Organic LETTERS
Letter
pubs.acs.org/OrgLett

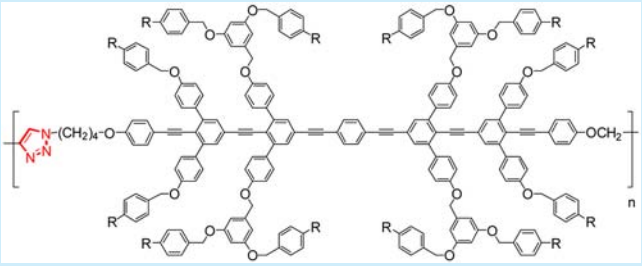
Synthesis and Higher-Order Structure of Linear Dendrimeric Assemblies

Saori Nishioka, Shirou Morita, Keiji Okada, Shuichi Suzuki, and Masatoshi Kozaki*

Graduate School of Science, Osaka City University, 3-3-138, Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

S *Supporting Information*

ABSTRACT: A series of linear covalent assemblies of dendrimers with conjugated backbones were synthesized by means of an iterative divergent and convergent method in which copper-catalyzed acetylene−azide cycloaddition reactions were used to form flexible linkages. UV−vis and fluorescence spectra indicate that dendrimeric assemblies have a strong propensity to adopt folded conformations in which conjugated backbones adopt planar conformations. The folded conformation is stabilized by strong attractive van der Waals and dipole−dipole interactions between the dendrimers.



Systematic integration of dendrimers is attractive for the construction of precisely designed nanoscale molecular devices.[1] Recently, we synthesized a shape-persistent assembly by using the intermolecular coupling of dendrimers with conjugated backbones.[2] In nature, proteins perform sophisticated biological operations with their ordered three-dimensional structures formed by folding the linear peptide chains into compact and specific conformations.[3] The folded form of protein is stabilized by van der Waals and dipole−dipole attractions. It might be possible to fabricate a compact three-dimensional structure by folding a linear dendrimeric assembly. Judging from a successful self-assembling production of periodic arrays with dendrons and dendrimers, it is possible to form intramolecular contacts between dendrimer units that provide sufficient van der Waals and dipole−dipole attraction for stabilization of the folded form.[4,5] Although the intermolecular aggregation of dendrons and polymers with dendritic side chains has been reported in the solid state, the intramolecular aggregation in solution is relatively unexplored. An effective synthetic method for the preparation of a linear assembly of dendrimers should be developed to test the folding approach for forming dendrimeric assemblies. Click chemistry is attractive for this purpose owing to its efficiency and versatility as required for connecting the dendrimers.[2b,6] Here, we design a powerful iterative divergent/convergent methodology to construct a linear assembly of dendrimers with precisely controlled lengths by using the copper-catalyzed acetylene−azide cycloaddition (CuAAC) reaction.[7] We obtained linear dimers, tetramers, and octamers of the dendrimer using the proposed method. Spectroscopic investigation of the conformation of the conjugated chain disclosed that the assemblies have a strong propensity to adopt folded conformations as they afford a unique stabilization effect.

The divergent/convergent synthesis based on the CuAAC reactions shown in Scheme 1 starts from monomer **D1** that has a bromo functional group at one end and a TMS-protected ethynyl group at the other end (Figure 1). Monomer **D1** was prepared by applying the previously reported convergent synthetic method for dendrimers with conjugated backbones (Schemes S1−S3).[8] Monomer **D1** was divided into two portions. In one portion, a bromo group was substituted by an azide group by heating **D1** with sodium azide in DMF to produce **D1-AZ** in 84% yield. In the other portion, the TMS protecting group in **D1** was removed by treatment with sodium carbonate in a methanol−dichloromethane solution to afford **D1-EN** in 95% yield. The CuAAC reaction of **D1-EN** and **D1-AZ** was carried out at room temperature using copper iodide, *N*,*N*-diisopropylethylamine, and THF as a catalyst, an additive, and a solvent, respectively, to afford dimer **D2** in 56% yield.[9]

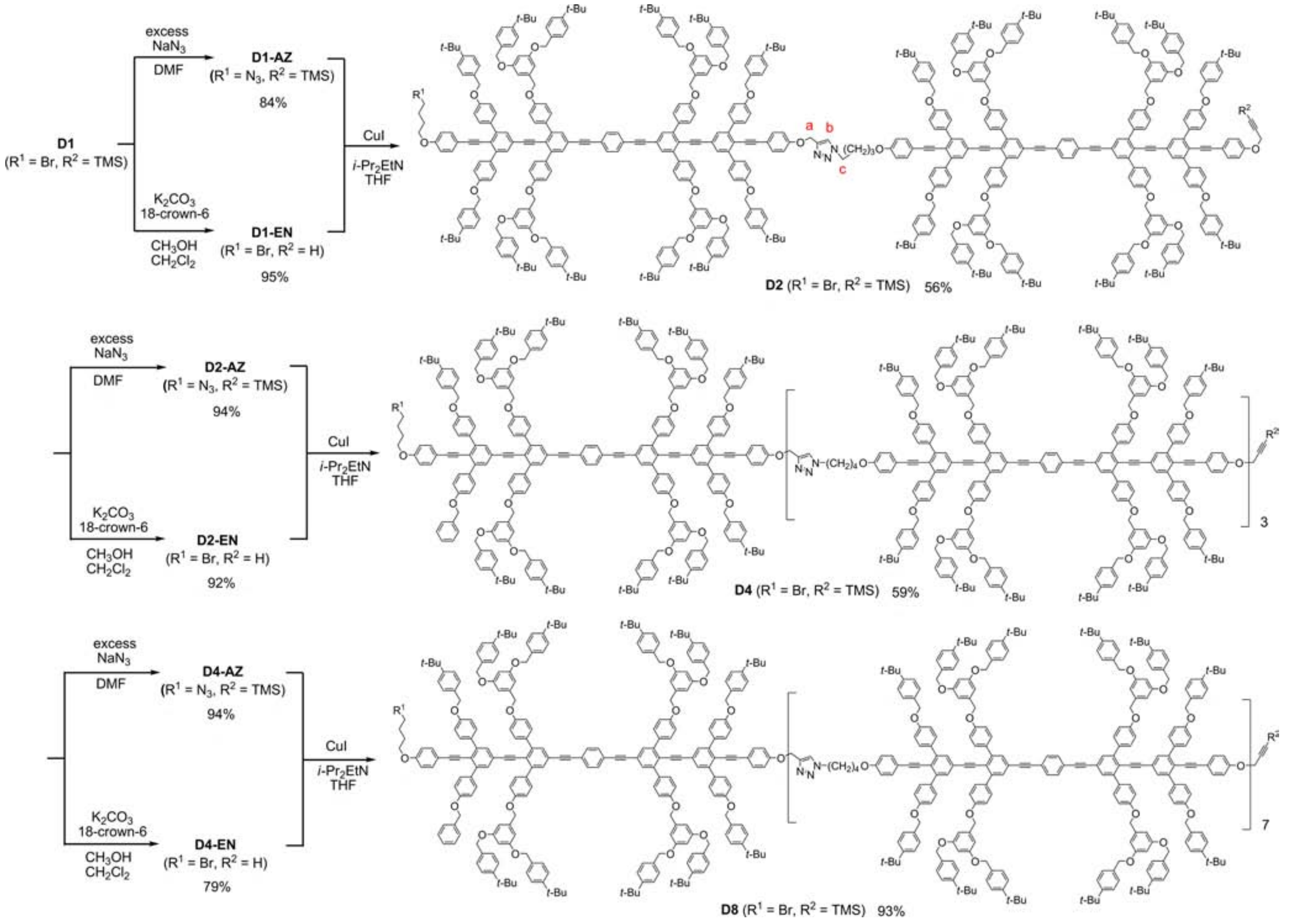
Dimer **D2** has identical terminals groups to **D1**. The activation processes similar to those described above were carried out for **D2** to form activated dimer **D2-EN** and **D2-AZ** in 92% and 94% yields, respectively. The CuAAC reaction of **D2-EN** and **D2-AZ** produced tetramer **D4** in 59% yield. Tetramer **D4** underwent analogous activation and CuAAC reaction processes to afford octamer **D8**.

^{1}H NMR spectra of **D1**, **D2**, **D4**, and **D8** in 1,1,2,2-tetrachloroethane-d_2 are shown in Figures S1 and S2. Although **D1**, **D2**, **D4**, and **D8** showed broad ^{1}H NMR signals at room temperature, their well-resolved signals were observed at 130 °C. The formation of the triazole ring in **D2** was undoubtedly confirmed by the isolated singlet signal at 7.47 ppm assignable to ring protons H_b (Scheme 1). In addition, characteristic signals for methylene units adjacent to the triazole ring were observed at 5.15 ppm (H_a) and 4.37 ppm (H_c) for **D2**. The corresponding signals were observed for both **D4** and **D8**. Except for the signals of the linkage units, **D2**, **D4**, and **D8** are nearly identical in spectral shape to **D1**. These results suggest

Received: April 18, 2015
Published: May 15, 2015

DOI: 10.1021/acs.orglett.5b01137
Org. Lett. 2015, 17, 2720−2723

Scheme 1. Iterative Convergent/Divergent Synthesis of Octamer D8



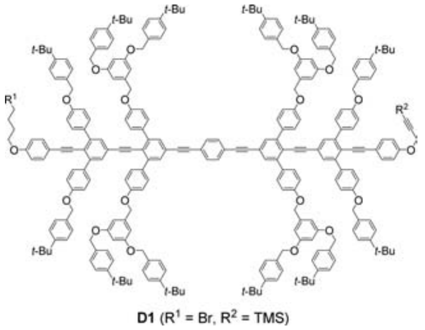


Figure 1. Chemical structure of **D1**.

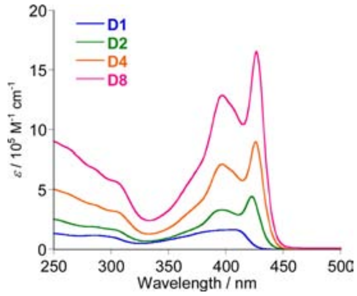


Figure 2. Absorption spectra of **D1** (blue), **D2** (green), **D4** (orange), and **D8** (red) measured in CH$_2$Cl$_2$ at 20 °C.

that dendrimer units in these assemblies show insignificant interaction in solution at 130 °C. In the MALDI-TOF MS, well resolved molecular ion peaks were observed for monomer **D1** (MW = 3936), dimer **D2** (7762), and tetramer **D4** (15 414) at m/z = 3937, 7763, and 15415, respectively (Figure S3). In addition, a series of fragment ions generated by the cleavage of an ether bond in dendritic chains was detected.[2] In the case of octamer **D8** (MW = 30 719), a broad peak centered at m/z = 30 608 was observed.

UV–vis absorption spectra of **D1**, **D2**, **D4**, and **D8** in dichloromethane at 20 °C are compared in Figure 2. In addition to the absorption of benzyl ether chains (285 nm), monomer **D1** also showed a $\pi-\pi^*$ absorption band owing to phenylene-ethynylene (PE) units (λ_{max} = 407 nm).[8] The spectral shape of the $\pi-\pi^*$ band of PE units is almost similar to that reported for PE oligomers with identical length in solution.[10] On the other hand, assemblies **D2**, **D4**, and **D8** showed completely different spectral shapes. PE units in **D2** showed a narrow absorption band at λ_{max} = 423 nm, besides showing a broad absorption band at λ_{max} = 396 nm. While there are negligible differences in the location of absorption maxima between **D2**, **D4**, and **D8**, molar absorptivity increases linearly with the number of dendrimer units. Similar spectra were observed in toluene and DMF. Surprisingly, the observed shapes of the absorption band for PE units in **D2**, **D4**, and **D8** in solution are similar to those reported for an amorphous spin-cast film of PE polymers and randomly oriented aggregates of PE oligomers and polymers in solution.[10] Bunz and co-workers have established that a narrow absorption band in the longer-wavelength region appears because of the planarization of PE chains.[11] These results indicate that PE chains in **D2**, **D4**, and **D8** adopt planar conformation and that they randomly aggregate in solution. The absorption spectra of **D2** show negligible concentration dependency at 20 °C when the concentration in dichloromethane varies from 2.72×10^{-6} M to 2.72×10^{-7} M (Figure S4). The negligible concentration dependency was also observed for both **D4** and **D8** as shown in Figure S4. These results suggest that the observed spectral feature arises mainly because of the intramolecular mechanism (vide infra).

The fluorescence spectra of **D2**, **D4**, and **D8** in degassed dichloromethane further support the aggregation of their PE unit assemblies (Figure 3). The excitation of PE units in **D1** at 395 nm resulted in the appearance of a structured band ($\lambda_{\text{EM-max}}$ = 425 nm, λ_{EM} = 450 nm (shoulder)) with a comparatively small Stokes shift. These observations are in accordance with those reported for nonaggregated PE oligomers with identical repeat units.[10] On the other hand, **D2** showed broad fluorescence bands at the longer-wavelength region ($\lambda_{\text{EM-max}}$ = 439 and 489 nm). These emission bands can be reasonably assigned to excimer-like interchain excited states of PE oligomers.[10,11] Because the diluted solution was used for the fluorescence measurement, the formation of intramolecular excimer-like states is proposed. A similar spectral feature was observed for both **D4** ($\lambda_{\text{EM-max}}$ = 442 and 486 nm) and **D8** ($\lambda_{\text{EM-max}}$ = 441 and 491 nm).

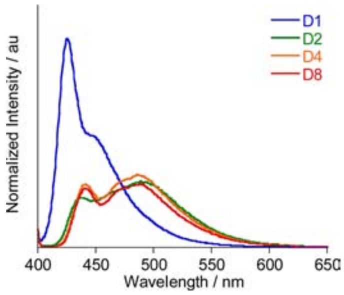


Figure 3. Fluorescence spectra of **D1** (blue), **D2** (green), **D4** (orange), and **D8** (red) measured in CH_2Cl_2 at rt (λ_{EX} = 395 nm). Fluorescence intensities are showed after normalizing the absorbance at excitation wavelength.

To gain mechanistic insight into the observed difference of the absorption spectra, the temperature dependency of the absorption spectra of **D1**, **D2**, **D4**, and **D8** was investigated in 1,1,2,2-tetrachloroethane by varying the temperature from −10 to 90 °C. The observed spectral changes of both **D1** and **D8** are summarized in Figure 4. The corresponding data for **D2** and **D4** are shown in Figure S5. Octamer **D8** has a broad absorption band with $\lambda_{\max}$ = 399 nm at 90 °C. The spectrum is similar to that observed for **D1** at 90 °C, indicating a negligible intramolecular interaction among dendrimer units in **D8** at 90 °C. When the temperature was lowered to −10 °C, a narrow band was observed at the longer-wavelength region ($\lambda_{\max}$ = 427 nm at −10 °C). The thermochromic changes for **D2** and **D4** were similar to those observed for **D8**, whereas **D1** showed a significantly different thermochromic behavior. Lowering the temperature of the **D1** solution resulted in a progressive red shift of the $\pi-\pi^*$ absorption band of PE units from $\lambda_{\max}$ = 399 nm at 90 °C to $\lambda_{\max}$ = 412 nm at −10 °C. A shaped absorption band with weak intensity newly appeared in the longer-wavelength region. Monomer **D1** showed a moderate change in its thermochromics compared to that shown by **D2**, **D4**, and **D8**.

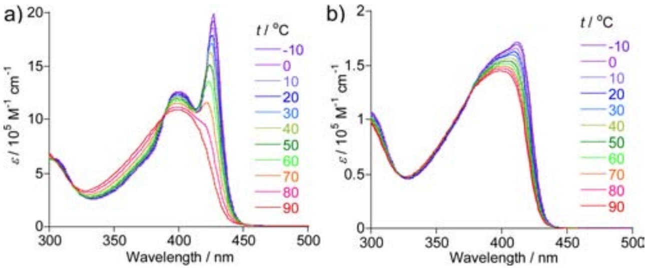


Figure 4. Variable-temperature UV−vis absorption spectra of (a) **D8** and (b) **D1** in $CHCl_2CHCl_2$.

We propose the following mechanism for the observed thermochromism in **D1**, **D2**, **D4**, and **D8**. The resemblance among the PE absorption bands of **D1**, **D2**, **D4**, and **D8** at 90 °C suggests that the PE units of the dendrimers do not have any significant preference for a particular conformation and each dendrimer unit behaves independently in solution. As the temperature decreases, the population of conformers with relatively planar conjugated chains increases owing to the van der Waals and dipole−dipole interaction between dendritic side chains in each dendrimer unit.[5,12] This intradendrimer mechanism seems to be responsible for the origin of the thermochromism of monomer **D1**. The moderate temperature dependency of **D1** absorption suggests that van der Waals and dipole−dipole interactions between dendritic branches provide a limited driving force for the transformation of twisted conformers to planar conformers (Figure 5a,b). Intense absorption bands at ca. 430 nm for **D2**, **D4**, and **D8** indicate a much higher population of planar conformers at low temperatures compared to that observed for **D1**. The well-established retrostructural analysis for the self-organization of the Percec-type dendrons suggests that dendrons with small solid angles adopt wedge-shaped conformations and self-assemble into columnar structures.[4] The analogous self-assembling process probably takes place in **D2**, **D4**, and **D8**. As the temperature decreases, the dendrimers prefer a planar conformation and the population of the folded assembly increases (Figure 5c,d). The additional strong driving force for the planarization of PE chains is most likely afforded by van der

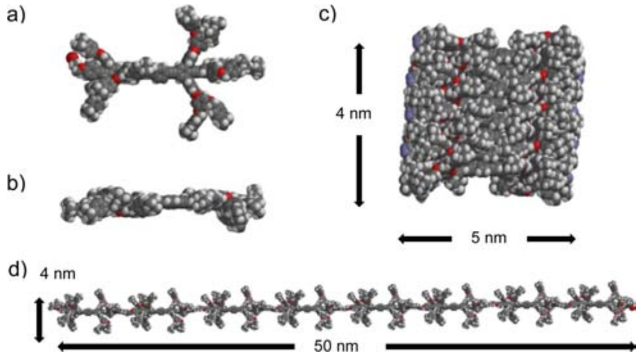


Figure 5. Computational model (PM3 and MMFF) of representative (a) nonplanar and (b) planar conformers of **D1** and (c) folded and (d) extended conformers of **D8**. Carbon, hydrogen, oxygen, and nitrogen atoms are gray, white, red, and blue, respectively.

Waals and dipole−dipole interactions between dendrimer units. As the assemblies are folded, dendrimer units are forced to adopt a planar structure. The more planar conformer furnishes stronger van der Waals and dipole−dipole attractions owing to the larger contact area. The PE units in the folded assemblies are locked into a planar conformation.

Dynamic light scattering (DLS) of **D8** in 1,1,2,2-tetrachloroethane (1.0×10^{-4} M) was measured at 20 and 60 °C to investigate the thermal effect on the higher-order structure of the linear assembly of dendrimers. The DLS data showed that the average particle sizes at 20 and 60 °C were about 11 and 360 nm, respectively (Figure S6). The approximate size of **D8** is estimated by PM3 and MMFF (Merck molecular force field) calculations as 50 nm × 4 nm × 4 nm and 4 nm × 4 nm × 5 nm for the fully extended and folded structure, respectively (Figure 5c,d).[13] With systematic error in a particle size in DLS data taken into consideration, the results are quantitatively consistent in the above thermochromic mechanism. Since a relatively high concentration of **D8** is used for the DLS measurement to maintain sufficient intensity of the scattered light, the effect of the intramolecular aggregation on the observed results cannot be ruled out.

In conclusion, we designed a folding approach for fabricating a dendrimeric assembly. Dendrimers were connected with flexible linkers by the iterative convergent and divergent method based on the CuAAC reaction. These assemblies adopt surprisingly stable folded structures in organic solvents. Notably, 1,1,2,2-tetrachloroethane is the best solvent for monitoring the thermally induced unfolding process. A partial unfolding was observed in toluene at 90 °C. It is surprising that the entropically unstable folded form is stabilized by relatively weak van der Waals and dipole−dipole interactions. In contrast, aggregation of the dialkyl substituted PE oligomer or polymer was observed in poor solvent or in the solid state.[11] These results suggest the presence of considerably strong attractive interactions between dendrimeric units. The large contact area of the planar dendrimer probably produces strong attractive van der Waals and dipole−dipole interactions. PE chains in the folded assembly are forced to adopt a planar conformation. Planar PE chains are reported as a superior molecular wire for both energy and charge transfers.[14] Thus, the PE network in the folded assembly is a promising scaffold for the construction of molecular devices.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization of all new compounds, spectra, absorption and fluorescence spectra, and DLS histograms. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01137.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kozaki@sci.osaka-cu.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS (No. 23350022) and financial support Grant-in-Aid for Scientific Research on Innovative Areas “New Polymeric Material based on Element-blocks” from MEXT (No. 25102536). We thank for Otsuka Electronics for DLS measurements.

■ REFERENCES

(1) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*; VCH: Weinheim, Germany, 2001. (b) Fréchet, J. M. J.; Tomalia, D. A.; *Dendrimers and other Dendritic Polymers*; John Wiley & Sons: New York, 2002. (c) Newkome, G. R.; Shreiner, C. *Chem. Rev.* **2010**, *110*, 6338−6442. (d) Astruc, D.; Boisselier, E.; Ornelas, C. *Chem. Rev.* **2010**, *110*, 1857−1959. (e) Kozaki, M.; Suzuki, S.; Okada, K. *Chem. Lett.* **2013**, *42*, 1112−1118.

(2) (a) Kozaki, M.; Tujimura, H.; Suzuki, S.; Okada, K. *Tetrahedron Lett.* **2008**, *49*, 2931−2934. (b) Kozaki, M.; Morita, S.; Suzuki, S.; Okada, K. *J. Org. Chem.* **2012**, *77*, 9447−9457.

(3) Petsko, G. A.; Ringe, D. *Protein Structure and Function*; New Science Press: London, 2004.

(4) (a) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.* **2009**, *109*, 6275−6540. (b) Rudick, J. G.; Percec, V. *Acc. Chem. Res.* **2008**, *41*, 1641−1652.

(5) For self-assembling dendrimers, see: (a) Apperloo, J. J.; Janssen, R. A. J.; Malenfant, P. R. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6916−6924. (b) Tomovic, Z.; Van Dongen, J.; George, S. J.; Xu, H.; Pisula, W.; Leclere, P.; Smulders, M. M. J.; De Feyter, S.; Meijer, E. W.; Schenning, A. *J. Am. Chem. Soc.* **2007**, *129*, 16190−16196.

(6) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (b) Macdonell, A.; Johnson, N. A. B.; Surman, A. J.; Cronin, L. *J. Am. Chem. Soc.* **2015**, *137*, 5662−5665. (c) Wan, J.; Huang, J. X.; Vetter, I.; Mobli, M.; Lawson, J.; Tae, H.-S.; Abraham, N.; Paul, B.; Cooper, M. A.; Adams, D. J.; Lewis, R. J.; Alewood, P. F. *J. Am. Chem. Soc.* **2015**, *137*, 3209−3212.

(7) For the iterative convergent−divergent approach, see: (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537−553. (b) Xu, Z.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537−4550.

(8) (a) Kozaki, M.; Okada, K. *Org. Lett.* **2004**, *6*, 485−488. (b) Kozaki, M.; Akita, K.; Okada, K. *Org. Lett.* **2007**, *9*, 1509−1512. (c) Uetomo, A.; Kozaki, M.; Suzuki, S.; Yamanaka, K.; Ito, O.; Okada, K. *J. Am. Chem. Soc.* **2011**, *133*, 13276−13279.

(9) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018−8021.

(10) Feng, F. D.; Yang, J.; Xie, D. P.; McCarley, T. D.; Schanze, K. S. *J. Phys. Chem. Lett.* **2013**, *4*, 1410−1414.

(11) (a) Bunz, U. H. F. *Acc. Chem. Res.* **2001**, *34*, 998−1010. (b) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605−1644. (c) Miteva, T.; Palmer, P.; Kloppenburg, L.; Neher, D.; Bunz, U. H. F. *Macromolecules* **2000**, *33*, 652−654. (d) Fiesel, R.; Halkyard, C. E.; Rampey, M. E.; Kloppenburg, L.; Studer-Martinez, S. L.; Scherf, U.; Bunz, U. H. F. *Macromol. Rapid Commun.* **1999**, *20*, 107−111. (e) Bunz, U. H. F. *Macromol. Rapid Commun.* **2009**, *30*, 772−805. (f) Bunz, U. H. F.; Imhof, J. M.; Bly, R. K.; Bangcuyo, C. G.; Rozanski, L.; Bout, D. A. V. *Macromolecules* **2005**, *38*, 5892−5896.

(12) (a) Li, W. S.; Jiang, D.-L.; Aida, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2943−2947. (b) Kozaki, M.; Akita, K.; Okada, K.; Islam, D.-M. S.; Ito, O. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1223−1237.

(13) Spartan ’14, Wavefunction, Inc., Irvine, CA.

(14) (a) Pettersson, K.; Kyrychenko, A.; Rönnow, E.; Linugdahi, T.; Mårtensson, J.; Albinson, B. *J. Phys. Chem. A* **2006**, *110*, 310−318. (b) Seminario, J. M.; Zacarias, A. G.; Tour, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 3970−3974. (c) Sugiyasu, K.; Honsho, Y.; Harrison, R. M.; Sato, A.; Yasuda, T.; Seki, S.; Takeuchi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14754−14756. (d) Sukegawa, J.; Schubert, C.; Zhu, X.; Tsuji, H.; Guldi, D. M.; Nakamura, E. *Nat. Chem.* **2014**, *6*, 899−905.