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Synthesis and Ring Size Effect of Macrocyclic Ethynylhelicene Oligomers

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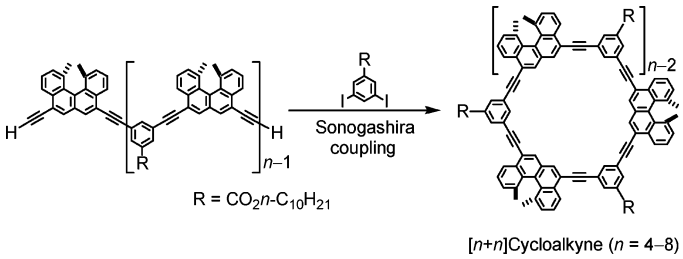
Received October 15, 2005



The cyclization of acyclic ethynylhelicene oligomers with decyl 3,5-diiodobenzoate under optimized conditions gave the corresponding optically active [*n*+*n*]cycloalkynes ($n = 4-8$) in high yields. Their structures were compared in terms of ring size by using ^{1}H NMR, UV−vis, and CD spectroscopies and vapor pressure osmometry (VPO). The UV−vis spectra exhibited an increase in absorbance in proportion to *n*. In contrast, the CD spectra of the macrocycles exhibited a large ring size effect, comparable $\Delta\epsilon$ values despite the increase in *n* and temperature-dependent properties of the [8+8]cycloalkyne. It was concluded that [4+4]cycloalkyne, [5+5]cycloalkyne, [6+6]cycloalkyne, and [7+7]cycloalkyne have rigid structures, while [8+8]cycloalkyne has a flexible structure.

Introduction

During our studies of the syntheses and properties of optically active helicenes, 1,12-dimethylbenzo[*c*]phenanthrene derivatives, the ethynylated oligomers of such derivatives turned out to aggregate in solution.[1−4] [3+3]Cycloalkyne, which is a cyclic derivative containing three helicenes and three *m*-phenylene moieties, forms strong and selective bimolecular aggregates in organic solvents, which is ascribed to the strong nonplanar $\pi-\pi$ interactions of the helicenes.[1a] On the basis of this finding, the aggregates of oligomeric [3+3]cycloalkyne were examined, the properties of which were highly dependent on the structure of the linker moiety.[2,3] As for acyclic oligomers, compounds with more than six helicenes form helix dimers, while those with less than seven helicenes form random coil structures in solution.[4] These studies showed that cyclic and acyclic ethynylhelicene oligomers could form diverse aggregate structures. However, there is as yet no study of the higher cyclic homologues of [3+3]cycloalkyne. Described here is the synthesis and spectroscopic properties of macrocyclic ethynylhelicene oligomers [*n*+*n*]cycloalkynes ($n = 4$, 5, 6, 7, and 8).[5,6]

The ring structure is important in organic chemistry. However, the ring size effect on the properties of compounds, particularly for large rings, is not yet well understood. Often, notable features appear for small ring compounds due to strain, and, above a certain ring number, the compounds exhibit similar properties independent of ring size. Such trends are also observed for ethynylarene macrocycles. Moore synthesized a series of

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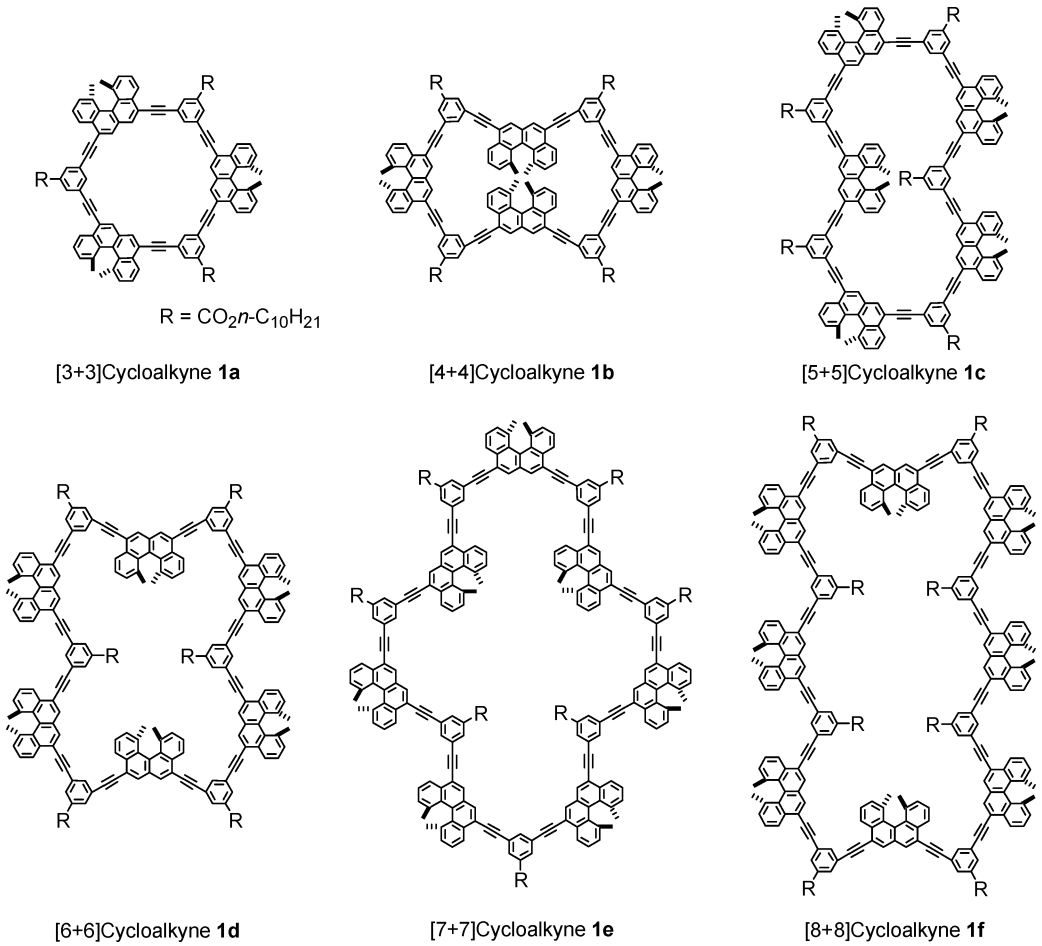
(5) Synthesis of enantiomerically pure conjugated ethynylarene macrocycles: (a) Neidlein, U.; Diederich, F. *Chem. Commun.* **1996**, 1493−1494. (b) Droz, A. S.; Diederich, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4224−4226. (c) An, D. L.; Nakano, T.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 171−173.

(6) In 1998, Fox synthesized an acetylene-bridged cyclic dimer derived from an optically active helicene: Fox, J. M.; Lin, D.; Itagaki, Y.; Fujita, T. *J. Org. Chem.* **1998**, *63*, 2031−2038.

10.1021/jo0521549 CCC: $33.50
Published on Web 12/20/2005

CHART 1



phenylacetylene macrocycles with different ring sizes, and showed the cyclic hexamer to self-aggregate in organic solvents.[7] The self- or hetero-aggregation of phenylene diethynylene macrocycles in solution was investigated by Tobe;[8] they indicated the aggregate formation of the cyclic hexamer. In both cases, macrocycles with large ring sizes showed a very weak aggregation, and the planar geometry and conformational rigidity of the hexamer were considered essential for the aggregation. Oda synthesized a series of cyclic *p*-phenylacetylenes [*n*]CPPAs ($n = 6-9$), and observed a broadening and bathochromic shift in emission spectra with a decrease in ring size due to the increased strain and rigidity of the compounds.[9] Diederich examined the ring size effect of radialenes linked by butadiyne.[10] The ring size effect is still obscure for large-ring compounds. We were therefore interested to compare higher [*n*+*n*]-cycloalkynes ($n \geq 4$) and [3+3]cycloalkyne in terms of ring size. CD could be used to study chiral ethynylhelicene macrocycles, which was not the case for the achiral ethynylarene macrocycles mentioned above.

Results and Discussion

Higher [*n*+*n*]cycloalkynes were synthesized by the method used for the [3+3]cycloalkyne **1a**,[1a] the cyclization by the Sonogashira coupling reaction[11] of acyclic ethynylhelicene oligomers[4] and the decyl 3,5-diiodobenzoate **3**. A toluene solution of the desilylated acyclic tetramer **2b** and **3** was added with a syringe-pump to a DMF/Et_3N (20/1) solution containing $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), CuI (60 mol %), Mes_3P (30 mol %), and *n*-Bu_4NI (400 mol %) over 3 h at 45 °C, and the reaction mixture was stirred for 3 h at that temperature giving the [4+4]-cycloalkyne **1b** in 28% yield (Table 1, entry 2). The yields of the higher [*n*+*n*]cycloalkynes, however, considerably decreased as ring size increased: **1e** and **1f** were obtained in less than 10% yields, which were accompanied by substantial amounts of insoluble polymers (Table 1, entries 3−6). The ineffectiveness was ascribed to the lower solubility of acyclic ethynylhelicene oligomers in DMF and to the formation of the helix dimer, particularly for **2e** and **2f**.[4]

After several trials, it was found that the yield of **1e** could be improved to 37% by using DMF/THF/Et_3N (10/10/1) solvent.

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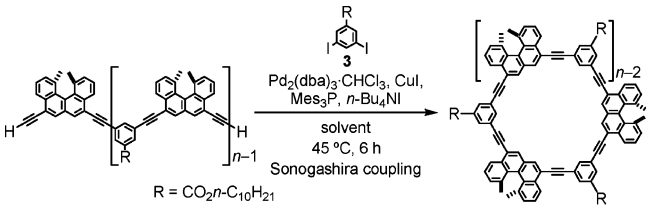
TABLE 1. Synthesis of [*n*+*n*]Cycloalkynes (*n* = 3−8)



n = 3 **2a**
n = 4 **2b**
n = 5 **2c**
n = 6 **2d**
n = 7 **2e**
n = 8 **2f**

[3+3]Cycloalkyne **1a**
[4+4]Cycloalkyne **1b**
[5+5]Cycloalkyne **1c**
[6+6]Cycloalkyne **1d**
[7+7]Cycloalkyne **1e**
[8+8]Cycloalkyne **1f**

entry	precursor	solvent	product	yield/%
1[a]	**2a**	DMF/toluene/Et_3N (20/1/1)	**1a**	54
2	**2b**	DMF/toluene/Et_3N (20/1/1)	**1b**	28
3	**2c**	DMF/toluene/Et_3N (20/1/1)	**1c**	32
4	**2d**	DMF/toluene/Et_3N (20/1/1)	**1d**	18
5	**2e**	DMF/toluene/Et_3N (20/1/1)	**1e**	8
6	**2f**	DMF/toluene/Et_3N (20/1/1)	**1f**	7
7	**2b**	DMF/THF/Et_3N (10/10/1)	**1b**	42
8	**2c**	DMF/THF/Et_3N (10/10/1)	**1c**	42
9	**2d**	DMF/THF/Et_3N (10/10/1)	**1d**	40
10	**2e**	DMF/THF/Et_3N (10/10/1)	**1e**	37
11	**2f**	DMF/THF/Et_3N (10/10/1)	**1f**	18

[a] See ref 1a.

2e is soluble in THF; THF is a solvent that rapidly dissociates the helix dimer of **2e**.[12] This is an interesting example showing that the inhibition of aggregation facilitated the chemical reaction. The cyclization of the other oligomers also proceeded effectively with use of the same solvent (Table 1, entries 7−11). The synthetic [*n*+*n*]cycloalkynes (*n* = 4−8) were characterized by NMR spectroscopy, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, and elemental analyses. These macrocycles were soluble in $CHCl_3$, CH_2Cl_2, toluene, and THF.

Reflecting the high degree of symmetry, the ^{1}H NMR (400 MHz, $CDCl_3$, 0.5 mM, 25 °C) spectra of [*n*+*n*]cycloalkynes (*n* = 3−8) were simple (Figure 1). In contrast to that observed in **1a**, no concentration dependence was observed in the ^{1}H NMR (400 MHz, $CDCl_3$, 0.1−5.0 mM, 25 °C) spectra of [*n*+*n*]-cycloalkynes (*n* = 4−8), which indicated the monomeric nature of these macrocycles in solution.[13] This was confirmed by vapor pressure osmometry (VPO) study (vide infra). The ^{1}H NMR (400 MHz, $CDCl_3$, 0.5 mM, 25 °C) spectra of [*n*+*n*]-cycloalkynes (*n* = 4−7) at the aromatic region were similar and temperature independent. In contrast, the chemical shifts of helicene H^a and *m*-phenylene H^b for the [8+8]cycloalkyne **1f** were slightly different from those for the other macrocycles, and notably the spectra of **1f** were temperature dependent: When the solution was cooled from 60 to −40 °C, aromatic protons shifted upfield and were broadened (Figure 2). In particular, H^a and H^b shifted upfield by ca. 0.2 ppm at −40 °C.

The UV−vis spectra ($CHCl_3$, 1 μM, 25 °C) of [*n*+*n*]-cycloalkynes (*n* = 3−8) except for **1b** indicated a linear increase in ϵ with *n* at λ_{max} 340 nm. The λ_{max} of **1b** was blue-shifted to 335 nm, which was probably due to the rigid and nonplanar structure of **1b** with a lower extent of conjugation (Figure 3). The slight differences observed for all the macrocycles at 370−400 nm might reflect the differences in the conformations of [*n*+*n*]cycloalkynes.

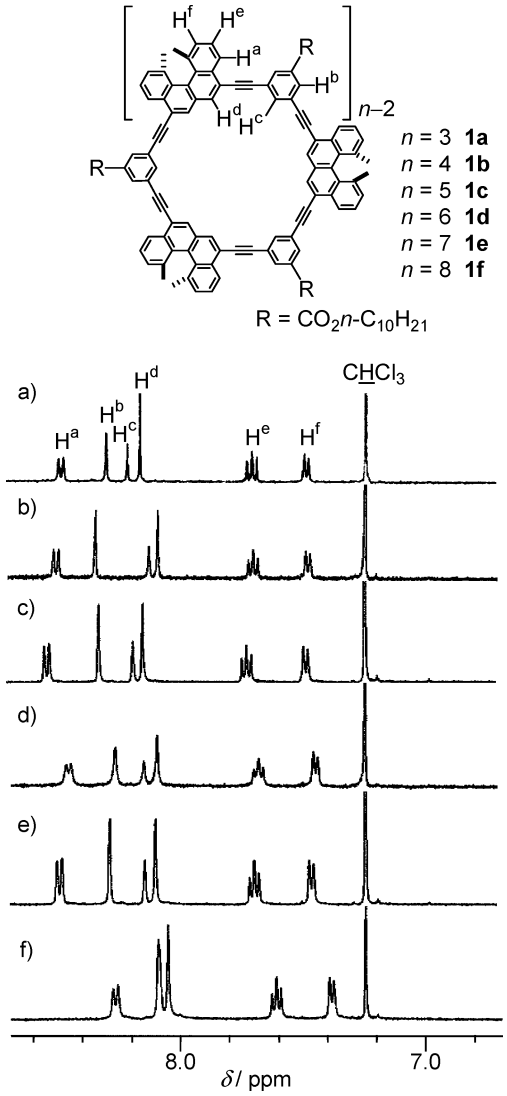


FIGURE 1. ^{1}H NMR spectra of the aromatic region (400 MHz, $CDCl_3$, 0.5 mM, 25 °C) of [*n*+*n*]cycloalkynes (*n* = 3−8): (a) **1a**, (b) **1b**, (c) **1c**, (d) **1d**, (e) **1e**, and (f) **1f**. The spectroscopic data of **1a** were previously reported.[1a]

The CD ($CHCl_3$, 5 μM, 25 °C) spectra of [*n*+*n*]cycloalkynes (*n* = 3−8) were intriguing (Figure 4). Despite the increasing number *n*, the higher [*n*+*n*]cycloalkynes (*n* = 4−8) exhibited even smaller $\Delta\epsilon$ than **1a**. The observation is highly contrasted to the acyclic oligomers (*n* = 2−6) exhibiting a simple increase in $\Delta\epsilon$.[4] This is an interesting large ring size effect of macrocyclic compounds: The increase in ring size does not show additivity or similarity to the acyclic compounds. This may be due to the rigid conformations of the ethynylhelicene macrocycles in solution, which very likely originate from the strong intramolecular interactions between helicenes. Such a large ring size effect also compares to that in the ethynylarene macrocycles noted in the Introduction. Ethynylhelicene oligomers are an interesting group of compounds that can aggregate in various modes.

The CD ($CHCl_3$, 5 μM) spectra of [*n*+*n*]cycloalkynes (*n* = 4−7) were essentially temperature independent[13] (5−60 °C) being consistent with the ^{1}H NMR spectra. For **1f**, however, its

(12) The unfolding of the helical heptamer was rapid in THF, and the CD (5 μM, 25 °C) spectrum observed 10 min after dissolution exhibited the formation of a monomeric random coil structure.

(13) See the Supporting Information.

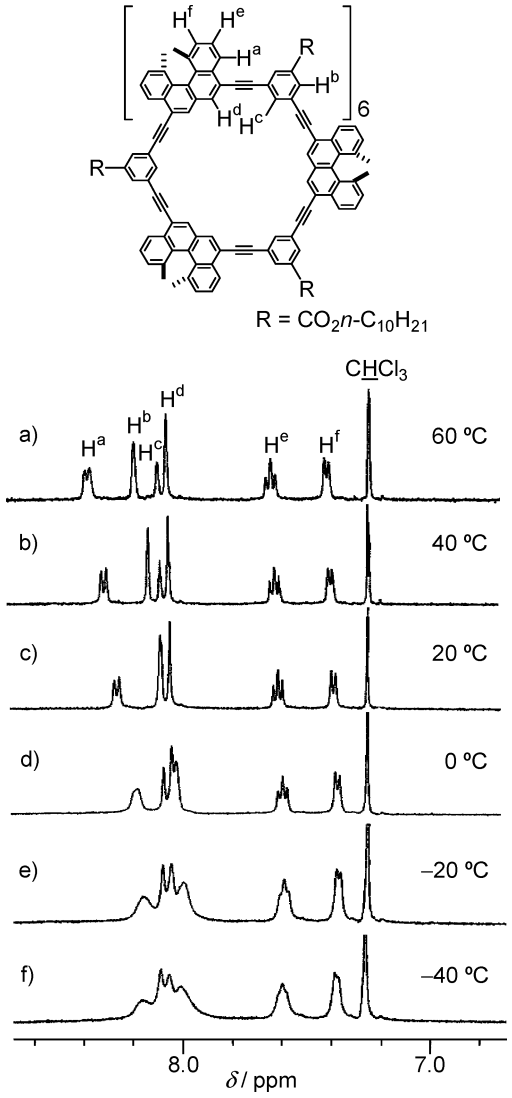


FIGURE 2. Temperature dependences of ^{1}H NMR spectra of the aromatic region (400 MHz, $CDCl_3$, 1 mM) of **1f** observed at (a) 60, (b) 40, (c) 20, (d) 0, (e) −20, and (f) −40 °C.

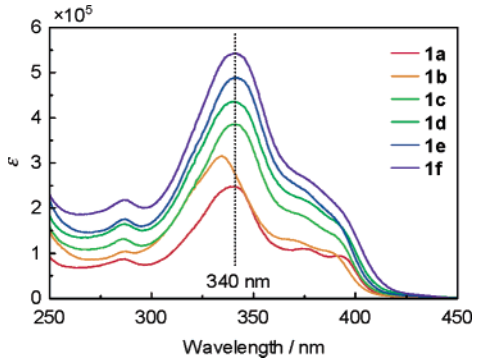


FIGURE 3. UV−vis spectra ($CHCl_3$, 1 μM, 25 °C) of [n+n]-cycloalkynes (n = 3−8). The spectroscopic data of **1a** were previously reported.[1a]

spectra at 60 °C exhibited a decrease in the extent of the Cotton effect at ca. 300 nm and a blue shift of λ_{max} from 400 to 390 nm (Figure 5). These results indicate that **1f** has some structural freedom to change its conformation with temperature, while the

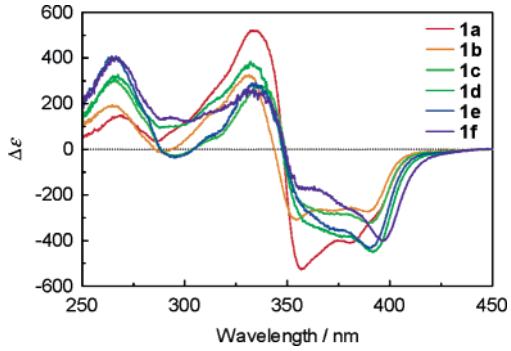


FIGURE 4. CD spectra ($CHCl_3$, 5 μM, 25 °C) of [n+n]cycloalkynes (n = 3−8). The spectroscopic data of **1a** were previously reported.[1a]

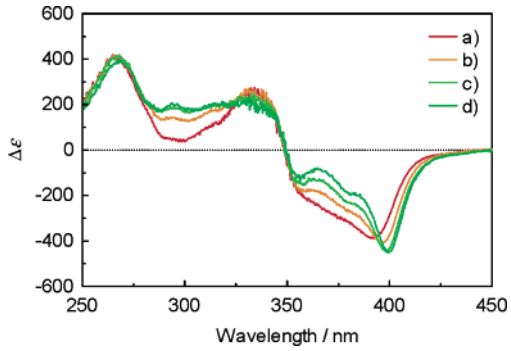


FIGURE 5. Temperature dependences of CD spectra ($CHCl_3$, 5 μM) of **1f** observed at (a) 60, (b) 25, (c) 5, and (d) −10 °C.

lower homologues have rigid structures. This is another notable large ring size effect of ethynylhelicene macrocycles.

No intermolecular aggregation was observed by VPO studies ($CHCl_3$, 5.0−5.4 mM, 35 °C) of the higher [n+n]cycloalkynes (n = 4−8). Thus, the aggregate formation of the ethynylhelicene macrocycles was observed only for the [3+3]cycloalkyne **1a**, which is consistent with the results obtained by Moore and Tobe:[7,8] Planar and rigid structures appear to be essential for the aggregation of the ethynylarene macrocycles.

We previously examined the spectroscopic properties of [n+n]cycloamides (n = 2−10), which were cyclic oligoamides containing n parts of an optically active helicene and n parts of a dianiline spacer.[14] [n+n]Cycloamides (n = 4−10) showed additivity in the CD spectra proportional to n, which suggested the compounds to possess flexible structures. The difference in the large ring size effect between [n+n]cycloalkynes and [n+n]-cycloamides indicates that the structures of macrocycles are considerably affected by spacer moieties. The development of a method of obtaining two types of compounds is interesting.

Conclusions

To summarize, a series of [n+n]cycloalkynes (n = 4−8) were synthesized effectively via the Sonogashira coupling reaction. Spectroscopic studies showed that [n+n]cycloalkynes (n = 4−7) have rigid structures, while the [8+8]cycloalkyne has a flexible structure. A notable large ring size effect was observed by CD, which may be due to the strong nonbonding interactions of nonplanar π-electron systems. It is interesting to study the structure of the higher [n+n]cycloalkynes ($n \geq 9$).

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Experimental Section

[7+7]Cycloalkyne 1e (General Procedures for Cyclization with Sonogashira Coupling Reaction). Under an argon atmosphere, a mixture of tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (3 mg, 0.003 mmol), purified cuprous iodide[15] (7 mg, 0.04 mmol), tris(2,4,6-trimethylphenyl)phosphine (7 mg, 0.02 mmol), tetrabutylammonium iodide (87 mg, 0.24 mmol), *N*,*N*-dimethylformamide (30 mL), tetrahydrofuran (25 mL), and triethylamine (3 mL) was freeze-evacuated three times in flask A. In flask B, a solution of the desilylated acyclic heptamer **2e**[4] (30 mg, 0.00816 mmol) and decyl 3,5-diiodobenzoate **3** (1.0 equiv, 4.19 mg, 0.00816 mmol) in tetrahydrofuran (5 mL) was freeze-evacuated three times, and the solution was added to flask A with a syringe-pump over 3 h at 45 °C. Then, the mixture was stirred for 3 h at that temperature. The reaction was quenched by adding saturated aqueous ammonium chloride, and the organic materials were extracted with toluene. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After evaporation of the solvents under reduced pressure, silica gel flash column chromatography ($CHCl_3$), recycling GPC (THF), and silica gel flash column chromatography (hexane/toluene) gave pure [7+7]-cycloalkyne **1e** (12.0 mg, 0.00305 mmol, 37%): mp >259 °C dec (toluene−methanol); $[\alpha]^{22}_D$ −716 (*c* 0.10, $CHCl_3$); MALDI-TOF MS *m*/*z* calcd for $[M + H]^+$ 3940.2, found 3939.8; VPO ($CHCl_3$, 5.0 mM, 35 °C) 3730 g·mol^{-1}; UV−vis ($CHCl_3$, 1 μM, 25 °C) λ_{max} (ϵ) 341 nm (4.9×10^5); CD ($CHCl_3$, 5 μM, 25 °C) λ ($\Delta\epsilon$) 264 (404), 295 (−34), 334 (284), 390 nm (−435); IR (KBr) 2204, 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 5 mM, 25 °C) δ 0.84 (21H, t, J = 6.7 Hz), 1.17−1.51 (98H, m), 1.82 (14H, tt, J = 8.0, 6.8 Hz), 1.95 (42H, s), 4.37 (14H, t, J = 6.8 Hz), 7.46 (14H, d, J = 7.0 Hz), 7.69 (14H, dd, J = 7.9, 7.0 Hz), 8.08 (14H, s), 8.14 (7H, d, J = 1.5 Hz), 8.28 (14H, d, J = 1.5 Hz), 8.49 (14H, d, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 5 mM, 25 °C) δ 14.3, 22.8, 23.35, 23.39, 26.2, 28.8, 29.5, 29.7, 32.0, 65.8, 89.3, 93.0, 119.7, 123.5, 124.1, 126.6, 126.9, 129.1, 129.8, 130.8, 130.9, 131.2, 132.0, 132.1, 136.7, 138.2, 165.2. Anal. ($C_{287}H_{266}O_{14}$) Calcd: C, 87.51; H, 6.81. Found: C, 87.77; H, 6.93.

[8+8]Cycloalkyne 1f. 1f (5.6 mg, 0.00124 mmol, 18%) was prepared from desilylated acyclic octamer **2f** (30 mg, 0.00708 mmol): mp >249 °C dec (toluene−methanol); $[\alpha]^{22}_D$ −370 (*c* 0.10, $CHCl_3$); MALDI-TOF MS *m*/*z* calcd for $[M + H]^+$ 4502.9, found 4502.1; VPO ($CHCl_3$, 5.0 mM, 35 °C) 3460 g·mol^{-1}; UV−vis ($CHCl_3$, 1 μM, 25 °C) λ_{max} (ϵ) 340 nm (5.4×10^5); CD ($CHCl_3$, 5 μM, 25 °C) λ ($\Delta\epsilon$) 264 (400), 301 (121), 331 (269), 396 nm (−400); IR (KBr) 2205, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 5 mM, 25 °C) δ 0.85 (24H, t, J = 7.0 Hz), 1.16−1.54 (112H, m), 1.76 (48H, s), 1.76−1.95 (16H, m), 4.26−4.43 (16H, m), 7.38 (16H, d, J = 6.8 Hz), 7.61 (16H, dd, J = 7.5, 6.8 Hz), 8.05 (16H, s), 8.08 (24H, s), 8.25 (16H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 5 mM, 25 °C) δ 14.3, 22.8, 23.3, 26.2, 28.9, 29.46, 29.54, 29.7, 32.0, 65.8, 89.3, 93.1, 119.6, 123.4, 124.1, 126.4, 126.6, 129.0, 129.9, 130.6, 130.8, 131.0, 131.78, 131,81, 136.6, 138.4, 165.1. Anal. ($C_{328}H_{304}O_{16}$) Calcd: C, 87.51; H, 6.81. Found: C, 87.29; H, 7.05.

Acknowledgment. The authors thank the Japan Society for the Promotion of Science (JPSP) for providing financial support. A fellowship to H.S. from JSPS for young Japanese scientists is also gratefully acknowledged.

Supporting Information Available: Characterization data for compounds **1b**−**d** and **2f**, variable-concentration ^{1}H NMR data and variable-temperature CD data, and copies of ^{1}H and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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