# Design, Synthesis, and Self-Assembly of Parallel Cyclobolaphile that Contains Four Amide Groups as a Linkage between Polar Head Groups and Hydrocarbon Chain: A Mimetic of Archaeal Membrane Lipid

Kazuhiro Miyawaki, Atsuhiro Harada, Toshiyuki Takagi, Motonari Shibakami*

Institute for Materials and Chemical Process, Institute of Advanced Industrial Science and Technology (AIST), Central 5th, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan
Fax +81(298)614547; E-mail: moto.shibakami@aist.go.jp

*Received 29 December 2002*

**Abstract:** Chiral 52-membered macrocyclic compound has been synthesized by utilizing intramolecular cyclization under Eglinton conditions [$Cu(OAc)_2$, pyridine]. Three structural features include: (i) two hydrocarbon chains containing diacetylene, (ii) a linkage that is composed of amide group, and (iii) two polar head groups. Self-assembly of this compound in a mixture of chloroform–methanol (1:1) produced organogel. Transmission electron micrograph revealed that UV-irradiated gel is featured by nanosize helicity.

**Key words:** archaeal lipid, diacetylene, mimetic, amide, helical ribbon, nanostructure, polymerization, organogel

The design and synthesis of well-defined nanoscale architecture via self-assembly is of great interest in materials research.[1] Biological cells that exemplify the assembly of nano- and microstructures of different sizes and functions provide inspiration for devising fundamentally new approaches toward nanoarchitecture design. Our own efforts in this area are based on the structural mimicry of macrocyclic membrane lipids found in archaea (Figure 1).[2] The reason that we have chosen to employ the lipids as a model involves their considerable resistance to extreme environment. We have recently synthesized bolaamphiphilic lipids (parallel and antiparallel cyclobolaphiles)[3,4] as a component of self-assemblies that have potential thermostability.[5] Three general features that are common to our lipids include: (i) two hydrocarbon chains that contain diacetylene group, (ii) a linkage that is composed of ether bond, and (iii) two polar head groups. An intriguing extension of the nanoarchitectural aspect of our assemblies can be envisaged, if the ether linkage would be replaced with amide. An amide group possessing the ability of hydrogen bond formation has been implicated as a driving force for self-assembly in the nanoarchitecture chemistry[6] as well as raft formation in biomembranes.[7] Thus one might imagine the combination of rigidity and noncovalent bonding that provided by diacetylene and amide group, respectively, should lead to well-defined nanofabrication. With this idea in mind, we have designed a novel cyclobolaphile that contains these structural elements **1** (Figure 2). In this paper, we report the synthesis of such a macrocyclic structure by adopting intramolecular cyclization under Eglinton conditions [$Cu(OAc)_2$, pyridine], the formation of organogel, and the helical structure of polymerized gel.

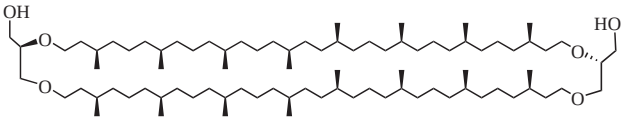
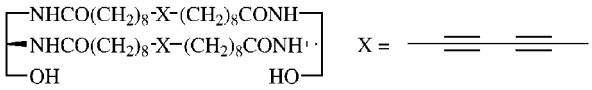



**Figure 1** Backbone of typical caldarchaeol.



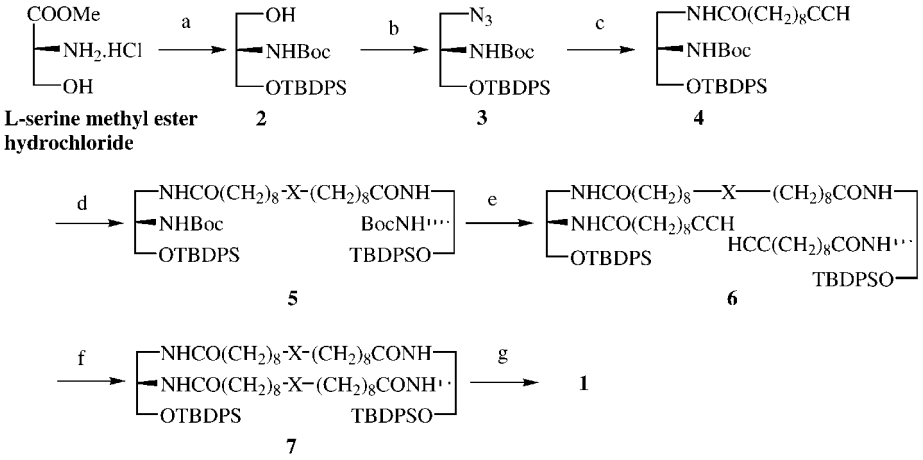

**1**

**Figure 2** Structure of **1**.

Scheme 1 outlines the synthetic approach to prepare cyclobolaphile **1**. In brief, protection of L-serine methyl ester hydrochloride with $Boc_2O$, followed by silylation of the free hydroxyl group and reduction of methyl ester group with lithium aluminum hydride ($LiAlH_4$) produced the desired alcohol **2** in 65% overall yields for the three steps.[8] Treatment of **2** with methanesulfonyl chloride (MsCl)/triethylamine, followed by displacement of the resulting mesylate with azide ion, afforded azide **3** in 66% overall yields for the two steps.[9] Reduction of **3** with Pd/C, followed by condensation of the resulting amine with $HOOC(CH_2)_8CCH$, gave terminal acetylene **4** in 87% overall yields for the two steps.[10] Subsequent subjection of **4** to a classical Glaser acetylene coupling method afforded diacetylene **5** in 91% yield. Removal of the Boc group using trifluoroacetic acid (TFA),[11] followed by condensation of the resulting amine with $HOOC(CH_2)_8CCH$ gave terminal acetylene **6** in 75% overall yields for the two steps. A significant task which remained was the construction of macrocyclic structure. Unfortunately, our first attempt that employed high-dilution Glaser acetylene coupling[5] resulted in failure. In the modified procedure,[12] a solution of **6** in pyridine was added to a stirred solution of $Cu(OAc)_2$ in pyridine over 4 hours at 120 °C, which successfully led to the formation of **7** in 55% yield.[13]

Synlett 2003, No. 3, Print: 19 02 2003.
Art Id.1437-2096,E;2003,0,02,0349,0352,ftx,en;U12302ST.pdf.

ISSN 0936-5214




**Scheme 1** *Reagents and conditions*: (a) (i) $Boc_2O$, pyridine, $Et_3N$, $CH_2Cl_2$, r.t., 2 h; (ii) TBDPSCl, imidazole, DMF, r.t., 11 h; (iii) $LiAlH_4$, THF, r.t., 20 min, 65% from L-serine methyl ester hydrochloride; (b) (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 3 h; (ii) $NaN_3$, DMSO, 80 °C, 1 h, 66% from **2**; (c) (i) $H_2$, Pd-C; (ii) 10-undecynoic acid, EDCI, HOBt·$H_2O$, $Et_3N$, $CH_2Cl_2$, r.t., 3 h, 87% from **3**; (d) TMEDA, CuCl, $O_2$, acetone, 60 °C, 11 h, 91%; (e) (i) TFA, $CH_2Cl_2$; (ii) 10-undecynoic acid, EDCI, HOBt·$H_2O$, $Et_3N$, $CH_2Cl_2$, r.t., 15 h, 75% from **5**; (f) $Cu(OAc)_2$, pyridine, 120 °C, 55%; (g) TBAF, $CHCl_3$, r.t., 6 d, 64%. MsCl = methanesulfonyl chloride, TBDPSCl = *tert*-butylchlorodiphenylsilane, HOBt = 1-hydroxybenzotriazole, TMEDA = tetramethylethylenediamine, TFA = trifluoroacetic acid, TBAF = tetrabutylammonium fluoride, $Boc_2O$ = di-*tert*-butyl dicarbonate, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Finally, desilylation of **7** with tetrabutylammonium fluoride (TBAF) gave diol **1** in 64% yield.[13,14]

In order to construct molecular assembly, we adopted gelation process.[6a] In brief, **1** (3.7 mg) was placed in a test tube, and dissolved in a 1:1 mixture of chloroform–methanol (0.3 mL) at 50–60 °C. The resulting transparent solution was then cooled to 25 °C, and white gel was formed. Once the gel is formed, it is stable and the test tube can be inverted without changing the shape of the gel. The gel was thermoreversible, i.e., it turned into clear, low-viscosity solution upon heating (50–60 °C) and gelation returned after cooling (25 °C). In view of the rigid framework and four amide groups that act simultaneously as hydrogen bond donor and acceptor, the diacetylene groups were expected to be aligned in a highly ordered state. With this assumption in mind, we exposed the organogel to short-wave UV (254 nm) at 25 °C, and observed the immediate colorless-to-purple transition in the gel. UV/Vis absorption spectra of the gel before and after UV irradiation are shown in Figure 3. The absorbance approximately at 579 nm indicated that photo-polymerization took place.[6b] These polymerization points to the existence of perfectly packed ordered structure of **1** capable of reacting topochemically.[15]

The TEM micrograph of the polymerized gel showed the formation of helical ribbons (Figure 4, a). Interestingly, only left-handed ribbons (width of 27 nm, pitch of 186 nm) are observed. Currently, we consider that this helicity stems from chirality of **1**.[6e] The TEM image also shows that the ribbons join at 'junction zones' to form networks (Figure 4, b).[6f] Such three-dimensional networks may explain the physical gelation of **1**.[6g]

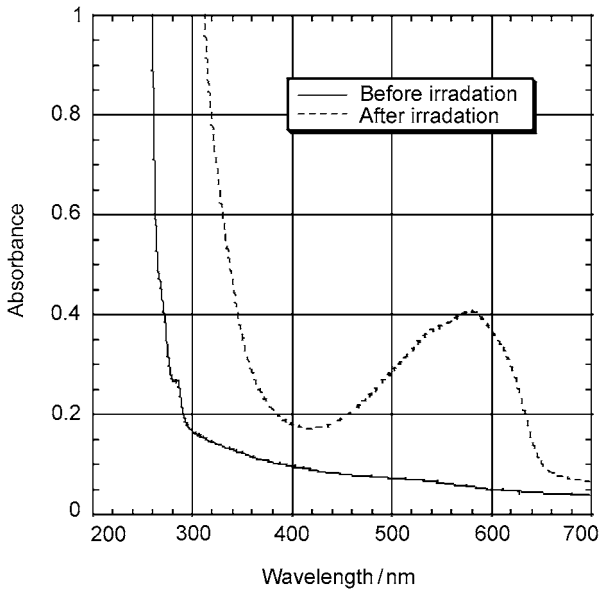



**Figure 3** UV/Vis absorption spectra of the gel that was made from **1** (UV irradiation at 254 nm for 3 min at 25 °C). The solvent was a mixture of chloroform /methanol (1/1, v/v). The concentration of **1** was 12.0 mM (before irradiation). Cell width was 2.0 mm. All spectra were recorded at 25 °C.

In conclusion, we have developed an efficient approach to the synthesis of chiral parallel cyclobolaphile **1** that has both, two diacetylene and four amide groups. We also have demonstrated that the UV-irradiated gel formed three-dimensional network structures composing of helical ribbons. Efforts aimed at exploiting the stereoisomers of **1** with a view toward synthesis and self-assembly are now under intense investigation in our laboratory.

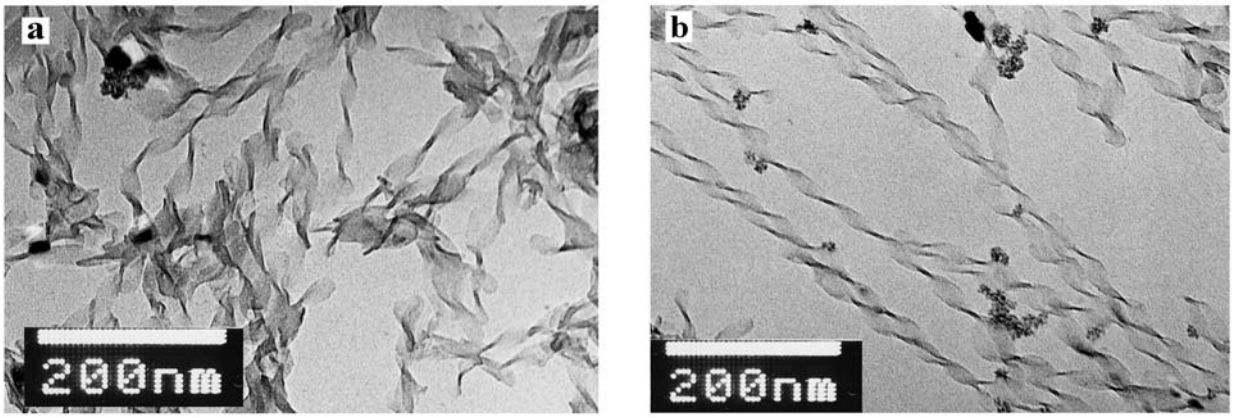



**Figure 4** Transmission electron micrographs of the polymerized gel that was prepared by UV-irradiation (10 min) of the organogel.

## Acknowledgment

We are grateful to Y. Sato (JEOL) for providing technical assistance with the electron microscopy. This research was supported by Industrial Technology Research Grant Program in 2001 from New Energy and Industrial Technology Development Organization (NEDO) of Japan.

## References

(1) (a) Schnur, J. M. *Science* **1993**, *262*, 1669. (b) Spector, M. S.; Price, R. R.; Schnur, J. M. *Adv. Mater.* **1999**, *11*, 337. (c) Schnur, J. M.; Ratna, B. R.; Selinger, J. V.; Singh, A.; Jyothi, G.; Easwaran, R. K. *Science* **1994**, *264*, 945. (d) Selinger, J. V.; Schnur, J. M. *Phys. Rev. Lett.* **1993**, *71*, 4091. (e) Spector, M. S.; Selinger, J. V.; Singh, A.; Rodriguez, J. M.; Price, R. P.; Schnur, J. M. *Langmuir* **1998**, *14*, 3493. (f) Spector, M. S.; Singh, A.; Messersmith, P. B.; Schnur, J. M. *Nano Lett.* **2001**, *1*, 375.

(2) (a) Kushwaha, S. C.; Kates, M.; Sprott, G. D.; Smith, I. C. P. *Biochim. Biophys. Acta* **1981**, *664*, 156. (b) Comita, P. B.; Gagosian, R. B.; Pang, H.; Costello, C. E. *J. Biol. Chem.* **1984**, *254*, 15234. (c) Eguchi, T.; Arakawa, K.; Terachi, T.; Kakinuma, K. *J. Org. Chem.* **1997**, *62*, 1924. (d) Eguchi, T.; Ibaragi, K.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 2689. (e) Aoki, T.; Poulter, C. D. *J. Org. Chem.* **1985**, *50*, 5634. (f) Menger, F. M.; Chen, X. Y. *Tetrahedron Lett.* **1996**, *37*, 323. (g) Eguchi, T.; Kano, H.; Kakinuma, K. *J. Chem. Soc., Chem. Commun.* **1996**, 365.

(3) (a) Amphiphilic molecules containing a polar head group at the end of a hydrophobic segment have been termed; 'bolaamphiphiles' or 'bolaphile'. While amphiphiles having a macrocyclic ring as a hydrophobic segment have been termed 'macrocyclic bolaamphiphiles' (see ref.[2f]), we prefer to adopt the abbreviated and more readily pronounce-able term, 'cyclobolaphile'. (b) For 'bolaamphiphiles' see: Fuhrhop, J.-H.; Mathiewu, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 100. (c) For 'bolaphiles' see: Jayasuriya, N.; Bosak, S.; Regen, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5844.

(4) On the analogy of the definition of 'parallel caldarchaeol' and 'antiparallel caldarchaeol' that have a parallel and antiparallel arrangement of glycerol units, respectively, we term cyclobolaphile with a parallel arrangement of glycerol units 'parallel cyclobolaphile', and that with an antiparallel arrangement 'antiparallel cyclobolaphile', see: Gräther, O.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1995**, 405.

(5) (a) Miyawaki, K.; Takagi, T.; Shibakami, M. *Synlett* **2002**, 1326. (b) Miyawaki, K.; Goto, R.; Takagi, T.; Shibakami, M. *Synlett* **2002**, 1467.

(6) (a) Hanabusa, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949. (b) Inoue, K.; Ono, Y.; Kanekiyo, Y.; Hanabusa, K.; Shinkai, S. *Chem. Lett.* **1999**, 429. (c) Hanabusa, K.; Okui, K.; Karaki, K.; Koyama, T.; Shirai, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1371. (d) Loos, M. D.; Esch, J. V.; Stokroos, I.; Kellogg, R. M.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 12675. (e) Rowan, A. E.; Nolte, R. J. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 63. (f) Terech, P.; Furman, I.; Weiss, R. G. *J. Phys. Chem.* **1995**, *99*, 9558. (g) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133.

(7) (a) Brown, D. A.; London, E. *J. Membr. Biol.* **1998**, *164*, 103. (b) Brown, R. *J. Cell. Sci.* **1998**, *111*, 1.

(8) (a) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115. (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Synthesis* **1997**, 1146.

(9) (a) Uenishi, J.; Hiraoka, T.; Yuyama, K.; Yonemitsu, O. *Heterocycles* **2000**, *52*, 719. (b) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145.

(10) Hayashi, Y.; Kinoshita, Y.; Hidaka, K.; Kiso, A.; Uchibori, H.; Kimura, T.; Kiso, Y. *J. Org. Chem.* **2001**, *66*, 5537.

(11) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413.

(12) (a) **Synthesis of 7:** A solution of $Cu(OAc)_2$ (138 mg, 0.762 mmol) and pyridine (56 mL) was stirred at 120 °C. To the reaction was then added a solution of **6** (100 mg, 0.076 mmol) in pyridine (5 mL) over 4 h at 120 °C. After cooling to r.t., pyridine was removed under reduced pressure. The resulting solution was allowed to stand at 120 °C for 11 h before the reaction mixture was quenched with sat. citric acid (50 mL), and then extracted with $CHCl_3$ (300 mL × 2). The organic phase was washed with brine, dried ($Na_2SO_4$), and concentrated to give a residue. Purification of the residue was done by flash chromatography ($SiO_2$, $CHCl_3$–MeOH, 20:1) to give 55 mg (55%) of **7** as colorless solid. (b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 385.

(13) (a) All new compounds gave satisfactory analytical and spectral data. Selected physical data are as follows. Compound **7**: Stage colorless solid, $[\alpha]_D^{22}$+4.87 (*c* 1.80, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 8 H), 7.45–7.41 (m, 12 H), 6.27 (d, *J* = 7.6 Hz, 2 H), 5.93 (t, *J* = 5.5 Hz, 2 H), 4.10–4.00 (m, 2 H), 3.79 (dd, *J* = 10.3, 3.7

Hz, 2 H), 3.62–3.53 (m, 4 H), 3.33–3.29 (m, 2 H), 2.22 (t, *J* = 6.9 Hz, 8 H), 2.12–2.20 (m, 8 H), 1.60–1.43 (m, 16 H), 1.38–1.30 (m, 8 H), 1.29–1.20 (m, 24 H), 1.06 (s, 18 H) ppm. $^{13}$C NMR: δ = 174.53, 173.98, 135.54, 133.07, 132.74, 130.01, 127.92, 127.89, 77.43, 65.35, 63.59, 51.45, 41.94, 36.76, 36.60, 29.22, 29.18, 28.91, 28.76, 28.29, 26.90, 25.64, 25.59, 19.26, 19.17 ppm. LRMS (FAB): *m/z* = 1310 $[M + H]^+$, 1252 $[M – (CH_3)_3C]^+$. Compound **1**: Stage colorless solid. $^1$H NMR [500 MHz, $CDCl_3/CD_3OD$ (1:1, v/v)]: δ = 7.37 (t, *J* = 5.9 Hz, 2 H), 7.10 (t, *J* = 7.9 Hz, 2 H), 3.73–3.65 (m, 2 H), 3.38 (dd, *J* = 11.6, 4.0 Hz, 2 H), 3.25 (dd, *J* = 11.6, 5.5 Hz, 2 H), 3.21–3.13 (m, 2 H), 3.12–3.04 (m, 2 H), 2.03 (t, *J* = 7.0 Hz, 8 H), 1.97 (t, *J* = 7.0 Hz, 8 H), 1.42–1.34 (m, 8 H), 1.33–1.26 (m, 8 H), 1.21–1.13 (m, 8 H), 1.12–1.05 (brs, 24 H) ppm. LRMS (FAB): *m/z* = 834 $[M + H]^+$. Because compounds **7** and **1** were easy to be polymerized by light, their elemental analyses could not be obtained as seen in analogous diacetylene compounds.

(b) Wang, G.; Hollingsworth, R. I. *Langmuir* **1999**, *15*, 3062.

(14) Our synthetic scheme should provide optically pure compound **1**. Our reason for this is 2-fold. First, the first step[8a] that can lead to racemization retained the stereochemical configuration of L-serine methyl ester hydrochloride {**2**: $[\alpha]_D^{21}$ +4.99 (*c* 3.55, $CHCl_3$), Lit.[8a] $[\alpha]_D$ +4.7 (*c* 1.2, $CHCl_3$)}. Second, intermediates (**2**–**7**) and the desired product (**1**) do not include carbonyl group that can cause epimerization at the chiral center.

(15) (a) Lopez, E.; O'Brien, D. F.; Whitesides, T. H. *J. Am. Chem. Soc.* **1982**, *104*, 305. (b) Pan, J. P.; Charych, D. *Langmuir* **1997**, *13*, 1365.