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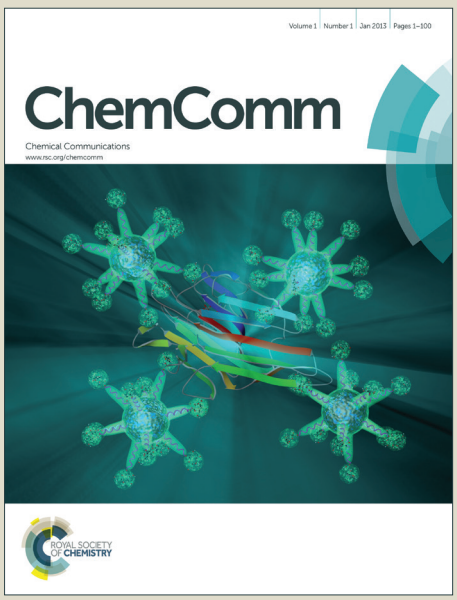

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ARTICLE TYPE

Novel Binding Regioselectivity in the Interpenetration of a Non-symmetric Axle into a Non-symmetric Pillar[5]arene Wheel

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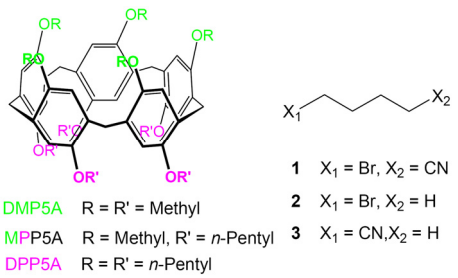
We describe the regioselective complexation of a non-symmetric 5-bromovaleronitrile axle by a non-symmetric pillar[5]arene bearing different alkyl (methyl and pentyl) rims, forming an oriented interpenetrated complex with the directionality of CN@methyl rim and Br@pentyl rim.

Molecular recognition plays a significant role in chemistry and biology.[1,2,3] The binding regioselectivity, i.e., controlling the directionality of the complexation, is considerably important in the host-guest interactions and biological interactions such as antigen−antibody, DNA−protein and saccharide−lectin bindings. Cyclodextrins and calixarenes, having "basket" structures and two very different rims, often showed regioselective geometries upon complexation with nonsymmetric molecules. While for a supramolecular container with similar rims, controlling the binding orientation of a nonsymmetric guest is extremely difficult.

Pillararenes, which are made up of hydroquinone units linked by methylene bridges at the 2 and 5 positions, have been emerging as new generation macrocyclic hosts in supramolecular chemistry due to their interesting host-guest properties[4,5] and potential applications in materials and biology.[6,7] Similar with cucurbiturils, pillararenes have two identical cavity portals and possess symmetrical architectures, and thus are not suitable hosts for the investigation on binding regioselectivity. Since it is relatively easy to get pillararene derivatives, we reason that non-symmetric pillar[5]arenes with different alkyl rims, which can be achieved by only one-step condensation reaction,[8] have the possibility to achieve host-guest regioselective complexation towards specially designed axial components. However, because there are only minor differences on structures and electronic effects of the alkyl substituents on the two rims, it is a big challenge to choose suitable guest molecule and to perfectly control the host-guest binding orientation.

Herein, it is demonstrated that an asymmetric pillar[5]arene (MPP5A, Scheme 1) containing five methyls on one side and five *n*-pentyls on the other one can highly regioselectively interact with asymmetric 5-bromovaleronitrile (**1**, Scheme 1) axle. The resulting interpenetrated complex has an unequivocal orientation that cyano (CN) is located at the methyl rim and bromo (Br) is located at the pentyl rim, which is investigated in both solution and the solid state.

The design of the axial component and the pillar[5]arene wheel was based on our previously reported results[9] that upon complexation with *per*-alkylated pillar[5]arenes, dihalo and



Scheme 1 Structures of the wheel/axle molecules.

dicyano guests exhibit absolutely reversed host selectivity. Specifically, the substitution of ten methyls for butyls/octyls in *per*-methylated pillar[5]arene (DMP5A), affording *per*-butylated pillar[5]arene/*per*-octylated pillar[5]arene (DBP5A/DOP5A), dramatically decreases the association constants (K_a) for 1,4-dicyanobutane guest by one order of magnitude.[9a] We have demonstrated that dipole–dipole forces play a significant role in the complexation between dinitriles and *per*-alkylated pillar[5]arenes.[9a] There exist multiple dipolar interactions between the guest's CN bonds and the host's alkoxy groups based on their antiparallel positions. Notice that the C−O bond of methoxy groups in DMP5A possesses larger dipole moment than DBP5A,[10] and then affords stronger dipole–dipole forces to the CN groups, resulting in stronger binding affinity.[9a] While for 1,4-dibromobutane, DBP5A and DOP5A give larger association constants, which are 2.7 and 2.6 times larger than that for DMP5A.[9b] Since the dominant driving force for the complexation is van der Waals dispersion forces, there may be more dispersive interactions between 1,4-dibromobutane and DBP5A/DOP5A bearing larger alkyl groups.[9b] According to the above observations, MPP5A host having two different rims (methyl and pentyl) is designed for the present study, and is expected to regioselectively bind with axle **1** with different terminal groups (Br and CN).

MPP5A host was obtained by condensation of 1-methoxy-4-penthoxybenzene monomer with paraformaldehyde in $CHCl_3$, $BF_3{\cdot}O(C_2H_5)_2$ as the catalyst. Its structure was characterized by ^{1}H NMR, ^{13}C NMR, 2D NOESY and HRMS. From ^{1}H NMR spectrum (Fig. S5), two single peaks (δ = 6.84 and 6.77 ppm) were found for the aromatic protons. This is reasonable since the chemical environments of the phenyl protons from the methyl side and the pentyl side are different. In the 2D NOESY analysis, no NOE correlations between the methyl and pentyl moieties can

be found, suggesting that the methyl groups should not be adjacent to the pentyl groups. More importantly, there are unequivocal correlations between the phenyl protons from the pentyl rim ($\mathbf{H_1}$) and methylene proton $\mathbf{H_5}$ of pentyl, and those for the aromatic protons from the methyl rim ($\mathbf{H_2}$) and methyl proton $\mathbf{H_4}$, which are denoted as the NOE cross-peaks A and B, respectively (Fig. S7). Moreover, no cross-peaks between $\mathbf{H_1}$ and $\mathbf{H_4}$ and between $\mathbf{H_2}$ and $\mathbf{H_5}$ were observed. Combining these 2D NOESY results with ^{1}H NMR spectral features mentioned above, we can definitely conclude the structure of nonsymmetrical MPP5A that all the methyl and pentyl moieties were completely separated. On the other hand, the structure of MPP5A was also unambiguously confirmed by a crystal structure of its host-guest complex, which will be discussed below.

Before investigating the binding behavior between nonsymmetrical wheel and nonsymmetrical axle **1**, the complexation of MPP5A and symmetric DMP5A and DPP5A towards mono-substituted butane guest, 1-bromobutane (**2**) and 1-butyl cyanide (**3**, Scheme 1), was firstly examined. Fast exchange on the NMR timescale was observed for these complexes. As can be seen from Fig. S8 and S9, upon addition of MPP5A host, the signals of guest **2** and **3** exhibit pronounced upfield shifts and broadening effects, revealing that the host engulfs the guest, which thus leads to an efficient shield toward guest protons. [11] The K_a values of **2** and **3** with three pillar[5]arene hosts were determined by ^{1}H NMR titration experiments in $CDCl_3$ (Table 1). As expected, DMP5A and MPP5A show similar binding strength towards guest **3** and the corresponding K_a values are 2.6 and 2.5 times larger than that for DPP5A. While for guest **2**, DMP5A gives the smallest K_a value, and MPP5A and DPP5A show similar binding affinities. These observations are consistent with our previously reported results[9a,b] and further indicate that the methyl side of pillar[5]arene is suitable for binding CN and the pentyl side is suitable for Br.

Table 1. Association constants (K_a) for the complexation of guest **1**–**3** with pillar[5]arenes in $CDCl_3$ at 298 K.

Guest	Host	K_a (M^{-1})
1	DMP5A	$(1.7 \pm 0.2) \times 10^4$ [a]
1	MPP5A	$(8.4 \pm 0.6) \times 10^4$ [a]
1	DPP5A	$(1.6 \pm 0.3) \times 10^4$ [a]
2	DMP5A	41 ± 3 [b]
2	MPP5A	75 ± 2 [b]
2	DPP5A	82 ± 4 [b]
3	DMP5A	$(5.7 \pm 0.4) \times 10^2$ [b]
3	MPP5A	$(5.5 \pm 0.3) \times 10^2$ [b]
3	DPP5A	$(2.2 \pm 0.1) \times 10^2$ [b]

[a] Determined by ^{1}H NMR single-point method. [b] Determined by ^{1}H NMR titration method.

The host-guest complexation of **1** and MPP5A was then examined. Fig. 1 show ^{1}H NMR spectra of **1** in $CDCl_3$ recorded in the absence and in the presence of approximately one equivalent of the host. Upon addition of MPP5A, the ^{1}H NMR spectrum (Fig. 1b) showed two different sets of signals, indicating the formation of a host-guest complex in a slow association/dissociation process on the NMR time scale. The resonances of the new species are in accord with the formation of an interpenetrated complex. All the peaks for the methylene protons of the axle exhibit substantial upfield shifts and broadening effects respect to the free guest ($\Delta\delta = -1.42 \sim -3.99$ ppm) as a consequence of inclusion-induced shielding effects. For symmetric DMP5A and DPP5A wheels, similar complexation induced NMR changes were observed when interacted with **1**, suggesting the formation stable interpenetrated complexes. The association constants for the three complexes were calculated by several independent measurements following the single-point method. Very interestingly, the K_a value for **1** with nonsymmetric MPP5A [$(8.4 \pm 0.6) \times 10^4$ M^{-1}] is 4.9 and 5.3 times larger than those for **1**⊂DMP5A and **1**⊂DPP5A, respectively. According to the above discussion on the host/guest design and our previously reported results, [9a,b] we can deduce that the strong binding strength of MPP5A and **1** is due to the positive cooperative effects of MPP5A's two different rims and there must exist binding regioselectivity in **1**⊂MPP5A, i.e., the axle's CN@the wheel's methyl rim and Br@pentyl rim, as depicted in Fig. 2. 2D NOESY and ROESY experiments of **1**⊂MPP5A at different temperatures (273K, 293 K and 308 K) were then performed to examine the regioselective complexation. However after several attempts, no intermolecular NOEs between the host's protons and the guest's methylene protons were observed. This is reasonable due to the very remarkable broadening effects for the methylene protons (Fig. 1b). [12]

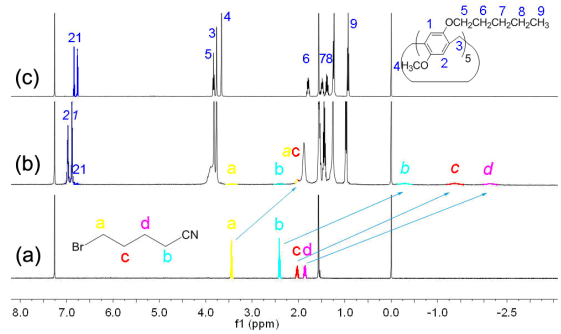


Fig. 1 ^{1}H NMR spectra (500 MHz, 298 K) of (a) **1**, (b) **1** + MPP5A, and (c) MPP5A in $CDCl_3$ at a concentration of 4.7–5.3 mM. Italics represent complexed host and guest.

Fortunately, we obtained single crystals of **1**⊂MPP5A complex suitable for X-ray analysis by slow evaporation of a solution of **1** and MPP5A in CH_2Cl_2/*n*-hexane solution at

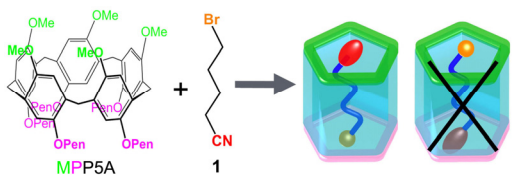


Fig. 2 Regioselective formation of interpenetrated complex between **1** and MPP5A.

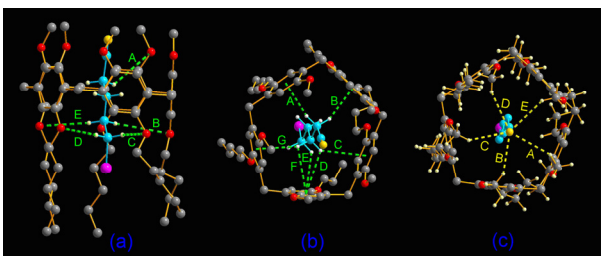


Fig. 3 Crystal structure of interpenetrated complex **1**⊂MPP5A. Dashes represent C–H···O/N/π hydrogen bonds. For details, see Fig. S10.

room temperature. As expected, the crystal structure revealed that guest **1** threaded the central cavity of MPP5A with the orientation of CN@methyl rim and Br@pentyl rim (Fig. 3 and S10), which is consistent with the result in solution. It was found that there are not only quintuple (weak) C−H···O hydrogen bonding interactions (Fig. 3a: A−E), but also septuple (weak) C−H···π interactions (Fig. 3b: A−G) between the host and the guest. Additionally, there exist several weak C−H···N interactions (Fig. 3c: A−E) between methyls of the wheel with nitrogen atom of the axle. These multiple non-covalent interactions suggest a good host-guest dimension matching, and certainly play an important role in the formation of the interpenetrated complex and its good regioselectivity.

In summary, a non-symmetric host MPP5A, with five methyls on one rim and five pentyls on the other one, has been synthesized and its complexation towards asymmetric 5-bromovaleronitrile guest has been investigated. Although the structural differences of its two rims are small, MPP5A can regioselectively engulf 5-bromovaleronitrile axle to form an interpenetrated complex with a specific directionality of CN@methyl rim and Br@pentyl rim. The self-sorted orientation is due to the reversed binding selectivity between methyl/pentyl rims and CN/Br groups, i.e., a clear preference for CN−methyl over CN−pentyl and for Br−pentyl over Br−methyl. We believe that the extension of this approach could lead to novel supramolecular assemblies with high-order topologies.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthesis, additional ^{1}H NMR spectra, crystal data and determination of the association constants. See DOI: 10.1039/b000000x

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