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Synthesis and Conformational Characteristics of Nonsymmetric Pillar[5]arene

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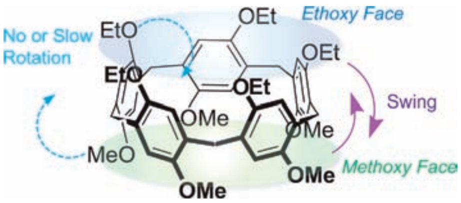
ABSTRACT



A new nonsymmetric pillar[5]arene of ethoxymethoxypillar[5]arene (EMpillar[5]arene) has been synthesized. By 2D ROESY analysis of EMpillar[5]arene, the ethoxy and methoxy moieties were completely separated at the upper and lower rims, respectively. Moreover, by the variable-temperature ^{1}H NMR measurements of EMpillar[5]arene, the rotational movement of phenolic units in EMpillar[5]arene was slow on the NMR time scale or did not occur.

Macrocycles such as cyclodextrins, cucurbiturils, and calixarenes continue to be the focus of considerable research activity because of their interesting conformational and physicochemical and host−guest properties. Cyclodextrin molecules have a rigid, well-defined nonsymmetric ring structure due to the intramolecular hydrogen bond between OH groups.[1] The structures of cucurbiturils are also rigid and highly symmetric.[2] In the case of calixarenes, they are flexible, vase-shaped nonsymmetric architectures and thus form various conformers.[3] Among them, we have first synthesized a new type of macrocycle and named it "pillar[5]arene" (Figure 1a).[4]

The composition of pillar[5]arene is almost the same as typical calixarenes. However, because its repeating units are connected by methylene bridges at the *para*-position, pillar[5]arene forms a unique symmetrical pillar architecture, which is different from the basket-shaped structure of the *meta*-bridged calixarenes. However, due to its highly symmetrical structure, proton signals from pillar[5]arene were observed as singlets at room temperature. Therefore, we could not obtain detailed information about the conformational characteristics of pillar[5]arene from the ^{1}H NMR

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(1) (a) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1918. (b) Hishiya, T.; Asanuma, H.; Komiyama, M. *J. Am. Chem. Soc.* **2002**, *124*, 570–575. (c) Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456–464. (d) Harada, A.; Hashidzume, A.; Yamaguchi, H.; Takashima, Y. *Chem. Rev.* **2009**, *109*, 5974–6023. (e) Ogoshi, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2007**, *129*, 4878–4879. (f) Ogoshi, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *Chem. Commun.* **2006**, 3702–3704.

(2) (a) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H. J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621–630. (b) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844–4870. (c) Ogoshi, T.; Inagaki, A.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2008**, 2245–2247. (d) Ogoshi, T.; Masuda, K.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2009**, *42*, 8003–8005.

(3) (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic: Dordrecht, the Netherlands, 1991. (c) Yamagishi, T.; Moriyama, E.; Konishi, G.; Nakamoto, Y. *Macromolecules* **2005**, *38*, 6871–6875. (d) Atwood, J. L.; Dalgarno, S. J.; Hardie, M. J.; Raston, C. L. *Chem. Commun.* **2005**, 337–339. (e) Castro, R.; Godinez, L. A.; Criss, C. M.; Kaifer, A. E. *J. Org. Chem.* **1997**, *62*, 4928–4935. (f) Ogoshi, T.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2007**, 4776–4778.

(4) (a) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022–5023. (b) Ogoshi, T.; Umeda, K.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2009**, 4874–4876.

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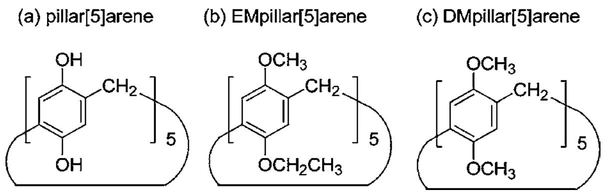
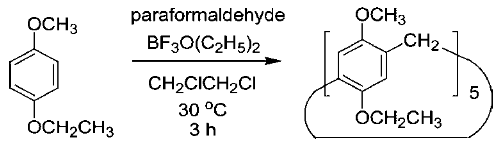


Figure 1. Pillar[5]arenes.

spectra. Here, in this letter, to reveal the conformational characteristics of pillar[5]arene by ^{1}H NMR measurements, we synthesized nonsymmetric novel pillar[5]arene. By using 1-ethoxy-4-methoxybenzene as a monomer, we successfully obtained nonsymmetric ethoxymethoxypillar[5]arene (EMpillar[5]arene, Figure 1b). By the variable-temperature ^{1}H NMR measurements, we revealed the conformational mobility of EMpillar[5]arene. Furthermore, using 2D ROESY analysis, we successfully characterized the 3D conformational structure of EMpillar[5]arene.

By reacting 1-ethoxy-4-methoxybenzene and paraformaldehyde in the presence of boron trifluoride diethyl etherate [$BF_3O(C_2H_5)_2$], we prepared a mixture of polymer and EMpillar[5]arene (Scheme 1).

Scheme 1. Synthesis of Nonsymmetric EMpillar[5]arene



Using silica gel column chromatography, we successfully isolated EMpillar[5]arene in high yield (36.6%). EMpillar[5]arene was highly soluble in organic solvents, such as acetone, toluene, chloroform, DMSO, and THF, while the solubility of dimethoxypillar[5]arene[4] (DMpillar[5]arene, Figure 1c) was poor in these solvents. The melting point of EMpillar[5]arene (131.2 °C) was much lower than that of DMpillar[5]arene (248.8 °C),[4] indicating the low crystallinity of EMpillar[5]arene. Due to the nonsymmetric structure of EMpillar[5]arene, EMpillar[5]arene showed low crystallinity and excellent solubility compared to DMpillar[5]arene. The structure of EMpillar[5]arene was characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, HSQC, FAB-mass, and elemental analysis (Supporting Information). Furthermore, using 2D ROESY analysis, we investigated the 3D conformational structure of EMpillar[5]arene (Figure 2).

In the 2D ROESY analysis of EMpillar[5]arene, there were no correlations between the methoxy and ethoxy moieties (Figure 2a, black rectangles), indicating that the methoxy moieties should not be located near the ethoxy moieties. The expanded 2D ROESY spectra are shown in Figure 2b. The ROE correlations were observed (pink circle) between the protons from the ethoxy moieties around 3.58−3.72 ppm (peaks d) and the phenyl protons around 6.88−7.00 ppm (peaks b), while the other correlations were also found (blue circle) between the protons from the methoxy moieties around 3.40−3.50 ppm (peaks e) and the phenyl protons around 6.95−7.07 ppm (peaks a). These observations indicate

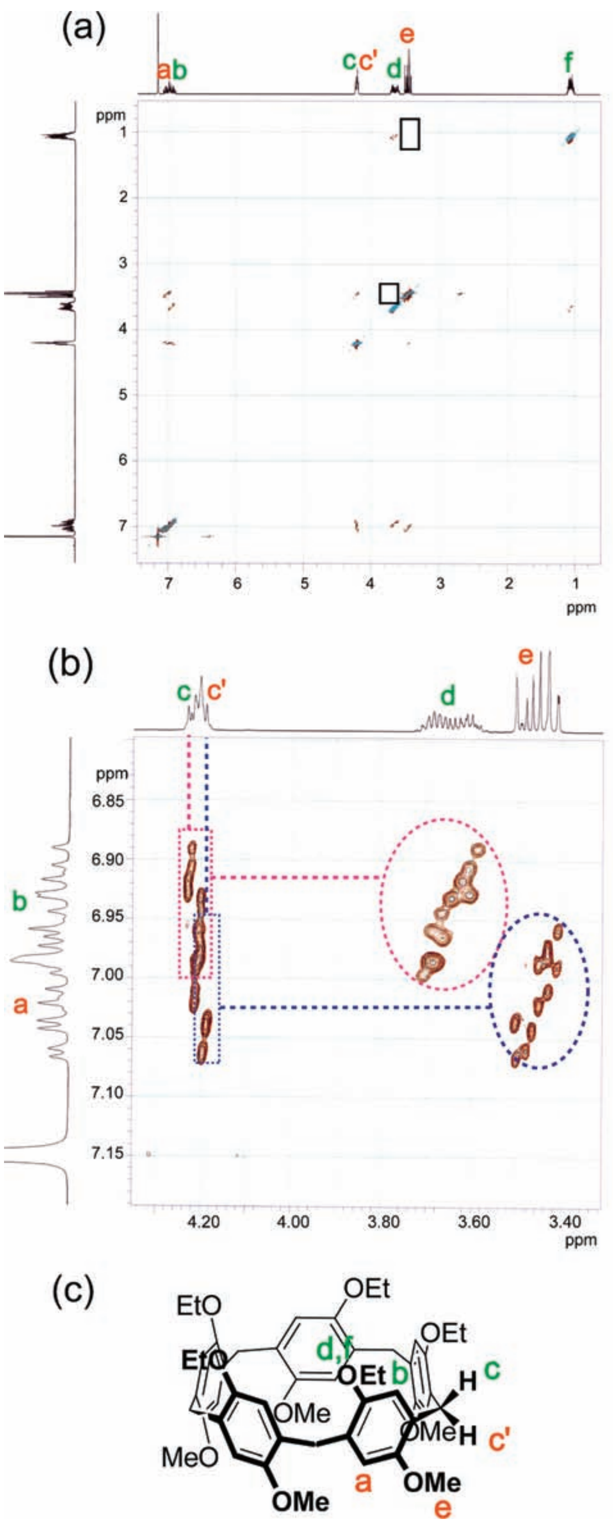


Figure 2. (a) 2D ROESY and (b) expanded 2D ROESY spectra of EMpillar[5]arene (10 mM) in benzene-d_6 at 8 °C. (c) The 3D conformational structure of EMpillar[5]arene.

that the proton peaks around 6.88−7.00 ppm and 6.95−7.07 ppm were ascribed to the phenyl protons from the methoxy-side (peaks a) and ethoxy-side (peaks b), respectively (in the range of 6.95−7.00 ppm, these proton signals were overlapped). Strong correlations between the ethoxy-side phenyl protons (peaks b) and the methylene bridge proton (peaks c) were observed (pink rectangle), whereas ROE correlations were hardly observed between the methoxy-side phenyl protons (peaks a) and the methylene bridge proton (peaks c). Clear ROE effects can also be observed (blue rectangle) between the methoxy-side phenyl protons (peaks a) and the methylene bridge proton (proton c′), while little correlations were found between the ethoxy-side phenyl protons (peaks b) and the methylene bridge proton (peaks c′). From these observations, the methoxy moieties were not located adjacent to the ethoxy groups. All the ethoxy and methoxy moieties were completely separated at upper and lower rims, respectively (Figure 2c).

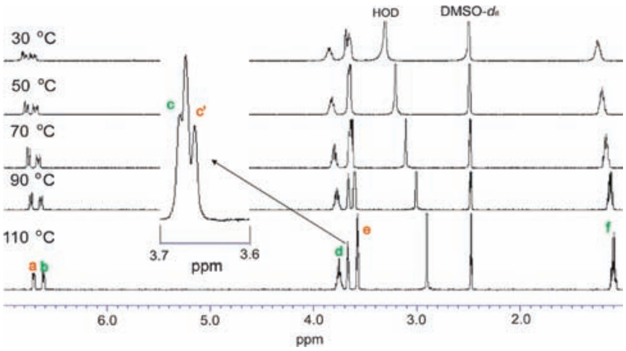


Figure 3. Variable-temperature ^{1}H NMR spectra of EMpillar[5]arene in DMSO-d_6.

As for the investigation of the conformational mobility of EMpillar[5]arene, the variable-temperature ^{1}H NMR measurements were carried out (Figure 3). At low temperatures (30−70 °C), the split proton signals from the phenyl, ethoxy, and methoxy moieties were observed, indicating slow swinging movement of the phenolic units on the NMR time scale (Figure 4). At high temperatures (90−110 °C), these signals became sharp, indicating that the swinging movement became fast. However, even at high temperatures, the signals from the methylene bridge protons (peaks c and c′) did not coalesce (Figure 3, inset). If the phenolic constituent units rotate fast on the NMR time scale, the peaks should become equivalent, and coalescence of the peaks should take place. Therefore, the observation strongly suggested that the rotational movement of the phenolic units should not take place or be slow on the NMR time scale (Figure 4).

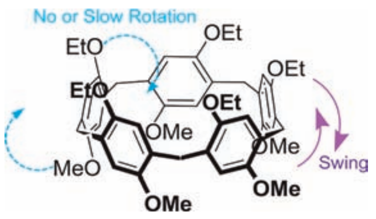


Figure 4. Schematic representation of the swinging and rotation movements of EMpillar[5]arene.

In conclusion, we successfully synthesized a new *para*-bridged nonsymmetric pillar[5]arene, EMpillar[5]arene, in high yield. Due to the nonsymmetric structure, EMpillar[5]arene showed low crystallinity and high solubility in organic solvents compared to DMpillar[5]arene. Due to the nonsymmetric structure of EMpillar[5]arene, we were able to elucidate the 3D conformational structure and mobility of pillar[5]arene. From the 2D ROESY spectra, it was found that the ethoxy and methoxy moieties of EMpillar[5]arene were completely separated at the upper and lower rims, respectively. Since C_4 symmetric calix[4]arenes were selectively obtained by using $BF_3O(C_2H_5)_2$ as Lewis acid,[5] the use of $BF_3O(C_2H_5)_2$ may be useful for the synthesis of the stereoselective macrocycles. Furthermore, by the variable-temperature ^{1}H NMR measurements, we successfully clarified the conformational characteristics of EMpillar[5]arene. The rotational movement of EMpillar[5]arene was slow on the NMR time scale or did not occur. The substituent moieties may affect the conformational characteristics of EMpillar[5]arene. For the further investigation of the swinging and rotation movements of pillar[5]arenes, we are studying the conformational characteristics of new pillar[5]arene derivatives having bulky substituents. The examination of the conformational characteristics may lead to the development of new functional systems based on pillar[5]arene.

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Supporting Information Available: Experimental procedures and full spectroscopic data for EMpillar[5]arene. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Mclldowie, M. J.; Mocerino, M.; Skelton, B. W.; White, A. H. *Org. Lett.* **2000**, *2*, 3869–3871.