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Synthesis of Pillar[5]arene Dimers and Their Cooperative Binding toward Some Neutral Guests

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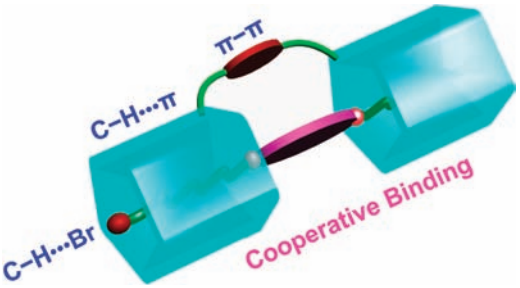
ABSTRACT



Three pillar[5]arene dimers, bridged by a flexible aliphatic chain (H1) or a relatively rigid phenylene unit (H2 and H3), were synthesized, with the possible synthetic strategies being discussed. The dimers could significantly enhance the binding affinities toward neutral model substrates in comparison with monomeric 1,4-dimethoxypillar[5]arene (H4) through the cooperative binding of two pillar[5]arene moieties. The molecular binding ability and selectivity are discussed from the viewpoints of the size/shape-fit concept and multiple recognition mechanism.

Pillararenes (PAs) are new symmetrical calixarene (CA) analogues, featuring hydroquinone units that are linked by methylene ($-CH_2-$) bridges. Unlike the conventional CA's "basket" structure, PAs possess the symmetrical pillar architecture with two identical cavity portals. This structural feature renders PAs superior to CAs in the construction of threaded complexes and tubular assemblies. On the other hand, PAs are more rigid than the traditional CAs, which may afford highly effective binding properties for specially designed guests.[1−3] Our previous works[3a,b] have reported the formation of a series of threaded complexes between pillar[5]arene (P5A) with cationic bis(pyridinium) derivatives, paraquat derivatives, and 1,4-bis(imidazolium)butanes. Recently, we[3c] have demonstrated that simple alkyl-substituted P5As can form stable interpenetrated complexes with neutral bis(imidazole) guests utilizing multiple hydrogen bonds and C−H···π interactions.

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(1) (a) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721–9723. (b) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Chen, X.; Huang, F. *Chem. Commun.* **2011**, *47*, 2417–2419. (c) Han, C.; Ma, F.; Zhang, Z.; Xia, B.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 4360–4363. (d) Si, W.; Hu, X.-B.; Liu, X.-H.; Fan, R.; Chen, Z.; Weng, L.; Hou, J.-L. *Tetrahedron Lett.* **2011**, *52*, 2484–2487. (e) Li, J.; Zhou, W.; Li, Y.; Liu, H.; Ouyang, C.; Yin, X.; Zheng, H.; Zuo, Z. *Tetrahedron Lett.* **2008**, *49*, 4857–4861.

(2) (a) Cragg, P. J.; Sharma, K. *Chem. Soc. Rev.*, DOI: 10.1039/c1cs15164a. (b) Ogoshi, T.; Hashizume, M.; Yamagishi, T. *Chem. Commun.* **2010**, *46*, 3708–3710. (c) Ogoshi, T.; Nishida, Y.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2010**, *43*, 3145–3147. (d) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022–5023.

(3) (a) Li, C.; Zhao, L.; Li, J.; Ding, X.; Chen, S.; Zhang, Q.; Yu, Y.; Jia, X. *Chem. Commun.* **2010**, *46*, 9016–9018. (b) Li, C.; Xu, Q.; Li, J.; Yao, F.; Jia, X. *Org. Biomol. Chem.* **2010**, *8*, 1568–1576. (c) Li, C.; Chen, S.; Li, J.; Han, K.; Xu, M.; Hu, B.; Yu, Y.; Jia, X. *Chem. Commun.* **2011**, *47*, 11294–11296. (d) Li, C.; Shu, X.; Li, J.; Chen, S.; Han, K.; Xu, M.; Hu, B.; Yu, Y.; Jia, X. *J. Org. Chem.* **2011**, *76*, 8458–8465.

(4) (a) Strutt, N. L.; Forgan, R. S.; Spruell, J. M.; Botros, Y. Y.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 5568–5671. (b) Zhang, H.; Strutt, N. L.; Stoll, R. S.; Li, H.; Zhu, Z.; Stoddart, J. F. *Chem. Commun.* **2011**, *47*, 11420–11422. (c) Ogoshi, T.; Demachi, K.; Kitajima, K.; Yamagishi, T. *Chem. Commun.* **2011**, *47*, 7164–7166.

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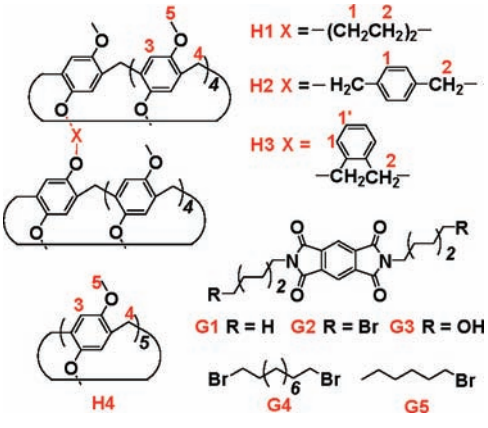
To improve the original binding abilities and molecular selectivities of native PAs and simple alkyl-substituted PAs, efforts have been devoted to the design and synthesis of functional P5A derivatives, such as monofunctionalized PAs,[4] decafunctionalized PAs[3d,5] and coPAs,[6] and to investigations into their molecular recognition behavior. Very recently, when we prepared this paper, Huang and co-workers[7] reported the first synthesis of a PA dimer and its formation of 1:2 complexes with *n*-octyltrimethyl ammonium hexafluorophosphate. The average association constant [$K_{av} = (6.0 \pm 0.4) \times 10^2\ M^{-1}$] is lower than the association constant ($K_a = 1695 \pm 115\ M^{-1}$) for the complexation between the 1,4-dimethoxypillar[5]arene (**H4**) monomer and the ammonium guest. This is reasonable considering there are no cooperative effects in such a dimeric system. Instead, a larger steric hindrance may be induced for the complexation between the dimer and the guest. Likewise, Ogoshi et al.[8] reported the selective binding of *n*-hexane by a P5A dimer, giving a smaller K_a value of $98 \pm 12\ M^{-1}$. Similarly, this should be due to no cooperative complexation because *n*-hexane is too short to be simultaneously located in both cavities of the dimer.

It is well-known that the essential function of macrocycle dimers is the cooperative effect. Compared with monomers, dimers often form stable complexes with guests through the intramolecular cooperative binding.[9] To our knowledge, the highly effective cooperative binding systems arising from P5A dimers have not been reported as yet. Herein, we report the synthesis of three novel P5A dimers, bridged by a flexible aliphatic chain (**H1**) or a relatively rigid phenylene unit (**H2** and **H3**) using different synthetic strategies, and their interesting host–guest properties toward some neutral guests (Scheme 1). Generally, calixarenes and their analogues interact strongly with cationic guests, except for calixpyrroles.[10] The P5A dimers used in this work significantly enhance the binding abilities toward neutral model substrates in comparison with monomeric 1,4-dimethoxypillar[5]arene (**H4**) through the cooperative binding of a single model substrate by two cavities located in close proximity.

Scheme 1. Structure of P5A Dimers and Neutral Guests



As shown in Scheme S1, four different synthetic strategies were attempted for the synthesis of P5A dimers. We first tried to prepare them through the direct cyclization of 1,4-bis(4-methoxyphenoxy)butane with paraformaldehyde, using $BF_3 \cdot O(C_2H_5)_2$ as the catalyst (Route 1). Nevertheless, the reactions were very complicated and no desired products were observed. We then explored a second route by cooligomerization of 1 equiv of 1,4-bis(4-methoxyphenoxy)butane and 8 equiv of 1,4-dimethoxybenzene (Route 2). Reactions proceeded very smoothly under similar conditions. However, the yield of dimer **H1** was relatively low (6%); the major product was monomer **H4** (45%). Moreover, cooligomerization of 1,4-bis((4-methoxyphenoxy)methyl)benzene/1,2-bis-((4-methoxyphenoxy)methyl)benzene and 1,4-dimethoxybenzene did not yield dimers **H2** and **H3**. Rather, monomer **H4** was the sole product. One possible reason is that 1,4-bis((4-methoxyphenoxy)methyl)benzene and 1,2-bis((4-methoxyphenoxy)methyl)benzene are more rigid than 1,4-bis(4-methoxyphenoxy)butane, which disfavors the cooligomerization.

Routes 3 and 4 rely on the nucleophilic substitution reactions between 1 equiv of dihalide with 2 equiv of (or excess) monohydroxyl P5A or parent P5A using K_2CO_3 or NaH as the base. Using route 3, the yields for dimer **H1**, **H2**, and **H3** are 65%, 86%, and 77% respectively, which are much better than those from route 2. Route 4, however, did not provide the desired dimers where parent P5A was used as the reactant. This is possibly due to the 10 hydroxyl groups in parent P5A, resulting in the formation of complex mixtures.

Each successful route has its own advantage. Route 2 provided the P5A dimers in one step from readily available starting materials, albeit in low yield, wherein dimers **H2** and **H3** with rigid linkers are not applicable. Route 3 offered the dimers **H1**–**H3** in good yields, but the key intermediate, monohydroxyl P5A, is not readily accessible, which was prepared from commercially avaible reagents in two steps.

The complexation of dimer **H2** with alkyl substituted pyromellitic diimide (PDI) derivative **G1** (Scheme 1) was first tested. There may be multiple C–H$\cdots\pi$ interactions[6a] between the guest's methylenes with the dimer's

(5) Hu, X.-B.; Chen, L.; Si, W.; Yu, Y.; Hou, J.-L. *Chem. Commun.* **2011**, *47*, 4694–4696.
(6) (a) Zhang, Z.; Luo, Y.; Chen, J.; Dong, S.; Yu, Y.; Ma, Z.; Huang, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1397–1401. (b) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285–3287. (c) Kou, Y.; Tao, H.; Cao, D.; Fu, Z.; Schollmeyer, D.; Meier, H. *Eur. J. Org. Chem.* **2010**, 6464–6470.
(7) Xia, B.; He, J.; Abliz, Z.; Yu, Y.; Huang, F. *Tetrahedron Lett.* **2011**, *52*, 4433–4436.
(8) Ogoshi, T.; Demachi, K.; Kitajima, K; Yamagishi, T. *Chem. Commun.* **2011**, *47*, 10290–10292.
(9) (a) Liu, Y.; Chen, Y. *Acc. Chem. Res.* **2006**, *39*, 681–691. (b) Li, Y.; Pink, M.; Karty, J. A.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17293–17295.
(10) Calixpyrroles have shown considerable promise in the area of anion recognition and sensing. (a) Lee, C.-H.; Miyaji, H.; Yoon, D.-W.; Sessler, J. L. *Chem. Commun.* **2008**, 24–34. (b) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55.

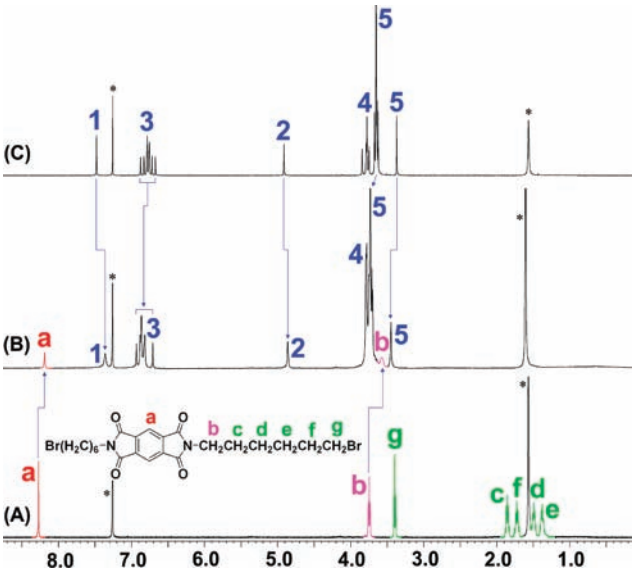


Figure 1. ^{1}H NMR spectra (500 MHz) of **G2** (4.8 mM) in the absence (A) and presence (B) of **H2** host (5.1 mM) in $CDCl_3$. For comparison, the spectrum of the uncomplexed **H2** is shown at the top (C). Asterisk = solvent/water.

P5A moiety and $\pi-\pi$ interactions between the guest's PDI unit with the dimer's phenylene linker. Due to the dimeric host containing two P5A moieties, it could be expected to form a nonclassical 1:1 [2]pseudorotaxane-type complex, in which the two methylene chains of the guest thread the two lateral P5A cavities of the dimer. However, upon addition of **H2**, very small shifts were observed for the protons of **G1** (Figure S15), suggesting very weak binding affinities. The association constant (K_a) could not be calculated for this complex. Similar results were found for the other two dimers (**H1** and **H3**) (Figures S16–S17).

We then explored whether and to what extent the introduction of other weak noncovalent interactions, such as a C–H···halogen or C–H···O hydrogen bond, would improve the host–guest complexation. Thus, PDI derivatives **G2** and **G3** containing terminal bromo and hydroxyl groups were examined (Scheme 1). Figure 1 shows the ^{1}H NMR spectra of **G2** in $CDCl_3$ recorded in the absence (Figure 1A) and presence of ~1 equiv of host **H2** (Figure 1B). The peaks for the methylene protons of **G2** exhibited substantial upfield shifts and broadening effects compared to the free axle. The $\Delta\delta$ value for H_b was −0.20 ppm. And the broadening effects were so remarkable that the proton signals of methylene H_c-H_g could not be observed in the ^{1}H NMR spectrum. Therefore, we can deduce that the methylenes of the guest molecule are included in the cavity of the host, which thus leads to efficient shielding of the guest protons.[11] The signals derived from the aromatic protons relative to the phenylene unit of the host and the PDI unit of the guest displayed upfield shifts ($\Delta\delta$ = −0.12 ppm for H_1 and 0.08 ppm for H_a) due to the ring current effects for face-to-face stacking.[12] This indicates the possible π-stacking interactions between phenylene and PDI. From the ^{1}H NMR results, we can deduce the formation of a 1:1 [2]pseudorotaxane-type complex between the host and guest, in which the two carbon chains of the guest thread the two lateral P5A cavities of the dimer. On the other hand, a Job plot based on proton NMR data demonstrated that the complex had a 1:1 stoichiometry (Figure S32). The association constant was determined to be $(1.3 \pm 0.2) \times 10^3$ M^{-1}, which was comparable with our previously reported values of the formation of pseudorotaxanes between the native P5A and dicationic guests.[3a,b] The much more effective binding of **H2** toward **G2** than **G1** is mainly because of the additional C–H···Br interactions between the host's methyl groups and the guest's bromine atoms, and the stronger C–H···π interactions due to the inductive effects of the bromo groups. For hydroxyl-substituted PDI derivative **G3**, similar **H2** complexation-induced effects were observed, indicating an analogous mode of binding. However, the K_a value for **G3**⊂**H2** was decreased by a factor of 3.3, compared with that for **G2**⊂**H2**. 2D NOESY and ROESY experiments were also performed for the **G2**⊂**H2** complex in $CDCl_3$, which did not reveal intermolecular NOEs between the host's P5A protons and the guest's methylene protons. This is reasonable due to the very remarkable broadening effects for the methylene protons. However, it is unexpected that the NOEs between the host's and guest's bridger protons are not observed in the NOESY and ROESY spectra.[13] UV–vis experiments were then performed. The complex **G2**⊂**H2** gave a charge transfer (CT) band (Figure S28). This is due to the π-stacking interaction between the guest's PDI unit with the dimer's phenylene linker, indicating the cooperative binding mode.

The binding behaviors of PDI derivatives **G2** and **G3** with 1,2-phenylene bridged **H3** were also investigated. Upon addition of **H3**, no obvious upfield shifts were observed for the signals of **G3**'s PDI aromatic proton (H_1) and **H3**'s 1,2-phenylene protons (H_1 and $H_{1'}$), which was very different from that for **H2**. This is explained by the fact that **H3** could not form the intramolecular cooperative binding modes[14] with **G2** and **G3** due to the short 1,2-phenylene unit, giving a very small K_a value [$(5.5 \pm 0.5) \times 10$ M^{-1} for **G2**⊂**H3** and $(3.4 \pm 0.3) \times 10$ M^{-1} for **G3**⊂**H3**, Table 1]. Similarly, there is no significant cooperative effect between dimer **H1** and PDI derivatives.

(11) (a) Arena, G.; Gentile, S.; Gulino, F. G.; Sciotto, D.; Sgarlata, C. *Tetrahedron Lett.* **2004**, *45*, 7091–7094. (b) Kon, N.; Iki, N.; Miyano, S. *Org. Biomol. Chem.* **2003**, *1*, 751–755. (c) Liu, Y.; Guo, D.-S.; Zhang H.-Y.; Ma, Y.-H.; Yang, E.-C. *J. Phys. Chem. B* **2006**, *110*, 3428–3434.

(12) Zych, A. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 8898–8909.

(13) Zhou, Q.-Z.; Jiang, X.-K.; Shao, X.-B.; Chen, G.-J.; Jia, M.-X.; Li, Z.-T. *Org. Lett.* **2003**, *5*, 1955–1958.

(14) Compared with macrocycle monomers, dimers often exhibit strong binding abilities with guests through the intramolecular cooperative binding. While the intermolecular cooperative binding modes result in the formation of assemblies. It is difficult to form molecular assemblies efficiently for **G2**/**G3**⊂**H3** complexes, due to the very small K_a values. In fact, the intramolecular cooperative binding behavior is the major subject of the present paper.

This may be attributed to the strict size/shape-fit between the host and the guest. With a relatively long linker, **H2** was able to adopt cooperative multiple binding with the PDI-derived **G2** and **G3**, as compared with the other two dimers. Moreover, the possible $\pi-\pi$ interactions between 1,4-phenylene and PDI further promote the host−guest inclusion complexation. These factors jointly contribute to the strongest binding ability. Investigations of the complexation between monomeric **H4** and PDI derivative **G2** and **G3** employing Job plots indicated the formation of 2:1 complexes believed to be of a [3]pseudorotaxane geometry. But the average association constants[15] are very small ($K_{av} < 50\ M^{-1}$) and cannot be calculated accurately.

Table 1. Association Constant (K_a/M^{-1}) for Complexation of Neutral Guests with P5A Dimers in $CDCl_3$ at 298 K

	H1	H2	H3	H4
G1	[a]	[a]	[a]	[a]
G2	$(1.1 \pm 0.1) \times 10^2$	$(1.3 \pm 0.2) \times 10^3$	$(5.5 \pm 0.5) \times 10$	[b]
G3	$(7.6 \pm 0.9) \times 10$	$(4.0 \pm 0.3) \times 10^2$	$(3.4 \pm 0.3) \times 10$	[b]
G4	$(8.2 \pm 0.8) \times 10^2$	$(7.6 \pm 0.9) \times 10$	$(3.6 \pm 0.4) \times 10$	$(4.5 \pm 0.3) \times 10$
G5	[b]	[b]	[b]	$(5.1 \pm 0.4) \times 10$

[a] NMR changes were too small to allow the calculation of K_a. [b] The host−guest complex had a 2:1 or 1:2 stoichiometry. But the K_{av} values[15] are very small ($50\ M^{-1}$) and cannot be calculated accurately.

For comparison purposes, we also examined an aliphatic dibromide guest, 1,10-dibromooctane (**G4**). As can be seen from Figure S22, upon addition of **H1**, the methylene protons of **G4** exhibit pronounced broadening effects and upfield shifts ($\Delta\delta = -0.43$ to -0.81 for H_{a-d}). The NMR changes of **G4** upon complexation with the other two dimers **H2** and **H3**, linked by rigid units, are not as remarkable as those for **H1**. The K_a values for **H2** and **H3** toward **G4** are dramatically reduced by factors of 11 and 23 compared with that for **H1** with a flexible methylene linker. It is well documented that the match in the degree of size between dimeric hosts and guests has a dominant effect on the stabilities of the corresponding complexes.[9] Apparently, **G4** is short compared to these three macrodicyclic hosts. **H1** shows a stronger binding affinity toward this shorter guest because its flexible methylene linker can bend, therefore enabling the guest to penetrate deeper into the two P5A cavities upon complexation and thus leading to strong hydrogen bond and C−H$\cdots\pi$ interactions between host and guest. It is also worth noting that the K_a value of **G4**⊂**H1** is remarkably increased by a factor of 18 compared with that of the complex between **G4** and monomer **H4**, which also indicates the significant cooperative binding between dimer **H1** and **G4**.

As expected, the hosts **H1**−**H4** could bind the monobromide, 1-bromohexane (**G5**), with a smaller K_a value. Job plots have shown a 2:1 binding stoichiometry with dimer **H1**−**H3** and a 1:1 stoichiometry with monomer **H4**. For the 1:1 complex **G5**⊂**H4**, the K_a was determined to be $(5.1 \pm 0.4) \times 10\ M^{-1}$. For 2:1 complexes **G5**$_2$⊂**H1**, **G5**$_2$⊂**H2**, and **G5**$_2$⊂**H3**, the K_{av} values[15] are very small ($< 50\ M^{-1}$) and cannot be calculated accurately.

In summary, three P5A dimers have been synthesized and the possible synthetic strategies to prepare pillararene dimers have been discussed. Compared with monomeric **H4**, the dimers have shown significant enhancement in binding strength toward some neutral guests through cooperative binding and multiple recognition. Appropriately controlling the linker length and rigidity and the introduction of heteroatoms to the guests could result in strong host−guest binding and high molecular selectivity. **H1** bearing a flexible linker shows a strong binding ability with short dibromide **G4** [$K_a = (8.2 \pm 0.8) \times 10^2\ M^{-1}$], with up to 11-, 23-, and 18-fold increases as compared with dimeric **H2**, **H3**, and monomeric **H4**. **H2** linked by a relatively rigid and long bridge displays the strongest binding ability with bromo-substituted PDI derivative **G2** [$K_a = (1.3 \pm 0.2) \times 10^3\ M^{-1}$], giving a reversed molecular selectivity for the **G2**/**G4** pair (up to 17-fold enhancement as compared with **H1**). These results provide a convenient and powerful tool for the design of effective dimeric pillararene receptors and further our understanding of the design and construction of new functional supramolecular systems.

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Supporting Information Available. Synthesis, NMR spectra, and Job plots. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707. (b) Connors, K. A. *Binding Constants*; J. Wiley and Sons: New York, 1987; pp 78−86. (c) Huang, F.; Zakharov, L. N.; Rheingold, A. L.; Ashraf-Khorassani, M.; Gibson, H. W. *J. Org. Chem.* **2005**, *70*, 809–813.