable solvent conditions.

Our results are consistent with those of Stone et al.,[20] who observed a discernible change in the stability of the helical conformation with respect to chain length for ester-functionalized mPPEs. In their study, the onset of helical stability was shown to occur at or near 12 repeat units and that stability improved with increasing chain length. The GPC-based estimations of mPPE chain length for oligomers examined in this study are listed in Table 1 and indicate that two of the three mPPE samples (mPPE1 and mPPE2L) have a sufficient number of aromatic rings to stabilize a helical conformation should that structure be favored under the specific solvent conditions. Because there is evidence of a stable helical structure for mPPE2S in aqueous solution, the p_mPPE2S and mPPE2S samples must be at least seven repeat units long (and are likely longer based on our GPC results), as this is the minimum number of repeat units needed to form a single helical turn with one π-stacking interaction. Although the properties of mPPE2S oligomers in aqueous solution show that this shorter system can fold into helical conformations, the spectroscopy data indicate that the helical conformation is not stable in alcohol solvents at that chain length. The mPPE2L sample, on the other hand, contains chains of sufficient length to support the formation of stable helical structures in alcohol solvents. Thus, our data suggest that helical structures can form with oligomers shorter than 12 monomers long, but that oligomers having lengths greater than 20 monomers long are significantly more stable, which is in agreement with prior experimental results for other mPPEs.[9]

Functional Group Effects on Folding

By comparing the folding behavior of mPPE1 and mPPE2, as well as between their protected amine precursors, we can deduce the effect of the primary structure of the mPPE copolymers on the stability of their helical conformations. Structurally, the only difference between the two materials is that mPPE1 contains a methoxy ($—OCH_3$) functional group at each position *para* to the amine substituents, whereas mPPE2 has a hydrogen in each of these positions. Further, the functional groups (*R*) are positioned, such that they would be oriented toward the interior regions of the helix (i.e., they are *endohelix* functional groups) when the mPPE exhibits a helical secondary structure, which would significantly limit their interaction with solvent molecules. Despite this fact, the experimental results show that this simple change from a methoxy group to a hydrogen atom can have a significant effect on the folding behavior of the respective mPPE. Although GPC results indicate that the chain length of the methoxy-functionalized polymer (mPPE1) is greater than that of the unfunctionalized mPPE2L, mPPE2L was found to fold into a helical conformation in nearly all tested alcohol solvents, while mPPE1 remained amorphous in each of the solvents. Similarly, when comparing the protected amine precursors p_mPPE1 and p_mPPE2L, the sample without methoxy substituents exhibited a propensity to fold into helical structures in acetonitrile and methanol, whereas the methoxy-containing polymer (p_mPPE1) did not.

The results described earlier are generally consistent with the conventional view of folding as a process of solvophobic collapse. In the helical conformation of mPPE1, the methoxy groups point toward the interior of the helical cavity and are shielded from the solvent molecules. In its unfolded state, the methoxy groups are exposed to the solvent. Thus, in polar solvents, the unfolded state of mPPE1 is stabilized by favorable solvent interactions. When the methoxy group is replaced with a hydrogen atom, as in mPPE2L, the site becomes less polar and, therefore, has less favorable interactions with polar solvent molecules. This leads to the solvophobic collapse of mPPE2L into a helix to minimize these interactions.

The above explanation is consistent with the results in Table 1 for the mPPEs in alcohol solvents. Yet, a puzzling

contradiction is given by the data in aqueous solution. Because water is more polar than the alcohol solvents, one would expect it to stabilize the unfolded or random conformations of mPPE1. According to our data, however, mPPE1 shows evidence of folding in aqueous solutions. This result proves that the relationship between primary and secondary structure in mPPEs is nontrivial and further confirms our previously published molecular dynamics simulation results.[5,7]

In addition to the solvophobic collapse arguments discussed previously, there is evidence that the ether groups attached to the aromatic rings (as present in mPPE1) can further destabilize the helical conformation by disrupting π-stacking interactions. Lahiri et al.[15] showed that mPPE macrocycles were unable to agglomerate when they contained ether substituents, and the corresponding mPPE oligomers did not fold into helices. Thus, it is possible that higher chain length mPPE1 materials may fold into helical structures in moderately polar solvents, but this assertion was not directly tested. In our previous work,[16] we reported a long-chain length mPPE having ether functional groups that was able to fold in acetonitrile. Also, the fact that a helical structure was observed for mPPE1 in aqueous solutions indicates that π-stacking is not impossible for the polymer. Thus, while we observe some level of destabilization of the helical structure due to ether substituents, we believe that the effect may be mitigated by controlling other factors, such as solvent and polymer chain length.

EXPERIMENTAL

All chemicals used in this study were commercially available and used as received: 3,5-diiodobenzoyl chlorine (98%, Spectra Group), 3,5-diiodobenzylnitrile (98%, Spectra Group), 3,5-diiodo-4-hydroxyl benzonitrile (98%, Acros Organic), triethyleneglycol monomethyl ether (TgOH, 95%, TCI America), tris–(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$, 97%, Acros Organics), *tetra-n*-butylammonium fluoride 1 M in THF with 5% water (*tetra-n*-butylammonium fluoride; TBAF, Acros Organics), diisopropyl azodicarboxylate (DIAD, 94%, Acros Organics), trimethylsilyl acetylene (TMSA, 98 + % GFS Chemicals), di-*tert*-butyl dicarbonate ((Boc)2CO, 97%, Sigma-Aldrich), and HCl 4 M/dioxane (Sigma-Aldrich). Toluene and tetrahydrofuran (THF) were dried with sodium (using benzophenone as an indicator) under N_2 atmosphere. Diiospropyl amine was dried with CaH_2 under N_2. Other solvents include hexane, ethylacetate, *N*,*N*-dimethyl formamide (DMF), DMSO, methanol, diethyl ether, dichloromethane, chloroform, acetonitrile, ethanol, 1-propanol, and 2-propanol (all ACS reagent grade from Sigma-Aldrich).

Flash column chromatography used 200–400 mesh silica gel, 60A from Sigma-Aldrich with N_2 pressure. Thin-layer chromatography used silica gel 60 F_{254} plates from Merck; chemical locations were determined using UV light. NMR spectra were obtained in the Chemistry Department at Clemson University (CU) using a 300 MHz Bruker Avance for both ^1H and ^{13}C spectra, with either $CDCl_3$ (99.8% atom D, Acros Organics) or DMSO-d_6 (99.9% atom D + 1% v/v TMS, Cambridge Isotope Laboratories) used as the solvent for NMR experiments. UV/VIS absorption spectra were measured using a Varian Bio 50 UV/VIS spectrophotometer, with a 1-cm path length quartz cell (Starna Cells). The absorbance was measured from 200 to 400 nm, using a 0.5-nm step between measurements. Fluorescence spectra were obtained at CU with a Photon International—Fluorescence Photometer system, using a quartz cell with a 1-cm path length (Starna Cells), an excitation wavelength of 290 nm, an emission scan from 300 to 500 nm, and a 1-nm step. All UV absorbance and fluorescence emission spectra were recorded at temperatures ranging from 20 to 25 °C. Low-resolution matrix-assisted laser desorption ionization (MALDI) experiments were performed on a Bruker Autoflex matrix-assisted laser desorption/ionization—time-of-flight mass spectrometer, using 2,4-dihydroxy benzoic acid (DHB) or 7,7,8,8-tetracyanoquinodimethane (TCNQ) as the matrix. Elemental analysis for carbon, hydrogen, and nitrogen was conducted using a Perkin Elmer CHNS/O analyzer 2400 and calibrated using acetanilide as a standard. Liquid chromatography-electron ionization (EI) mass spectrometry was conducted on a modified Extrel (Pittsburgh, PA) Benchmark Thermabeam LC/MS quadrupole mass spectrometer at CU.[31] The LC mobile phase was 50:50 methanol/milliQwater, with a flow rate of 1 mL/min. The particle beam interface, which delivers the dry analyte particles to the EI source, consists of a nebulizer and a momentum separator. The nebulizer temperature was at 100 °F with a He sheath gas. The momentum separator was heated to 144 °F, and the EI source block was heated to 275 °F. The EI filament voltage was 70 eV, and detection was achieved with an electron multiplier at 1400 V. GPC was conducted in the Material Science Department at CU using a Water Breeze system equipped with a UV/VIS detector. It was calibrated using narrow molecular weight distribution polystyrene standards (from 400 to 1,000,000 Da). The specific GPC method involved isocratic chloroform flow at 1 mL/min, a UV detector set at 254 nm, and an HR 5E SEC column (range from 2 K to 4 $\times$ 10^6 Da).

Figure 3 depicts the synthesis procedure used in this study. The chemicals (1)–(5) and the mPPEs were synthesized following procedures in published literature.[16,22,23,32]

Reaction procedure to synthesize amine functionalized mPPEs. Reagents: (a) 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TgOH), CH_2Cl_2, triethylamine (TEA), r.t, 24 h, 56%; (b) TMSA, $Pd_2(dba)_3$, CuI, $P(Ph)_3$, diisopropyl amine (DIPA), toluene, 78 °C, 24 h; then TBAF, THF, 2 h, 66%; (c) CH_3OH, $P(Ph)_3$, DIAD, r.t., 24 h, 77%; (d) BH_3·THF, THF, reflux, 24 h; then $(Boc)_2CO$, DMF, NaOH, H2O, 24 h, 70% (5), 52% (6); (e) $Pd_2(dba)_3$, CuI, $P(Ph)_3$, DIPA, toluene, 78 °C, 24 h; (f) HCl 4M/dioxane, CH_2Cl_2, 0 °C, 2 h.

2-(2-(2-Methoxyethoxy)ethoxy)ethyl 3,5-diiodobenzoate (1)

To a 50-mL round-bottomed flask (dried then cooled under N_2) was added dichloromethane (25 mL) and TEA (0.78 mL, 3 equiv.). 3,5-Diiodobenzoyl chloride (1 g, 2.46 mmol) was then slowly added to the above solution, followed by TgOH

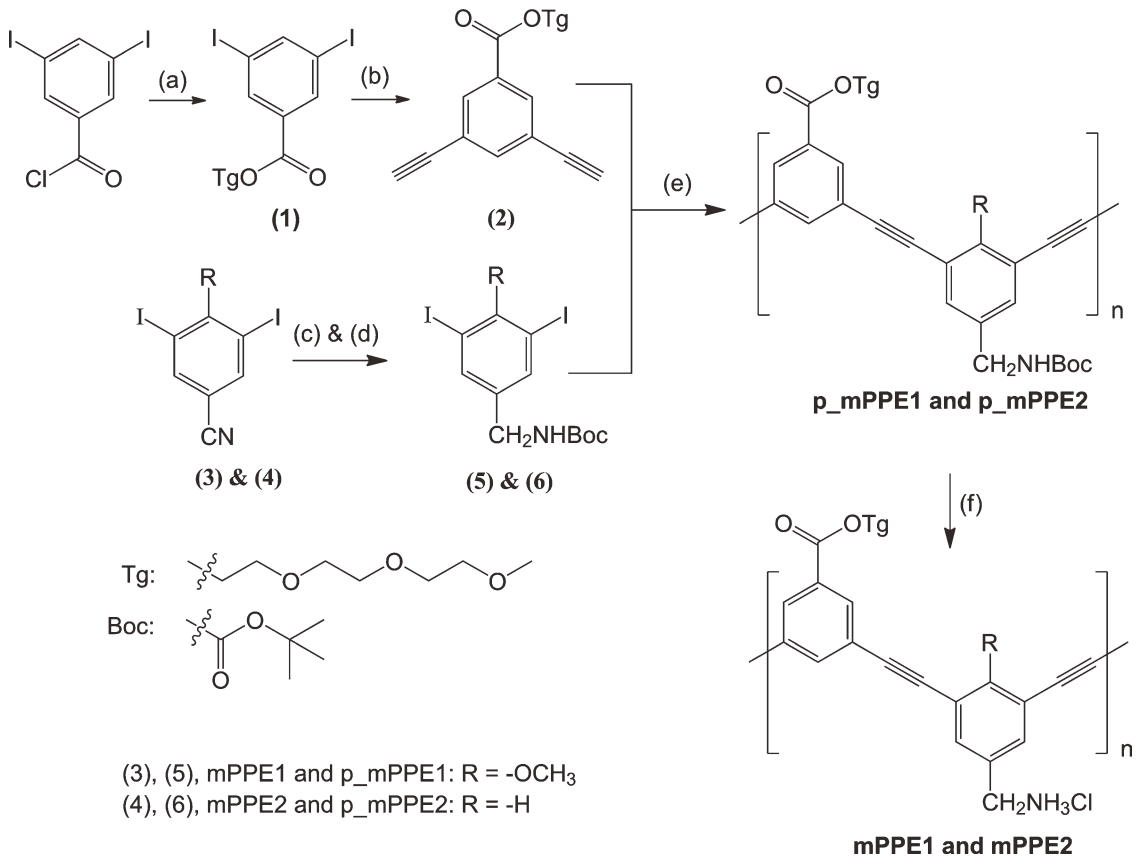

FIGURE 3 Reaction procedure to synthesize amine functionalized mPPEs. Reagents: (a) 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TgOH), CH_2Cl_2, TEA, r.t, 24 h, 56%; (b) TMSA, Pd2(dba)3, CuI, P(Ph)3, DIPA, toluene, 78 °C, 24 h; then *tetra-n*-butylammonium fluoride (TBAF), THF, 2 h, , 66%; (c) CH_3OH, P(Ph)3, diisopropyl azodicarboxylate (DIAD), r.t., 24 h, 77%; (d) BH3•THF, THF, reflux, 24 h; then (Boc)2CO, *N,N*-dimethylformamide (DMF), NaOH, H_2O, 24 h, 70% (5), 52% (6); (e) Pd2(dba)3, CuI, P(Ph)3, DIPA, toluene, 78 °C, 24 h; (f) HCl 4M/dioxane, CH_2Cl_2, 0 °C, 2 h.

(0.5 mL, 1.25 equiv.) under continuous stirring at 0 °C (immersed in an ice bath). Next, the ice bath was removed, the solution was allowed to warm to room temperature, and stirring was continued for an additional 24 h. The resulting solution was washed with a 20% NH_4Cl solution (using distilled water—repeated two times), and the organic layer was collected and dried with anhydrous Na_2SO_4. Dichloromethane was removed using a rotary vacuum evaporator to collect crude product as a yellow solid. The crude product was purified using flash column chromatography with 1:1 v/v hexane/ethyl acetate as the eluent to collect 0.72 g of product as white crystals (1.38 mmol, yield 56%). TLC R_f = 0.25 (1:2 v/v hexane/ethyl acetate), ^{1}H NMR (300 MHz, $CDCl_3$, δ): ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.34 (d, J = 1.6 Hz, Ar H, 2H), 8.24 (t, J = 1.6 Hz, Ar H, 1H), 4.47 (t, J = 4.7 Hz, —COO—CH_2—CH_2—, 2H), 3.84 (t, J = 4.7 Hz, —COO—CH$_2$—CH_2—O—, 2H), 3.65–3.72 (m, —O—CH_2—CH_2—O—CH_2—CH$_2$—O—CH$_3$, 6H), 3.54–3.57 (m, —CH_2—O—CH$_3$, 2H), 3.39 (s, 3H, —CH$_2$—OCH_3); ^{13}C NMR (300 MHz, $CDCl_3$, δ): 163.5, 149.2, 137.7, 133.2, 94.3, 71.9, 70.6, 70.5, 68.9, 64.7, and 59.0. MALDI DHB matrix (m/z) $[M+H]^+$ calcd for $C_{14}H_{19}O_5I_2^+$ 520.932; found, 521.592; $[M+Na]^+$ calcd for $C_{14}H_{18}O_5I_2Na^+$ 542.914; found, 543.708. LC–MS EI (70 Ev), m/z (relative intensity): 429.95 (2), 399.12 (91), 355.34 (100), 327.55 (49), 260.38 (44), 230.79 (31), and 201.81 (31). Anal. Calcd. for $C_{14}H_{18}I_2O_5$ (520.102): C 32.33; H 3.49. Found: C 32.27; H 3.20.

2-(2-(2-Methoxyethoxy)ethoxy)ethyl 3,5-diethynylbenzoate (2)

To a 100-mL round-bottomed flask (dried then cooled under N_2, equipped with a magnetic bar) was added 2-(2-(2-methoxyethoxy)ethoxy)ethyl 3,5-diiodobenzoate [chemical (1)] (1.0 g, 1.92 mmol), $Pd_2(dba)_3$ (35.3 mg, 0.02 equiv.), CuI (14.7 mg, 0.04 equiv.), and triphenyl phosphine ($P(Ph)_3$) (101.3 mg, 0.2 equiv.). The flask was sealed, purged with N_2, and evacuated (repeated three times) to remove any moisture. Next, dried DIPA (6.2 mL), dried toluene (61.3 mL), and TMSA (1.060 mL, 4 equiv.) were added using syringes. The solution was stirred and heated to 78 °C in an oil bath for 48 h. The resulting solution was cooled to room temperature and passed through a short silica gel column, using ethyl acetate as the eluent. Solvent was removed by rotary vacuum evaporator to produce a yellow oil crude product. The crude product was purified via flash column chromatography, using ethyl acetate as the eluent, to collect the final

product as yellow oil. This oil was then dissolved in tetrahydrofuran (50 mL). To this solution was added TBAF (1.0 M in THF with 5% water; 5.4 mL), and the mixture was stirred at room temperature for 15 min. The black solution was passed through a short silica gel column, using ethyl acetate as the eluent to collect the crude product as orange oil. The crude product was then purified by flash column chromatography and eluted with 1:2 v/v hexane/ethyl acetate to collect 0.40 g of a dark yellow solid (1.26 mmol, yield 66%). TLC R_f = 0.3 (1:2 v/v hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14 (s, Ar H, 2H), 7.77 (s, Ar H, 1H), 4.49 (t, J = 4.7 Hz, —COOCH_2—CH$_2$—, 2H), 3.85 (t, J = 4.7 Hz, —COOCH$_2$—CH_2—O—, 2H), 3.65–3.74 (m, —O—CH_2—CH_2—O—CH_2—CH$_2$—O—CH$_3$,6H), 3.54–3.57 (m, —CH_2—O—CH$_3$, 2H), 3.38 (s, —CH$_2$—OCH_3, 2H), 3.17 (s, —C≡CH, 2H). ^{13}C NMR (300 MHz, $CDCl_3$, δ): 164.9, 139.4, 133.3, 130.8, 123.0, 81.8, 79.0, 72.0, 70.7, 70.6, 69.1, 64.6, and 59.0. MALDI DHB matrix (m/z) $[M + H]^+$ calcd for $C_{18}H_{21}O_5^+$ 317.139; found, 317.237; $[M + Na]^+$ calcd for $C_{18}H_{20}O_5Na^+$ 339.121; found, 339.297. LC–MS EI (70 Ev), m/z (relative intensity): 227 (7), 212.08 (16) , 196.93 (100) 181.96 (6), 153.05 (28), and 125.44 (4). Anal. Calcd. for $C_{18}H_{20}O_5$ (316.353): C 68.34; H 6.37. Found: C 67.98; H 6.10.

3,5-Diiodo-4-methoxybenzonitrile (4)

To a 250-mL round-bottomed flask with a magnetic stir bar was added dried THF (100 mL). The solvent was cooled to 0 °C via immersion in an ice bath. Then 4-hydroxy-3,5-diiodobenzonitrile (2.0 g, 5.39 mmol) was added to the solvent, followed by methanol (0.26 mL, 1.3 equiv.), and P(Ph)$_3$ (2.119 g, 1.5 equiv.). DIAD (1.7 mL, 1.6 equiv.) was slowly added in small portions under continuous stirring to avoid any temperature excursions above 0 °C. After all chemicals were added, the ice bath was removed, and the solution was stirred for 24 h and allowed to warm to room temperature. The solvent was removed using a rotary vacuum evaporator. Then, 50 mL of diethyl ether was added to the flask, and the mixture was stirred at room temperature overnight. The resulting mixture was filtered and a slightly yellow filtrate solution isolated. Diethyl ether was removed from the filtrate solution using a vacuum evaporator to yield a crude pale yellow solid product. The yellow solid was dissolved in dichloromethane and purified via flash column chromatography using 5:1 v/v hexane/dichloromethane as the eluent, yielding 1.6 g of white crystalline product (4.16 mmol, yield 77%). TLC (diethyl ether) R_f = 0.7. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.10 (s, Ar H, 2H), and 3.95 (s, Ar—OCH_3, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, δ): 163.1, 143.1, 115.3, 111.7, 90.8, and 61.0. MALDI TCNQ matrix (m/z) or M^+ calcd. for $C_8H_5ONI_2^+$ 384.846; found, 385.600. LC–MS EI (70 Ev), m/z (relative intensity): 383.22 (73), 386.31 (33), 340.43 (7), 258.24 (6), 242.57 (100), 227.84 (15), 214.8 (8), and 127.18 (2). Anal. calcd. for $C_8H_6I_2NO$ (384.950): C 24.96; H 1.57; N 3.63. Found: C 25.35; H 1.24; N 3.69.

3,5-Diiodo-4-methoxybenzonitrile (5) and (6)

To a 500-mL round-bottomed flask (equiped with a magnetic stir bar, immersed in an ice bath) was added dried THF (100 mL) and BH_3·THF 1M (100 mL). 3,5-Diiodo-4-methoxybenzonitrile (2.20 g, 5.72 mmol) [chemical (3), for mPPE1] or 3,5-diiodobenzonitrile (2.20 g, 6.20 mmol, for mPPE2) was dissolved in 20 mL THF and then added to the BH_3 solution in small portions in order to ensure that the temperature did not rise above 0 °C. Several boiling stones were added to the flask, a condenser was attached, and the solution was refluxed for 24 h. Then the solution was cooled to room temperature, and methanol (30 mL) was slowly added to completely deactivate any excess BH_3 (hydrogen bubbles were expected). The solvent was removed from the resulting solution by rotary evaporation; the remaining solid was washed with methanol (20 mL) and then evaporated (repeated three times). Methanol (20 mL) was added into the flask to form a milky mixture. The flask was cooled to 0 °C in an ice bath, and HCl gas was slowly bubbled through the solution for 15 min. Later, diethyl ether (50 mL) was added, and HCl was bubbled for ~15 min or until the solution became clear. Additional diethyl ether (250 mL) was added, and a slightly brown solid (amine salt) precipitated from the solution. The solid was filtered, washed with diethyl ether (10 mL; repeated three times), and dried under vacuum to collect the amine salt for mPPE1 (2.10 g, 5.10 mmol, yield 89%) or the amine salt for mPPE2 (1.53 g, 3.87 mmol, yield 62%). Note that the amine salt must be protected immediately to avoid degradation.

tert-Butyl 3,5-diiodophenyl-4-methoxybenzylcarbamate (5)

To a 25-mL round-bottomed flask was added the amine salt (2.10 g, 5.10 mmol) from the reduction procedure, $(Boc)_2CO$ (1.50 g, 1.4 equiv.), DMF (10 mL), and solid NaOH (0.38 g, ~2.0 equiv.). The mixture was stirred for 15 min and then distilled water (2 mL) was added in one portion. The flask was covered with aluminum foil and stirred overnight at room temperature. After 24 h, distilled water (10 mL) was added, and then the mixture was filtered and washed with excess distilled water to obtain the protected amine product as a white solid (1.75 g, 3.58 mmol, yield 70%). ^{1}H NMR (300 MHz, $CDCl_3$, δ):7.68 (s, Ar H, 2H), 4.88 (br s, NH), 4.21 (d, J = 5.4 Hz, —CH_2—NH—, 2H), 3.85 (s, Ar—OCH_3, —3H), 1.45 (s, C— (CH_3)$_3$, 9H); ^{13}C NMR (300 MHz, $CDCl_3$, δ): 157.5, 156.1, 138.6, 91.4, 60.7, 43, 28.4. MALDI DHB matrix (m/z) $[M+Na]^+$ calcd for $C_{13}H_{17}I_2NO_3Na^+$ 511.920; found, 512.530. LC–MS EI (70 Ev), m/z (relative intensity): 430 (61), 386.2 (24), 371.3 (36), 359.36 (4), 261.41 (100), 246.55 (43), 230.75 (23), and 202.78 (9). Anal. Calcd. for $C_{13}H_{17}I_2NO_3$ (489.091): C 31.93; H 3.50; N 2.86. Found: C 32.88; H 3.83; N 2.84.

tert-Butyl 3,5-diiodophenylbenzylcarbamate (6)

To a 25-mL round-bottomed flash was added the amine salt (1.53 g, 3.87 mmol) from the reduction procedure, $(Boc)_2CO$ (1.15 g, 1.4 equiv.), DMF (10 mL), and solid NaOH (0.31 g, ~2 equiv.). The mixture was stirred for 15 min, and then distilled water (5 mL) was added in one portion. The mixture became homogeneous for a short time, but later turned to a milky solution. The flask was covered with aluminum foil and stirred overnight at room temperature. After 24 h, distilled water (10 mL) was added, and the mixture was filtered to collect a crude product as white solid product. The

product was purified via flash column chromatography, where it was eluted first with hexane and then with ethyl acetate. The product-containing fractions (confirmed using TLC) were vaporized to collect the final protected amine as a white solid (0.92 g, $M = 459.037$ Da, 2.00 mmol, yield 52%). TLC (hexane: ethyl acetate 1:1 (v/v)) $R_f = 0.48$. ^{1}H NMR 300 MHz, $CDCl_3$, δ): 7.96 (t, $J = 1.5$ Hz, Ar H, 1H), 7.59–7.60 (m, Ar H, 2H), 4.90 (br s, —NH—), 4.22 (d, $J = 5.5$ Hz, —CH_2—NH—, 2H), and 1.48 (s, —C(CH_3)$_3$, 9H); ^{13}C NMR (300 MHz, $CDCl_3$, δ):146.8, 144.00, 143.2, 135.6, 94.9, 43.2, and 28.4. MALDI DHB matrix (m/z) $[M+Na]^+$ calcd for $C_{12}H_{15}I_2NO_2Na^+$ 481.909; found, 483.496. LC–MS EI (70 Ev), m/z (relative intensity): 401.18 (53), 383.28 (1.8), 356.33 (17), 341/43 (20), 275.18 (27), 257.39 (11), 231/68 (100), and 215.92 (15). Anal. Calcd. for $C_{12}H_{15}I_2NO_2$ (459.065): C 31.40; H 3.29; N 3.05. Found: C 32.25; H 3.25; N 2.95.

p_mPPE1 and p_mPPE2

To a 25-mL round-bottomed flask (dried, then cooled under N_2, equipped with a magnetic stir bar) was added (chemical (6) for p_mPPE3) or (chemical (7) for p_mPPE4) (100 mg), (2) (66.5 mg, 1.0 equiv.), $Pd_2(dba)_3$ (3.8 mg, 0.02 equiv.), CuI (1.6 mg, 0.04 equiv.), and $P(Ph)_3$ (10.6 mg, 0.2 equiv.). The flask was sealed, purged with N_2, and evacuated (three times) to remove any moisture. Then dried DIPA (0.8 mL) and dried toluene (8.0 mL) were added using syringes. The solution was heated to 78 °C and stirred in an oil bath for 24 h. The final dark brownish yellow solution was filtered through a short silica gel column to remove the catalyst, eluted with 9/1 v/v chloroform/isopropanol to collect a clear, yellow solution containing the polymer and monomers. This solution was concentrated, and the polymer was separated from the monomer by flash column chromatography, where it was initially eluted with a 1:2 v/v hexane/ethyl acetate solution and then with a 9:1 v/v chloroform/isopropanol mixture. The polymer-containing fractions were concentrated, precipitated in hexane, then filtered, and washed with hexane to collect the final polymer as a pale yellow solid. Final recovery of p_mPPE3 and p_mPPE4 was 94.5 and 112 mg, respectively.

p_mPPE1

^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.19 (br s, Ar H), 7.88 (br s, Ar H**),** 7.47 (br s, Ar H, 2H), 5.01 (br s, —NH), 4.53–4.56 (br m, —COOCH_2), 4.23 (br s, —CH_2—NH—), 4.19 (br s, —OCH_3), 3.87–3.90 (br m, COOCH_2—CH_2—O—, 2H), 3.65–3.74 (br m, —O—CH_2—CH_2—O—CH_2—CH_2—O—CH_3), 3.55–3.58 (br m, —CH_2—O—CH_3), 3.37 (br s, CH_2—O—CH_3), and 1.49 (br s, —C(CH_3)$_3$). GPC result: $M_w = 21735$ Da, $M_n = 9622$ Da, $M_p = 9481$ Da, and polydispersity = 2.26. Small amounts of very high molecular weight polymer were also detected (they were beyond the range of the polystyrene standards).

p_mPPE2

^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.13–8.15 (br m, Ar H), 7.80–7.85 (br m, Ar H), 7.63 (br s, Ar H), 7.47 (br s, Ar H), 5.10 (br s, —NH), 4.52 (br s, —COOCH_2^-), 4.35 (br s, —CH_2—NH—), 3.88 (br s, —COO—CH_2—CH_2—O—), 3.66–3.74 (m, —O—CH_2—CH_2—O—CH_2—CH_2—O—CH_3), 3.53–3.56 (m, —CH_2—O—CH_3), 3.36 (s, —CH_2—OCH_3), and 1.51 (s, —C(CH_3)$_3$). GPC results: for long-chain length fraction $M_w = 12{,}591$ Da, $M_n = 6822$ Da, $M_p = 8661$, and Da, Pd = 1.85; for short-chain length fraction: $M_w = 8376$ Da, $M_n = 3818$ Da, $M_p = 3812$ Da, and Pd = 2.19. Small amounts of very high-molecular weight polymer were also detected (they were beyond the range of the polystyrene standards).

mPPE1 and mPPE2

To a 25-mL round-bottomed flask (dried, then cooled under N_2, equiped with a magnetic stir bar, and immersed in an ice bath) was added HCl 4 M/dioxane (2 mL). Later, a solution-containing p_mPPE3 (or p_mPPE4; 10 mg in 3 mL of chloroform) was slowly added. The mixture was stirred at 0 °C for 1 h; during that time, the clear yellow solution turned to a milky solution, and yellow precipitate was observed. The yellow suspension was filtered; the solid was washed on the filter paper with diethyl ether (three times, 50 mL each). The solid was dissolved in methanol (10 mL), concentrated, and then reprecipitated by adding diethyl ether (50 mL). The resulting mixture was filtered and washed with diethyl ether to collect the final product as a pale yellow solid (7.5 mg).

mPPE1

^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.54 (br s, —NH_3+), 8.02–8.08 (br m, Ar H), 7.79–7.87 (br m, Ar H), 4.45 (br s, —COOCH_2—), 4.18 (br s, —OCH_3), 4.04 (br s, —CH_2—NH—), 3.78–3.97 (br m, —CH_2—O—CH_2—), 3.50–3.60 (br m, —CH_2—O—CH_2—), and 3.17 (s, —OCH_3).

mPPE2

^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.62 (br s, —NH_3+), 7.83–8.26 (br m, Ar H), 4.43 (br s, —COOCH_2—), 4.08–4.12 (br m, —CH_2—NH—), 3.77 (br s, —CH_2—O—CH_2—), 3.50–3.62 (br m, —CH_2-O—CH_2—), and 3.18 (s, —OCH_3).

2-(2-(2-Methoxyethoxy)ethoxy)ethyl 3,5-bis(phenylethynyl)benzoate

To a 25-mL round-bottomed flask (dried, then cooled under N_2, equipped with a magnetic stir bar) was added 2-(2-(2-methoxyethoxy)ethoxy)ethyl 3,5-diiodobenzoate [chemical (1), 200 mg, 0.38 mmol], ethynylbenzene (117.2 mg, 3.0 equiv.), $Pd_2(dba)_3$ (9.6 mg, 0.02 equiv.), CuI (4.0 mg, 0.04 equiv.), and $(P(Ph)_3)$ (27.2 mg, 0.2 equiv.). The flask was sealed, purged with N_2, and then evacuated (three times) to remove any moisture. Dried DIPA (1.67 mL) and dried toluene (16.5 mL) were subsequently added using syringes. The solution was stirred at 78 °C in an oil bath for 24 h. The solution was later cooled to room temperature and passed through a short silica gel column (using ethyl acetate as the eluent). Solvent was removed using a rotary vacuum evaporator to collect crude product as yellow oil. The crude product was later purified by flash column chromatography and eluted with 1:2 v/v hexane/ethyl acetate to collect the final product as a yellow oil. TLC (1:2 v/v hexane/ethyl acetate) $R_f = 0.63$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.18 (d, $J = 1.4$ Hz, Ar H, 2H), 7.88 (m, $J = 1.4$ Hz, Ar H, 2H), 7.55–7.59 (m, Ar H, 4H), 7.38–7.40 (m, Ar H, 6H), 4.54 (t, $J = 4.7$ Hz, —COOCH_2—, 2H), 3.89 (t, $J = 4.7$ Hz, —COOCH$_2$—CH_2—O—, 2H), 3.67–3.75 (m, —O—CH_2—CH_2—O—CH_2—CH$_2$—O—CH$_3$,

6H), 3.54–3.57 (m, —CH_2—O—CH_3, 2H), and 3.38 (s, —OCH_3, 3H).^{13}C NMR (300 MHz, $CDCl_3$, δ): 138.5, 132.2, 131.8, 130.9, 128.8, 128.5, 124.1, 90.9, 87.6, 71.93, 70.7, 70.6, 69.1, 64.6, and 59.0. GPC results: M_w = 623 Da, M_n = 688 Da, M_p = 667 Da, and Pd = 1.1. MALDI DHB matrix (m/z) $[M + H]^+$ calcd for $C_{30}H_{29}O_5^+$ 469.201; found, 469.741; $[M + Na]^+$ calcd for $C_{30}H_{28}O_5Na^+$ 491.183; found, 491.839. LC–MS EI (70 Ev), m/z (relative intensity): 408.32 (4), 364.6 (18), 347.7 (67), 320.9 (88), 304 (100), 290.22 (14), and 275.1 (95). Anal. Calcd. for $C_{30}H_{28}O_5$ (468.548): C 76.90; H 6.02. Found: C 74.82; H 5.80.

CONCLUSIONS

We report the synthesis of two new mPPE copolymers (mPPE1 and 2) that contain both ester and amine functional groups, with the distinguishing feature being that one of the mPPEs is also methoxy functionalized (mPPE1). These two polymers are not only soluble in water and many other common protic solvents, but are also able to fold into helical conformations in water. Thus, these mPPEs could potentially be candidates for new biological applications. The folding behaviors are also reported for these two mPPEs and their precursors, which contain amine-protecting groups in a range of aprotic and protic polar solvents. Experimental results show that an endohelix methoxy functional group can significantly destabilize the helical structure, but steric interactions between these groups were not a factor. The chain length of the polymers was also found to play a decisive role in determining secondary structure. For example, the longer chain length sample of mPPE2 exhibited helical structures in acetonitrile and several alcohol solvents, while shorter chain length samples of the same polymer did not fold in these solvents. These results provide further insight into the process of secondary structure formation by mPPEs and related polymers.

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