JOC*Note*

A Clue to Elusive Macrocycles: Unusually Facile, Spontaneous Polymerization of a Hexagonal Diethynylbenzene Macrocycle

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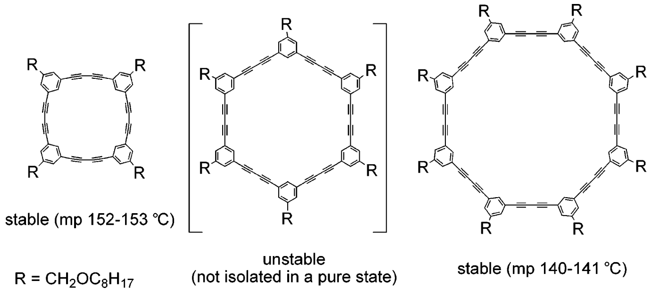
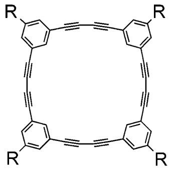
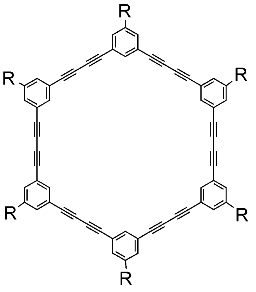


A hexagonal diethynylbenzene macrocycle having exterior octyloxymethyl groups undergoes spontaneous polymerization at room temperature to form hardly soluble materials, in contrast to the corresponding dehydrotetramer and dehydrooctamer, which are stable enough to show their melting points at higher than 140 °C.

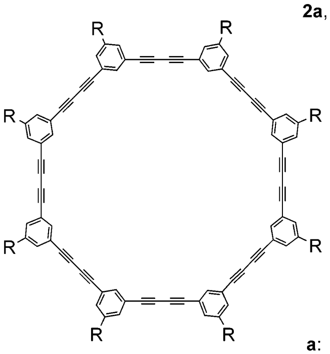
Macrocyclic phenylene ethynylene and phenylene butadiynylene dehydrooligomers constitute a central class of shape-persistent macrocycles and dehydrobenzoannulenes that have been attracting much interest principally because of their self-organizing properties[1] and optoelectronic applications,[2] respectively. These compounds are typically prepared by Cu(II)-mediated oxidative coupling reactions between terminal alkynes or by Pd(0)-catalyzed cross-coupling between sp and sp^2 carbons. However, it has been sometimes observed that macrocycles of certain ring size were elusive, especially in the case of phenylene butadiynylene macrocycles,[3,4] even though they did not seem to be particularly disfavored in terms of enthalpy (i.e., ring strain) and entropy of the ring formation. This unusual behavior can be attributed to (i) low solubility of the macrocycle, which hampers isolation, (ii) steric requirement for coordination to the transition metal centers, which would raise the transition state energy of the ring formation, or (iii) consumption of the product due to secondary reactions. Although in some cases the reason for the elusive macrocycle was ascribed to its low solubility,[4e] the second and third instances have not been proven experimentally. During the course of preparation of diethynylbenzene macrocycles (DBMs)[3,5] having extraannular alkoxymethyl substituents, we encountered a case for the third instance, which is the topic of this Note, though the reason for the unusual behavior is not understood. Namely, the dehydrohexameric macrocycle **2a** underwent spontaneous polymerization, while the corresponding tetramer **1a** and octamer **3a** were robust enough to show their melting points at ca. 140−150 °C. This Note also reports an alternative route to unsymmetrically substituted dehydrodimer unit **8** through the use of (trimethylsilyl)butadiyne (TMSB).



1a, **1b**



2a, **2b**



3a, **3b**

a: R = $CH_2OC_8H_{17}$
b: R = $CO_2C_8H_{17}$

As a part of our study on the one- and two-dimensional self-assembly of DBMs such as **1b**−**3b**,[3a,5a,c] we planned to prepare octyloxymethyl-substituted DBMs **1a**−**3a**.[6] To this end, we first improved the synthetic method for the key intermediate, dehydrodimer unit **8**, by the use of (trimethylsilyl)butadiyne

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[1] For recent reviews, see: (a) Grave, C.; Schlüter, A. D. *Eur. J. Org. Chem.* **2002**, 3075−3098. (b) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807−818. (c) Höger, S. *Chem.*−*Eur. J.* **2004**, *10*, 1320−1329. (d) Höger, S. In *Acetylene Chemistry, Chemistry, Biology and Material Science*; Diederich F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 427−452.

[2] For recent reviews, see: (a) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81−130. (b) Marsden, J. A.; Palmer, G. I.; Haley, M. M. *Eur. J. Org. Chem.* **2003**, 2355−2369. (c) Bunz, U. H. F. *Top. Curr. Chem.* **1999**, *201*, 131−161. (d) Bunz, U. H. F.; Rubin, Y.; Tobe, Y. *Chem. Soc. Rev.* **1999**, *28*, 107−119. (e) Youngs, W. J.; Tessier, C. A.; Bradshaw, J. D. *Chem. Rev.* **1999**, *99*, 3153−3180.

[3] For *m*-diethynylbenzene macrocycles, see: (a) Tobe, Y.; Utsumi, N.; Kawabata, K.; Naemura, K. *Tetrahedron Lett.* **1996**, *37*, 9325−9328. (b) Tobe, Y.; Utsumi, N.; Nagano, A.; Sonoda, M.; Naemura, K. *Tetrahedron* **2001**, *57*, 8075−8083.

[4] For dehydrobenzo[18]annulene, see: (a) Eglinton, G.; Galbraith, A. R. *Proc. Chem. Soc., London* **1957**, 350−351. (b) Behr, O. M.; Eglinton, G.; Raphael, A. R. *Chem. Ind.* **1959**, 699−700. (c) Eglinton, G.; Galbraith, A. R. *J. Chem. Soc.* **1960**, 3614−3625. (d) Zhou, Q.; Carroll, P. J.; Swager, T. M. *J. Org. Chem.* **1994**, *59*, 1294−1301. (e) Wan, W. B.; Brand, S. C.; Pak, J. J.; Haley, M. M. *Chem.*−*Eur. J.* **2000**, *6*, 2044−2052.

[5] (a) Tobe, Y.; Utsumi, N.; Nagano, A.; Naemura, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 1285−1287. (b) Tobe, Y.; Nagano, A.; Kawabata, K.; Sonoda, M.; Naemura, K. *Org. Lett.* **2000**, *2*, 3265−3268. (c) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350−5364.

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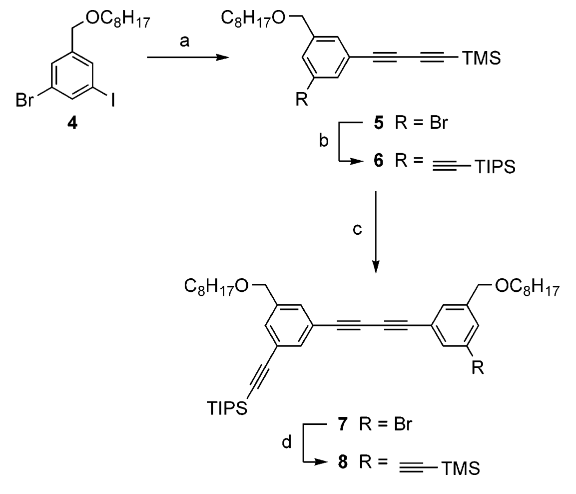
SCHEME 1[a]



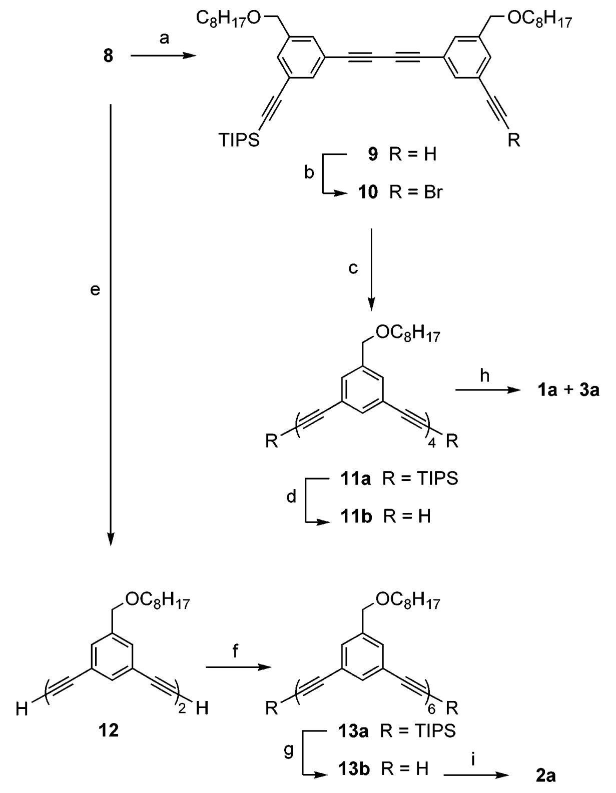
[a] Reagents and conditions: (a) $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, PPh_3, Et_3N, TMSB, 50 °C, 90%; (b) $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, PPh_3, Et_3N, TIPSA, 75 °C, 91%; (c) K_2CO_3, THF, MeOH, rt, then $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, PPh_3, Et_3N, **4**, 50 °C, 96%; (d) $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, PPh_3, Et_3N, TMSA, 75 °C, 96%.

(TMSB)[7] as shown in Scheme 1. Namely, Pd-catalyzed coupling of TMSB at room temperature with 1-bromo-3-iodo-5-(octyloxymethyl)benzene (**4**) derived from the known alcohol[8] gave monosubstituted product **5** selectively in 90% yield. Subsequent coupling of **5** with (triisopropylsilyl)acetylene (TIPSA) gave **6** (91%). Selective removal of the TMS group of **6** afforded the corresponding arylbutadiyne derivative, which was used without isolation for the subsequent Pd-catalyzed coupling reaction with **4** because of its anticipated lability,[9] giving bromide **7**. Another coupling of **7** with (trimethylsilyl)acetylene (TMSA) afforded the dehydrodimer unit **8** (96%). This procedure thus provides a highly selective and high-yielding route to the unsymmetrically substituted dehydrodimer **8**.

Selective removal of the TMS group of **8** (to give **9**) followed by bromination with NBS/$AgNO_3$ furnished bromoalkyne **10** in 96% yield (Scheme 2). Oxidative coupling of **9** gave linear tetramer **11a** in 86% yield, from which deprotection of both TIPS groups afforded **11b** (95%). Cross coupling of 2 equiv of **10** with terminal alkyne **12** derived from **8** by removal of both silyl groups afforded linear dehydrohexamer **13a** in 26% yield. Deprotection of the TIPS groups of **13a** with TBAF gave **13b** (89%).

Now the stage was set for the intramolecular cyclization of the linear dehydrotetramer **11b** and dehydrohexamer **13b**. Oxidative coupling of **11b** with $Cu(OAc)_2$ under high dilution conditions afforded cyclic dehydrotetramer **1a** and dehydrooctamer **3a** in 10 and 1% yields, respectively, which were separated with preparative HPLC. These compounds are stable enough to show their melting points at 152−153 and 140−141 °C, respectively, without decomposition.[10] In contrast to the corresponding macrocycle **1b** having exterior ester substituents,[3a,5a,c] DBM **1a** did not exhibit self-association behavior in $CDCl_3$, as indicated by the absence of the chemical shift change within the concentration range of 2.2×10^{-2} to 1.6×10^{-4} M.

SCHEME 2[a]



[a] Reagents and conditions: (a) K_2CO_3, THF, MeOH, rt, 96%; (b) $AgNO_3$, NBS, acetone, rt, 99%; (c) $Cu(OAc)_2$, pyridine, rt, 86%; (d) TBAF, THF, rt, 95%; (e) TBAF, THF, rt, 96%; (f) $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, $(i\text{-}Pr)_2NH$, **10**, benzene, rt, 26%; (g) TBAF, AcOH, THF, benzene, rt, 89%; (h) $Cu(OAc)_2$, pyridine, benzene, rt, 10% for **1a**, 1% for **3a**; (i) $Cu(OAc)_2$, pyridine, benzene, rt.

In a remarkable contrast, when cyclization of linear dehydrohexamer **13b** was carried out and worked up in a similar manner, a considerable amount of yellow solid insoluble in chloroform was formed, although the reaction mixture before workup exhibited an HPLC peak most likely due to cyclic dehydrohexamer **2a**, as shown in Figure 1a. The $CHCl_3$-soluble part of the solid was subjected to preparative GPC ($CHCl_3$ eluent) to give a $CHCl_3$ solution containing **2a**. An HPLC analysis of the solution showed that it was reasonably pure (Figure 1b). The retention time of the peak in Figure 1b is consistent with that of **2a**, since it appears between those of cyclic dehydrotetramer **1a** and dehydrooctamer **3a** as shown in Figure 2. The solvent of this solution was removed quickly, and the ^1H NMR spectrum of the residue was taken as a $CDCl_3$ solution containing insoluble precipitates. The ^1H NMR spectrum showed signals due to the aromatic protons at δ 7.48 (d)

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(6) For shape-persistent macrocycles having alkoxymethyl groups, see: (a) Lehmann, U.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3483−3487. (b) Henze, O.; Lentz, D.; Schlüter, A. D. *Chem.−Eur. J.* **2000**, *6*, 2362−2367. (c) Henze, O.; Lentz, D.; Schäfer, A.; Franke, P.; Schlüter, A. D. *Chem.−Eur. J.* **2002**, *8*, 357−365. (d) Grave, C.; Lentz, D.; Schäfer, A.; Samorì, P.; Rabe, J. P.; Franke, P.; Schlüter, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 6907−6918.

(7) Bartik, B.; Dembinski, R.; Bartik, T.; Arif, A. M.; Gladysz, J. A. *New J. Chem.* **1997**, *21*, 739−750.

(8) Höger, S.; Bonrad, K.; Mourran, A.; Beginn, U.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651−5659.

(9) In general, 1-arylbutadiynes with some exceptions are known to undergo spontaneous polymerization readily upon standing at ambient temperature. For example, see: (a) Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1991**, *113*, 9803−9810. (b) Wan, W. B.; Haley, M. M. *J. Org. Chem.* **2001**, *66*, 3893−3901 and references therein.

(10) DSC analysis of **1a** revealed that it exhibited a melting transition at 147.1 °C with an endotherm of 12.85 mJ mg^{-1} followed by a large irreversible exotherm of −216.3 mJ mg^{-1} at 194.1 °C due to polymerization, giving dark brown solid.

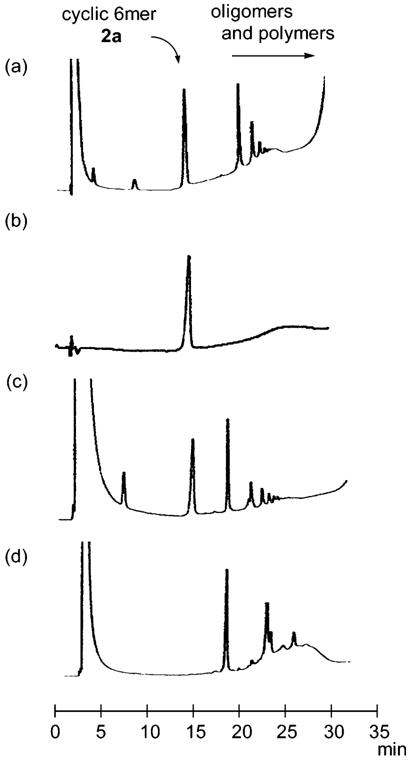

FIGURE 1. Chromatograms of HPLC analysis. (a) Reaction mixture of cyclization of **13b** after 24 h. (b) Purified cyclic dehydrohexamer **2a** by preparative GPC ($CHCl_3$ solution). (c) Sample for the ^1H NMR spectrum ($CDCl_3$ solution) immediately after NMR measurement. (d) The same sample after leaving at room temperature for 4 days. Conditions: an ODS column using CH_3CN/CH_2Cl_2 as an eluent, first with 50/50 (v/v) (0−10 min) then with a gradient to 0/100 (v/v) (10−30 min).

and 7.65 (t) ppm beside broadened peaks presumably due to polymeric materials. The observed chemical shifts are again between those of **1a** (δ 7.27 (d) and 7.80 (t)) and **3a** (δ 7.50 (d) and 7.59 (t)), consistent with dehydrohexamer **2a**. An HPLC analysis of the $CDCl_3$ solution after the NMR measurement indicated that, although it contained a substantial amount of high molecular weight materials, **2a** remained as one of the major components (Figure 1c). Removal of the solvent resulted in the complete loss of the peak due to **2a** as shown in Figure 1d. The low solubility of the $CHCl_3$-insoluble solid hampered its characterization. However, the absence of dark color as well as its IR (KBr) spectrum, which exhibits an absorption at 2221 cm^{-1}, indicates that most of the butadiyne units remained intact; the degree of polymerization must be minimal. The LD-TOF mass spectrum (see the Supporting Information) of this material showed peaks due to oligomers of **2a** up to its hexamer. These results clearly showed that cyclic dehydrohexamer **2a** survives only in a dilute solution owing to its spontaneous polymerization upon concentrating its solution.

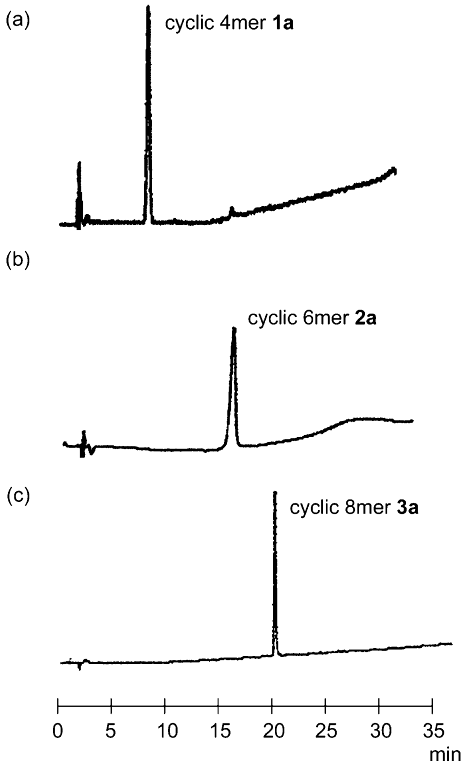

FIGURE 2. Chromatograms of HPLC analysis. (a) Cyclic dehydrotetramer **1a**. (b) Most likely cyclic dehydrohexamer **2a**. (c) Cyclic dehydrooctamer **3a**. Conditions: same as those in Figure 1.

Thus we found a remarkable difference between the kinetic stabilities of DBMs **1a**−**3a** which depend critically on the ring size. The extremely high reactivity of **2a** may be ascribed to its solid-state packing geometry, because topochemical polymerization of butadiyne derivatives has been well-known.[11] However, we are not aware of the occurrence of such a high propensity toward polymerization. These results may provide a new clue to elusive macrocycles that were not isolated.

Experimental Section

Cyclization of Linear Dehydrotetramer 11b: Cyclic Dehydrotetramer 1a and Dehydrooctamer 3a. To a solution of $Cu(OAc)_2$ (546 mg, 3.00 mmol) in 200 mL of pyridine/benzene (3:2, v/v) was added dropwise a solution of **11b** (320 mg, 300 μmol) in 100 mL of the same solvent with a Hershberg dropping funnel over 24 h under dark. After additional stirring at room temperature for 3 h, the solvent was removed in vacuo, the green residue was passed through a short plug of SiO_2, and the solvent was removed to afford crude products. The residue was purified by flash chromatography to be followed by preparative HPLC, which afforded **1a** (white solid, 32.0 mg, 10%) and **3a** (pale yellow solid, 5.6 mg, 0.9%).

1a: mp 152−153 °C; ^1H NMR (270 MHz, $CDCl_3$, 30 °C) δ 7.80 (t, $J = 1.1$ Hz, 4H), 7.27 (d, $J = 1.1$ Hz, 8H), 4.40 (s, 8H), 3.46 (t, $J = 6.7$ Hz, 8H), 1.62 (quint, $J = 6.7$ Hz, 8H), 1.42−1.25 (m, 40H), 0.89 (t, $J = 6.7$ Hz, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$, 30 °C) δ 140.3, 139.7, 128.9, 122.4, 82.5, 75.5, 71.7, 70.9, 31.9, 29.8, 29.5, 29.4, 26.3, 22.8, 14.2; IR (KBr) 2214, 1100, 880, 758, 694 cm^{-1}; MS (MALDI-TOF) m/z 1065.6 ($M^+ + H$). Anal. Calcd for $C_{76}H_{88}O_4$: C, 85.67; H, 8.32. Found: C, 85.44; H, 8.40.

3a: mp 140−141 °C; ^1H NMR (600 MHz, $CDCl_3$, 30 °C) δ 7.59 (t, $J = 1.2$ Hz, 8H), 7.50 (d, $J = 1.2$ Hz, 16H), 4.46 (s, 16H), 3.47 (t, $J = 7.2$ Hz, 16H), 1.63 (quint, $J = 6.7$ Hz, 16H), 1.38−1.25 (m, 80H), 0.89 (t, $J = 7.2$ Hz, 24H); ^{13}C NMR (150 MHz, $CDCl_3$, 30 °C) δ 140.0, 135.3, 132.0, 122.3, 80.7, 74.5, 71.6, 71.0, 31.8, 29.7, 29.4, 29.3, 26.2, 22.7, 14.1; IR (KBr) 2220, 2145, 1113, 863, 680 cm^{-1}; MS (MALDI-TOF) m/z 2129.2 (M^+).

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[11] Most of the known topochemical polymerizations of butadiyne derivatives are limited to dialkyl-substituted derivatives. See: (a) Wegner, G. *Z. Naturforsch. B* **1969**, *24*, 824−832. (b) Enkelmann, V. *Adv. Polym. Sci.* **1984**, *63*, 91−136. However, to our knowledge, one example of the light-induced polymerization of a diaryl-substituted butadiyne exists: (c) Baldwin, K. P.; Matzger, A. J.; Scheiman, D. A.; Tessier, C. A.; Vollhardt, K. P. C.; Youngs, W. J. *Synlett* **1995**, 1215−1218.

Cyclization of Linear Dehydrohexamer 13b. Detection of Cyclic Dehydrohexamer 2a. To a solution of $Cu(OAc)_2$ (32.0 mg, 176 μmol) in 25 mL of pyridine/benzene (3:2, v/v) was added dropwise a solution of linear hexamer **13b** (128 mg, 80.0 μmol) in 25 mL of the same solvent over 16 h, while the flask was covered with an aluminum foil. After additional stirring at room temperature for 8 h, the solvent was removed in vacuo, and the green residue was passed through a short plug of SiO_2. When the solution was concentrated to about 3 mL, yellow precipitates were formed, which were filtered off by a membrane filter (PTFE, pore size 0.5 μm) to afford 41.5 mg of a yellow powder. The filtrate was subjected to preparative HPLC to afford a chloroform solution of cyclic dehydrohexamer **2a**. In another run of the same scale, a $CHCl_3$ solution containing **2a** was obtained by subjecting a $CHCl_3$-soluble part of the crude product to preparative GPC. When the solvent was removed in vacuo from this solution, to observe ^{1}H NMR spectrum, 15.0 mg of yellow powder was obtained. ^{1}H NMR measurement was carried out immediately after dissolving in a $CDCl_3$ solution that still contained some precipitates (Figure S1 of the Supporting Information). The ^{1}H NMR spectrum (270 MHz, $CDCl_3$, 30 °C) exhibited peaks at δ 7.65 (t, $J = 1.4$ Hz), 7.48 (d, $J = 1.4$ Hz), 4.46 (s), and 3.48 (t, $J = 6.8$ Hz). Removal of the solvent gave again a $CHCl_3$-insoluble solid whose MALDI-TOF mass spectrum is shown in Figure S2 of the Supporting Information.

After leaving the dehydrohexamer **2a** at room temperature for 4 days, the peak corresponding to **2a** in chromatogram disappeared, at the same time forming $CHCl_3$-insoluble materials. On the other hand, in the HPLC chromatogram, new peaks including the one with a retention time of 18.5 min appeared as shown in Figure 1c,d. However, because of the small quantity of the $CHCl_3$-soluble materials, we were unable to analyze these peaks.

Supporting Information Available: Experimental procedures, characterization of new compounds not listed in the main text, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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