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Tetrahedron

Lewis acid-catalyzed synthesis of dodecamethoxycalix[4]arene from 1,3,5-trimethoxybenzene and its conformational behavior and host–guest property

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ABSTRACT

Lewis acid-catalyzed condensation of 1,2- and 1,3-dimethoxybenzenes with paraformaldehyde afforded an *ortho*-bridged cyclic trimer (**1**) and a *meta*-bridged cyclic tetramer (**2**), respectively. Furthermore, condensation of 1,3,5-trimethoxybenzene with paraformaldehyde in the presence of Lewis acid catalyst successfully rendered the first dodecamethoxy-substituted calix[4]arene (**3**) with high yield. From X-ray crystallography, it was found that **3** formed the partial cone conformation. The conformational behavior of **3** in the solution was investigated by variable temperature ^{1}H NMR measurements. The partial cone structure observed in the solid state was retained in the solution at low temperatures. Furthermore, because of the slow conformational exchanges of **3** on the NMR time scale, bimodal conformational exchanges were found. The host–guest property of **3** with the electron accepting guest, tetracyano-ethylene (TCNE) was examined by UV–Vis measurements, and the ability to associate with the **3**-TCNE complex was three times higher than that of the **2**-TCNE complex. The observation is due to the superior electron donating property and slow conformational exchanges of **3** compared with those of analogous **2**.

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1. Introduction

Calixarenes have attracted substantial attention in recent years. This can be attributed to their unique structural and conformational properties allowing their use in the synthesis of supramolecular architectures.[1] For the synthesis of calixarenes, the classical procedure reported by Gutsche et al. is the base catalyzed condensation of phenolic compounds. The other synthetic procedure uses Lewis acid catalysts. Due to the versatility and facility of Lewis acids in organic synthesis, the application of Lewis acids for the synthesis of calixarenes has received considerable attention.[2–6] Successful Lewis acid-catalyzed synthesis of new calixarenes has been demonstrated by Iwanek et al.[2] By using the Lewis acid catalyst, novel C_4 symmetric calix[4]resorcinarene has been reported by Mocerino et al.[3] Among these studies, we have recently synthesized new cyclic compounds of pillar[5]arenes by condensation of 1,4-dimethoxybenzene with the Lewis acid catalyst.[5] Pillar[5]arenes form a unique symmetrical pillar architecture, that is, able to stably capture guest molecules. For the synthesis of pillar[5]arene, boron trifluoride diethyl etherate [BF$_3$·O(C$_2$H$_5$)$_2$] was an appropriate Lewis acid. Due to the weak acidity of BF$_3$·O(C$_2$H$_5$)$_2$, the

condensation should proceed gradually and then react intermediately to form stable macrocycles. The use of BF$_3$·O(C$_2$H$_5$)$_2$ in calixarenes or calixresorcinarenes synthesis has also been examined.[6] Therefore, in this study, by using BF$_3$·O(C$_2$H$_5$)$_2$ as Lewis acid, we investigated the condensation of various di- and trimethoxybenzenes with paraformaldehyde. The Lewis acid-catalyzed condensation of 1,2- and 1,3-dimethoxybenzene produced cyclotriveratrylene (Fig. 1, **1**) and octamethoxycalix[4]resorcinarene (Fig. 1, **2**), respectively. Furthermore, by the Lewis acid condensation of 1,3,5-trimethoxybenzene, the novel *meta*-bridged macrocyclic tetramer of 4,6,10,12,16,18,22,24,25,26,27,28-dodeca-methoxycalix[4]arene (Fig. 1, **3**) was obtained. Due to the bulky dodeca-methoxy substituents on the upper and lower rims, **3** should show unique conformational characteristics and host–guest properties compared to typical calixarenes and calixresorcinarenes.
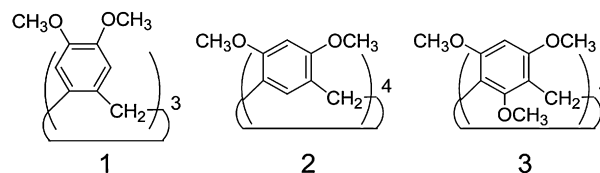

Figure 1. Macrocycles prepared from Lewis acid-catalyzed condensation of methoxybenzenes with paraformaldehyde.

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In this research, we revealed conformational behavior and the host–guest property of **3** compared to those of **2**, which had a similar structure except for the lack of tetra-methoxy substituents on the lower rim.

2. Results and discussion

2.1. Lewis acid-catalyzed condensation of dimethoxybenzenes

GPC elution traces after Lewis acid-catalyzed condensation of dimethoxybenzenes with paraformaldehyde are shown in Figure 2a and b. As a Lewis acid, we employed boron trifluoride diethyl etherate [$BF_3 \cdot O(C_2H_5)_2$]. In both 1,2- and 1,3-dimethoxybenzenes, the sharp peaks were observed at 22.5 and 22.0 mL, respectively, indicating that particular oligomers were selectively obtained. By washing with acetone, *ortho*-bridged cyclic trimer, cyclotriveratrylene (**1**) and *meta*-bridged cyclic tetramer, octamethoxycalix[4]resorcinarene (**2**) were successfully isolated. These macrocycles were characterized completely by ^{1}H NMR and FAB-Mass measurements. While these macrocycles are known compounds, this procedure is the facile and improved method to obtain high yield of macrocycles **1** (54.8%) and **2** (84.8%) compared with the other synthetic methods.[7]

2.2. Lewis acid-catalyzed condensation of trimethoxybenzenes

Lewis acid-catalyzed condensation of trimethoxybenzenes with paraformaldehyde was investigated using GPC measurements (Fig. 2c–e). $BF_3 \cdot O(C_2H_5)_2$ was used as a Lewis acid. In 1,2,3-trimethoxybenzene, a broad peak at the elution volume of 17–20 mL was observed (Fig. 2c), strongly suggesting the formation of polymer. In the case of 1,2,4-trimethoxybenzene, multiple peaks at an elution volume of 20–23 mL were found (Fig. 2d), indicating the preparation of the mixture of oligomers. On the other hand, by the condensation of 1,3,5-trimethoxybenzene, a sharp peak at 21.8 mL was mainly seen (Fig. 2e). The observation indicates that a particular oligomer is selectively obtained by using 1,3,5-trimethoxybenzene. The product was successfully *re*-crystallized from acetone. From X-ray crystallography (Fig. 3), it was found that the crystalline was the cyclic tetramer of 1,3,5-trimethoxybenzene (**3**). 1,3,5-Trimethoxybenzene units were connected by methylene bridges at *meta*-positions. The structure of **3** was the partial cone conformation (three benzene rings 'up' and one 'down'). From these observations, it was confirmed that cyclic tetramer (**3**) was obtained by condensation of 1,3,5-trimethoxybenzene and paraformaldehyde using Lewis acid catalyst. On the other hand, the reaction of 1,2,3- and 1,2,4-trimethoxybenzenes with Lewis acid catalyst produced
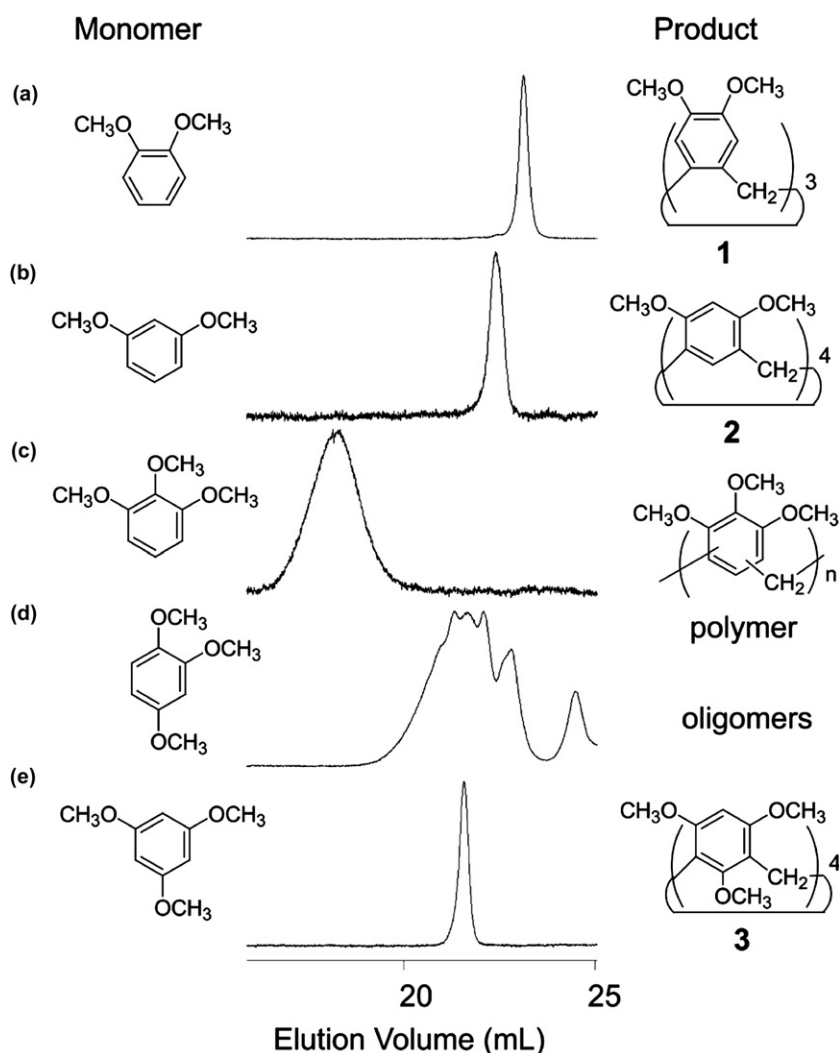

Figure 2. GPC traces of the obtained products from (a) 1,2-dimethoxybenzene, (b) 1,3-dimethoxybenzene, (c) 1,2,3-trimethoxybenzene, (d) 1,2,4-trimethoxybenzene and (e) 1,3,5-trimethoxybenzene.
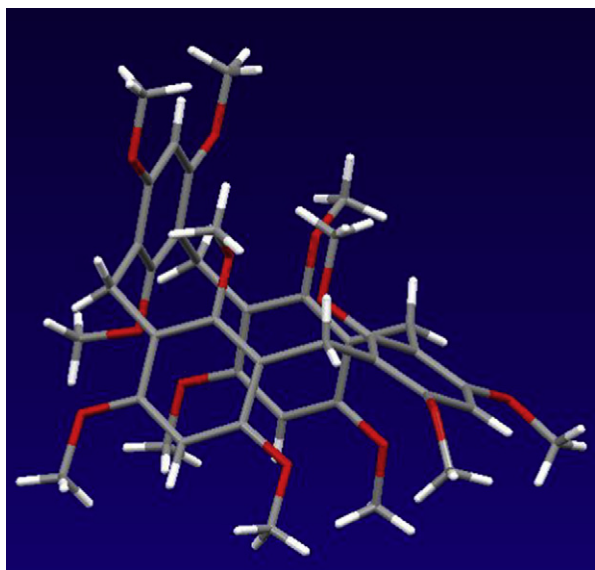
Figure 3. The crystal structure of **3**.

polymer and oligomers, respectively. The difference in reactivity was depended upon the substituent position of the methoxy groups. Since the 1,3,5-trimethoxybenzne has 3 equiv reactive positions on the aromatic ring, the reaction proceeds cleanly. Two isomers of 1,2,3- and 1,2,4-trimethoxybenzenes do not have equal reaction sites: therefore, these two isomers should produce a complex mixture of polymer and oligomers.

To examine the mechanism for the formation of the macrocyclic **3**, the reactions with the other Lewis acids were carried out. By using the other Lewis acids such as aluminum (III) chloride, iron (III) chloride, and tin (IV) chloride, polymers formed and **3** was not obtained selectively (Supplementary data). Since the acidity of these Lewis acid is stronger than that of $BF_3 \cdot O(C_2H_5)_2$, the reactions took place effectively and thus formation of the polymers should occur. When the weak $BF_3 \cdot O(C_2H_5)_2$ catalyst was used for the reaction, the condensation should proceed gradually and then the intermediate should form thermally stable macrocyclic tetramer of **3**.

2.3. Conformational behavior of 3

To examine the conformational behavior of the **3** in the solution, measurements of the variable temperature ^1H NMR were carried out (Fig. 4a).
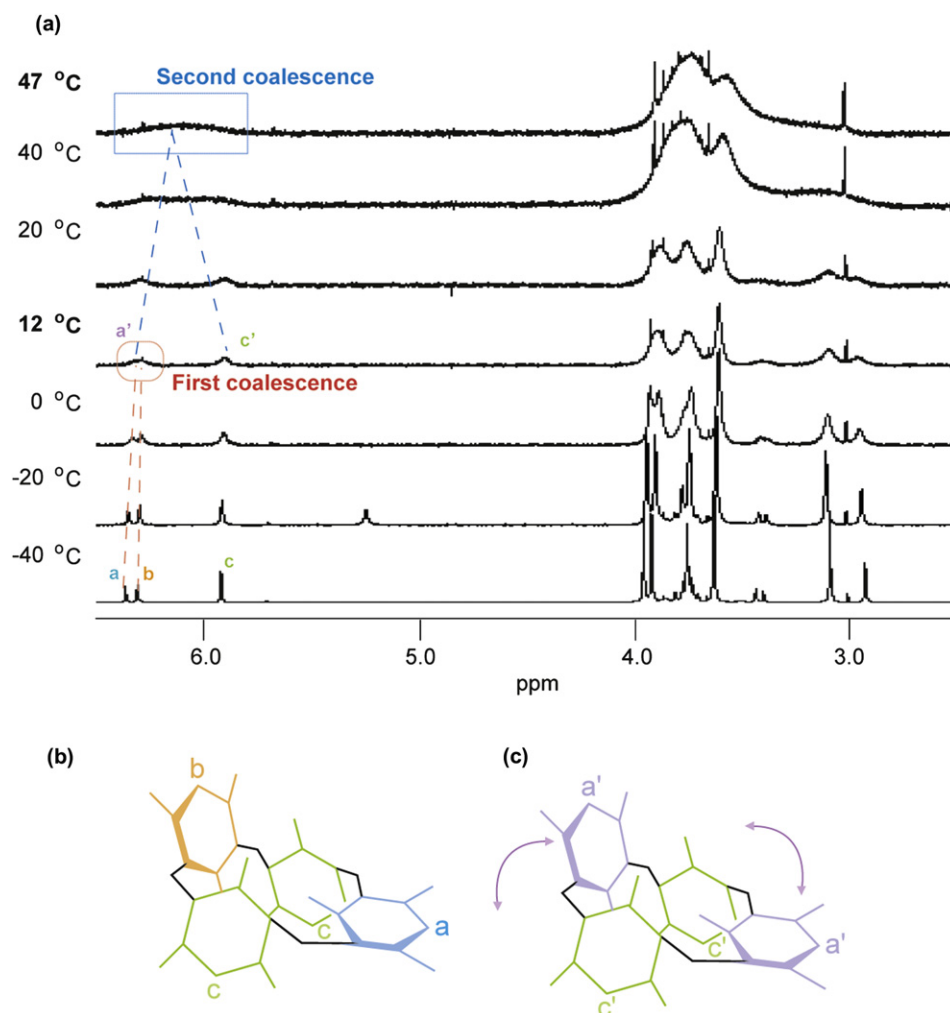

Figure 4. (a) Variable temperature ^1H NMR spectra of **3** in $CDCl_3$. (b) The arrangement of the benzene proton peaks at low temperature. (c) First exchange process of **3**. The peak at 5.23 ppm in Figure 4 (a) at −20 °C should correspond to toluene formed the complex with **3** or noise from the device.

In CDCl$_3$ at 20 °C, proton resonances from the **3** were largely broadened. At low temperatures, these peaks became sharp and split. The result indicates that conformational exchanges of the **3** were slow on the NMR time scale at low temperatures. In the ^{1}H NMR spectrum of **3** in CDCl$_3$ at -40 °C, three singlets [δ=5.92 (2H), 6.29 (1H), 6.35 (1H)] were found, indicating that the partial cone conformation adopted in the solid state should be retained in the solution at the temperature. (The assignment of these peaks is shown in Fig. 4b). At 12 °C, the first coalescence of both the singlets [δ=6.29 (proton a) and 6.35 (proton b)] was observed. The coalescence behavior derived from the equilibrium between the two equivalent species of the partial cone conformation was attributed to the flipping of face-to-face 'flat' and 'down' benzene rings (first exchange process, Fig. 4c). From the coalescence temperature, a free-energy barrier of 60.3 kJ/mol was calculated for the exchange process. As the temperature increased, the second coalescence of the singlets [δ=6.29 (proton a$'$) and 5.89 (proton c$'$)] was found. The second coalescence behavior corresponded to the conformational exchange from a partial cone to cone. From the second coalescence temperature, a free-energy barrier for the conformational inversion was determined to be 62.9 kJ/mol. In the case of **3** in toluene-d_8, the first and second coalescence temperatures were found at 24 °C and 66 °C, respectively (Fig. 5).
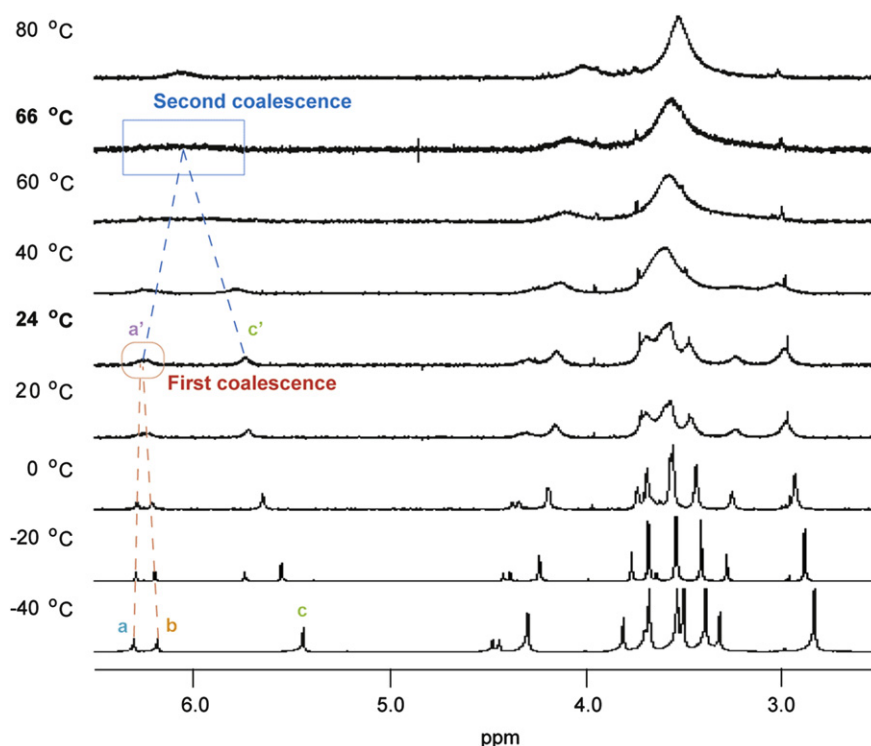
methoxy groups on the lower rim of **3** extremely lowered the conformational exchanges of **3** considerably.

2.4. Host–guest property of 3

Since **3** is composed of an electron donor of 1,3,5-trimethoxybenzene, the formation of the host–guest complex with a strong electron acceptor of tetracyanoethylene (TCNE) was examined. We measured UV–Vis absorption spectra of TCNE upon the addition of **3** (Fig. 6).

When **3** was added to the TCNE solution, a new peak around 718 nm was observed. Since there were no absorption peaks around this region in both TCNE and **3**, it was assumed that the peak was derived from the charge–transfer complex between TCNE and **3**. The stoichiometry of the host–guest complex between **3** and TCNE was determined by Job plots[8] (Fig. 7, left). The peak top was observed in molar fraction: X_{guest}=0.5, indicating the formation of a ratio of 1:1 host–guest complex. To determine the association constant of the complex, titration experiments were conducted by adding **3** to the TCNE solution. From the Benesi–Hildebrand treatment (Fig. 7, right), the association constant of the **3**-TCNE complex was found to be 60 M^{-1}. As a control experiment, we measured the association constant between the 1,3,5-trimethoxybenzene

Figure 5. Variable temperature ^{1}H NMR spectra of **3** in toluene-d_8.

From the coalescence temperatures, free-energy barriers for the first and second exchange processes in toluene-d_8 were determined to be 61.2 kJ/mol and 66.1 kJ/mol, respectively, which were higher than those in CDCl$_3$. These data indicate that conformational inversion of **3** in toluene-d_8 was slower than that in CDCl$_3$. In the case of **2**, which had a similar structure to **3** except for the lack of the methoxy groups in the lower rim, the proton peaks of **2** in toluene-d_8 did not change even at a low temperature (Supplementary data). The foundation indicates that conformational exchanges of **2** were fast on the NMR time scale at low temperatures. From these observations, it was found that the steric hindrance of the substituted

(monomer) and TCNE. The association constant of the 1,3,5-trimethoxybenzene–TCNE complex determined by the Benesi–Hildebrand method was 6 M^{-1} (Supplementary data), indicating that the association ability of **3** with TCNE was almost 10 times higher than that of 1,3,5-trimethoxybenzene. While various charge–transfer complexes between TCNE and electron donors have been reported, their general association constants are not so high (under 20 M^{-1}).[9] Accordingly, the complexation ability of **3** with TCNE is superior to usual donor molecules. The macrocyclic structure of **3** should enhance the association ability with TCNE. In the case of **2**, the association constant of the **2**-TCNE complex calculated by the
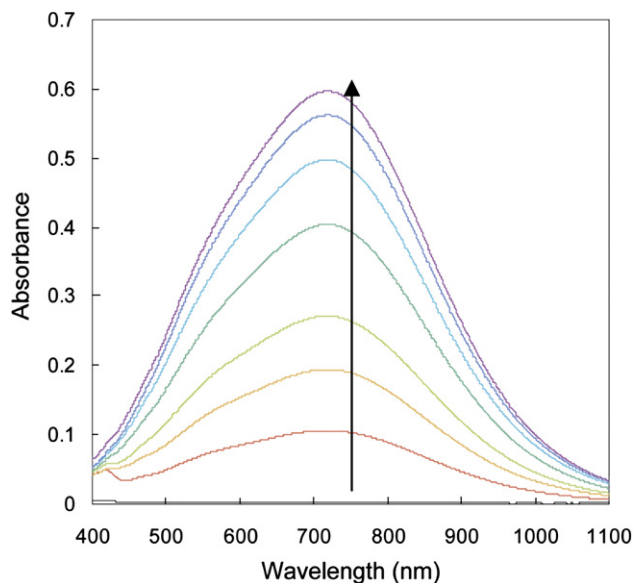
Figure 6. Absorption spectra of TCNE (3.33 mM) in chloroform upon addition of **3**. The concentration of **3** varied from 0 to 18.3 mM.

temperatures. As the temperature was raised, bimodal conformational exchanges of **3** were found from variable temperature ^{1}H NMR measurements. Furthermore, due to the superior electron donating property and slow conformational exchanges of **3**, **3** formed a strong complex with the electron accepting guest of TCNE.

4. Experimental

4.1. Materials

All solvents and reagents were used as supplied.

4.2. Measurements

The ^{1}H NMR spectra were recorded at 270 MHz and 400 MHz and ^{13}C NMR spectra were recorded at 67.5 MHz and 100 MHz with a JEOL-JNM EX270 and EL400 spectrometers, respectively. The FTIR spectra were obtained using a JASCO FT-IR460 plus infrared spectrometer. Gel permeation chromatography (GPC) analysis was carried out on Shodex GPC LF804 by using THF as an eluent at 25 °C at a flow rate of 1 mL min^{-1} after calibration with the standard polystyrene samples. The absorption spectra were recorded with a JASCO V-630 spectrophotometer at room temperature.
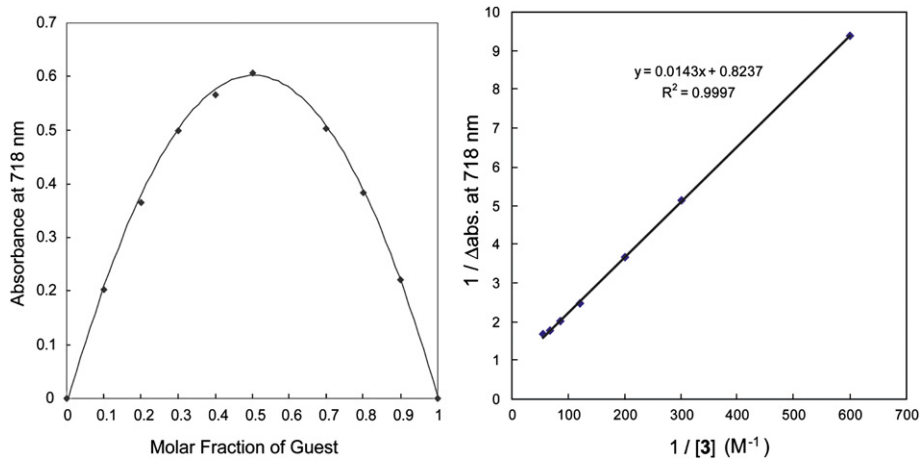

Figure 7. Job (left) and Benesi–Hildebrand (right) plots for **3** and TCNE.

Benesi–Hildebrand plots was 20 M^{-1} (Supplementary data). The association constant of **3**-TCNE complex was three times higher than that of the **2**-TCNE complex. The observation is due to the superior electron donating property and slow conformational exchanges of **3** compared with those of **2**. **3** was perceived to be a useful host for the electron accepting guests.

3. Conclusion

We investigated Lewis acid-catalyzed condensation of various methoxybenzenes with paraformaldehyde. In the case of 1,2- and 1,3-dimethoxybenzenes, the macrocycles **1** and **2** were selectively obtained. By using 1,3,5-trimethoxybenzene as a monomer, the novel cyclic tetramer of **3** was synthesized at a high yield. From these results, it was found that the Lewis acid-catalyzed condensation of methoxybenzenes was a facile and useful procedure at obtaining macrocycles. Conformational exchanges of the new **3** were extremely slow on the NMR time scale at low temperatures compared to that of the analogous **2**. Due to dodeca-methoxy substituents of **3**, the partial cone conformation observed in the solid state X-ray structure was retained in the solution at low

4.3. Cyclotriveratrylene (1)

Paraformaldehyde (0.31 g, 10 mmol) was added under nitrogen atmosphere to a solution of 1,2-trimethoxybenzene (1.38 g, 10 mmol) in 1,2-dichloroethane (20 mL). The reaction flask was capped and nitrogen bubbled through the solution for 30 min. Following this, boron trifluoride diethyl etherate [BF$_3$·O(C$_2$H$_5$)$_2$, 1.25 mL, 10 mmol] was added to the solution and the mixture was stirred at 30 °C for 3 h. The solution was poured into methanol and the resulting precipitate was collected using a filtration. After washing with acetone, cyclotriveratrylene (**1**) was obtained (Yield: 54.8%). ^{1}H NMR (CDCl$_3$, 270 MHz, 25 °C, ppm): δ 6.83 (s, 6H, phenyl), 4.80 (d, 3H, methylene), 3.84 (s, 18H, methoxy), 3.58 (d, 3H, methylene). FAB mass m/z=450 (M$^+$).

4.4. Octamethoxycalix[4]resorcinarene (2)

This compound was prepared from 1,3-dimethoxybenzene (1.38 g, 10 mmol), paraformaldehyde (0.31 g, 10 mmol) and boron trifluoride diethyl etherate [BF$_3$·O(C$_2$H$_5$)$_2$, 1.25 mL, 10 mmol] under the same conditions as those used for the preparation of **1**. After

washing with acetone, **2** was obtained (Yield: 84.8%). ^{1}H NMR (CDCl$_3$, 270 MHz, 25 °C, ppm): δ 6.41 (s, 4H, phenyl), 6.18 (s, 4H, phenyl), 3.77 (s, 24H, methoxy), 3.69 (s, 8H, methylene). FAB mass m/z=600 (M$^+$).

4.5. 4,6,10,12,16,18,22,24,25,26,27,28-dodecamethoxy-calix[4]arene (3)

This compound was prepared from 1,3,5-trimethoxybenzene (1.68 g, 10 mmol), paraformaldehyde (0.31 g, 10 mmol) and boron trifluoride diethyl etherate [BF$_3$•O(C$_2$H$_5$)$_2$, 1.25 mL, 10 mmol] under the same conditions as those used for the preparation of **1**. The solid material obtained was *re*-crystallized from acetone to yield **3** as a white solid. (Yield: 43.5%). ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C, ppm): δ 6.50–5.70 (br s, 1H, phenyl), 4.20–3.30 (br s, 32H, methylene and methoxy), 3.20–2.70 (br s, 12H, methoxy). ^{1}H NMR (DMSO-d_6, 270 MHz, 100 °C, ppm): δ 6.14 (s, 1H, phenyl), 3.62 (s, 24H, methoxy), 3.50 (s, 8H, methylene), 3.33 (s 12H, methoxy). ^{13}C NMR (CDCl$_3$, 67.5 MHz, 25 °C, ppm): δ 159.6, 156.0, 116.4, 91.9 (phenyl), 61.0, 55.7 (methoxy group), 16.8 (methylene bridge). Anal. Calcd for C$_{40}$H$_{48}$O$_{12}$: C, 66.65; H, 6.71. Found: C, 66.50; H, 6.72. FAB mass m/z=720 (M$^+$). FTIR (KBr): 1229 cm^{-1} (s, C–O–C, antisymmetric stretching), 1032 cm^{-1} (s, C–O–C, symmetric stretching). Melting point (T_m): 291.2 °C.

Acknowledgements

Appendix. Supplementary data

^{1}H and ^{13}C NMR spectra of **3**, X-ray crystallographic data in CIF format, GPC traces of the products from 1,3,5-trimethoxybenzene with aluminum (III) chloride, iron (III) chloride, and tin (IV) chloride, variable temperature ^{1}H NMR spectra of **2**, absorption spectra of TCNE with 1,3,5-trimethoxybenzene and **2**, Benesi–Hildebrand plots for determination of association constants of TCNE with 1,3,5-trimethoxybenzene and **2** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.059.

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