

Silica bound co-pillar[4+1]arene as a novel supramolecular stationary phase

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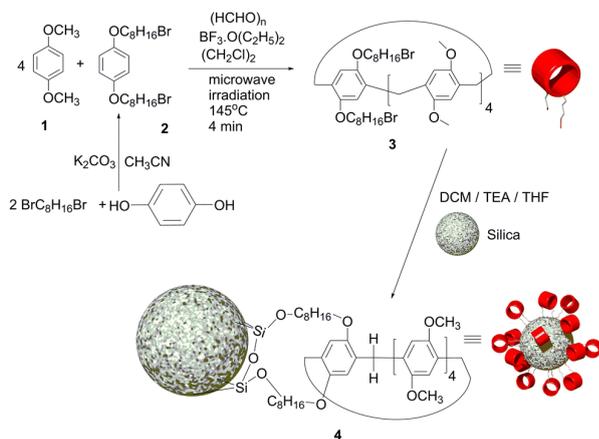
A novel co-pillar[4+1]arene incorporating two bromo-octyl substituents has been synthesised for the first time, using microwave irradiation in high yield (88%) in under four minutes, and bound to the surface of chromatographic silica particles. The resulting new stationary phase has been successfully utilised to separate xylene isomers *via* liquid chromatographic techniques.

Purification of organic geometrical isomers, in industry and fundamental research alike, is often problematic due to similarities in physical properties, both in industry and fundamental research alike.¹ Chromatographic techniques are therefore often adopted to facilitate their separation; however, normal and reverse stationary phases require extensive method development in order to attempt even separation of the simplest of isomers.²

Supramolecular host-guest interactions between functional groups, together with size complementarity, have been widely utilised to selectively bind specific geometric isomers.³ While this approach to separation *via* stepwise complexation and crystallisation is viable for selective isomers, it is inherently restricted to single geometric isomers and therefore has limited application for *in situ* separation of multiple sets of isomers.⁴

Several research groups have reported the synthesis and separation applications of combining the supramolecular host-guest properties of the bowl-like macrocycles, such as calix[n]arene and cyclodextrin macrocycles, bound to chromatographic silica.⁵ These novel stationary phases have demonstrated good potential for separating hydrocarbons.⁵

Pillar[n]arene macrocycles are tubular cavitands with hydrophobic cores typically made up of methylene bridged 1,4-di-alkoxy-substituted aromatics rings providing two functionalised outer rims.⁶ The tubular construct of these macrocyclic host molecules enables them to thread linear guests.⁷ This host-guest interaction has been utilised to develop electrochemical sensors, wherein the pillar[5]arene macrocycles have been attached to the surface of gold nanoparticles and electrodes.⁸ Herein, we report a new one-step microwave synthesis of a novel co-pillar[4+1]arene that contains two bromooctyl substituents, its attachment to chromatographic silica and a comparative study of this new stationary phase in the separation and purification of a mixture of *o*-xylene, *m*-xylene, *p*-xylene, toluene and ethylbenzene using flash column chromatography. In addition, we also study *in silico* the host-guest interactions of the different xylene geometric isomers, toluene and ethylbenzene with the dimethoxypillar[5]arene.



Scheme 1. Synthetic route to co-pillar[4+1]arene stationary phase, **4**.

Traditional methods for the synthesis of pillar[5]arene and modified pillar[5]arenes can take 3-48 hours with only moderate yields.^{6,8} Following the initial 16% low yielding synthesis of copillar[4+1]arene by the Huang group in 2010, the race was on to find an improved synthetic protocol route.⁹ Meier *et al.* replaced the traditional BF_3 etherate catalyst with FeCl_3 in CH_2Cl_2 and demonstrated an increased yield of 50-85% in 4-24 hours.¹⁰ Latterly there has been a desire by supramolecular chemists to adopt green methodologies.¹¹ Herein we demonstrate the use of microwave-induced synthesis to prepare a novel co-pillar[4+1]arene.

1,4-Di-(8'-bromooctyloxy)benzene, **2**, was obtained from hydroquinone and 1,8-dibromooctane *via* a modified literature procedure,¹² as shown in Scheme 1. Co-pillar[4+1]arene **3** was synthesised from the

condensation of four molar equivalents of 1,4-dimethoxybenzene **1**, one molar equivalent of **2**, five molar equivalents of paraformaldehyde in the presence of boron trifluoride etherate suspended in dichloroethane in a sealed microwave reaction vial. The reaction was heated to 145°C with stirring over 4 minutes using a Biotage® Initiator 60 microwave reactor. The reaction was allowed to cool to room temperature and the crude reaction mixture was triturated with acetone and the pure product collected as a white solid product under vacuum in 88.5% yield.

In order to validate this new green synthetic approach to making co-pillar[4+1]arene macrocycles in high yield, the same condensation reaction was repeated using traditional methodologies.¹³ The reagents were refluxed under ambient pressure for 4 hours. The product **3** was isolated from the reaction mixture as described above in a 26.3% yield.

The co-pillar[4+1]arene **3** was subsequently attached to chromatographic silica (Interchim general purpose grade, particle size 50 µm and pore size 500 Å) using a modified procedure.¹³ Thermogravimetric analysis studies confirmed a mass loading of the co-pillar[4+1]arene **3** at 16% w/w.

The co-pillar[4+1]arene bonded flash silica **4** (12 g) was dry packed into an empty Interchim® flash cartridge and primed with cyclohexane, ethyl acetate and methanol in order to equilibrate the column. The eluent was collected at various column volume intervals to check elution of co-pillar[4+1]arene from the silica bound co-pillar[4+1]arene flash column. The mass spectrometric analysis of eluents confirmed that there was no leaching of co-pillar[4+1]arene **3** from the silica bound co-pillar[4+1]arene **4** stationary phase.

The individual xylene isomers and toluene were loaded (1.0 mL) directly onto the co-pillar[4+1]arene silica flash cartridge (12 g) and run *via* an optimised mobile phase isocratic elution of methanol/ethyl acetate (21 mL min⁻¹ 10:90, 15 min). The individual retention times of *m*-xylene (a), toluene (b), *o*-xylene (c), *p*-xylene (d) can be seen Figure 1.

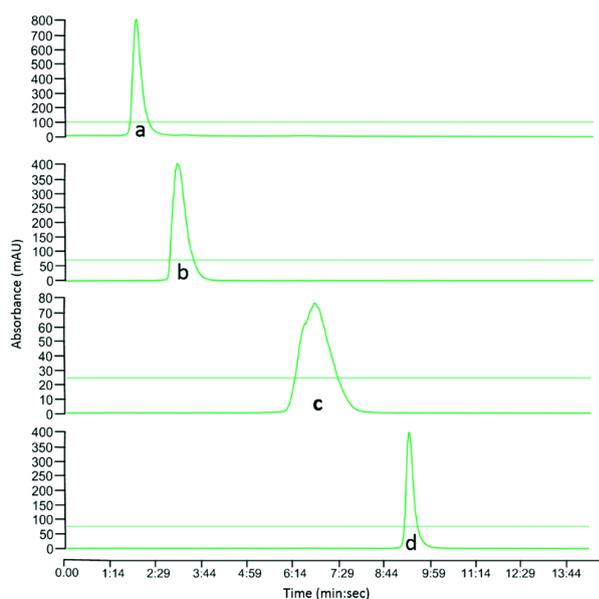


Fig. 1 Separation of xylene isomers and toluene standards; *m*-xylene (a), toluene (b), *o*-xylene (c) and *p*-xylene (d) on co-pillar[4+1]arene bound-silica stationary phase.

In order to validate the newly developed co-pillar[4+1]arene stationary phase, we have studied the separation of a mixture of xylenes, ethylbenzene and toluene (1.0 mL, Fisher Scientific CAS number:108-88-3 and 1330-20-7) on both normal phase Interchim® flash column (12 g) and the silica bound co-pillar[4+1]arene flash column (12 g) using the same isocratic mobile phase elution method (methanol/ethyl acetate, 10:90, at 21 mL min⁻¹, 15 min). The normal phase column resulted in a single sharp peak which eluted all five eluents together as shown in Figure 2A. Whereas the co-pillar[4+1]arene bound-silica **4** flash column separated out the mixture into five discrete bands (together as shown in Figure 2B), which were collected and analysed by ¹H-NMR. The elution order of the Fisher Scientific xylene and toluene sample mixture was found to be ; *m*-xylene (a), toluene (b), *o*-xylene (c), *p*-xylene (d) and ethylbenzene (e) as shown in Figure 2B.

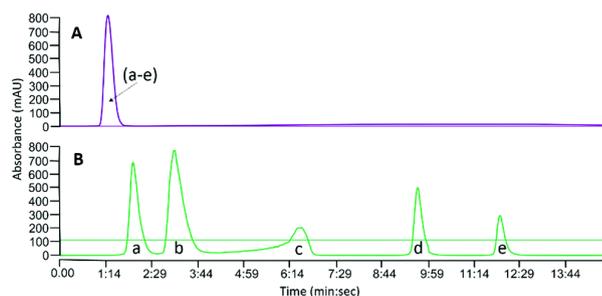


Fig. 2 Separation of Fisher Scientific xylene and toluene sample mixture; *m*-xylene (a), toluene (b), *o*-xylene (c), *p*-xylene (d) and ethylbenzene (e) on normal phase Interchim® flash column (A) and co-pillar[4+1]arene bound-silica stationary phase (B).

The xylene ratios observed from the co-pillar[4+1]arene bound-silica **4** flash column were quantified and found to be in line with the supplier certificate of analysis. The ratios of *m*-xylene, *o*-xylene, *p*-xylene and ethylbenzene were 45%, 24%, 20% and 10%. It was noted that the *o*-xylene isomer resulted in a broader peak shape compared to the other isomers.

Table 1 Correlation between the chromatographic experimental retention times and the DFTB-D3/3ob-3-1 binding energies of toluene, ethylbenzene and xylene isomers embedded in pillar-5-arene

Guest	Experimental retention time (min:s)	Binding Energy (kcal mol ⁻¹)
<i>m</i> -Xylene	1:59	-22.19
Toluene	3:05	-22.31
<i>o</i> -Xylene	6:25	-23.50
<i>p</i> -Xylene	9:33	-25.97
Ethylbenzene	11:45	-26.74

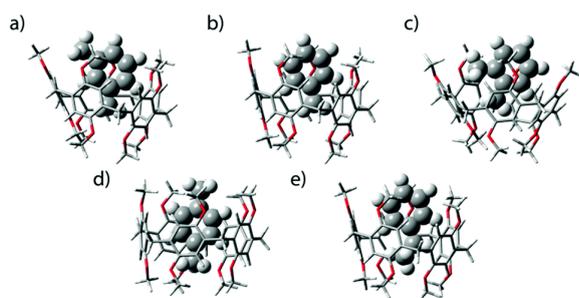


Fig.3 Optimized geometries of *meta*-xylene (a), toluene (b), *ortho*-xylene (c), *para*-xylene (d) and ethylbenzene (e) guests docking into the upper rim of the dimethoxy pillar[5]arene.

To further understand the chromatographic separation results that result from the host-guest interactions, we studied the binding energies of three xylene isomers, toluene and ethylbenzene in the pillar[5]arene host. Binding energies of toluene, ethylbenzene and the three xylene isomers in the pore of the pillar-5-arene molecule were calculated using the Density Functional Tight Binding (DFTB) method implemented in DFTB+ version 1.3.¹⁵ To determine the likely binding motifs for each molecule@pillar combination, 500 initial starting geometries were generated using the Kick3 stochastic structure generator and optimised using the 3ob-3-1 parameter set including -D3 dispersion, as show in figure 3.¹⁶

The results of the binding energy study, show in table 1, perfectly correlate with the observed experimental separation results. Ethylbenzene with a calculated binding energy of (-26.74 kcal/mol) showed the highest retention time towards the chromatographic separation through host-guest interactions while *m*-xylene (-22.19 kcal/mol) with the lowest binding energy eluted most quickly from the chromatographic flash column. When

looking at the optimized geometries of the host-guest interactions (Figure 3), it is apparent that the *ortho* isomer significantly distorts the pillar[5]arene cavity from a tube like morphology into a boat like conformer (Figure 3c). This conformational transformation of the host molecule, as it binds the guest, results in a kinetic distributional change that slows down the uptake and release of the *o*-xylene guest and subsequent boarder peak shape.

In conclusion we have demonstrated, for the first time, that co-pillar[4+1]arene **3** can be effectively synthesised using studies indicate differential bindings for the different xylene isomers to the co-pillar[4+1]arene. Thus, the co-pillar[4+1]arene **3** will improve the efficiency of the separation and refining of aromatic hydrocarbons, and may find industrial application given the large volume of these compounds that are used as starting materials in the chemical industry.

The authors wish to acknowledge the support and advice of Mr. Colin Banks, Dr. Dinga Wonanke A.D. and Dr. Raghu Kothur.

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