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Concentration-dependent supramolecular self-assembly of A1/A2-asymmetric-difunctionalized pillar[5]arene†

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A series of A1/A2-bromoalkoxy-and-hydroxy-difunctionalized pillar[5]arenes were synthesized by the removal of the pillar[5]arene-bearing benzyl group using catalytic hydrogenation. The difunctionalized pillar[5]arene bearing 8-bromooctoxy and benzyloxy substituents at the A1/A2 positions formed pseudo[1]rotaxane at low concentration and double-threaded supramolecular dimer at high concentration. The supramolecular self-assembly behavior has been probed with multiple methods including varying (variable) concentration ^{1}H NMR spectroscopy, diffusion-ordered spectroscopy (DOSY), dynamic light scattering (DLS) measurements, isothermal titration calorimetry (ITC), and single-crystal X-ray analysis.

Introduction

Mechanically interlocked molecules (MIMs) such rotaxanes/pseudorotaxanes have been extensively synthesized and studied in past decades and have found many applications in the design of molecular machines,[1] chemical probes[2] and drug delivery.[3] The reversible exchange behavior of pseudorotaxanes, which consist of macrocyclic systems with threaded linear components, plays an important role in the design and fabrication of MIMs based artificial molecular machines and supramolecular polymers.[4] Thus, macrocyclic hosts such as cyclodextrins,[5] calixarenes,[6] cucurbiturils,[7] cyclophanes,[8] and more recent pillar[*n*]arenes[9] plays an important role in construction of MIMs. Pillar[*n*]arenes in particular, attracted great interest for their unique structural features, versatile synthetic manipulation, and exceptional ability to selectively encapsulate different kinds of guest molecules.[10,11]

Pseudo[1]rotaxanes are the simplest form of threaded structures which are mechanically self-interlocked macrocyclic systems with reversible exchange behavior between threaded and open forms. Many pseudo[1]rotaxane based pillar[5]arene have been reported taking advantage of the highly symmetrical rigid structure and electron-donating cavities.[9,12] For example, monofunctionalized pillar[5]arene bearing imidazolium moiety that formed stable pseudo[1]rotaxane event at high concentration has been reported.[13] The concentration independent nature of self-inclusion was also shown with neutral mono-urea-functionalized pillar[5]arene, however in solid state formed double-threaded dimer.[14] In contrast, the concentration dependence behavior of pseudo[1]rotaxane was demonstrated using monofunctionalized pillar[5]arene derivative containing a viologen moiety, which self-complexation at low concentration, assembled into supramolecular daisy chain polymers and eventually organogels upon the increasing of its concentration.[15] More recent, concentration dependence nature between the formation of pseudo[1]rotaxane and interlocked-dimer was also been demonstrated using pillar[5]arene bearing ethylene glycol bridged pyridine, in addition to the acid/base control of the dimer between the shrinking state to extension state.[16]

In this work, we report the synthesis of series of A1/A2 asymmetric-difunctionalized pillar[5]arenes bearing bromoalkyl and hydroxy groups. The synthesized difunctionalized-pillar[5]arene with long 8-bromooctoxy chain and benzyloxy substituents formed two different size aggregates depending on the concentration. The concentration-dependent supramolecular transition between pseudo[1]rotaxane and double-threaded dimer was investigated by variable concentration ^{1}H NMR spectroscopy, diffusion-ordered spectroscopy (DOSY), dynamic light scattering (DLS) measurements, isothermal titration calorimetry (ITC) and X-ray single crystal diffraction studies.

Results and discussion

Synthesis

Macrocyclic compounds with different functionality enable selective manipulations to the macrocycle frame and the synthesis of materials with various architectures. Recently, difunctionalized pillar[5]arene with hydroxy and amino groups at the A1/A2 have been synthesized by controlled de-*O*-methylation of permethylated pillar[5]arene using oxidation-followed-by-reduction strategy.[17] Taking advantage of our previously report approach for the synthesis of hydroxylated pillar[5]

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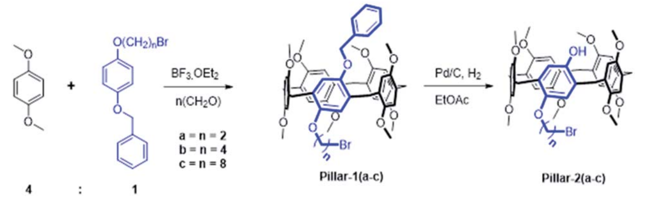
arenes,[11] a series of asymmetric A1/A2 difunctionalized pillar[5]arenes were synthesized. The approach involves co-cyclization of hydroquinone derivatives of 1,4-dimethoxybenzene and 1-benzyloxy-4-bromoalkoxybenzenes with paraformaldehyde in the presence of $BF_3 \cdot OEt_2$, as shown in Scheme 1. The copillararenes, **Pillar-1(a–c)** were isolated by silica gel column chromatography, and their corresponding hydroxylated pillar[5]arenes were obtained after removal of the benzyl protecting group by catalytic hydrogenation under mild reaction conditions using palladium on charcoal in anhydrous ethyl acetate.

NMR studies

^{1}H NMR spectra of pillar[5]arenes based on 2-bromoethoxy (**Pillar-1a**) and 4-bromobutoxy (**Pillar-1b**) at 298 K show peaks corresponding to different proton resonances (ESI†). In contrast, ^{1}H NMR spectrum of 8-bromooctoxy based pillar[5]arene (**Pillar-1c**) show high upfield shift of resonances for methylene protons of the long 8-bromooctoxy arm. In spectrum of **Pillar-1c** at 298 K no significant upfield shift for methylene protons H1 and H2 were observed, whereas protons H4, H5, H6, H7 and H8 (0.62, −0.35, −1.35, −0.88 and 1.29 respectively) exhibit unusual high field shift which indicate these protons located in central position of pillar[5]arene cavity (Fig. 1a). The methylene protons H5 and H6 show as broad signals due to rapid movement of these groups with respect to NMR time scale. To achieve better-quality signals, the movement was reduced by lowering temperature to 233 K which resulted in higher upfield shifts of the 8-bromooctoxy substituent (Fig. 1b). The peaks assignment was based on ^{1}H–^{1}H–COSY experiments at 298 K and 233 K (ESI†). Further evidence of the encapsulation of the octyl chain deep inside the macrocycle cavity in solution was obtained from 2D ROSY experiment at 233 K in chloroform-d_3 which shows strong correlations between all of the octyl protons H4-8 and the aromatic protons H6 as well as bridging methylene protons H12 of the copillar[5]arene unit (ESI†). Variable temperature ^{1}H NMR experiments from −233 to 328 K in chloroform-d_3 show that the octyl chain is encapsulated in the pillararene cavity in studied temperature rage (ESI†).

To investigate the inclusion behavior of the 8-bromooctoxy chain in pillar[5]arene cavity as self-inclusion or double-threaded dimer (interpenetration structure) or *n*-mer, ^{1}H NMR spectra at different concentrations (1–100 mM) of **Pillar-1c** were measured (ESI†). The data clearly demonstrate that **Pillar-1c** is concentration dependent, suggesting that **Pillar-1c** exist in different size aggregates. Fig. 2 shows representative examples of ^{1}H NMR spectra of **Pillar-1c** aromatic regions at 2- and 50 mM concentrations in chloroform-d_3 at 298 K. The chemical shift data show the presence of two main size aggregates, one below the 4 mM concentration and other around the 50 mM concentrations. At low concentration, the ^{1}H NMR concentration study implies that **Pillar-1c** exists predominantly as self-inclusion complex "pseudo[1]rotaxane" and at higher concentration the result indicate the existence of intermolecular complexation "double threaded dimer", which is evidence by the unusually high chemical upfield shift observed for alkyl chain. In addition, the intermolecular threaded supramolecular formation at high concentration is indicated by the observed downfield chemical shit experienced by aromatic protons of pillaraene frame as a result of the close proximity to the de-shielding region of the adjacent pillararene system (Fig. 2). These observations are similar to results previously reported for pillar[5]arenes with long side chains.[15,16] The presence of monomer to dimer in 1 : 1 ratio was estimated *ca.* 25 mM from a plot of concentration *versus* chemical shift (ESI†).



Scheme 1 Synthesis of A1/A2 difunctionalized bromo-hydroxy pillar[5]arenes.

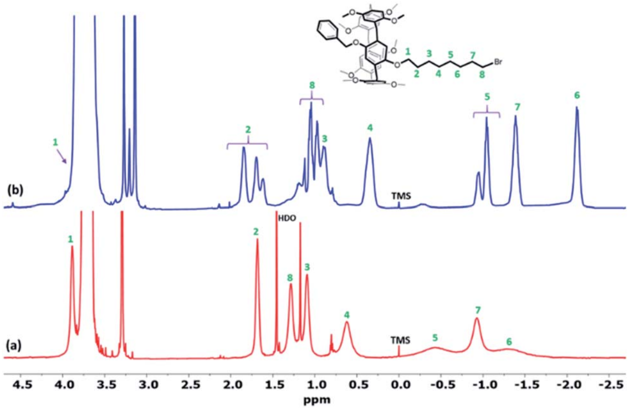


Fig. 1 Partial ^{1}H NMR spectra (600 MHz, $CDCl_3$) of **Pillar-1c** at 298 K (a) and 233 K (b).

The self-assembly behavior of compound **Pillar-1c** at different concentrations in chloroform-d_3 was further studied

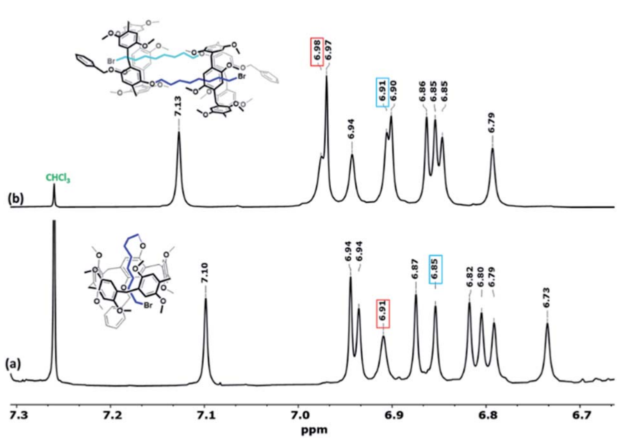


Fig. 2 Partial ^{1}H NMR spectra of pillararene aromatic frame (600 MHz, $CDCl_3$, 298 K) of **Pillar-1c** at 4 mM (a) and 50 mM (b).

by two-dimensional diffusion-ordered ^{1}H NMR (DOSY) experiments.[4c,18-20] The DOSY spectrum at 2, 50 and 100 mM concentrations revealed one set of signals, manifesting only one aggregate size in solutions. A change in the diffusion coefficient (D) should be observed in the DOSY spectra because larger aggregates have larger hydrodynamic radii (R), and R is inversely proportional to D according to the Strokes–Einstein equation [$D = k_BT/(6\pi\eta R)$], where T denotes the temperature, k_B is the Boltzmann constant, and η is the dynamic viscosity of the solvent. As the concentration of **Pillar-1c** increased from 2 mmol L^{-1} to 50 mmol L^{-1}, the value of weight-averaged diffusion coefficients (D) decreased from 1.08×10^{-9} to 5.17×10^{-10} m^2 s^{-1} ($D_2/D_{50} = 2.01$). This decrease was sufficient to suggest the change of the average dimension of aggregates with increase the concentration. The calculated hydrodynamic diameters at 2- and 50 mM are 0.76 and 1.58 nm, which correspond to monomeric and dimeric copillar[5]arene assemblies, respectively. At higher concentration of 100 mM, no significant change of the D (4.86×10^{-10} m^2 s^{-1}) was observed which indicated no further change of average dimension of the aggregates (Table 1).

The number-averaged degree of aggregation "supramolecular assembly" could be roughly approximated using the diffusion coefficient obtained from DOSY measurements by assuming that all assemblies are hydrodynamically spherical according to the Stokes–Einstein equation [$N \approx 1/(D/D_{\text{ref}})^3$].[4c] The number-averaged degree of aggregation "N" is proportional to the reciprocal of the cubic root of the diffusion coefficient, where D and D_{ref} are the diffusion coefficients of dimer and monomer, respectively. The average degree of supramolecular assembly was calculated to be 2, which corresponds to dimer formation. This simple but rough calculation confirms the presence of double threaded dimeric supramolecular assembly at high concertation. Even though the hydroxy derivative **Pillar-2c** show threaded 8-bromooctoxy chain as evidence from the high upfield shift in the ^{1}H NMR, analyses were complicated by the presence of the hydroxy functional group on the cavity rim (ESI†).

DLS measurement

DLS experiments were conducted in chloroform at 298 K to investigate the supramolecular assembly of **Pillar-1c** at two different concentrations. DLS measurements are mainly suitable for spherical models and can only give qualitative results about supramolecular assemblies. However, the DLS measurements of the hydrodynamic diameter (D_h) show pronounced scattering intensities at the two measured concentrations (2 and 50 mM) of **Pillar-1c**. Fig. 3 shows histograms of the D_h distributions for the supramolecular self-assembly at the two different concentrations. In the 2 mM solution, the measured D_h distribution centered at 0.72 nm which is consistent with the D_h value of self-inclusion complex. While, the centered D_h distribution for the 50 mM solution doubled to 1.50 nm indicating the presence of double-threaded supramolecular dimer. The DLS measurements clearly indicate the supramolecular self-assembly of **Pillar-1c** is pronouncedly concentration dependent, which is in agreement with NMR data.

Table 1 The hydrodynamic diameter calculated from DOSY experiments for **Pillar-1c**

Sample conc. (mM)	log D (log m^2 s^{-1})	D (10^{-10} m^2 s^{-1})	Diameter[a] (nm)
2	−8.97	10.8	0.76 (0.72)[b]
50	−9.29	5.17	1.58 (1.50)[b]
100	−9.31	4.86	1.68

[a] Diameter calculated using Strokes–Einstein equation. [b] Centered hydrodynamic diameter calculated from DLS measurement.

ITC studies

The ITC technique has been successfully employed to study the reversible noncovalent interactions of the supramolecular assemblies in solution.[21–25] Recently, we reported self-assembled linear supramolecular polymer based on pillar[5]arene driven by guest halogen–halogen interactions,[4c] the supramolecular assembly in solution was investigated by dilution ITC experiments which involve sequential injections of concentrated solution of supramolecular system into a cell containing pure solvent. Similarly, the concentration-dependent double threaded supramolecular dimer was studied by dilution ITC experiments. At high concentration (50 mM), the dimer is present predominately and the exchanged heat is a measure of the dissociated dimer and it is characteristic of the dissociation event. When the concentration is sufficiently low, there is no further disassembly of the supramolecular dimer and only the heat of dilution remains.

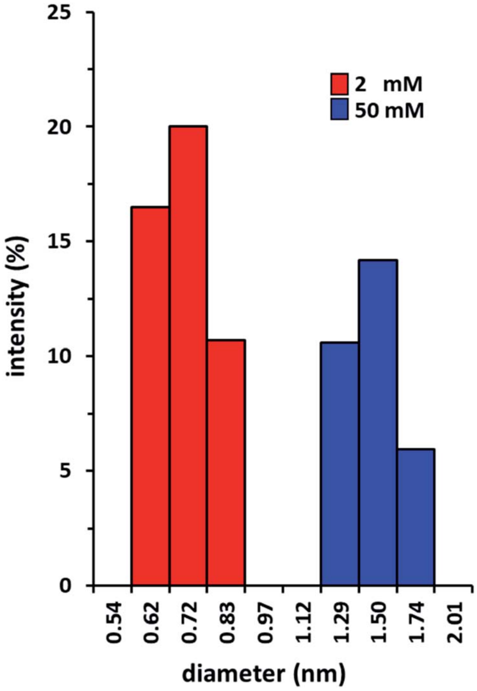


Fig. 3 Hydrodynamic radii distributions of **Pillar-1c** in chloroform at two different concentrations (2, and 50 mM).

The ITC dilution data for the dissociation of **Pillar-1c** dimer into chloroform at 2 and 50 mM are shown in Fig. 4. A plot of heat rate (μJ s^{-1}) against time (min) shows a series of peaks where the area under the endothermic heat peaks gives the enthalpy (ΔH) of dissociation (Fig. 4a). At high concertation (50 mM), the integrated heat data fit to a dimer dissociation model with positive value of $\Delta H_{\text{diss}} = 11.53$ kJ mol^{-1} and dissociation equilibrium constant of $K_{\text{diss}} = 2.27 \times 10^{-2}$ M (Fig. 4b). In addition, the positive value of Gibbs free energy ($\Delta G = 11.42$ kJ mol^{-1}) obtained from ITC dilution experiment indicate the formation of doubl-threaded supramolecular dimer at high concentration is a spontaneous process. In contrast, ITC dilution experiments at low concentration (**Pillar-1c** at 2 mM), no significant dimer dissociation was observed as evidence of the endothermic heat pulses (Fig. 4a). The ITC experiment results are in agreement with data obtained from DOSY experiments and DLS measurements.

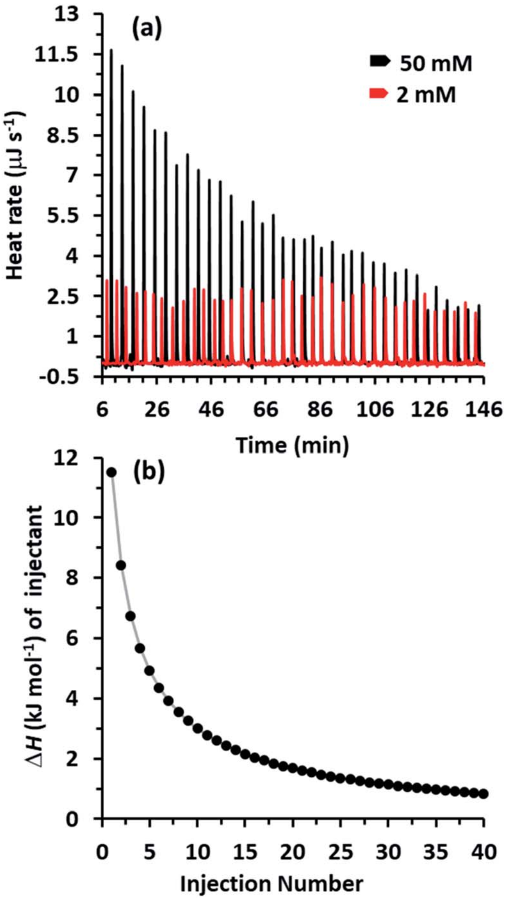


Fig. 4 ITC dilution raw heats for sequential injection in chloroform at 298 K for 2 (red) and 50 (black) mM of **Pillar-1c** (a), and the integrated heat data for **Pillar-1c** at 50 mM fitted to a dimer dissociation model (b).

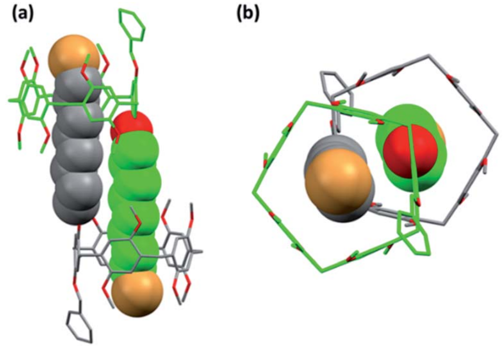


Fig. 5 Supramolecular double-threaded dimer of **Pillar-1c**. (a) The top view, and (b) the side view. Red, grey (or green) and yellow denote oxygen, carbon and bromine, respectively. Hydrogen atoms are omitted for clarity.

Crystallography

Single crystals of **Pillar-1a** suitable for X-ray diffraction studies were grown by slow vapor diffusion of hexanes into CH_2Cl_2/1-bromooctane solutions (10/1 v/v), whereas X-ray single crystal structures of pillar[5]arene **Pillar-(1b)** were obtained by the slow evaporation method using dichloroethane Single crystals of **Pillar-1c** suitable for X-ray diffraction studies were grown by slow vapor diffusion of acetone into chloroform solution. No suitable crystals of the hydroxy-pillar[5]arene derivatives (**Pillar 2a–c**) could be obtained for X-ray analysis. For **Pillar-1a**, the 1-Bromooctane molecules were included in the pillar[5] arene cavity and the pillararenes are aligned in a face-to-edge manner in the crystal network (ESI†). These host–guest complexes were stabilized by C–H···π and C–H···O interactions. The asymmetric unit of **Pillar-1b** crystal is observed to be half of the molecular structure and it was complicated by positional disorder for both benzyloxy and 1-bromobutoxy substituents. The crystal refinement was carried out by assigning half occupancy for constituent atoms of two fragments. Since the occupancy of the substituents are half at each site, the completed structure has both substituents (benzyloxy and 1-bromobutoxy) at both of the pillararene rim (ESI†).

The crystal structure of **Pillar-1c** shows the formation of a supramolecular double-threaded dimer where the bromooctyl chains is threaded inside the cavity of the adjacent pillar[5]arene (Fig. 5). The formation of interlocked structure in the solid state were previously reported with mono-urea-functionalized pillar[5]arene and copillar[5]arene with long bromodceyl group in the solid state.[14,26] The dimer formation is induced by C–H···π and C–H···O interactions between the octyl chain and the host. The encapsulation characteristics demonstrated in the solid state by the single-crystal X-ray diffraction technique agree with the results obtained from ^{1}H NMR concentration experiments, DOSY and DLS measurements which indicate the formation of a supramolecular double-threaded dimer or [*c*2]daisy chain type structure at high concertation.

Experimental

Materials and methods

Nuclear Magnetic Resonance (NMR) spectroscopy measurements were carried out by Bruker Avance II 600 MHz (Germany), spectrometer. Electron impact ionization (EI) mass spectrometry was performed using Thermo Scientific DFS High Resolution GC/MS (Germany) mass spectrometer. Electro-spary ionization in high resolution mode was done using Waters Xevo G2-S Qtof, (Germany) LC MS/MS mass spectrometer. The single crystal data analysis was made by R-AXIS RAPID II, Rigaku, (Japan) diffractometer. The data were collected at 150 K (Oxford cryosystems, UK). Flash column chromatography was performed using silica gel (Silica gel 60, 40–60 mesh ASTM, EMD Millipore, Merck KGaA, Germany). 4-Benzyloxyphenol was synthesized according to literature procedure.[11] DMF, acetonitrile and dichloroethane were distilled before use. All other reagents and solvents were of reagent grade purity and used without further purification.

Preparation of single crystals for X-ray diffraction

The single crystal diffraction data were collected on an R-AXIS RAPID diffractometer (Rigaku, Japan) at 150 K using the Crystal-Clear software package. The structures were solved by direct methods and expanded using Fourier techniques. The structure refinement was performed using SHELXL-2017/1. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed at calculated positions and refined using the riding model. The crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as a supplementary publication (CCDC 2000224–2000226).

DLS measurements

Samples of the **Pillar-1c** at different concentrations (2 and 50 mM in $CHCl_3$) were analyzed on a Zetasizer Nano Range, Malvern PANalytical (UK) at 298 K. All DLS measurements were performed at a scattering angle of 90°. Sample solutions were prepared by filtering each component solution through a 0.2 μm polytetrafluoroethylene (PTFE) syringe filter into a clean scintillation vial.

ITC measurements

All ITC studies were carried out on an Affinity ITC, TA Instruments (USA). The data were analyzed using NanoAnalyze (Version 3.10.0). In the ITC dimer-dissociation experiments, a 10 mM solution of the self-assembled **Pillar-1c** system in $CHCl_3$ was placed in a syringe and automatically titrated as 2 μL per injection at a time interval of 240 s into a reaction cell loaded with pure $CHCl_3$ (300 μL). The dissociation of the self-assembled aggregates was accompanied by non-constant heat signals along with a constant heat of dilution. A control experiment was performed using 2 mM **Pillar-1c** chloroform solution under similar experimental conditions against pure $CHCl_3$. All the titrations were conducted at 298 K.

Synthesis of 1-benzyloxy-4-bromoalkoxybenzenes (1–4)

1-(Benzyloxy)-4-(2-bromoethoxy)benzene (1). 4-Benzyloxyphenol (2 g, 10 mmol) was dissolved in dry DMF (30 mL) at room temperature, and anhydrous potassium carbonate (2.76 g; 20 mmol) was added. Then 1,2-dibroethane (1.20 mL, 14 mmol) was added, and the mixture was heated at 80 °C overnight. The product was precipitated in ice cold water and purified by column chromatography using dichloromethane/hexane mixture (65 : 35 v/v). Yield 2.4 g, 78%. ^1H NMR (600 MHz, $CDCl_3$) δ: 3.63 (t, $J = 6.0$ and $J = 6.6$ Hz, 2H), 4.26 (t, $J = 6.0$ and $J = 6.6$ Hz, 2H), 5.04 (s, 2H), 6.87 (m, 2H), 6.92 (m, 2H), 7.33 (m, 1H), 7.40 (m, 2H), 7.44 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 29.5, 69.0, 70.9, 116.1, 116.3, 127.7, 128.1, 128.8, 137.4, 152.6, 153.8. HRMS: (m/z): calcd for $[M^+]$: 306.0250 (for $C_{15}H_{15}O_2Br$); found 306.0250.

1-(Benzyloxy)-4-(4-bromobutoxy)benzene (2). 4-Benzyloxyphenol (2 g, 10 mmol) was dissolved in dry DMF (30 mL) at room temperature, and anhydrous potassium carbonate (2.76 g; 20 mmol) was added. Then 1,4-dibromobutane (1.96 mL, 14 mmol) was added, and the mixture was heated at 80 °C overnight. The product was precipitated in ice cold water and purified by column chromatography using dichloromethane/hexane mixture (65 : 35 v/v). Yield 3.1 g, 92%. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.94 (m, 2H) 2.09 (m, 2H), 3.51 (t, $J = 6.6$ and $J = 6.6$ Hz, 2H), 3.97 (t, $J = 6.6$ and $J = 6.0$ Hz, 2H), 5.04 (s, 2H), 6.85 (m, 2H), 6.92 (m, 2H), 7.34 (m, 1H), 7.40 (m, 2H), 7.43 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 28.2, 29.7, 33.7, 67.7, 70.9, 71.0, 115.6, 116.1, 116.1, 127.7, 128.1, 128.8, 137.5, 153.3, 153.5. HRMS: (m/z): calcd for $[M^+]$: 334.0563 (for $C_{17}H_{19}O_2Br$); found 334.0564.

1-(Benzyloxy)-4-(8-bromooctoxy)benzene (3). 4-Benzyloxyphenol (2 g, 10 mmol) was dissolved in dry DMF (30 mL) at room temperature, and anhydrous potassium carbonate (2.76 g; 20 mmol) was added. Then 1,8-dibromooctane (2.64 mL, 14 mmol) was added, and the mixture was heated at 80 °C overnight. The product was precipitated in ice cold water and purified by column chromatography using dichloromethane/hexane mixture (60 : 40 v/v). Yield 3.4 g, 85%. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.38 (m, 4H), 1.47 (m, 4H), 1.77 (m, 2H), 1.87 (m, 2H), 3.42 (m, 2H), 3.92 (t, $J = 7.2$ and $J = 6.6$ Hz, 2H), 5.04 (s, 2H), 6.85 (m, 2H), 6.93 (m, 2H), 7.34 (m, 1H), 7.39 (m, 2H), 7.44 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 25.8, 26.1, 28.2, 28.3, 28.8, 28.8, 28.9, 29.0, 29.2, 29.4, 29.5, 32.9, 33.0, 34.1, 34.2, 68.1, 68.7, 70.9, 115.6, 116.0, 127.7, 128.1, 128.7, 137.5, 153.1, 153.7. HRMS: (m/z): calcd for $[M^+]$: 390.1189 (for $C_{21}H_{27}O_2Br$); found 390.1189.

Synthesis of A1/A2-benzyloxybromoalkoxy difunctionalized-pillar[5]arenes 1(a–c)

Pillar-1(a). Paraformaldehyde (1.5 g, 50 mmol) was added to a solution of 1,4-dimethoxybenzene (2.2 g, 16.0 mmol) and 1-benzyloxy-4-(2-bromoethoxy)benzene (306 mg, 1 mmol) in dry dichloromethane (120 mL) under nitrogen atmosphere. Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$), (2.0 mL, 16 mmol) was then added to the solution and the mixture was stirred at 30 °C for 1 h. After this time, methanol (50 mL) was poured into the reaction mixture and the solution was concentrated then dissolved in dichloromethane (100 mL). The resulting organic solution was washed with aqueous $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and subjected to purification by silica gel chromatography (dichloromethane/hexanes (75 : 25 v/v)) to give **Pillar-1(a)** as a white solid (240 mg, 26%), ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.37 (s, 3H), 3.55 (t, $J = 6.0$, 6.6, 2H), 3.61 (s, 3H), 3.69 (s, 3H), 3.72 (m, 15H), 3.79 (s, 2H). 3.82 (m, 4H), 3.85 (d, $J = 8.4$, 4H) 4.15 (t, $J = 6.0$, 6.6, 2H), 4.97 (s, 2H), 6.72 (s, 1H), 6.80 (m, 3H), 6.82 (s, 1H), 6.85 (m, 4H), 6.93 (s, 1H), 7.36 (m, 3H), 7.43 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 29.5, 29.8, 29.8, 30.1,30.2, 53.2, 55.6, 55.8, 55.9, 56.0, 56.2, 69.0, 70.5, 114.1, 114.1, 114.2, 114.2, 114.3, 115.1, 116.0, 127.4, 127.8, 127.9, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 128.8, 129.3, 138.1, 149.4, 150.8, 150.9, 150.9, 151.0. HRMS: (*m*/*z*): calcd for [M^+]: 918.2973 (for $C_{52}H_{55}O_{10}Br$); found 918.2971.

Pillar-1(b). Paraformaldehyde (1.5 g, 50 mmol) was added to a solution of 1,4-dimethoxybenzene (2.2 g, 16.0 mmol) and 1-benzyloxy-4-(4-bromobutoxy)benzene (335 mg, 1 mmol) in dry dichloromethane (120 mL) under nitrogen atmosphere. Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$), (2.0 mL, 16 mmol) was then added to the solution and the mixture was stirred at 30 °C for 1 h. After this time, methanol (50 mL) was poured into the reaction mixture and the solution was concentrated then dissolved in dichloromethane (100 mL). The resulting organic solution was washed with aqueous $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and subjected to purification by silica gel chromatography (dichloromethane/hexanes (65 : 35 v/v)) to give **Pillar-1(b)** as white solid (330 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.76 (s, 4H), 3.04 (s, 2H) 3.32 (s, 3H), 3.63 (d, $J = 8.4$, 6H), 3.69 (m, 13H), 3.78 (s, 2H), 3.81 (s, 8H), 3.87 (s, 2H), 4.91 (s, 2H), 6.72 (s, 2H), 6.81 (m, 5H), 6.85 (s, 1H), 6.87 (s, 1H), 6.88 (s, 1H), 7.34 (m, 3H), 7.40 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 28.6, 29.7, 29.8, 30.0, 30.3, 33.6, 55.5, 55.9, 56.0, 56.1, 56.2, 56.3, 56.4, 56.4, 67.6, 70.6, 114.1, 114.2, 114.2, 114.3, 114.3, 114.4, 115.2, 115.3, 127.4, 127.8, 128.2, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 128.6, 138.2, 150.2, 150.3, 150.9, 150.9, 150.9, 151.0. HRMS: (*m*/*z*): calcd for [M + H_2O]: 964.3397 (for $C_{54}H_{59}O_{11}Br$); found 964.3345.

Pillar-1(c). Paraformaldehyde (1.5 g, 50 mmol) was added to a solution of 1,4-dimethoxybenzene (2.21 g, 16.0 mmol) and 1-benzyloxy-4-(*n*-bromo)octyloxy benzene (391 mg, 1 mmol) in dry dichloromethane (120 mL) under nitrogen atmosphere. Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$), (2.0 mL, 16 mmol) was then added to the solution and the mixture was stirred at 30 °C for 1 h. After this time, methanol (50 mL) was poured into the reaction mixture and the solution was concentrated then dissolved in dichloromethane (100 mL). The resulting organic solution was washed with aqueous $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and subjected to purification by silica gel chromatography (dichloromethane/hexanes (65 : 35 v/v)) to give **Pillar-1(c)** as a white solid (410 mg, 41%).^{1}H NMR (600 MHz, $CDCl_3$) δ: −1.35 (s, 2H), −0.90 (s, 2H), −0.45 (s, 2H), 0.67 (s, 2H), 1.18 (s, 2H), 1.34 (s, 2H), 1.80 (s, 2H), 3.36 (s, 3H), 3.85 (m, 31H), 3.98 (s, 2H), 5.01 (s, 2H), 6.79 (s, 1H), 6.86 (m, 3H), 6.92 (m, 2H), 6.95 (s, 1H), 6.99 (m, 2H), 7.16 (s, 1H), 7.36 (m, 1H), 7.45 (t, $J = 7.8$, 7.2, 2H), 7.63 (d, $J = 7.3$, 2H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 26.8, 27.5, 29.1, 29.3, 29.6, 29.9, 34.0, 55.1, 55.4, 55.4, 55.5, 55.5, 55.5, 55.8, 70.0, 113.1, 113.1, 113.2, 113.3, 113.6, 114.1, 114.4, 127.8, 127.9, 128.1, 128.2, 128.4, 128.6, 128.8, 138.3, 149.5, 149.6, 150.2, 150.2, 150.3, 150.3, 150.5, 150.7, 150.8. HRMS: (*m*/*z*): calcd for [M^+]: 1002.3913 (for $C_{58}H_{67}O_{10}Br$); found 1002.3912.

Synthesis of A1/A2-benzyloxybromoalkoxy difunctionalized-pillar[5]arenes 2(a–c)

Pillar-2(a). To a solution of the starting material **Pillar-1(a)** (100 mg, 0.11 mmol) in anhydrous ethyl acetate (30 mL) was added Pd/C (20 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 24 h in the hydrogenation chamber. The catalyst was filtered through Celite. The Celite pad was washed with ethyl acetate (30 mL × 2). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (99 : 1 v/v, CH_2Cl_2/methanol) to afford the desired product **Pillar-2(a)** as a white solid (yield 83 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.53 (s, 3H), 3.62 (m, 15H), 3.73 (m, 6H), 3.81 (m, 12H), 4.19 (t, $J = 6.0$, $J = 6.6$, 2H), 6.62 (d, $J = 5.4$, 2H), 6.65 (s, 1H), 6.69 (m, 2H), 6.75 (m, 4H), 6.90 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 28.2, 29.0, 29.6, 29.8, 29.9, 30.0, 30.0, 30.1, 30.3, 31.1, 32.1 55.6, 55.9, 56.0, 56.1, 56.2, 56.2, 56.3, 56.4, 56.6, 69.9, 113.2, 114.0, 114.0, 114.3, 114.5, 114.6, 114.7, 114.7, 114.8, 115.5, 119.2, 123.7, 125.5, 126.8, 128.0, 128.3, 128.5, 128.5, 128.6, 128.6, 129.5, 129.7, 131.1, 133.6, 148.6, 148.8, 149.5, 150.0, 151.0, 151.0, 151.1, 151.1, 151.2, 151.3, 152.1. HRMS: (*m*/*z*): calcd for [M + H_2O]: 846.2615 (for $C_{45}H_{51}O_{11}Br$); found 846.2672.

Pillar-2(b). To a solution of the starting material **Pillar-1(b)** (100 mg, 0.11 mmol) in anhydrous ethyl acetate (30 mL) was added Pd/C (20 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 24 h in the hydrogenation chamber. The catalyst was filtered through Celite. The Celite pad was washed with ethyl acetate (30 mL × 2). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (99 : 1 v/v, CH_2Cl_2/methanol) to afford the desired product **Pillar-2(b)** as a white solid (yield 81 mg, 90%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.70 (s, 2H), 3.14 (S, 2H), 3.54 (s, 3H), 3.62 (m, 4H), 3.65 (m, 10H), 3.76 (m, 11H), 3.81 (m, 10H), 6.69 (m, 5H), 6.79 (s, 2H), 6.84 (m, 1H), 6.88 (s, 1H), 6.93 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 28.2, 28.5, 28.8, 29.2, 29.6, 29.6, 29.9, 30.3, 31.1, 33.5, 55.6, 55.9, 56.0, 56.1, 56.1, 56.2, 56.4, 56.6, 68.0, 113.3, 113.8, 113.9, 114.2, 114.3, 114.4, 114.5, 114.7, 119.1, 123.6, 125.3, 127.1, 128.0, 128.0, 128.3, 128.4, 128.5, 128.5, 128.8, 129.5, 129.6, 130.0, 133.6, 146.7, 147.7, 148.8, 150.3, 150.9, 150.9, 150.9, 151.0, 151.0, 151.1, 151.2, 151.2, 152.0. HRMS: (*m*/*z*): calcd for [M + H_2O]: 874.2928 (for $C_{47}H_{55}O_{11}Br$); found 874.2988.

Pillar-2(c). To a solution of the starting material **Pillar-1(c)** (100 mg, 0.11 mmol) in anhydrous ethyl acetate (30 mL) was added Pd/C (20 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 24 h in the hydrogenation chamber. The catalyst was filtered through Celite. The Celite pad was washed with ethyl acetate (30 mL × 2). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (99 : 1 v/v, CH_2Cl_2/methanol) to afford the desired product **Pillar-2(c)** as a white solid (yield 85 mg, 93%).^{1}H NMR (600 MHz, $CDCl_3$) δ: −0.09 (s, 2H), 0.28 (s, 2H) 0.38 (s, 2H), 0.97 (s, 2H), 1.29 (m, 2H), 1.75 (m, 2H), 2.24 (s, 2H), 3.68 (s, 3H), 3.71 (m, 14H) 3.79 (m, 14H), 3.84 (s, 3H), 3.95 (m, 2H), 6.65 (s, 1H), 6.71 (s, 1H), 6.78 (m, 3H), 6.82 (m, 4H), 6.93 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 25.2, 27.2, 27.8, 28.7, 28.9, 29.1, 29.6, 29.8, 29.9, 31.0, 32,1, 34.0, 55.7, 55.8, 55.8, 55.8, 55.9, 55.9, 56.0, 56.3, 68.5, 113.0, 113.6, 113.8, 113.8, 113.9, 113.9, 113.9, 114.0, 114.2, 114.4, 119.4, 125.7, 127.3, 127.9, 128.2, 128.3, 128.3, 128.4, 128.5, 129.3, 129.9, 147.2, 149.0, 149.8, 150.7, 150.8, 150.8, 150.9, 150.9, 151.6. HRMS: (*m*/*z*): calcd for [M^+]: 912.3443 (for $C_{51}H_{61}O_{10}Br$); found 912.3448.

Conclusions

In summary, A1/A2-difunctionalized pillar[5]arenes bearing bromoalkoxy and hydroxy substituents were synthesized by the co-cyclization of hydroquinone derivatives followed by the removal of the benzyl protected group using catalytic hydrogenation over palladium on charcoal in anhydrous ethyl acetate. The 8-bromooctoxy substituent in the pillar[5]arene rim (**Pillar-1c**) undergo self-inclusion as evidence by the unusual high upfield proton chemical shift. ^{1}HNMR concentration experiments demonstrated that the inclusion behavior of long chain 8-bromooctoxy substituent is concentration-dependent, suggesting the presence of two main size aggregates. The formation of pseudo[1]rotaxane and double-threaded supramolecular dimer at low and high concentrations respectively was confirmed by single-crystal X-ray diffraction analysis, DOSY, DLS and ITC measurements. Currently further studies and modifications of the A1/A2-bromoalkyloxy-hydroxy-functionalized pillar[5]arenes host to develop new supramolecular systems and functional materials are underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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