Pergamon

Tetrahedron Letters 41 (2000) 10055–10060

TETRAHEDRON
LETTERS

Cyclophane-type bis-calix[4]arenes: efficient synthesis via quadruple cycloadditive macrocyclization and conformational study

Gil Tae Hwang and Byeang Hyean Kim*

Department of Chemistry, Center for Integrated Molecular Systems, Pohang University of Science and Technology, Pohang 790-784, South Korea

Received 17 August 2000; revised 21 September 2000; accepted 12 October 2000

Abstract

Cyclophane-type bis-calix[4]arenes were synthesized very efficiently using quadruple cycloadditive macrocyclization as a key reaction and their conformational studies were carried out by solution NMR experiments and X-ray crystallography. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: calixarenes; cyclophanes; conformation; nitrile oxides.

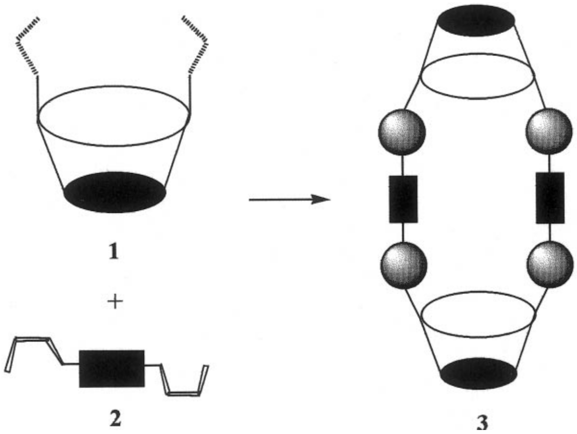
Three-dimensional macrocycles (3D-macrocycles) play an essential role in supramolecular chemistry[1] and it is very important to develop efficient synthetic pathways toward them. We have envisioned a new pathway for 3D-macrocycles by using quadruple cycloadditive macrocyclization (QCM)[2] as a key step (Scheme 1). Compound **1** is a bis-dipolarophile with a calixarene, cyclodextrin, or porphyrin moiety and compound **2** is a bis-dipole with nitrile oxide functionality. Reaction between **1** and **2** may give very efficiently 3D-macrocycle **3** in a one-pot procedure if the required reaction geometry and transition states for QCM are allowed. Compared to other macrocyclization methods, this modular QCM approach has several advantages: (1) few steps and good overall yields; (2) excellent stereoselectivity due to the well-defined transition state of [3+2] dipolar cycloaddition; (3) accessibility to structural diversity by changing bis-dipole and bis-dipolarophile components.

Calix[4]arenes[3] are macrocyclic building blocks constructed from phenols and formaldehydes. There have been many attempts to design and synthesize receptor molecules with enforced cavities by using calix[4]arenes as a key structural motif. The representatives are double or multiple calix[4]arenes[4] which are covalently constructed through upper rim–upper rim linkage,[5] lower rim–lower rim fashion,[6] or noncovalently generated through hydrogen bonding.[7] How-

---

* Corresponding author. Tel: 82-54-279-2115; fax: 82-54-279-3399; e-mail: bhkim@postech.ac.kr

PII: S0040-4039(00)01818-9

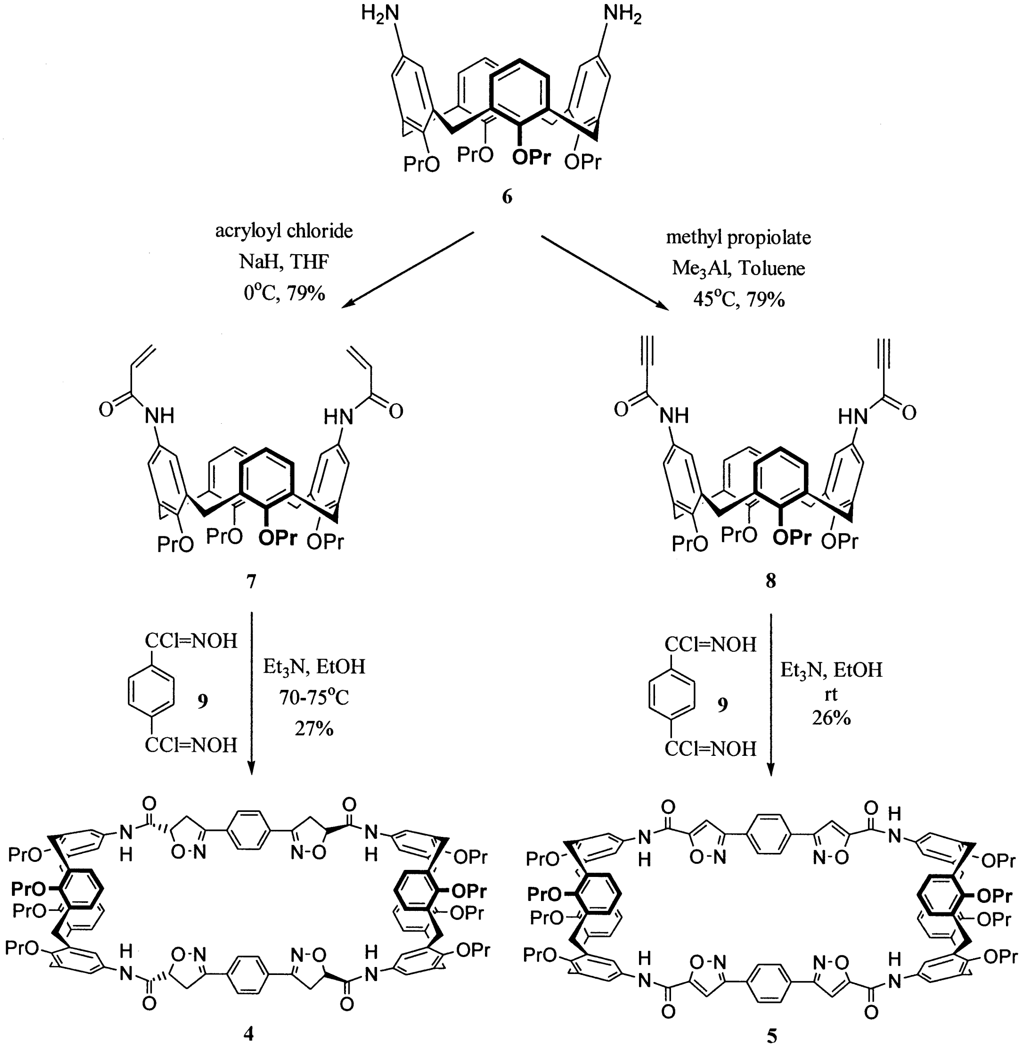


Scheme 1.

ever, in most cases the yields of bis-calix[4]arenes are very low due to the preference of intramolecular cross-link to the intermolecular dimerization. We report here an efficient synthesis of cyclophane-type bis-calix[4]arenes **4** and **5** by using QCM as a key step. Also reported are the crystal structure of compound **4**, and NMR studies for the solution conformation of calix[4]arenes. To our knowledge, there is no precedent for the synthesis of bis-calix[4]arenes by using QCM as a key reaction.

Synthetic routes for the bis-calix[4]arenes **4** and **5** are shown in Scheme 2. *N*-Acryloylation and *N*-propiolation of the diamine **6**[8] afforded the bifunctional dipolarophiles **7** and **8**, respectively. Cycloadditions between the dihydroximoyl chloride **9**[2] and compound **7** in the presence of triethylamine in ethanol then provided the bis-calix[4]arene **4** in 27% isolated yield, which corresponds to a 72% yield per cycloaddition. Similarly, the bis-calix[4]arene **5** was prepared by cycloadditions between compounds **8** and **9** in 26% yield. Both bis-calix[4]arenes **4** and **5** were prepared in only two steps from diamine **6** in 21% overall yield. In the case of the imino bis-calix[4]arenes recently reported by us,[5f] the isolated yield of bis-calix[4]arene from terephthaldehyde was 19%. Therefore this QCM method is comparable to the condensation method for macrocycles with the *para*-related (terephthaldehyde based) linkers. The structures of bis-calix[4]arenes **4** and **5** were identified by elemental analysis, mass spectroscopy, IR, UV, ^{1}H, and ^{13}C NMR.[9] Full characterization data of bis-calix[4]arenes **4** and **5** suggest that these compounds are quadruple cycloadducts between terephthaldinitrile oxide and the corresponding bifunctional dipolarophiles **7** and **8**, respectively.

The ^{1}H NMR spectra of bis-calix[4]arenes **4** and **5** were temperature dependent (Fig. 1). The signals for the aromatic protons of the substituted aromatic rings (ArH_{sub}) are shifted downfield as the temperature decreases, whereas the aromatic protons of the unsubstituted aromatic rings (ArH_{unsub}) are shifted upfield. Furthermore, bis-calix[4]arene **4** showed a remarkable solvent dependence of signal patterns for the aromatic protons of the calix[4]arene. From these phenomena we speculate that bis-calix[4]arenes **4** and **5** are conformationally mobile. To investigate the possibility of the pinched cone conformation,[10] we determined the distances between the equatorial proton of the methylene group of the calix[4]arene and the two neighboring aromatic protons by using the initial rate approximation[11] through NOESY spectroscopy. We found that all of the bifunctional dipolarophiles and bis-calix[4]arenes **4** and **5** have the pinched cone conformation in the solution state. Bis-calix[4]arene **4** in particular has a highly distorted pinched cone conformation (Table 1).



Scheme 2.

To confirm the suggested structure in the solution state and get direct evidence for the pinched cone conformation, we carried out the X-ray crystallographic study. The X-ray diffraction-grade single crystals of the bis-calix[4]arene **4** were grown by slow evaporation of DMSO/$CHCl_3$ (1:1 v/v) solution. The X-ray crystal structure[9] (Fig. 2) clearly shows the chemical structures of **4** including the relative stereochemistry of the four stereogenic centers and reveals the overall topological shape with an inversion center (*i*) of the bis-calix[4]arene **4**. This bis-calix[4]arene is a nanometer-sized macrocycle (2.2 nm long). In the bis-calix[4]arene **4**, two aromatic rings substituted with amido groups are almost parallel (interplanar angle 16.3°), and the other two are almost perpendicular (interplanar angle 89.0°) to each other. These interplanar angles suggest that the bis-calix[4]arene has a highly distorted pinched cone conformation in the solid-state. These solid-state conformational results are parallel with the solution conformational data obtained by NMR.

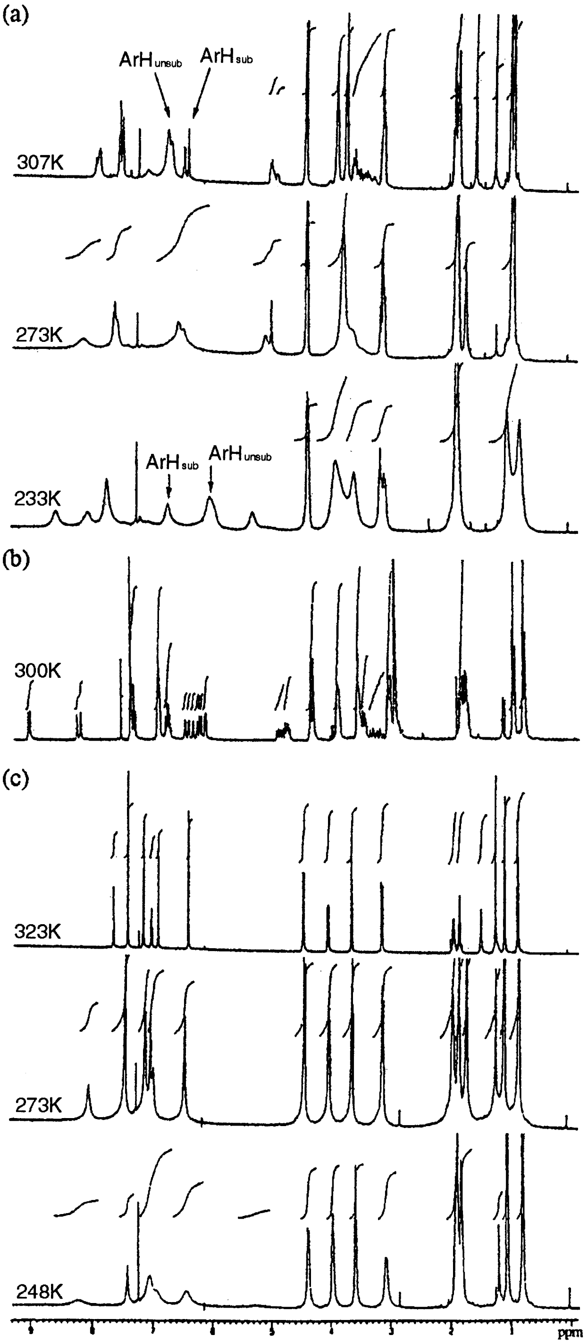
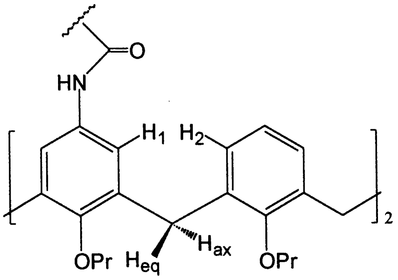


Figure 1. Variable temperature ^{1}H NMR spectra of bis-calix[4]arenes **4** and **5**. (a) ^{1}H NMR (500 MHz) spectra of **4** in $CDCl_3$. ArH_{sub} and ArH_{unsub} represent the aromatic protons of the substituted aromatic rings and unsubstituted rings, respectively. (b) ^{1}H NMR spectrum (300 MHz) of **4** in $CDCl_3$/DMSO-d_6 3:2 v/v at 300 K. (c) ^{1}H NMR spectra (500 MHz) of **5** in $CDCl_3$

Table 1
The distances (Å) between the H_{eq} and the neighboring aromatic protons of bis-calix[4]arenes **4** and **5**



Bis-calix[4]arene[a]	**4**[b]	**5**
H_1	2.81–3.53[c] (2.54–2.64)	2.52
H_2	2.43 (2.33–2.49)	2.39

[a] Bis-calix[4]arene **4** was determined in $CDCl_3$/DMSO-d_6 1:1 v/v and **5** was determined in $CDCl_3$ at rt.

[b] The distance obtained from the X-ray crystal structure is in the parenthesis.

[c] Calculated distance range of four distinct H_1 protons.

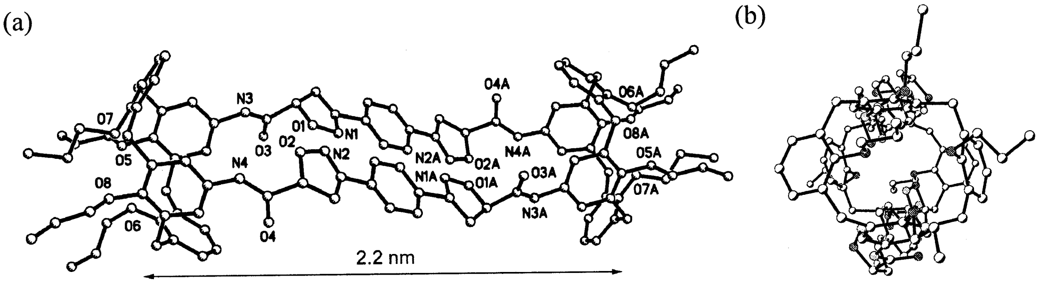


Figure 2. X-Ray crystal structure of bis-calix[4]arene **4**: (a) side view; (b) top view. One dimethyl sulfoxide solvent molecule and hydrogen atoms are omitted for clarity

In summary, we successfully applied the quadruple cycloadditive macrocyclization to the synthesis of novel, three-dimensional, cyclophane-type bis-calix[4]arene **4** and **5**. Solution NMR experiments and X-ray crystal study showed that the conformation of cyclophane-type bis-calix[4]arene to be a pinched cone.

Acknowledgements

This work was supported by the Korea Science and Engineering Foundation (1999-123-001-3). We are grateful to Professor Kimoon Kim and Mr. Jungseok Heo for their help in X-ray crystallography.

References

1. (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995. (b) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; The Royal Society of Chemistry: Cambridge, 1994.
2. (a) Kim, B. H.; Jeong, E. J.; Jung, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 6390. (b) Lee, C. W.; Hwang, G. T.; Kim, B. H. *Tetrahedron Lett.* **2000**, *41*, 4177.
3. For reviews see: (a) Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1. (b) Gutsche, C. D. *Calixarenes*, *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989; Vol. 1. (c) Gutsche, C. D. *Calixarenes Revisited*, *ibid*, 1998.
4. For reviews see: (a) Asfari, Z.; Weiss, J.; Vicens, J. *Synlett* **1993**, 719. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.
5. (a) Struck, O.; Chrisstoffels, L. A. J.; Lugtenberg, R. J. W.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, *62*, 2487. (b) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. L. *J. Chem. Soc.*, *Chem. Commun.* **1991**, 936. (c) Araki, K.; Sisido, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 8297. (d) Böhmer, V.; Goldmann, H.; Vogt, W.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, *30*, 1391. (e) Asfari, Z.; Vicens, J.; Weiss, J. *Tetrahedron Lett.* **1993**, *34*, 627. (f) Hwang, G. T.; Kim, B. H. *Tetrahedron Lett.* **2000**, *41*, 5917.
6. (a) McKervey, M.; Owens, M.; Schulten, H.-R.; Vogt, W.; Böhmer, V. *Angew. Chem.*, *Int. Ed. Engl.* **1990**, *29*, 280. (b) Lhoták, P.; Kawaguchi, M.; Ikeda, A.; Shinkai, S. *Tetrahedron* **1996**, *52*, 12399. (c) Schmitt, P.; Beer, P. D.; Drew, M. G. B.; Sheen, P. D. *Angew. Chem.*, *Int. Ed. Engl.* **1997**, *36*, 1840. (d) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 6070.
7. (a) Castellano, R. K.; Kim, B. H.; Rebek Jr., J. *J. Am. Chem. Soc.* **1997**, *119*, 12671. (b) Castellano, R. K.; Rebek Jr., J. *J. Am. Chem. Soc.* **1998**, *120*, 3657. (c) Struck, O.; Verboom, W.; Smeets, W. J.; Spek, A. L.; Reinhoudt, D. N. *J. Chem. Soc.*, *Perkin Trans. 2* **1997**, 223. (d) Hamann, B. C.; Shimizu, K. D.; Rebek Jr., J. *Angew. Chem.*, *Int. Ed. Engl.* **1996**, *35*, 1326. (e) Shimizu, K. D.; Rebek Jr., J. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12403. (f) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476.
8. Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683.
9. Selected spectroscopic data of **4** and **5**. Compound **4**: mp >238°C dec.; ^{1}H NMR (300 MHz, $CDCl_3$) 8.00 (br d, 4H; NH), 7.61–7.54 (m, 8H; ArH), 6.71 (m, 14H; ArH), 6.52 (d, 2H, $J=7.1$ Hz; ArH), 6.44 (s, 4H; ArH), 5.07–5.01 (m, 4H; CH), 4.43 (d, 8H, $J=13.3$ Hz; $ArCH_2Ar$), 3.88 (t, 8H, $J=7.3$ Hz; OCH_2), 3.62–3.20 (m, 8H; $NCCH_2$), 3.18–3.09 (m, 8H; $ArCH_2Ar$), 1.98–1.84 (m, 16H; $C\underline{H}_2CH_3$), 1.02–0.86 (m, 24H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 168.1, 156.9, 136.0, 135.0, 131.0, 130.7, 130.5, 128.8, 127.6, 122.9, 119.8, 79.5, 77.6, 39.3, 31.4, 23.6, 10.8, 10.7; MS (FAB) $m/z=1781.8$ (M^++1), 1780.7 (M^+); anal. calcd for $C_{108}H_{116}N_8O_{16}\cdot 4H_2O$: C, 69.96; H, 6.74; N, 6.04. Found: C, 70.13; H, 6.77; N, 6.02. Compound **5**: mp >249°C dec.; ^{1}H NMR (300 MHz, $CDCl_3$), 7.82 (s, 4H; NH), 7.37 (s, 8H; ArH), 7.13 (d, 8H, $J=7.4$ Hz; ArH), 6.83 (s, 4H; CH), 6.38 (s, 8H; ArH), 4.41 (d, 8H, $J=13.4$ Hz; $ArCH_2Ar$), 3.99 (t, 8H, $J=8.1$ Hz; OCH_2), 3.59 (t, 8H, $J=6.6$ Hz; OCH_2), 3.10 (d, 8H, $J=13.4$ Hz; $ArCH_2Ar$), 1.97–1.77 (m, 16H; $C\underline{H}_2CH_3$), 1.04 (t, 12H, $J=7.3$ Hz; CH_3), 0.82 (t, 12H, $J=7.4$ Hz; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 163.7, 162.1, 158.0, 152.9, 152.3, 136.8, 134.3, 130.9, 129.2, 127.0, 122.5, 119.0, 104.7, 77.2, 31.1, 23.5, 22.9, 10.8, 9.8; MS (FAB) $m/z=1773.8$ (M^++1), 1772.7 (M^+); anal. calcd for $C_{108}H_{108}N_8O_{16}\cdot 2H_2O$: C, 71.66; H, 6.24; N, 6.19. Found: C, 71.60; H, 6.48; N, 6.30. *Crystal data* for **4**: $C_{108}H_{116}N_8O_{16}\cdot C_2H_6SO$, $M=1860.22$, crystal system: triclinic, space group: $P\bar{1}$, $a=9.9175(9)$ Å, $\alpha=87.248(2)°$, $b=10.6381(10)$ Å, $\beta=81.458(2)°$, $c=30.730(3)$ Å, $\gamma=71.205(2)°$, $V=3035.2(5)$ Å^3, $Z=1$, $D_{\text{calcd}}=1.018$ g cm^{-3}, $T=188(2)$ K, Siemens SMART diffractometer with CCD detector, Mo Kα ($\lambda=0.71073$ Å), $\mu=0.85$ cm^{-1}, of 12412 measured data, 8866 were independent ($R_{\text{int}}=0.0699$), R_1 [$I>2\sigma(I)$]$=0.2481$, wR_2 (all data)$=0.5358$ and GOF$=2.644$.
10. For recent examples of the pinched cone conformation of bis-calix[4]arene, see Refs. 5a and 7c.
11. For the first study of the pinched cone conformations of calix[4]arenes in the solution state using initial rate approximation, see Ref. 7f.