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Regulating Molecular Recognition with C-Shaped Strips Attained by Chirality-Assisted Synthesis

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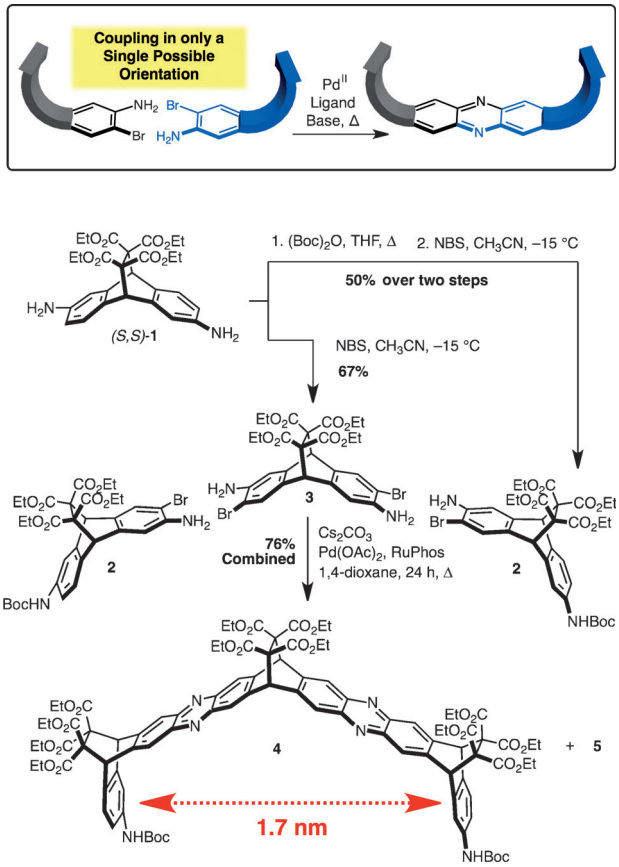
Abstract: *Chirality-assisted synthesis (CAS) is a general approach to control the shapes of large molecular strips. CAS is based on enantiomerically pure building blocks that are designed to strictly couple in a single geometric orientation. Fully shape-persistent structures can thus be created, even in the form of linear chains. With CAS, selective recognition between large host and guest molecules can reliably be designed de novo. To demonstrate this concept, three C-shaped strips that can embrace a pillar[5]arene macrocycle were synthesized. The pillar[5]arene bound to the strips was a better host for electron-deficient guests than the free macrocycle. Experimental and computational evidence is provided for these unique cooperative interactions to illustrate how CAS could open the door towards the precise positioning of functional groups for regulated supramolecular recognition and catalysis.*

Our work based on chirality-assisted synthesis (CAS) represents a fundamental step towards precise molecular-shape control,[1] which is critical for selective supramolecular recognition,[2] self-assembly,[3] and catalysis.[4] Many proteins, for example, achieve their functions by adopting specific folds under physiological conditions. Distinct from biological constructs, however, de novo designed synthetic materials often need to operate under various experimental conditions in a more atom-economic fashion. It is therefore essential to find new ways to control molecular shapes.

Molecular strips,[5] which are composed of many fused rings and thus adopt well-defined structures, are promising candidates for this endeavor. Whereas such structures often function as clips[6] and tweezers,[7] the challenging formation of fused rings with intricate stereochemistry still presents major limitations for the directed synthesis of bent strips as single stereoisomers.[8] Consequently, only a few non-cyclic, shape-persistent strips, with inner diameters on the order of 1 nm, have been created to date.[1a,5a,7,9] Diastereoselective cycloadditions have been used as the key steps in most of these syntheses, but excellent[1a] diastereoselectivity is often difficult to maintain for even larger building blocks.[7] Therefore, more voluminous, strip-like structures have only been created[10] in the form of symmetric dendrimers, for which the diastereoselectivities of the coupling reactions have no influence on the shapes of the products formed.

CAS provides a fundamentally distinct approach to generally control the directionality of bent molecular strips. It employs enantiopure building blocks that can only couple in a single geometric orientation (Scheme 1). As a result, the chirality of the building blocks controls the direction of growth for the molecular strips. As the stereochemical outcome of the coupling reactions is determined by two covalent bonds formed with predictable regioselectivity, CAS is unaffected by the chemical substituents and size of the molecular strips. Therefore, in the absence of freely rotatable bonds in the structural backbone, the shapes and supramolec-



Scheme 1. Chirality-assisted coupling of *ortho*-bromoanilines, leading to the C-shaped molecular strip **4**. Chirality-assisted synthesis (CAS) is enabled by the use of enantiopure starting materials to form only a single stereoisomer. RuPhos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl.

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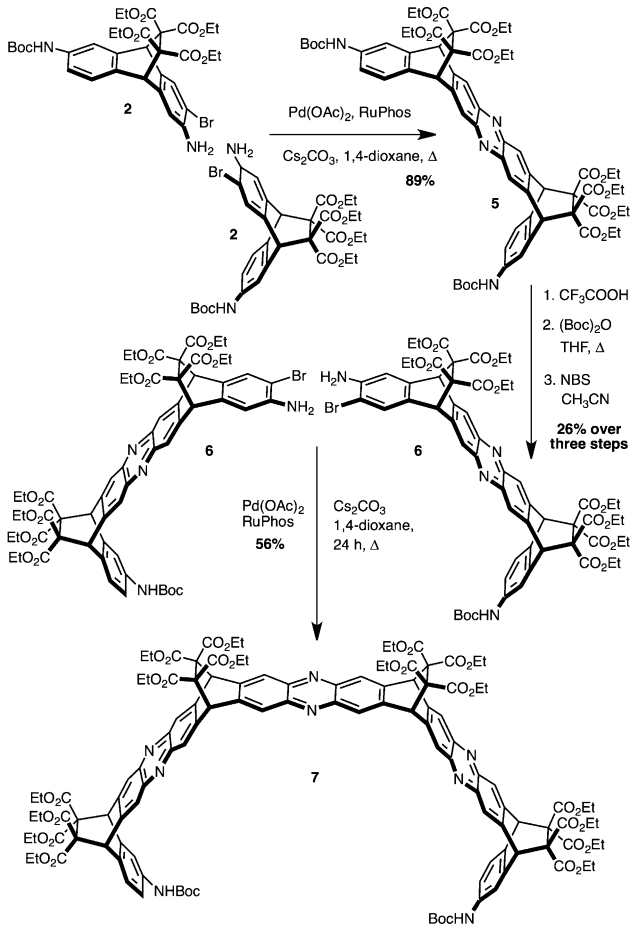

Scheme 2. Chirality-assisted couplings are applied twice in the synthesis of **7**.

ular interactions of the strips can be predicted precisely using computer-aided design.

We utilize CAS to create large, chiral, C-shaped molecular strips of various lengths with cavities in the form of truncated, polygonal prisms (Schemes 1 and 2). Given their preorganized binding sites, our strips are strong candidates for new types of shape-selective supramolecular recognition. Through computer-aided design and NMR spectroscopy, we discovered that the strips bind to the outside of pillar[5]arene macrocycles[11] in a manner similar to how a five-sided bolt head fits into a pentagonal wrench. Furthermore, by embracing pillararenes, the C-shaped strips are able to regulate the interactions of pillararene hosts with conventional guests,[12] for example, electron-deficient viologen derivatives. Thus, our discovery not only offers a general way to control the shapes of large molecules, but also adds a new dimension to the regulated supramolecular recognition of macrocyclic hosts.

We started our investigations with the synthesis of the enantiomerically pure CAS building block **1**. We found that **1** can be readily prepared as a racemic mixture from anthracene in three primary steps, a Diels–Alder cycloaddition with electron-deficient tetraethyl ethylenetetracarboxylate[13] followed by nitration and reduction of the nitro groups. Separation of the enantiomers of **1** was achieved by mixing racemic **1** and enantiopure 2,3-dibenzoyl-D-tartaric acid in a 1:3 molar ratio. This procedure leads to a colorless gel in CH_3CN, whose fibers are enriched with the (*S*,*S*)-enantiomer of **1**,[14] which allowed us to isolate (*S*,*S*)-**1** in 96% *ee*[15] by washing the gel with pure CH_3CN, followed by a second diastereoselective gelation and washing step. As no chromatography is needed for the synthesis or isolation of enantiopure **1**, both enantiomers of this central CAS building block can now be prepared on multigram scale.

Next, we established proof of principle for the CAS coupling reactions with the synthesis (Scheme 1) of the chiral strips **4** and **5**. The CAS couplings are enabled by regioselective Pd-catalyzed aminations[16] of *ortho*-bromoanilines, giving rise to directionally defined phenazine linkages. To synthesize **4** in a stereoselective fashion, we thus subjected (*S*,*S*)-**1** to electrophilic aromatic bromination, which resulted in the regioselective formation of bis(*ortho*-bromoaniline) **3**. To precisely control the lengths of the CAS coupling products, we attached a *tert*-butyloxycarbonyl (Boc) protecting group to one of the amino groups of (*S*,*S*)-**1**.[17] Regioselective electrophilic aromatic bromination with *N*-bromosuccinimide (NBS) followed by Pd-catalyzed cross-coupling with **3** then led to the desired strips **4** and **5**.

The products of the CAS coupling reactions naturally emerge as single enantiomers. Thus, no additional chiral resolutions are needed for further growth of the strips. To prove this concept, we launched a second CAS coupling round, this time starting from **5** (Scheme 2). Again, the Pd-catalyzed couplings occurred in a completely stereospecific manner to generate the chiral strip **7** as a single stereoisomer. Compound **7** represents[8] one of the largest fully shape-persistent bent strips synthesized to date, and yet, thanks to its 16 ethyl ester groups pointing outward, it is soluble in a variety of solvents, even in mixtures of acetonitrile and water.

Given their large chiral cavities, **4** and **7** are able to act as selective hosts for bulky macrocyclic guests. According to computer modeling, both strips possess shapes that closely match the contours of pillararene[18] macrocycles. Therefore, we envisioned that our strips might bind these popular hosts,[12] which have already found many applications.[19] To test this hypothesis, we synthesized[18b] the pillar[5]arene macrocycle **P[5]** (Figure 1), which contains ten triethylene glycol methyl ether substituents.

When comparing (Figure 1) the ^{1}H NMR spectrum of pure **P[5]** in 5:1 CD_3CN/D_2O (v/v) with the corresponding spectra of 1:1 mixtures of **P[5]** and **4** as well **P[5]** and **7**, we observed clear evidence for binding between the strips and **P[5]**: First and foremost, the ^{1}H NMR resonance labeled P, which corresponds to the aromatic protons of **P[5]**, was shifted upfield and also broadened significantly in the presence of both **4** or **7**. Furthermore, with strip **7**, the P resonance was also clearly split into two signals, which was most likely caused by the interaction[20] of the inherent chiralities of **7** and **P[5]**. Moreover, all of the NMR resonances corresponding to the aromatic protons of strips **4** and **7** also shifted significantly when **P[5]** was added. This result is in line with **P[5]** undergoing π–π stacking with all of the phenazine groups of the strips as the complexes form.[21]

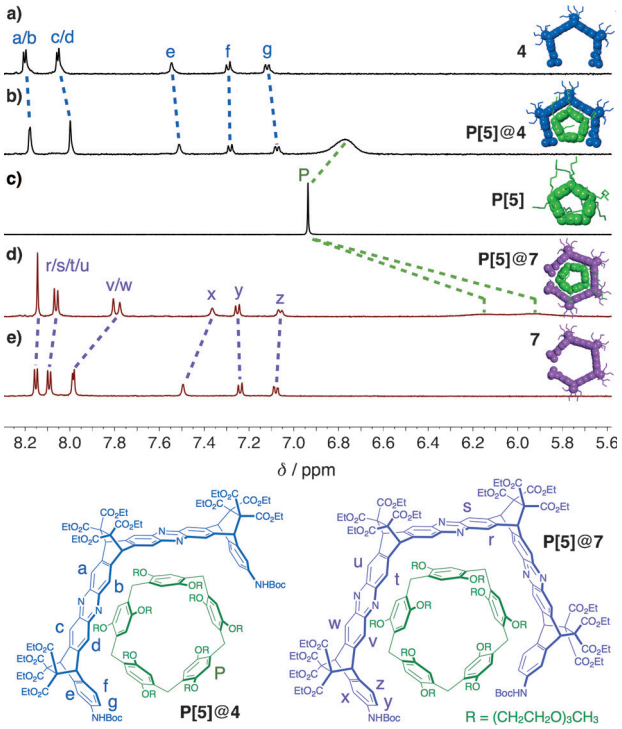

Figure 1. Partial ^{1}H NMR spectra (500 MHz, CD_3CN/D_2O (5:1, v/v), 298 K) showing the chemical shifts of the aromatic protons of a) pure strip **4**, b) **4** mixed with **P[5]** in a 1:1 molar ratio, c) pure **P[5]**, d) **7** mixed with **P[5]** in a 1:1 molar ratio, and e) pure **7**. The ^{1}H NMR resonances corresponding to the different protons of the phenazine ring were assigned (see the Supporting Information) with the help of 2D homonuclear correlation (COSY) ^{1}H NMR spectroscopy. Although **P[5]** equilibrates[20] between two main enantiomeric conformations, only its (R_p,R_p,R_p,R_p,R_p) enantiomer is shown.

NMR spectroscopy also revealed a series of rapidly increasing association constants for the **P[5]@5**, **P[5]@4**, and **P[5]@7** complexes. As Job Plots (see the Supporting Information) for **P[5]@4** and **P[5]@7** indicated a 1:1 binding stoichiometry, we fit the complex association constants (K_a) to a 1:1 binding model. The measured K_a values (Figure 2a) clearly show a near-exponential increase of the binding affinities with increasing length of the molecular strips. This result leads to a micromolar affinity for the longest strip **7** with **P[5]** and also confirms our hypothesis that **4**, **5**, and **7** are indeed bound to the outside of **P[5]**, a process driven by solvophobic and π–π stacking interactions.

To further explore how our molecular strips recognize **P[5]**, we employed molecular dynamics (MD) simulations with the OPLS2005 force field. Both **P[5]@4** and **P[5]@7** were found to be stable in four independent 40 ns simulations (see the Supporting Information). We were also able to observe the detailed dynamic processes involved in the binding of **7** to **P[5]** through binding experiments in silico, starting with completely separated **7** and **P[5]** in a periodic box. Our construct, which contains three free molecules of **7** and **P[5]** in a CH_3CN/H_2O solvent mixture (5:1, v/v), was simulated with two replicas. Both simulations showed that at least one **P[5]@7** complex formed within 60 ns. For example, in one simulation, a strip started to wrap around a pillararene macrocycle after a 30 ns long search (Figure 2b). As soon as the **P[5]@7** complex was formed, it remained stable with maximized π–π stacking for the rest of the simulation, as indicated by the small centroid distance and axis angle. These MD simulation results are in good agreement with our NMR data and suggest that the recognition between our strips and **P[5]** is stable and specific.

The binding of **4** and **7** to the outside of **P[5]** leaves the central cavity of the pillararene open for supramolecular complexation with a third guest. Our molecular strips thus have the potential to act as synthetic regulatory agents that are capable of fine-tuning the recognition of macrocyclic hosts with a variety of guests. To investigate this possibility, we titrated bis(octyl)viologen dibromide (**VBr-1**) into CD_3CN/D_2O (5:1, v/v) solutions of **P[5]@4** and **P[5]@7**. The resulting changes[22] in the ^{1}H NMR chemical shifts (Figure 3) revealed that surrounding **P[5]** with **4** or **7** actually leads to significantly enhanced[23] affinities for **VBr-1** to bind inside[24] the cavity of **P[5]**. Remarkably, this effect of positive cooperativity in a rare[25] ternary supramolecular complex also seems to increase in magnitude with increasing elongation of the molecular strip.[26] Accordingly, our finding opens the door to

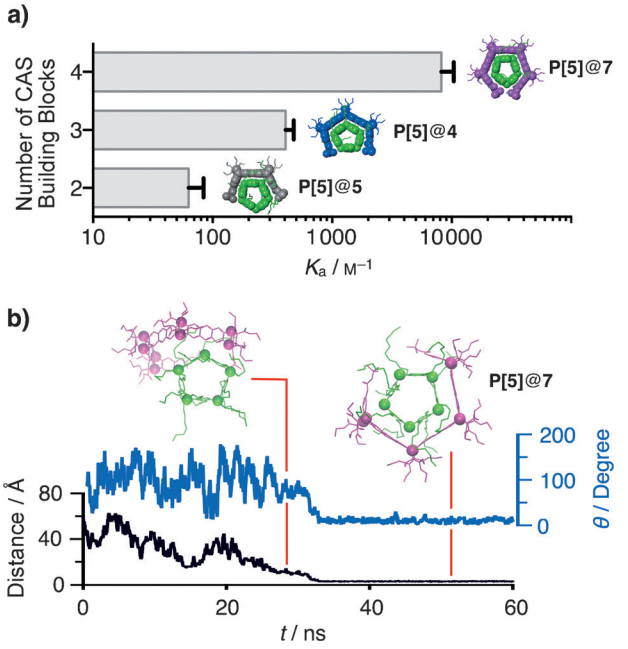

Figure 2. a) Plot of the experimental association constants, K_a, versus the strip size for supramolecular complexes formed between **P[5]** and the molecular strips **4**, **5**, and **7**. All K_a values were determined by ^{1}H NMR titrations in CD_3CN/D_2O solution (5:1, v/v) at 298 K (see the Supporting Information). Error bars represent the standard errors of the non-linear least squares regression analyses. b) Graphical illustration of an MD binding experiment between molecular strip **7** and **P[5]**, using all-atom MD simulations. In the initial model, **P[5]** and **7** were over 5 Å apart in a 9×9×9 nm^3 periodic box, containing CH_3CN/H_2O (5:1, v/v) as the solvent. The Figure illustrates the time evolution of 1) the distance between the strip and ring centroids as well as 2) the angle (θ) between the central axes of strip **7** and the **P[5]** ring. Binding occurs after approximately 30 ns, as indicated by the drop in both the distance and the angle. The points in time to which the snapshots of the binding transition and the stable complex structure correspond are indicated by red lines.

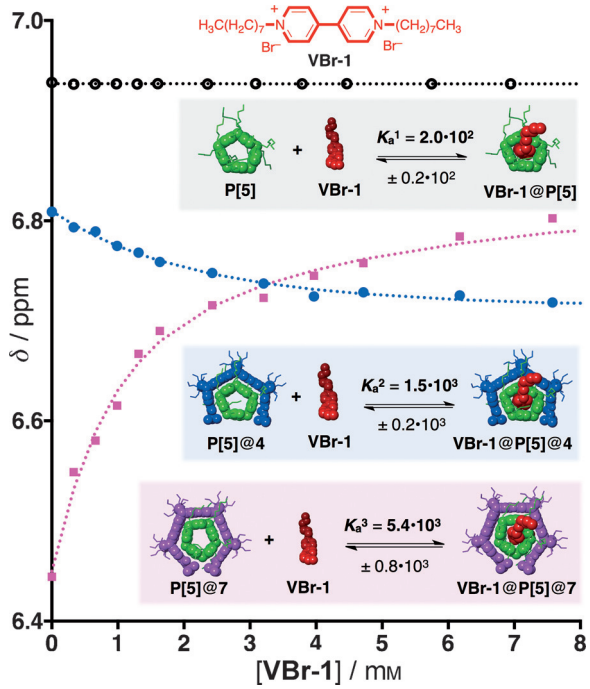

Figure 3. The binding of **VBr-1** to the cavity of **P[5]** is modulated in a cooperative sense by the molecular strips **4** and **7** embracing **P[5]**. The observed changes in the **VBr-1@P[5]** association constants K_a1, K_a2, and K_a3 are illustrated by plotting the mean ^{1}H NMR (500 MHz, CD_3CN/D_2O (5:1, v/v), 298 K) chemical shift of the aromatic protons of **P[5]** against the **VBr-1** concentration. All values and standard errors for the binding constants are given in M^{-1}. Binding constants were obtained (see the Supporting Information) by non-linear fitting to the chemical shifts of multiple protons attached to **P[5]** and, if applicable, **4** or **7**.

a new fundamental dimension of synthetic supramolecular chemistry, where traditional host–guest interactions can be modulated in predictable ways with embracing regulatory receptors.

In summary, we have introduced chirality-assisted synthesis as an effective means to precisely control the shapes of large molecular strips. As illustrated by ^{1}H NMR spectroscopy and MD simulations, our preorganized structures bind to the outside of pillar[5]arene macrocycles in a novel complexation mode, which is stabilized by π–π stacking interactions and solvophobic effects. By embracing a pillararene macrocycle, the strips act as modulators that increase the affinity of electron-deficient guests to bind inside the cavity of the macrocycle. Thus our findings not only provide access to a new synthetic method for precise nanoscale shape control, but also open the door to enhanced supramolecular interactions, with traditional macrocyclic hosts becoming guests of even larger preorganized materials. We are currently working towards the chirality-assisted synthesis of general molecular strips, which may act as catalysts to site-selectively modify man-made and biological polymers.

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[14] The absolute configuration of (*S*,*S*)-**1** was assigned by comparing experimental and calculated (B3LYP/6-31G*) vibrational circular dichroism spectra (see the Supporting Information).

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[17] Although this initial protection step resulted in a statistical mixture of 1) starting material **1** (19%), 2) mono-Boc-protected *N*-Boc-**1** (54%), and 3) the di-Boc-protected analogue *N*,*N*-diBoc-**1** (27%), simple, high-yielding deprotection and recycling of the *N*,*N*-diBoc-**1** side product further increased the overall yield of *N*-Boc-**1** to 79%.

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[20] As **7** was present as a single enantiomer and **P[5]** as a racemic mixture of interconverting enantiomers (see: N. L. Strutt, S. T. Schneebeli, J. F. Stoddart, *Supramol. Chem.* **2013**, *25*, 596 – 608), two diastereoisomeric complexes with distinct chemical shifts, namely (S_P,S_P,S_P,S_P,S_P)-**P[5]@7** and (R_P,R_P,R_P,R_P,R_P)-**P[5]@7**, were likely formed in this case. Integration of the corresponding ^{1}H NMR resonances indicated that both diastereoisomeric complexes were present in approximately equal amounts. Therefore, no significant induction of planar chirality was observed for **P[5]** upon complexation with the chiral strips.

[21] When titrating *N*,*N*′-diBoc-**1** into a CD_3CN/D_2O solution (5:1, v/v) of **P[5]**, no detectable changes in the ^{1}H NMR chemical shifts were observed, neither for the proton resonances of **P[5]**, nor for the ones of *N*,*N*′-diBoc-**1**. Consequently, this result rules out the possibility that the Boc protecting groups of strips **4** and **7** are simply binding to the cavity of **P[5]**.

[22] The aromatic ^{1}H NMR resonances of pillararenes generally shift downfield upon binding to viologens (see Ref. [18b]). Our results are consistent with this trend given the fitted (see the Supporting Information) aromatic **P[5]** proton resonances of 6.15 ± 0.01 ppm for **P[5]@4**, 6.24 ± 0.04 ppm for **VBr-1@P[5]@4**, 3.90 ± 0.02 ppm for **P[5]@7**, as well as 6.53 ± 0.03 ppm for **VBr-1@P[5]@7**. The apparent upfield shift of the resonances of the aromatic **P[5]** protons in the presence of **4** (Figure 3) is simply caused by the positive cooperativity, which leads to an increased fraction of **P[5]** bound to **4** upon addition of **VBr-1**.

[23] We observed an association constant for the **VBr-1@P[5]** complex of ca. $200\,M^{-1}$ in CD_3CN/D_2O (5:1, v/v). This value is lower than what has been reported previously for the same complex in pure water (see Ref. [18b]), indicating that hydrophobic effects might be a significant driving force for the binding of **VBr-1** to **P[5]**.

[24] To 1) confirm that **VBr-1** is indeed binding inside the cavity of **P[5]** in the ternary complexes and 2) rule out significant changes in the **P[5]@4** and **P[5]@7** association constants caused by changes in salt concentration, we also titrated sterically hindered bis(3,5-dimethylbenzyl)viologen dibromide (**VBr-2**) into a solution of **P[5]@4** in CD_3CN/D_2O (5:1, v/v). Consistent with our hypothesis, no changes in the ^{1}H NMR chemical shifts were observed (see the Supporting Information) for these negative control experiments, as the 3,5-dimethylbenzyl substituents of **VBr-2** are too large to allow for the sliding of **VBr-2** into the cavity of **P[5]**.

[25] T. Kawase, K. Tanaka, N. Shiono, Y. Seirai, M. Oda, *Angew. Chem. Int. Ed.* **2004**, *43*, 1722 – 1724; *Angew. Chem.* **2004**, *116*, 1754 – 1756.

[26] Whereas the physical reasons for these observations are still under investigation, the positive cooperativity could be of an entropic nature; binding of the clips to the outside of a pillararene likely rigidifies the macrocycle, which would reduce the loss of entropy upon complexation with viologen.

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