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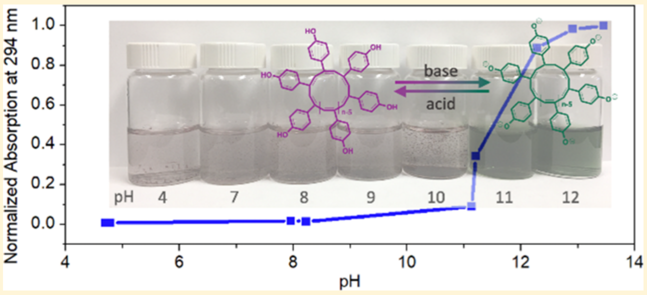
# pH-Responsive Water-Soluble Cyclic Polymer

Zhihui Miao,[†] Tomohiro Kubo,[‡] Digvijayee Pal,[‡] Brent S. Sumerlin,*[,‡] and Adam S. Veige*[,†]

[†]Center for Catalysis, Department of Chemistry, and [‡]Center for Macromolecular Science & Engineering and George & Josephine Butler Polymer Research Laboratory, Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida 32611, United States

*Supporting Information*

**ABSTRACT:** Cyclic polymers possess different properties compared to their linear analogues of the same molecular weight, such as smaller hydrodynamic volumes and higher glass transition temperatures ($T_g$). Cyclic poly(4-ethynylanisole) (**cPEA**) was synthesized via a catalytic ring-expansion of 4-ethynylanisole. The catalyst employed was a tungsten complex supported by a tetraanionic pincer ligand. Evidence of the cyclic topology comes from gel permeation chromatography, dynamic light scattering, static light scattering, and solution viscometry. Demethylation of **cPEA** with boron tribromide affords cyclic poly(4-ethynylphenol) (**cPEP-OH**). **cPEP-OH** exhibits pH-responsive water solubility, being soluble in aqueous solutions at elevated pH and becoming insoluble under acidic conditions. The linear equivalent of **cPEP-OH** was also synthesized, and it exhibits similar pH responsiveness.



Synthetic polymers such as poly(ethylene glycol), poly(vinyl alcohol), and poly(2-hydroxyethyl methacrylate) have been employed as drug carriers, contact lens, and polymer scaffolds for tissue engineering for decades.[1−3] Polymer materials are greatly expanding the field of biomaterials and their applications due to their relative ease of preparation, a wide range of chemical compositions, readily tuned physical properties, and a variety of structural and topological designs.[1] Polymers with a cyclic topology have no end groups and reduced conformational mobility, and thus possess different physical properties compared to linear polymers with the same chemical compositions and molecular weights.[4−7] Cyclic polymers have smaller hydrodynamic volumes,[8] reduced radii of gyration,[9] and, as a consequence exhibit lower intrinsic viscosities in solution,[10] and longer retention times in gel permeation chromatography (GPC) analysis in comparison to linear polymers of the same molecular weight.[11] In bulk, cyclic polymers exhibit higher density[12] and higher glass transition temperatures.[13] Cyclic polymers often exhibit different properties in a biological complex, such as longer in vivo circulation times[14] and higher tumor uptake[14−16] as drug carriers and increased stability,[17] higher efficiency, and reduced cytotoxicity as gene carriers.[18,19]

For many biomaterial applications, polymers need to be water-soluble. Linear phenolic polymers exhibit water solubility in basic aqueous solutions. Including pH-responsive water solubility, natural polyphenols demonstrate radical scavenging properties, antioxidant activities, and biocompatibility.[20−22] Synthetic polymers bearing phenol moieties find application as diagnostic and drug therapy agents,[22,23] drug delivery,[22,24] adhesives,[24,25] and self-healing materials.[23,26] Though challenging to synthesize and sparsely reported in the literature, water-soluble cyclic polymers present an exciting opportunity considering their varied and potentially advantageous properties. One strategy for their synthesis includes ring closing of readily water-soluble linear polymers. Vitali and Masci[27] first synthesized cyclic poly(ethylene oxide) (cPEO) in 8% yield via ring closing of linear poly(ethylene oxide) (PEO). Using more favorable ring closing conditions, Yu et al.[28,29] improved the cPEO yield to 93%, and Ishizu and Akiyama[30] synthesized cPEO by intramolecular Williamson etherification with near-quantitative conversion. Additional reports have described the grafting of hydrophobic components to cPEO to afford amphiphilic polymers.[31,32] An alternative strategy to prepare water-soluble or stimuli-responsive cyclical polymers includes grafting hydrophilic components to hydrophobic ring polymers to adjust their water solubility.[14]

Other reports have described the synthesis and investigation of stimuli-responsive cyclic polymers. Linear poly(*N*-isopropyl acrylamide) (PNIPAM) is a thermoresponsive water-soluble polymer and exhibits water solubility below its lower critical solution temperature (LCST). Stöver et al.[33,34] reported that the LCST of linear PNIPAM depends on molecular weight and end groups, ranging from 32 to 45 °C, where the hydrophobic end groups lead to lower LCST and hydrophilic ones increase LCST. Interestingly, without end groups, cyclic PNIPAM exhibits a 7 °C decrease in LCST compared to some linear analogs.[35,36] Many weak polyelectrolytes can transform

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between their water-soluble ionized form and insoluble neutral form, depending on the pH.[37] For example, cyclic poly(2-vinylpyridine)[38] and cyclic poly(2-dimethylamino-ethyl methacrylate)[19] dissolve in acidic aqueous solutions.

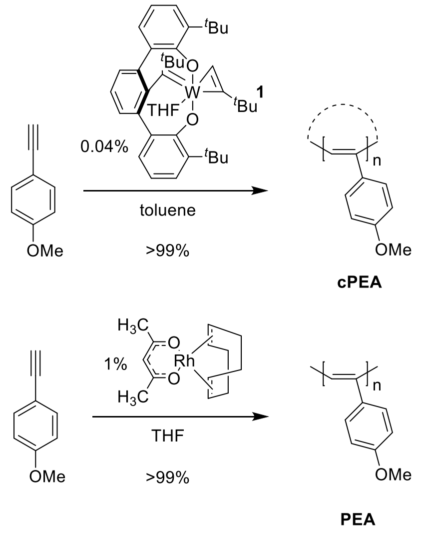
Despite the few examples reported in the literature, there remains much to improve upon in water-soluble polymers with unique topologies. For example, most of the cyclic water-soluble polymers prepared to date require ring closing of water-soluble linear polymers.[14,27−30] This method requires high dilution and suffers from the inherent presence of linear impurities that accompany incomplete cyclization or oligomerization.[39,40] Moreover, any postpolymerization modification[41] of cyclic polymers must be conducted with consideration of the linkage used to accomplish ring closing.[42] Ring expansion, another common method for cyclic polymer synthesis, does not require dilution;[7,40,43,44] however, because this approach is limited to a few select catalyzed polymerization mechanisms, monomer diversity and functionality can be limited. Eliminating the requirement for ring closing of a linear polymer, we reported catalyst **1** which is capable of polymerizing alkynes via ring expansion to give cyclic polyacetylenes[45] or cyclic polyolefins.[46] Using catalyst **1**, we now report the synthesis and characterization of the first pH-responsive cyclic polyphenol.

## ■ RESULTS AND DISCUSSION

Combining 4-ethynylanisole with catalyst **1** in a ratio of 2500:1 in toluene at ambient temperatures produces cyclic poly(4-ethynylanisole) (**cPEA**) as an orange solid in >99% yield in just 30 min. The polymerization is exothermic, and the solution color changes immediately from light yellow to bright orange. Obtained in >99% yield as well, the synthesis of the corresponding linear polymer requires combining 4-ethynylanisole with acetylacetonato(1,5-cyclooctadiene)rhodium(I)[47] in a 100:1 ratio in tetrahydrofuran (THF) at ambient temperatures. Interestingly, the solution color only turns yellow, and the polymer obtained after precipitating from methanol is light yellow (Scheme 1).

Evidence of a cyclic topology was obtained by GPC with static light scattering (SLS) and viscometry detection. Cyclic polymers have smaller hydrodynamic radii as compared to analogous linear polymers of the same molecular weight. Therefore, cyclic polymers that elute at the same time as equivalent linear polymers have higher molecular weights.[45,48] Supporting the cyclic topology assignment, both polymer architectures elute with maxima at ∼18 min (Figure 1); however, the $M_n$ for **PEA** and **cPEA** are of 79.3 kDa ($Đ$ = 1.60) and 96.5 kDa ($Đ$ = 1.43), respectively. The phenomenon holds over a broad molecular weight range as depicted in Figure 2.

**Scheme 1. Synthesis of Cyclic and Linear Poly(4-ethynylanisole)**



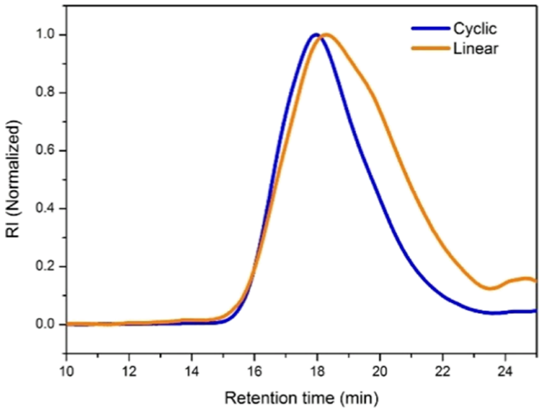


**Figure 1.** GPC traces of cyclic (blue) and linear (orange) poly(4-ethynylanisole) in THF at 35 °C.

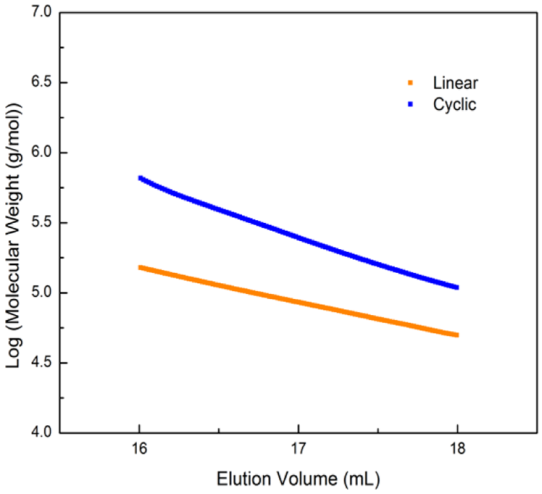


**Figure 2.** log (molecular weight) vs elution volume plot for cyclic (blue) and linear (orange) poly(4-ethylnylanisole).

Additional evidence for a cyclic topology comes from the radius of gyration measurements. Theory predicts that the radius of gyration ($\langle R_g^2 \rangle$) of a cyclic polymer is half of its linear analog.[9] Experimental data supports the $\langle R_g^2 \rangle$ ratio between cyclic and linear polymers.[48] In this case, $\langle R_g^2 \rangle_{\text{cyclic}}/\langle R_g^2 \rangle_{\text{linear}}$ = 0.50 ± 0.03 over a wide range of molecular weights (80.0−200 kDa), as depicted in Figure 3.

Cyclic polymers also exhibit lower intrinsic viscosity ($[\eta]$) compared to their linear analogues.[45,49,50] Figure 4 depicts a Mark−Houwink−Sakurada (MHS) plot of **cPEA** and **PEA**, which resulted in MHS $a$ values of 0.694 and 0.664, respectively, indicating that the two polymers behave similarly as relatively flexible polymers in THF.[51] As expected, the

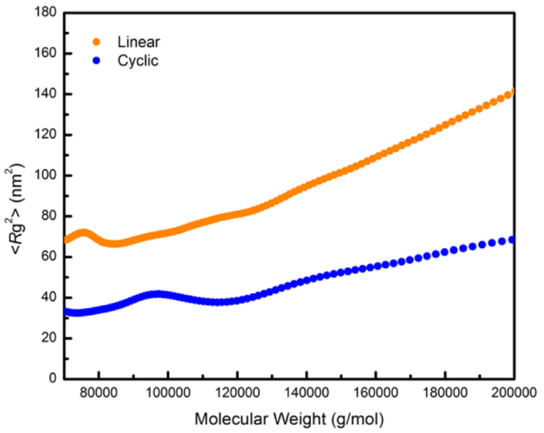


**Figure 3.** Comparison of mean square radius of gyration $\langle R_g{}^2 \rangle$ of cyclic (blue) and linear (orange) poly(4-ethynylanisole) vs molecular weight.

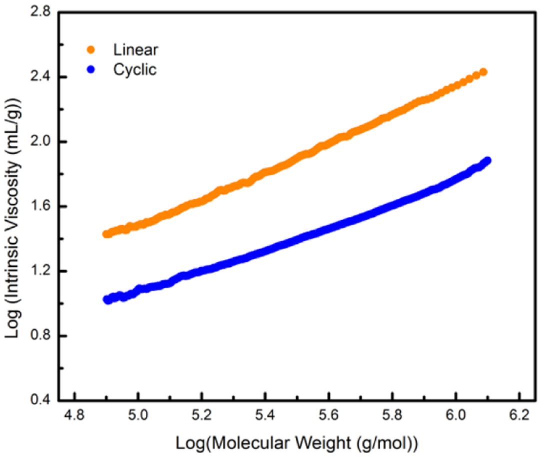


**Figure 4.** MHS plot that compares intrinsic viscosities [$\eta$] over a range of molecular masses for cyclic (blue) and linear (orange) poly(4-ethynylanisole) samples reported in THF at 35 °C.

intrinsic viscosity of the cyclic polymer is consistently lower than that of the linear polymer, a well-known phenomenon attributed to the compact chains induced by the macrocyclic structure. Over the molecular weight range of $7.90 \times 10^4$ to $1.00 \times 10^6$ Da, $[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}} = 0.33 \pm 0.06$ (Figure 4). Many experimental studies and theoretical estimations on the intrinsic viscosity ratio between cyclic and linear polymers give varied results.[50] Early theoretical estimations suggest the ratio under theta conditions ($a = 0.5$) is ∼0.65,[10,52] while more advanced estimations by Rubio suggest a ratio of 0.58 ± 0.01.[53] The experimental results are inconsistent, ranging from ∼0.5 to ∼0.8,[8,11,50] depending on molecular weight,[8,54] as well as polymer−solvent systems.[11,55] Linear impurities could be the major reason behind this inconsistency of intrinsic viscosity ratios in different studies. For example, linear impurities greatly affect the melt viscosity of cyclic polymers.[56] Similarly, linear impurities could affect the measured intrinsic viscosity of cyclic polymers in solutions.[50] Most previous studies on cyclic polymers rely on ring-closure methods, where linear impurities are unavoidable and hard to remove, preventing a reasonable consensus. Cyclic polymers made through ring expansion methods consistently exhibit lower intrinsic viscosities ($[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}}$ close to 0.4),[39,45,46,57,58] similar to the results obtained in this study for **cPEA**.

Interestingly, **PEA** and **cPEA** exhibit different colors when dissolved in solution at identical concentrations. Figure 5 depicts the UV−vis spectra of **PEA** and **cPEA** (THF, 0.5 $\mu$M). A previous study on cyclic poly(4-vinylbenzylcarbazole) revealed that the cyclic topology enhanced the fluorescence intensity of the pendent fluorophore.[59] However, the colors of **cPEA** and **PEA** come from their conjugated backbone. A potential property not yet fully explored or exploited is that cyclic polymers should exhibit longer effective conjugation lengths and higher extinction coefficients because of their more constrained geometry and fewer degrees of freedom.[60] Some preliminary evidence to support that claim is the red-shift for **cPEA** and its more intense absorption near 400 nm.

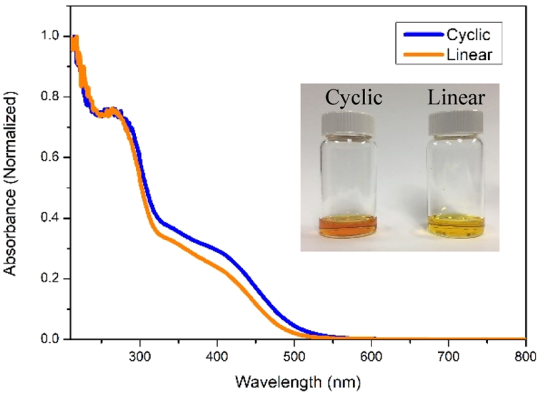
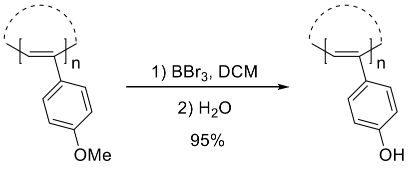


**Figure 5.** UV−vis spectra of cyclic (blue) and linear (orange) poly(4-ethynylanisole) samples (5 mM) reported in Table 1 in THF in the range from 210 to 800 nm; inside picture shows the cyclic and linear poly(4-ethynylanisole) samples in THF (5 mM).

Subjecting **cPEA** to boron tribromide, a demethylation reagent, produces alkaline-soluble cyclic poly(4-ethynylphenol) (**cPEP-OH**) (Scheme 2). Dissolving **cPEA** in dichloromethane results in an orange solution. Upon adding $BBr_3$, the solution turns purple. Quenching the reaction with water after 5 h followed by adding the resulting solution to stirring methanol yields a purple, homogeneous solution, as the polymer is now methanol-soluble, consistent with previously reported linear polyhydroxyphenylacetylene.[61] Concentrating the resulting methanol solution and adding it to stirring hexanes provides a red-purple polymer precipitate in 95% yield. The color is consistent with previously reported poly(p-hydroxyphenylacetylene).[61] Demethylation was 95% efficient as determined by $^1$H NMR spectroscopy by monitoring the residual methoxy resonance at 3.5 ppm. In addition, a Fourier-transform infrared spectroscopy spectrum of the polymer exhibits a broad absorption centered at 3010 cm$^{-1}$ for the phenolic OH stretching vibrations. Performing the same procedure for the linear polymer provides linear poly(4-ethynylphenol) (**PEP-OH**). Both the linear and cyclic **PEP-**

**Scheme 2. Synthesis of Cyclic Poly(4-ethynylphenol) via Demethylation of Cyclic Poly(4-ethynylphenol) with $BBr_3$**



**OH** are red-purple solids, and their methanol solutions exhibit minimal absorption near 400 nm (Figure 6), indicating a short

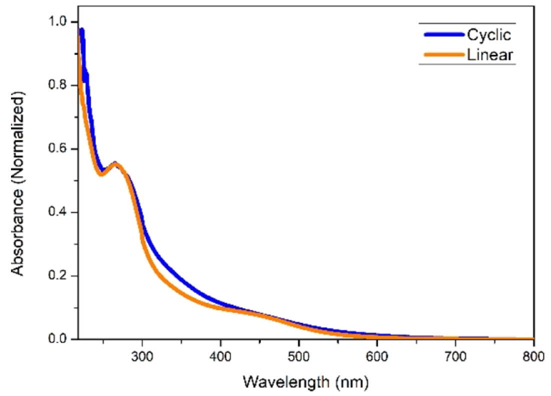


**Figure 6.** UV−vis spectra of cyclic (blue) and linear (orange) poly(4-ethynylphenol) in methanol.

backbone conjugation length, but no obvious difference between the cyclic and linear versions, other than a slight increase in intensity between 300 and 400 nm for **cPEP-OH**.

The topology of **PEP-OH** and **cPEP-OH** should remain after demethylation, as boron tribromide is not reactive toward C═C double bonds. **PEP-OH** and **cPEP-OH** are insoluble in THF; their molecular weights were measured by a GPC equipped with a multi-angle light scattering detector and *N*,*N*-dimethylacetamide as the mobile phase. The GPC data reveal molecular weights close to their precursors (Table 1). Both

**Table 1. Number-Average Molecular Weight ($M_n$) and Dispersity ($Đ$) of Cyclic and Linear Poly(4-ethynylanisole)**

| sample | $M_n$ (Da) | $Đ$ |
|---|---|---|
| **PEA** | 79 300 | 1.60 |
| **cPEA** | 96 500 | 1.43 |
| **PEP-OH** | 72 300 | 1.41 |
| **cPEP-OH** | 86 900 | 1.18 |

**PEP-OH** and **cPEP-OH** are insoluble in neutral aqueous solution. However, transforming the polymers by deprotonating the phenol groups creates highly water-soluble polyelectrolytes. A green solution forms by adding **cPEP-OH** to a sodium hydroxide solution at pH of 11. With the phenol groups deprotonated to phenoxide, **cPEP-OH** transforms to poly(sodium 4-ethynylphenoxide) (**cPEP-ONa**), a green polyanion. The color is consistent with a previously reported linear polyanion derived from poly(hydroxyphenylacetylene).[61] Acidifying the aqueous solution protonates the polyanion to its neutral form, and **cPEP-OH** precipitates as a purple solid below pH = 10, as depicted in Figure 7, demonstrating its pH-responsive water solubility. Monitoring the UV−vis spectra of **cPEP-OH** in 10 aqueous solutions with different pH values (Figure 8) shows the trend of polymer solubility as the pH changes. As the pH increases, the resulting polyanion dissolves to give a green solution and an obvious absorption at 655 nm. When the pH drops below 11, the polymer is insoluble. Plotting the absorbance at 294 nm versus pH reveals a sharp increase in solubility that suggests a p$K_a$ = 11 (Figure 9). Linear **PEP-OH**, prepared with a similar $M_n$ reveals nearly identical pH-responsiveness.

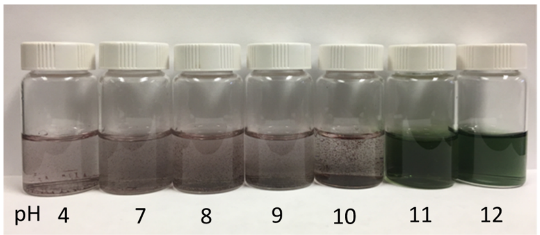


**Figure 7.** Color of cyclic poly(4-ethynylphenol) in different pH aqueous solutions: insoluble purple solids suspended in solutions with a pH lower than 11 and green solutions with a pH greater than 11.

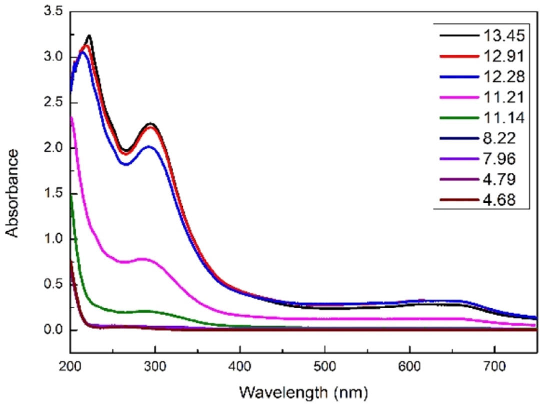


**Figure 8.** UV−vis spectra of cyclic poly(4-ethynylphenol) in different pH aqueous solutions.

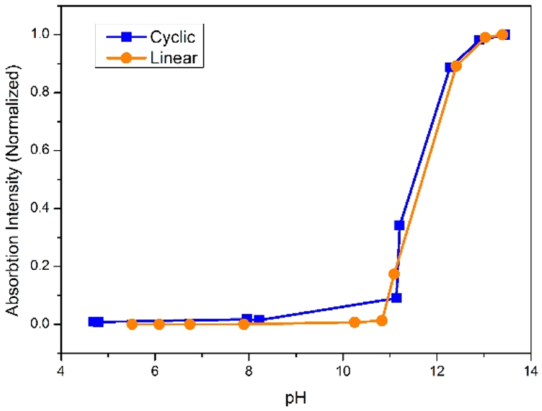


**Figure 9.** Absorption intensity at 294 nm of cyclic and linear poly(4-ethynylphenol) samples in different pH aqueous solutions plotted against the pH value.

## ■ CONCLUSIONS

This study reports the first example of ring-expansion polymerization to prepare pH-responsive cyclic polymers. Comparing the solution size and intrinsic viscosity of **cPEA** and **PEA** provides evidence for cyclic topology. Interestingly, **cPEA** and **PEA** in solution and the solid-state have different colors, suggesting a longer conjugation length for **cPEA**. Postpolymerization demethylation of **cPEA** exposes phenol groups in the cyclic polymer. This was an important realization because monomer 4-ethynylphenol is incompatible with catalyst **1**, due to the acidity of the phenol group. The cyclic polyphenol **cPEP-OH** exhibits pH-responsive water solubility, though its response is nearly identical to the linear version. Because the thermal properties of cyclic versus linear polymers are potentially more dramatic, future efforts will focus on creating thermally responsive cyclic polymers and delineating the possibility that cyclic polymers are inherently more conjugated.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.9b01307.

Full experimental procedures, NMR spectra, GPC data, and UV–vis spectra (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: sumerlin@chem.ufl.edu (B.S.S.).
*E-mail: veige@chem.ufl.edu (A.S.V.).

### ORCID

Tomohiro Kubo: 0000-0003-3913-5845
Brent S. Sumerlin: 0000-0001-5749-5444
Adam S. Veige: 0000-0002-7020-9251

### Author Contributions

Z.M. synthesized **cPEA**, **PEA**, **cPEP-OH**, and **PEP-OH**, characterized all the polymers via NMR spectroscopy and via UV–vis spectroscopy, studied the pH responsibility of **cPEP-OH** and **PEP-OH** via the UV–vis absorption measurement. T.K. and D.P. characterized **cPEA**, **PEA**, **cPEP-OH**, and **PEP-OH** with GPC, dynamic light scattering, SLS, and solution viscometry. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. A.S.V. and B.S.S. directed the research and edited the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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