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The properties of host-guest complexes based on macrocycles such as cyclodextrins,1 crown ethers,2 calixarenes3 and cucurbiturils4 have been studied extensively. The development of methods for the high yield synthesis of macrocyclic host homologues possessing different cavity sizes has extended this field of chemistry considerably, because of different host-guest properties depending on their cavity sizes. The selective synthesis of the macrocyclic homologues, however, is generally difficult under the kinetically controlled cyclization process.

The use of template compounds (thermodynamically controlled cyclization process) is therefore necessary for the selective synthesis of particular homologues.

Pillar[n]arenes, which were first reported by our group in 2008,5 are one of new macrocyclic compounds at the core of supramolecular chemistry. Cyclic pentamer pillar[5]arene5,6 was prepared in high yields by the condensation reaction of 1,4-dialkoxybenzene with paraformaldehyde and BF3•OEt2 in 1,2-dichoroethane (DCE) because DCE acts as a templating solvent. The high yield synthesis of pillar[5]arenes led to rapid developments in the chemistry of pillar[5]arenes.5-7 Pillar[6]arenes, which are cyclic hexamers, have been synthesized, but their yields were not high (<45%) even in the optimized condition because the cyclization process is under kinetically control.5,10 The low yields encountered for the synthesis of pillar[6]arenes compared to pillar[5]arenes represent bottle-neck in terms of further expanding the field of pillar[6]arenes chemistry. Herein, we described our research towards developing a thorough understanding of the exact role of the template effect of solvents on the synthesis of a pillar[6]arene. Based on the thermodynamically controlled cyclization process, we successfully synthesized a pillar[6]arene in high yield, and a co-pillar[6]arene by co-cyclization approach for the first time.

![Cyclic pentamer pillar[5]arene](attachment://Figure1a.png)

**Figure 1** (a) Synthesis of pillar[5]- and pillar[6]arenes from dialkoxybenzene monomers (M1-M4). (b) pillar[n]arenes with tri(ethylene oxide) groups (TEOn)[n] = 5; TEO[6] = 6.

DCE is a suitable solvent for the synthesis of pillar[5]arenes. Pillar[5]arene P1[5] (Fig. 1) was obtained in high yield (71%) when DCE was used as the solvent with 1,4-dimethoxybenzene (M1) as the monomer (Table 1, entry 1). The cavity size of pillar[5]arenes is ca. 5.5 Å and generally fits linear alkanes containing electron-with-drawing groups.6 The linear dihaloalkane DCE therefore fit well into pillar[5]arene cavity and acts as the template for the synthesis of pillar[5]arene, indicating thermodynamically controlled cyclization process. In contrast, the reaction of 1,4-diethoxybenzene (M2) with paraformaldehyde in the presence of BF3•OEt2 in chloroform (Table 1, entry 2) resulted in a mixture of pillar[5-10]arenes,10 with P2[5] and P2[6] being isolated in yields of 20 and 15%,
Table 1. Solvent Effects

<table>
<thead>
<tr>
<th>Entry</th>
<th>Monomer</th>
<th>Solvent</th>
<th>Pillar[n]arenes (Yield%)</th>
<th>n = 5</th>
<th>n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>M1</td>
<td>DCE</td>
<td>P3[5] (71)</td>
<td>P1[6] (0)</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>M3</td>
<td>DCE</td>
<td>P3[5] (3)</td>
<td>P3[6] (0)</td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>M3</td>
<td>Chloroform</td>
<td>P3[5] (10)</td>
<td>P3[6] (0)</td>
<td></td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>M3</td>
<td>CyC6</td>
<td>P3[5] (0)</td>
<td>P3[6] (0)</td>
<td></td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>M3</td>
<td>Cl-CyC6</td>
<td>P3[5] (3)</td>
<td>P3[6] (87)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Same reaction condition in Ref. 6b. <sup>b</sup>Same reaction condition in Ref. 9. <sup>c</sup>Detail experimental conditions are shown in ESI.

which prevented the pillar[5]arene from forming stable complexes. This indicates the cyclization is carried out under kinetic control. In this study, several other reaction solvents capable of fitting the pillar[6]arene cavity were also investigated for the synthesis of pillar[6]arenes. The cavity size of pillar[6]arenes is greater than that of pillar[5]arenes at ca. 7.5 Å and this large cavity size allows pillar[6]arenes to bind various of bulky hydrocarbons. Based on the host-guest chemistry of pillar[6]arenes, it was envisaged that bulky hydrocarbon solvents would be ideal solvents for the synthesis of pillar[6]arenes. Thus, we evaluated the use of cyclohexane (CyC6), chlorocyclohexane (Cl-CyC6), cyclooctane and decaline as solvents. 1,4-Bis(methylcyclohexyl) ether/benzene (M3) was used as a monomer in these reactions to overcome the poor solubility of 1,4-diakloxybenzenes in the hydrocarbon solvents because this monomer M3 contained bulky lipophilic moieties that would enhance its solubility in the hydrocarbon solvents. We initially examined the reaction of M3 in DCE under the same conditions used for the high yield synthesis of pillar[5]arene (Table 1, entry 1). Although the condition was suitable for the synthesis of pillar[5]arene, the yield of P3[5] was much lower at 3% (Table 1, entry 3). This low yield was attributed to steric hindrance from the bulky cyclohexylmethyl groups, which would have prevented the formation of P3[5] but also P3[6]. When M3 was reacted in chloroform, P3[5] and P3[6] were formed with yields of 10 and 8%, respectively (Table 1, entry 4). Chloroform does not act as a template for the synthesis of both pillar[5]- and pillar[6]arenes, thus the reaction in chloroform resulted in the formation of P3[5] and P3[6]. This result therefore displayed a similar trend to that of the reaction of M2 in chloroform (Table 1, entry 2). Pleasingly, when Cl-CyC6 was used as the solvent with M3, the pillar[6]arene P3[6] was isolated as the major product in 87% yield (Table 1, entry 6). This high yield represents a significant improvement over those previously reported for the synthesis of pillar[6]arenes (35–45%). This method therefore allowed for the selective and high yield synthesis of pillar[6]arene using Cl-CyC6 as a bulky hydrocarbon solvent. Several other bulky hydrocarbon solvents were also investigated, including CyC6 (Table 1, entry 5), but did not afford any of the desired pillar[6]arene products. The use of halogenated solvents is also suitable for the synthesis of pillar[n]arenes, because the cavities of pillar[n]arenes are electron rich spaces and can therefore readily accommodate guest molecules containing electron-withdrawing groups such as cyano and halogen moieties. The halooalkane Cl-CyC6 would therefore be included in the pillar[6]arene cavity where it would act as a template for the synthesis of pillar[6]arene. As with pillar[6]arenes, P3[6] also forms host-guest complex with a DABCO cation<sup>9</sup> (Fig. S2) and deprotection of cyclohexylmethyl groups by BBr<sub>3</sub> afforded per-hydroxylated pillar[6]arene in high yield (yield 95%).

![Fig. 2](image_url) 1H NMR spectra of (a) DCE, and 1:1 mixtures of DCE with (b) TEO[5] or (c) TEO[6]. (d) Cl-CyC6, and 1:1 mixtures of Cl-CyC6 with (e) TEO[5] or (f) TEO[6] at 25 °C.

In attempt to examine the solvent template effect on the selective formation of pillar[5]- and pillar[6]arenes, we measured the 1H NMR spectra of mixtures of DCE and Cl-CyC6 with P3[5] and P3[6] in CDCl<sub>3</sub> (Figs. S3 and S4). It was not possible, however, to detect clear peak shifts in these spectra because of the complexation was too weak in CDCl<sub>3</sub>. We recently found that pillar[5]- and pillar[6]arenes carrying tri(ethylene oxide) chains (Fig. 1b, TEO[5] and TEO[6]) exist as liquids at room temperature.<sup>11</sup> We proceeded to evaluate the bulk state host-guest complexation process by 1H NMR with guest molecules using TEO[5] and TEO[6] as solvents. The proton signal from the ethylene moiety of DCE in the bulk state was observed at 3.64 ppm (Fig. 2a). When DCE was mixed with TEO[5] (Fig. 2b), the signal of the ethylene moiety underwent a significant upfield shift of 2.53 ppm. In contrast, no upfield shift was observed for this peak in a 1:1 mixture of DCE and TEO[6] (Fig. 2c). These results indicated that DCE formed a strong complex with TEO[5] in the bulk state but not with TEO[6]. In contrast, when Cl-CyC6 and TEO[5] were mixed (Fig. 2e), only small up-field shifts were observed in the proton signals belonging to Cl-CyC6. In the case of a mixture of Cl-CyC6 and TEO[6] (Fig. 2f), large upfield shifts were observed in the signals belonging to Cl-CyC6. Cl-CyC6 can form much stronger interaction with TEO[6] than that with TEO[5]. From these results, DCE acts as a template for
pillar[5]arenes but not for pillar[6]arenes, and Cl-CyC6 behaves as a template for the synthesis of pillar[6]arenes but not for pillar[5]arenes. DFT calculations (Fig. S5) also supported these experimental data. Based on the solvent template effect and the reversible reaction behaviour, we examined the “dynamic” interconversion between the pillar[5]arene and pillar[6]arene with BF₃·OEt₂. Firstly, we examined conversion of P3[5] to P3[6] in DCE. The reaction was monitored by ¹H NMR measurements (Fig. 4a). At 25 °C, the ring-opening reaction of P3[6] did not proceed, but, when the mixture was heated at 80 °C, new peaks corresponding to from P3[5] and the oligomers were observed. It was necessary to heat the reaction to provide the energy required to overcome the kinetic barrier to the ring-opening reaction. A decrease in the ratio of P3[6] together with an increase in the ratio of P3[5] was subsequently observed as the reaction progressed, indicating P3[6] was converted to P3[5]. We also examined the conversion of P3[5] to P3[6] in Cl-CyC6 (Fig. 4b). Heating at 80 °C was also required for the cleavage of the P3[5] ring. As the reaction proceeded, we observed a decrease in the amount of P3[5] together with a simultaneous increase in the amount of P3[6], even though the ratio of oligomers in the reaction mixture was high. This result indicated that P3[5] was converted to P3[6]. By contrast, conversions did not take place (Fig. S5) in combinations of host-guest complexes (P3[5] in DCE or P3[6] in Cl-CyC6), meaning “freezing” by inclusion of a template solvent. We can reversibly interconvert using different template solvents, in that P3[6] can be converted to P3[5] using DCE, P3[5] can be converted back to P3[6] using Cl-CyC6.

The co-cyclization method, which involves the co-cyclization of different monomers, represents a useful approach for the synthesis of functionalized pillar[5]arenes. This method, however, cannot be applied to the synthesis of functionalized pillar[6]arenes because pillar[5]arenes are formed as the major

To examine the mechanism of the reaction leading to the pillar[6]arene using Cl-CyC6 (Table 1, entry 6), we monitored the size-exclusion chromatography (SEC) profiles of the products obtained from the reaction over time (Fig. 3a). After 1 min, peaks from P3[6] and P3[5] were observed with retention times of 19.0 and 19.5 min. Peaks for the corresponding oligomers were also observed in the range of 17–20 min. As the reaction proceeded, the sizes of the peaks corresponding to P3[5] and the oligomers decreased, where the peak corresponding to P3[6] increased in size. After 1.5 min, we detected peaks from P3[6] and the oligomers. Beyond this time point, the trace remained largely unchanged. The reaction was also monitored using ¹H NMR (Fig. 3b). After 20 sec, the proton signal from M3 (green diamonds), pillar[5]arene P3[5] (blue circles), pillar[6]arene P3[6] (red squares) and oligomers (black triangles) determined by ¹H NMR of the reaction mixtures over time.

![Fig. 3 Monitoring the reaction of entry 6 (Table 1). (a) SEC traces, (b) partial ¹H NMR spectra (CDCl₃, 25 °C) and (c) ratios of M3 (green diamonds), pillar[5]arene P3[5] (blue circles), pillar[6]arene P3[6] (red squares) and oligomers (black triangles) determined by ¹H NMR of the reaction mixtures over time.](image-url)

![Fig. 4 Interconversion between pillar[5]arene P3[5] and pillar[6]arene P3[6]. Ratios of P3[5] (blue circles), P3[6] (red squares) and the oligomers (black triangles) by cleaving (a) P3[6] in DCE and (b) P3[5] in Cl-CyC6 at 80 °C, which were monitored by ¹H NMR analysis of the reaction mixtures over time.](image-url)
products when DCE is used as the solvent. In this study, however, we found that pillar[6]arene was formed as the major product using Cl-CyC6. We investigated the development of a co-cyclization method for the synthesis of co-pillar[6]arene (Fig. 5). The condition with much amount of M4 is best for the synthesis of co-pillar[6]arene P3[5]P4[1]. A mixture of M3 and M4 (M3 : M4 = 1 : 16) with paraformaldehyde and BF3·OEt2 was stirred in Cl-CyC6 at room temperature. After purification by column chromatography, co-pillar[6]arene P3[5]P4[1] was isolated in 9% yield, which was higher than the yields observed for homopillar[n]arenes P3[5] (1%) and P3[6] (8%). The use of Cl-CyC6 as a solvent therefore allowed for the first synthesis of P3[5]P4[1] by co-cyclization method.

In conclusion, we demonstrated the template effect of different solvents towards the formation of pillar[5]- and pillar[6]arenes, and discovered that Cl-CyC6 is a good solvent for synthesis of pillar[6]arenes. Cl-CyC6 is an inexpensive and commercially available solvent, and we therefore believe that our new procedure could be used to provide better access to pillar[6]arenes. We have also demonstrated for the first time the synthesis of co-pillar[6]arene using the co-cyclization method. The success of this solvent-templated synthesis for the construction of pillar[6]arenes suggests that a similar strategy could be applied to the selective synthesis of the other pillar[n]arene homologues with larger ring sizes. This is currently underway in our laboratory.

Notes and references

12 Due to the weak association constant between Cl-CyC6 and pillar[5]arenes should be low.
13 Z. Zhang, B. Xia, C. Han, Y. Yu and F. Huang, Org. Lett., 2010, 12, 3285.