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Hybrid [*n*]Arenes through Thermodynamically Driven Macrocyclization Reactions

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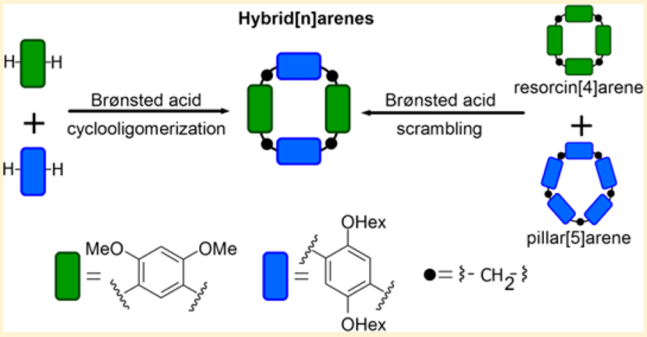
Supporting Information

ABSTRACT: Hybrid [*n*]arenes, the class of medium-sized macrocyclic compounds consisting of different alkoxybenzene units, were obtained by a simple, one-pot, direct condensation of two different alkoxybenzenes with formaldehyde catalyzed by a Brønsted acid (trifluoroacetic acid). We have shown that, under Brønsted acid catalysis, this reaction is reversible and therefore governed by the relative stability of the products. The main macrocyclic products are hybrid [*n*]arenes consisting of four alkoxybenzene units of [2 + 2] or [3 + 1] stoichiometry. However, an unusual [3 + 2] hybrid macrocycle was also obtained as a main product of the condensation between 1,4-dimethoxybenzene, 1,3,5-trimethoxybenzene, and formaldehyde. The stability of the hybrid products and the reversibility of the reaction were further confirmed by a scrambling experiment, involving pillar[5]arene and per-*O*-methylated resorcin[4]arene. The scrambling experiment has given hybrid macrocycles in yields comparable with those obtained in condensation reactions. NMR spectra and X-ray structures of hybrid [*n*]arenes indicate that 1,2- and 1,3-dialkoxybenzene units are flexible parts of macrocyclic rings. However, the 1,4-dialkoxybenzene units present considerable steric hindrance, resulting in the formation of isomers and inherently chiral macrocycles due to inhibited rotation. The recognition properties toward various organic cations were also determined. Highly selective recognition of the *N*-methylpyridinium cation was observed for the [3 + 2] hybrid macrocycle.



INTRODUCTION

The discovery[1−4] and realization of the potential[5,6] of cyclic phenolic oligomeric compounds called calix[*n*]arenes was undoubtedly one of the milestones for supramolecular chemistry. On the basis of their skeleton, many supramolecular functional architectures have been constructed.[7−10] As it seemed the pool of basic macrocyclic skeletons was complete, surprisingly, in 2008, a new, very simple macrocylic polyphenolic building block was discovered. Ogoshi et al. presented the pillar[5]arene, a simple macrocylic product of the reaction between 1,4-dimethoxybenzene and formaldehyde.[11] More recently, Schneebeli et al. obtained the family of asar[*n*]arenes,[12] and Chen et al. obtained biphen[*n*]arenes.[13] During a very short period of time, many groups reported numerous applications of these new macrocycles including sensing,[14−17] construction of rotaxanes,[18−20] supramolecular polymers,[21−24] switches,[25−27] or artificial channels.[28] Such a great interest indicates that new semirigid supramolecular scaffolds having cavities that may serve as binding pockets are still sought after.

Cyclic oligomers of phenols are commonly obtained by condensation between alkoxybenzenes or hydroxybenzenes with aldehydes. Calix[*n*]arenes and resorcin[4]arenes, featuring free OH groups, are readily prepared from the corresponding phenolic monomers by a condensation of the respective hydroxybenzenes with a large range of aldehydes using Brønsted acid or Brønsted base catalysis. Other macrocycles, for example, cyclotricatechylenes or pillar[5]arenes, cannot be obtained directly from phenolic precursors. Instead, they have to be obtained through their *O*-alkylated derivatives by Lewis acid catalyzed condensation of alkoxybenzenes with aldehydes (e.g., $BF_3 \bullet Et_2O$,[29] $SnCl_4$,[30] or $Sc(OTF)_3$[31,32]). Brønsted acids can also be successfully used as catalysts for the formation of cyclic products from alkoxybenzenes and aldehydes as shown by the work of Moravcová and co-workers,[33] Moore et al.,[34] as well as Weinelt and Schneider.[35] A strategy utilizing benzyl alcohols as surrogates of aldehyde functions has also been reported for synthesis of *O*-alkylated derivatives, for example, octamethoxyresorcin[4]arenes[36] or phlouroglucinols,[37] using trifluoroacetic acid (TFA) as a catalyst. Recently, we have also found out that pillar[5]arenes can be synthesized by a Brønsted acid mediated direct reaction of alkoxybenzene and formaldehyde.[38] The important finding was that the reaction is reversible under Brønsted acid catalysis (TFA in that case). Therefore, thermodynamic stability of the products is of crucial importance for the reaction outcome. In the case of deca-*O*-alkylpillar[5]arenes, solvent molecules (dichloromethane or 1,2-dichloroethane but not $CHCl_3$) effectively template the synthesis of pillar[5]arenes by a combination of hydrogen···π

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and halogen···π bonds. Other reports have also suggested that, under highly acidic conditions, the reaction of alkoxybenzenes with aldehydes is thermodynamically controlled.[39] For example, Urbaniak and Iwanek have shown that octa-*O*-alkylresorcin-[4]arenes can be postsynthetically isomerized in the presence of TFA.[40] It should be noted that these observations have only been applied to the synthesis of known macrocycles (also available by other condensation methods) and have not been used thus far for obtaining new macrocyclic scaffolds. In the current paper, we show that thermodynamically controlled reactions of various alkoxybenzenes with formaldehyde can be used for effective formation of new hybrid macrocycles.

RESULTS AND DISCUSSION

Synthesis. In the current approach, we have combined two different alkoxybenzenes (**1**−**4**, Figure 1) with formaldehyde in one-pot reactions. In a typical experiment, two different polyalkoxybenzenes were mixed in 0.1 M/0.1 M ratio with an equimolar amount of paraformaldehyde (0.2 M) in TFA/chloroform (5−20% v/v). By applying this procedure, [2 + 2] hybrid macrocycles **5**−**9** and **13** were obtained as the main products in 26 ÷ 53% yields (Table 1 and Figure 2). It should

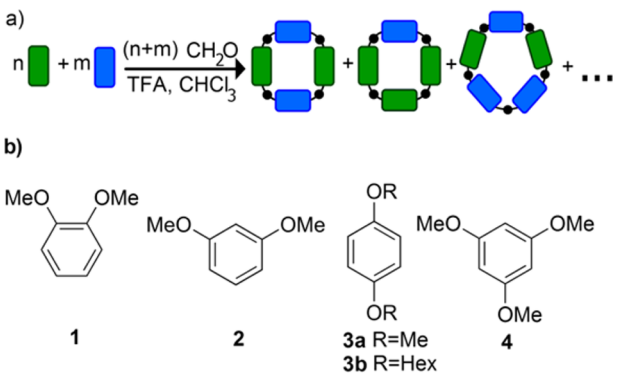

Figure 1. (a) Synthesis of hybrid macrocycles; (b) substrates used in macrocyclization reactions.

Table 1. Synthesis of Macrocycles 5−12 Using Two Different Substrates with Yields Given in Parentheses

substrate	1	2	3a/3b
1	**10** (85%)	**8** (40%) **9** (47%)	–[a]
2		**11** (85%)	(**5** + **6**) (53%) **7** (26%)
3a/3b			**12** (85%)

[a]No defined products detected.

be noted that the current yields can be considered quite high for macrocyclization reactions. For comparison, asar[*n*]arenes[12] were obtained in yields up to 12%, and biphen[*n*]arenes[13] were obtained in yields up to 22%. In the case of 1,3-dimethoxybenzene and 1,4-dihexoxybenzene, a mixture of two [2 + 2] products (**5** and **6**) was obtained in 53% total yield. The products proved to be diastereoisomers (for the structural explanation, see the next section). Although our initial approach concentrated on macrocycles having the same number of units of each type, in some cases, in addition to the expected [2 + 2] products, we observed formation of considerable amounts of less symmetrical macrocycles. In order to improve the yields of their formation, the stoichiometry of

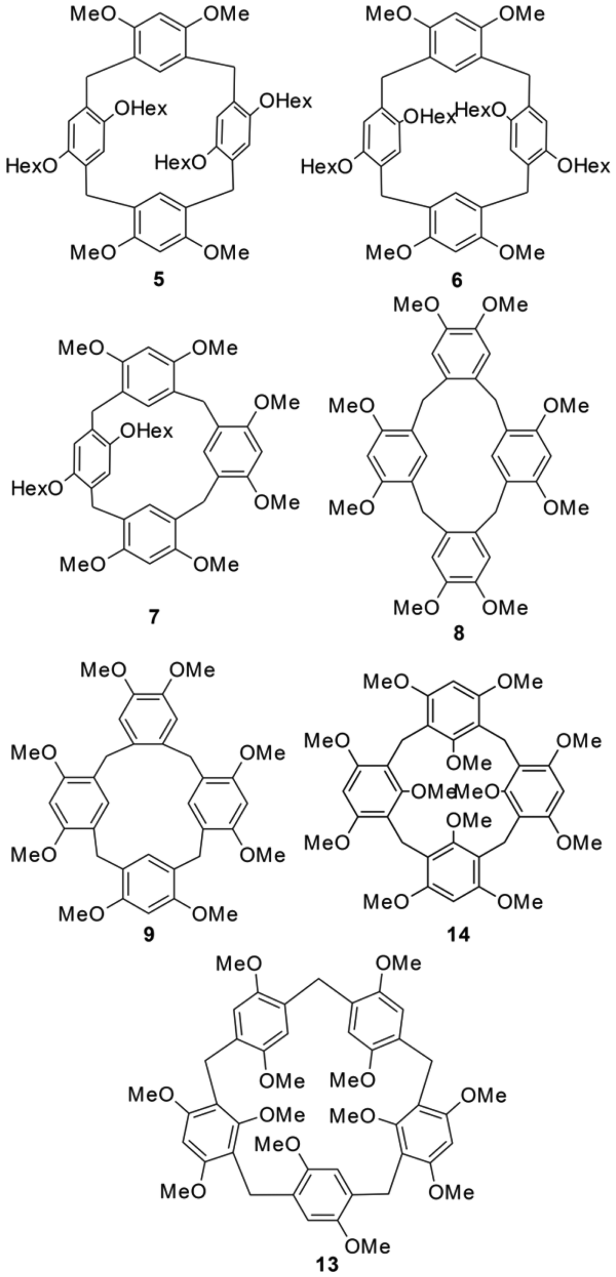

Figure 2. Hybrid [*n*]arenes obtained by one-pot macrocyclization reactions.

reagents was modified accordingly. In this way, the [3 + 1] macrocycle **9**, consisting of three 1,3-dimethoxybenzene units and one 1,2-dimethoxybenzene, was obtained in 47% yield, and macrocycle **7** containing three 1,3-dimethoxybenzene units and one 1,4-dihexoxybenzene unit was obtained in 26% yield. Interestingly, an unusual [3 + 2] stoichiometry was observed for the condensation of 1,3,5-trialkoxybenzene **4** and 1,4-dimethoxybenzene **3a** yielding macrocycle **13** as a main product (35% yield). It should also be noted that nonhybrid macrocyclic products, containing only one type of alkoxybenzene unit, like knowns **10**, **11**, and **12**, are also obtained in high yields (85%) using this procedure.

The synthetic approach described assumes that the macrocyclization reaction is reversible under the current conditions and the hybrid products are thermodynamically preferred. To prove the reversibility of the reaction, we performed a control

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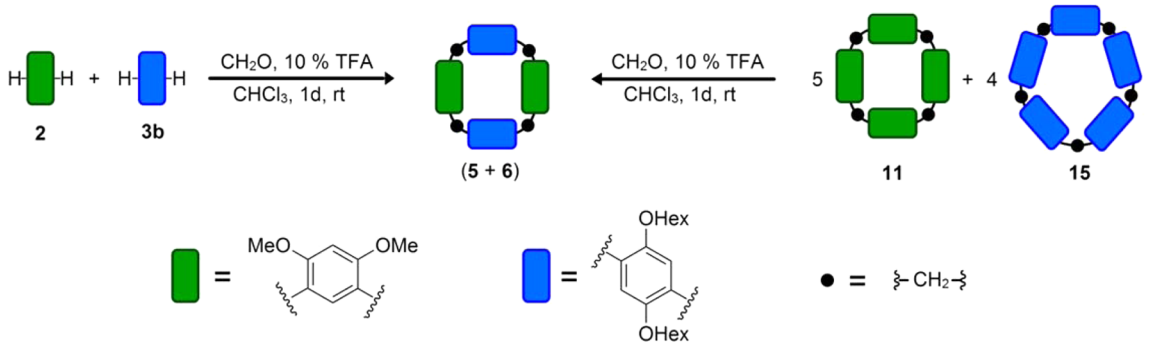

Figure 3. Scrambling experiment.

"scrambling" experiment (Figure 3). Two macrocyclic products, pillar[5]arene (**15**) and methoxyresorcin[4]arene (**11**), were used as substrates. In the presence of TFA and formaldehyde, the reaction between **11** and **15** yielded the hybrid diastereoisomeric products **5** and **6** in 53% yield (isolated product), while the initial macrocycles were completely used up. This result proves that the reaction is reversible and the distribution of the products is thermodynamically controlled. Moreover, it is the first example of scrambling between alkoxybenzene-type macrocycles. Additionally, ^{1}H NMR spectra of the crude reaction mixtures (containing all products) in the diagnostic ranges (7−5.8 ppm, range of aromatic protons; 4.40−3.40 range of methylene and alkoxy protons) are highly similar (Figure S36, Supporting Information). It is important to note that addition of a portion of formaldehyde is required for the scrambling reaction to proceed. This result indicates that the presence of a suitable amount of "free" formaldehyde is crucial for the effective equilibration of the first step of the reversible Friedel−Crafts reaction. Therefore, it may be supposed that, under the current conditions, equilibration is reasonably fast only at the early stages of the macrocyclization reaction. However, after the free formaldehyde is used up, equilibration may be too slow to be effective.

The wide range of substrates successfully converted into macrocycles shows that the current conditions are applicable for obtaining various O-alkylated hybrid [*n*]arenes in a direct way. We have also tested if the current procedure can be applied for substrates featuring free OH groups. Such macrocycles are highly desirable, since they can be readily functionalized. The reactions of 1,2-, 1,3- or 1,4-dihydroxybenzene or phlorogluocinol with formaldehyde under our standard conditions ($CHCl_3$, TFA) or under literature conditions ($MeOH/H_2O/HCl$) failed to give macrocyclic products. These results show that hybrid macrocycles featuring free OH groups cannot be synthesized directly but only via the respective alkoxy derivatives.

Conformational Features. The hybrid approach can be a powerful method for obtaining macrocycles with modulated shapes.[41−46] In the current case, the macrocyclic rings obtained by the hybrid approach have medium sizes (14÷23-membered rings). Such rings exhibit various degrees of flexibility resulting in diverse conformational and even configurational features. A spectacular manifestation of inhibited ring rotation is observed in the case of macrocyles **5** and **6** that were synthesized in the reaction between **2**, **3a**, and formaldehyde. The isomers were chromatographically separated (1:2 ratio) and analyzed by NMR and X-ray crystallography. Isomers **5** and **6** proved to have the same number of signals in the NMR spectra in agreement with either D_2 or C_{2h} symmetry. Considering the size of the macrocyclic ring (18-membered) and its relative rigidity, we assumed that the observed isomerism comes from inhibited rotation of 1,4-dialkoxy units through the macrocyclic ring (Figure 4a).

Our hypothesis was confirmed through analysis of splitting in ^{1}H NMR spectra and X-ray crystallography. Two separate signals were observed for hydrogen atoms of methylene bridges with characteristic geminal coupling constants (Figures S1 and S4, Supporting Information). X-ray analyses indicate that, for both **5** and **6**, 1,3-dialkoxy units (green, Figure 4b, c) are coplanar and parallel to the main macrocyclic plane (defined by four methylene bridges), while 1,4-dialkoxy units (blue, Figure 4b, c) are perpendicular to the main macrocyclic planes. Van der Waals representation of molecules of **5** and **6** shows that there is almost no room inside the macrocyclic rings of **5** and **6** (Figure 4b). Even assuming that 1,3-dialkoxy units can rotate out of the plane of the macroring, the short distance between 1,4-dialkoxy units (5.0 Å) fixes their relative positions. The stability of the isomers has been experimentally confirmed by their successful chromatographic separation and the fact that they do not interconvert in $CDCl_3$ solution even after a few weeks. It is also interesting to note that **5**, which has D_2 symmetry, is inherently chiral (although currently only obtained as a mixture of enantiomers).

For **7**, the presence of only a single 1,4-dialkoxybenzene unit (Figure 5) results in a partially averaged geometry (as seen in the NMR spectra, Figure S6, Supporting Information). Hydrogen atoms of the methylene bridges positioned next to 1,4-dihexoxybenzene are differentiated and exhibit a geminal coupling (J = 15.9 Hz). On the other hand, signals of methylene hydrogen atoms that are positioned between 1,3-dimethoxybenzene units appear as a singlet in the ^{1}H NMR spectrum. The X-ray structure of **7** shows a distorted "boat" conformation of the macrocyclic ring (Figure 5b). The molecule of **7**, even in the idealized boat conformation, is devoid of symmetry elements, rendering all methylene protons diastereotopic. Thus, averaging of some signals of methylene protons can be explained by fast flipping of 1,3-dimethoxybenzene units. However, the splitting of the signals of the two other methylene groups units at room temperature indicates a lack of rotation and suggests chirality of **7**.

For the compounds that do not contain 1,4-dialkoxybenzene units, for example, **8** and **9** (Figure 3), the flexibility of the macrocyclic rings is much higher. In the case of **8** and **9**, their ^{1}H and ^{13}C NMR spectra contain a reduced number of signals, and the methylene bridges appear as singlets (for **9**) or as a broad singlet (for **8**) (Figures S11−S13, S15, and S16,

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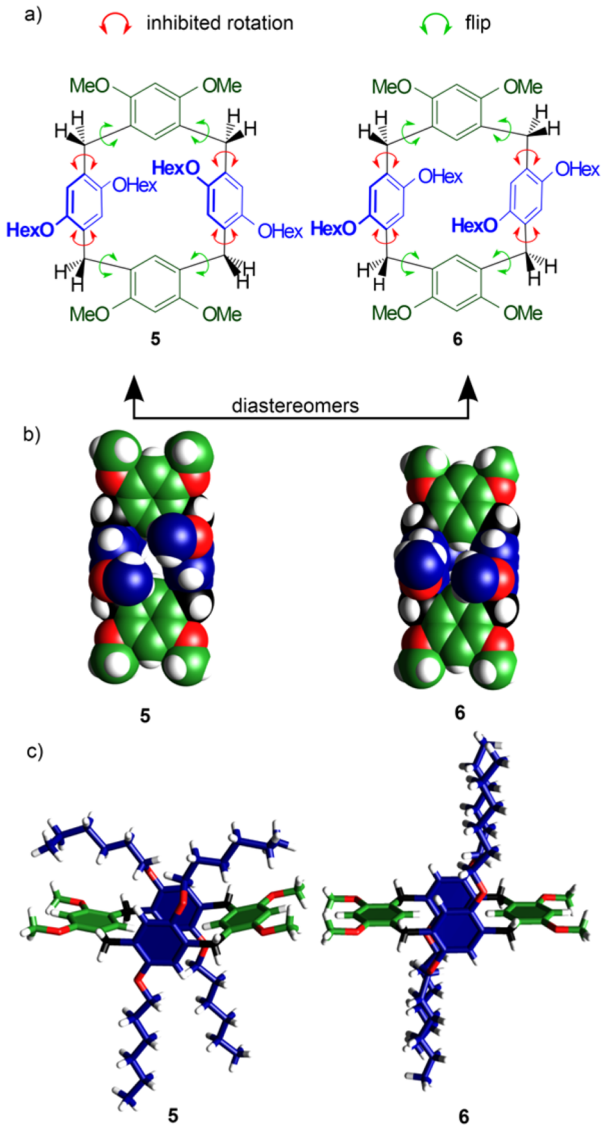

Figure 4. (a) Conformational features of **5** and **6**; (b) van der Waals representations of macrocyclic rings of **5** and **6** (X-ray structures; atoms of *n*-hexyl groups were removed for clarity); (c) X-ray structures of **5** and **6** in stick representations (green: 1,3-dimethoxybenzene units; blue: 1,4-dihexoxybenzene units).

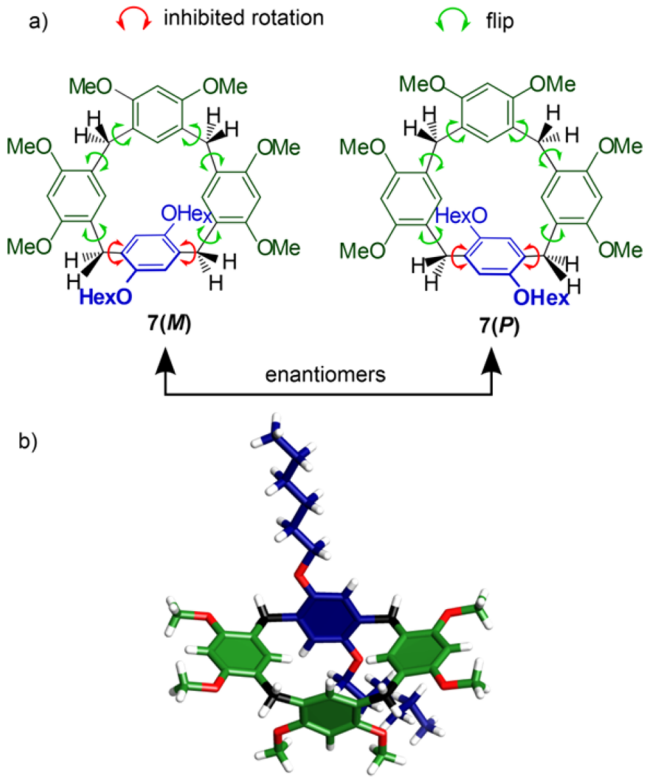

Figure 5. (a) Conformational features of **7**; (b) X-ray structure of **7**.

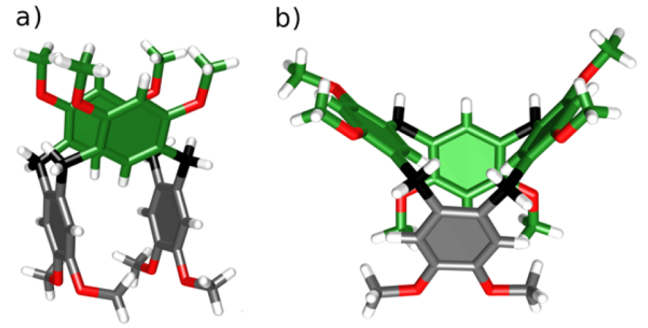

Figure 6. X-ray structures of (a) **8** and (b) **9** (green: 1,3-dimethoxybenzene units; gray: 1,2-dimethoxybenzene units).

Supporting Information). The X-ray structures indicate that both macrocyclic rings exhibit boat conformations in the solid state (Figure 6). Analysis of the ring distances suggests that a full rotation of any of the aromatic rings through the macroring is not possible. However, partial flipping of all aromatic rings is probable, resulting in averaging of the NMR signals. Similar dynamic behavior was also observed for [3 + 2] macrocycle **13** being the largest macrocycle obtained. In this case, all signals for protons of the methylene bridges are singlets (Figure S18, Supporting Information). The halving of the number of signals ($^1/_2$) is in agreement with dynamically averaged C_{2v} symmetry.

The X-ray structure of **13** shows the presence of a molecular cavity that is filled with a solvent guest molecule (MeCN in this case, Figure 7). The mode of interaction between the host and the guest is typical for electron-rich cavitands and involves complexation of hydrophobic CH_3 groups inside the aromatic cavity. Three out of five neighboring aromatic rings form a pocket for guest binding with short $C_{MeCN}\cdots centroid_{ring}$ distances of 3.7, 3.6, and 3.7 Å. A short C−H···N intramolecular distance is also observed between N (MeCN) and the OCH_3 group of the symmetry-related molecule (N···C 3.2 Å).

Summing up the conformational features of the new macrocycles, it can be noticed that 1,2- and 1,3-dialkoxy units can easily flip even across relatively small macrocyclic rings. However, the 1,4-dialkoxy unit presents considerable steric hindrance. For some macrocyclic rings, rotation of this unit is not possible. Therefore, formation of various isomers can be observed, and symmetry features of this unit may even generate inherent chirality of the macrocycles.

Recognition Properties. The recognition properties of the synthesized macrocycles were tested using guests **16**−**19** containing imidazolium- and pyridinium-type ions (Figure 8). The guest molecules were chosen using the criterion of importance (based on the extensive presence of imidazolium and pyridinium fragments in bioactive substances and in structural motifs of mechanically bound molecules) and

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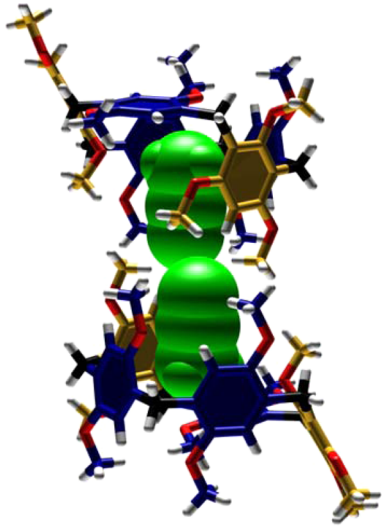

Figure 7. X-ray structure of **13** with MeCN inside the cavity (blue: 1,4-dimethoxybenzene units; gold: 1,3,5-trimethoxybenzene units; MeCN in van der Waals representation).

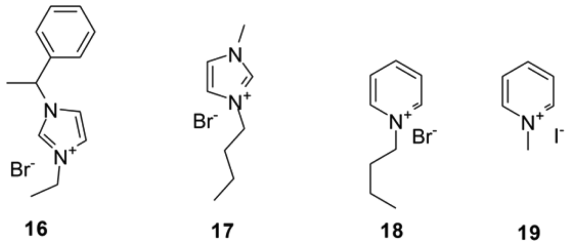

Figure 8. Guest molecules.

favorable noncovalent interactions between electron-rich alkoxybenzene walls of the host molecules with guests being organic cations.

Association constants were determined by ^{1}H NMR titration followed by nonlinear curve fitting as implemented in HYPNMR.[47] All signals that exhibited detectable changes of chemical shifts were fitted simultaneously. The reasonable fits have only been obtained by assuming formation of 1:1 and 1:2 (H/G) complexes. The results indicate that, in all cases, macrocycles **5**–**9** exhibited high binding constants of positively charged organic ions (Table 2), albeit with low selectivity. A notable exception is the largest macrocycle **13**. For **13**, no detectable interaction with guests **16**–**18** was observed. On the other hand, **13** interacts selectively with *N*-methylpyridinium iodide **19** (Figure 9). *N*-Methylpyridinium iodide **19** has a very limited solubility in $CDCl_3$. However, upon gradual addition of **19** to the solution of macrocycle **13**, dissolution up to 1 equiv of guest **19** was observed, and substantial changes in the ^{1}H NMR spectra were recorded. Upon further addition of **19**, the excess amount of guest remained undissolved. Analysis of complexation induced shifts indicated that the signals of hydrogen atoms positioned *ortho* to the nitrogen atom were substantially upfield shifted (>−2.8 ppm) in agreement with deep inclusion of this part in the aromatic cavity (Figure S51, Supporting Information). On the contrary, the signals of hydrogen atoms positioned *para* were only slightly affected by complexation indicating that this part of the molecule is not surrounded by the aromatic walls. Considerable changes were also observed for the signals of the macrocycle, suggesting a conformational change upon complexation.

Table 2. Association Constants between Hosts (5–9) and Guests (16–18)[a]

host		guest		
		16	**17**	**18**
5	$\log\beta_1$	2.48	2.78	2.44
	$\log\beta_2$	4.95	5.58	4.70
6	$\log\beta_1$	2.60	2.92	2.29
	$\log\beta_2$	4.79	5.59	4.69
7	$\log\beta_1$	2.56	2.76	2.27
	$\log\beta_2$	5.02	4.92	4.66
8	$\log\beta_1$	1.82	1.73	n.d.
	$\log\beta_2$	n.d.	n.d.	n.d.
9	$\log\beta_1$	2.33	2.67	n.d.
	$\log\beta_2$	4.62	4.73	n.d.

[a]n.d.: not detectable.

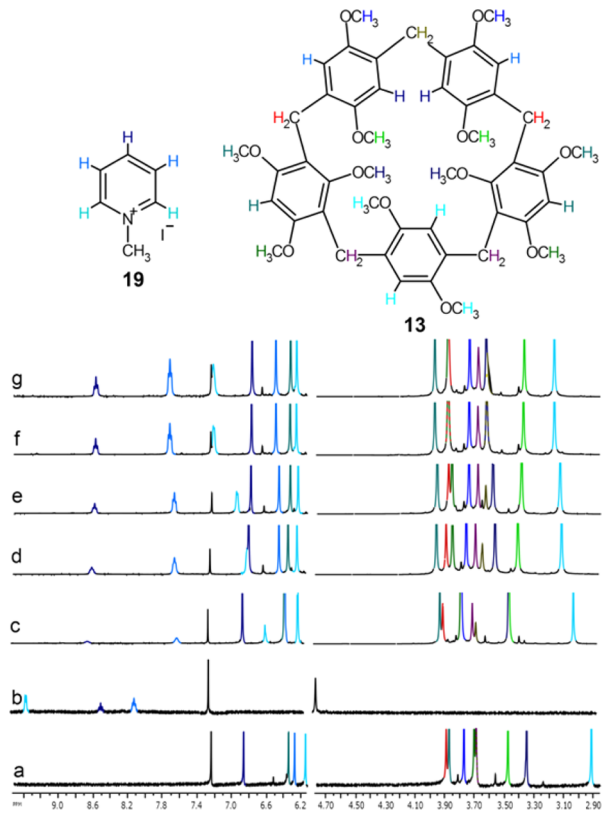

Figure 9. Complexation of **19** by **13**. ^{1}H NMR spectra of (a) **13**, (b) saturated solution of **19**, (c) **13** + **19** (0.25 equiv), (d) **13** + **19** (0.5 equiv), (e) **13** + **19** (0.75 equiv), (f) **13** + **19** (1 equiv), (g) **13** + **19** (excess) in $CDCl_3$ at 298 K.

CONCLUSIONS

It is commonly perceived that even simple macrocyclic products can present a considerable synthetic challenge due to the numerous complications in their synthesis and often low cyclization yields. Therefore, the number of easy-to-prepare macrocyclic scaffolds is quite limited. On the other hand, there is a continuing need for new semirigid macrocyclic compounds for the construction of new supramolecular systems. In this paper, we have shown that construction of new cyclic phenolic oligomers can be effectively achieved by a hybrid approach. It

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would seem that such an approach has much less chance of success than the synthesis macrocycles consisting of identical units. However, we have proven that, by using thermodynamically driven acid-catalyzed condensations, it can be very effective. The obtained products extend the pool of relatively easy available macrocycles for various applications in supramolecular chemistry. We predict that the rich chemistry of the phenolic group, including O-substitution, allows for easy functionalization of the currently obtained skeletons for their further modifications. Presence of two different types of units in one macrocycle allows for potential applications as "biased" supramolecular structures,[48,49] and differentiation of reactivity enables selective introduction of orthogonal or multiple functions.

EXPERIMENTAL SECTION

General Procedures. *Procedure A.* To a solution of polyalkoxybenzene A (10 mmol) in $CHCl_3$ (50 mL), paraformaldehyde (10 mmol) and TFA (5 mL) were added. The reaction was refluxed for 2 h. During the reaction, the color of the mixture changed from colorless to dark purple, dark blue, or dark green (depending on a specific substrate). The reaction was cooled down to room temperature (rt), and excess of Na_2CO_3 was added to neutralize the TFA. The mixture was filtered off and evaporated to dryness. The products were isolated by chromatography (30 g of silica gel, $CHCl_3$/ethyl acetate or hexane).

Procedure B. To a solution of polyalkoxybenzene A (5 mmol) and B (5 mmol) in $CHCl_3$ (50 mL), paraformaldehyde (10 mmol) and TFA (5 or 20 mL) were added. The reaction was refluxed (2 h to 4 days), and the progress was monitored by thin-layer chromatography (TLC). During the reaction, the color of the mixture changed from colorless to dark purple, dark blue, or dark green (depending on a specific set of substrates and conditions). The reaction was cooled down to rt, and an excess of Na_2CO_3 was added to neutralize the TFA. The mixture was filtered off and evaporated to dryness. The products were isolated by chromatography (50−200 g of silica gel, $CHCl_3$/ethyl acetate or hexane). After chromatography, some products were recrystallized from acetone or MeCN.

Procedure C. To a solution of polyalkoxybenzene A (7.5 mmol) and B (2.5 mmol) in $CHCl_3$ (50 mL), paraformaldehyde (10 mmol) and TFA (2.5 or 10 mL) were added. The reaction was refluxed (2 h to 4 days), and the progress was monitored by TLC. During the reaction, the color changed from colorless to dark purple, dark blue, or dark green (depending on specific substrates). The reaction was cooled down to rt, and an excess of Na_2CO_3 was added to neutralize the TFA. The mixture was filtered off and evaporated to dryness. The products were isolated by chromatography (silica gel, $CHCl_3$/ethyl acetate or hexane). After chromatography, some products were recrystallized from acetone or MeCN.

Scrambling Procedure. To a solution of *per*-hexoxypillar[5]arene **15**, (0.584 g, 0.4 mmol) and *per*-methoxylresorcin[4]arene **11** (0.300 g, 0.5 mmol) in $CHCl_3$ (50 mL) and TFA (10 mL), paraformaldehyde (20 mg) was added. The reaction was refluxed for 1 day, and the progress was monitored by TLC and NMR. During the reaction, the color changed from colorless to dark purple. After 1 day, the reaction was cooled down to rt, and an excess of Na_2CO_3 was added to neutralize the TFA. The mixture was filtered off and evaporated to dryness. The products (**5** and **6**) were isolated by chromatography as a mixture of diastereoisomers (silica gel, first hexane/$CHCl_3$ 1:1, next gradient $CHCl_3$−$CHCl_3$/ethyl acetate 100:1). Yield: 42%, 0.371 g.

Compounds **5** and **6**: Obtained from **3b** (0.69 g) and **2** (1.39 g) by procedure B (5 mL of TFA; 2 h). Purified by chromatography (200 g of silica gel; eluent: first, hexane/$CHCl_3$ 1:1, next gradient, $CHCl_3$−$CHCl_3$/ethyl acetate (100:1)). Yields: **5**: 0.39 g (36%); **6**: 0.78 g (17%).

Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$-*d*): 6.52 (4H, s); 6.49 (2H, s); 6.03 (2H, s); 6.15 (4H, d, *J* = 16 Hz); 3.91 (12H, s); 3.74 (4H, q); 3.50 (4H, q); 3.43 (4H, d, *J* = 16 Hz); 1.48 (24H, m); 0.84 (6H, t). ^{13}C NMR (100 MHz, $CDCl_3$-*d*): 155.5; 151.5; 127.4; 127.2; 121.2; 116.6; 94.3; 69.4; 55.7; 31.5; 29.7; 29.4; 28.9; 25.6; 22.6; 14.0. ESI q-TOF MS: $C_{56}H_{81}O_8$ calcd.: 881.5931, found: 881.5940.

Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$-*d*): 6.54 (4H, s); 6.51(2H, s); 6.02 (2H, s); 4.13 (4H, d, *J* = 15.9 Hz); 3.91 (12H, s); 3.71 (4H, q); 3.46 (8H, m); 1.48 (8H, m); 1.18 (24H, m); 0.84 (12H, t). ^{13}C NMR (100 MHz, $CDCl_3$-*d*): 155.5; 151.6; 127.4; 127.0; 121.2; 116.5; 94.2; 69.4; 55.7; 31.7; 29.6; 28.8; 25.6; 22.6; 14.0. ESI q-TOF MS: $C_{56}H_{81}O_8$ calcd.: 881.5931, found: 881.5928.

Compound **7**: Obtained from **2** (1.02 g) and **3b** (compound B, 0.696 g) by procedure B (5 mL of TFA; 2 h). Purified by chromatography (200 g of silica gel; eluent: first, hexane/$CHCl_3$ 1:1, next gradient $CHCl_3$−$CHCl_3$/ethyl acetate (100:2)). Yield: 0.57 g (26%). ^{1}H NMR (500 MHz, $CDCl_3$-*d*): 6.76 (1H, s); 6.51 (2H, s); 6.50 (2H, s); 6.40 (1H, s); 6.00 (2H, s); 4.17 (2H, d, *J* = 15.9 Hz); 3.914 (6H, s); 3.906 (6H, s); 3.71 (6H, m); 3.70 (6H, s); 3.52 (2H, m); 3.44 (2H, d *J* = 15.9 Hz); 1.52 (4H, m); 1.23 (12H, m); 0.86 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$-*d*): 157.6; 155.4; 151.3; 134.4; 127.8; 127.6; 121.8; 121.7; 120.3; 116.4; 96.5; 94.8; 69.2; 56.0; 55.9; 55.8; 31.6; 29.5; 29.1; 28.2; 25.6; 22.6; 14.0. ESI q-TOF MS: $C_{46}H_{60}O_8Na$ calcd.: 763.4183, found: 763.4183.

Compound **8**: Obtained from 1,3-dimethoxybenzene (compound A, 1.02 g) and 1,2-dimethoxybenzene (compound B, 0.34 g) by procedure B (20 mL of TFA; 2 h; 50 g of silica gel; eluent: gradient $CHCl_3$−$CHCl_3$/ethyl acetate (100:3)). Yield: 0.544 g (40%). ^{1}H NMR (400 MHz, $CDCl_3$): 6.57 (4H, s); 5.99 (2H, s); 5.34 (2H, s); 3.78 (12H, s); 3.73 (12H, s). ^{1}H NMR (400 MHz, $CDCl_3$-*d*, 233 K): 6.57 (4H, s); 5.99 (2H, s); 5.34 (2H, s); 3.89 (4H, d, *J* = 15.5 Hz); 3.78 (12H, s); 3.73 (12H, s); 3.30 (4H, d, *J* = 15.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): 154.6; 147.3; 131.4; 130.50; 130.47; 120.09; 115.60; 115.58; 93.1; 56.3; 55.3; 31.2. ESI q-TOF MS: $C_{36}H_{41}O_8$ calcd.: 601.2801, found: 601.2809.

Compound **9**: Obtained from 1,3-dimethoxybenzene (compound A, 1.02 g) and 1,2-dimethoxybenzene (compound B, 0.34 g) by procedure C (20 mL of TFA; 2 h; 50 g of silica gel; eluent: gradient $CHCl_3$−$CHCl_3$/ethyl acetate (100:3)). Yield: 0.64 g (47%). ^{1}H NMR (400 MHz, $CDCl_3$-*d*): 6.47 (2H, s); 6.30 (2H, s); 6.37 (1H, s); 6.34 (1H, s); 5.75 (2H, s); 3.87 (6H, s); 3.81 (6H, s); 3.79 (4H, s); 3.74 (6H, s); 3.72 (6H, s); 3.69 (4H, s). ^{13}C NMR (100 MHz, $CDCl_3$-*d*): 157.0; 155.8; 155.7; 146.9; 133.5; 131.0; 129.8; 121.6; 120.3; 113.6; 95.3; 94.2; 55.71; 55.65; 29.9; 26.8. ESI q-TOF MS: $C_{36}H_{40}O_8Na$ calcd.: 623.2608, found: 623.2621.

Compound **10** (CTV): Obtained from 1,2-dimethoxybenzene (1.38 g, 10 mmol) by procedure A (30 g of silica gel, eluent: $CHCl_3$/ethyl acetate (100:2)). Yield: 1.28 g (80%). NMR and MS spectra are in agreement with literature data.[26]

Compound **11** (*per*-methoxyresorcin[4]arene): Obtained from 1,3-dimethoxybenzene (1.38 g, 10 mmol) by procedure A (30 g of silica gel, eluent: $CHCl_3$/ethyl acetate (100:2)). Yield: 1.28 g (80%). NMR and MS spectra are in agreement with literature data.[26]

Compound **12** (*per*-methoxypillar[5]arene): Obtained from 1,4-dimethoxybenzene (1.38 g, 10 mmol) by procedure A (30 g of silica gel, eluent: gradient $CHCl_3$−$CHCl_3$/MeOH (100:2)). Yield: 1.20 g (80%). NMR and MS spectra are in agreement with literature data.[26]

Compound **13**: To a solution of 1,4-dimethoxybenzene (0.828 g, 6 mmol) and 1,3,5-trimethoxybenzene (0.672 g, 4 mmol) in $CHCl_3$ (50 mL), paraformaldehyde (0.300 g, 10 mmol) and TFA (10 mL) were added. The reaction was refluxed for 3 days, and the progress was monitored by TLC ($CHCl_3$/ethyl acetate 100:5). During the reaction, the color changed from colorless to dark purple. The reaction was cooled down to rt, and an excess of Na_2CO_3 was added to neutralize the TFA. The mixture was filtered off and evaporated to dryness. The products were isolated by chromatography (75 g of silica gel, eluent: gradient $CHCl_3$−$CHCl_3$/ethyl acetate (100:6)). After chromatography, the product was recrystallized from MeCN to obtain **13** as white crystals. Yield: 0.567 g, 3.5 mmol (35%). ^{1}H NMR (400 MHz, $CDCl_3$): 6.89 (2H, s); 6.36 (2H, s); 6.29 (2H, s); 6.16 (2H, s); 3.90 (4H, s); 3.89 (6H, s); 3.79 (6H, s); 3.71 (6H, s); 3.70 (4 + 2H, s); 3.49 (6H, s); 3.39 (6H, s); 2.90 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 158.8; 157.3; 156.9; 151.5; 151.3; 150.2; 129.1; 127.7; 126.8; 116.3; 115.0; 113.6; 111.7; 91.7; 61.0; 56.7; 55.8; 55.5; 55.1; 32.3;

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22.7; 21.2. ESI q-TOF MS: $C_{47}H_{58}NO_{12}$ calcd.: 828.3959, found: 828.3962.

Compound **14**: Obtained from 1,3,5-trimethoxybenzene (1.68 g) by procedure A (30 g of silica gel, eluent: CH_2Cl_2). Yield: 1.428 g (80%). NMR and MS spectra are in agreement with literature data.[29]

Crystallographic Part. CCDC 1024332−1024337 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for ***5****.* $C_{56}H_{80}O_8$, M = 881.20, 0.33 × 0.17 × 0.07 mm^3, triclinic, space group P-1 (No. 2), a = 8.7786(3), b = 13.1685(4), c = 23.0265(7) Å, α = 78.201(2), β = 88.483(2), γ = 81.806(2)°, V = 2579.03(14) Å^3, Z = 2, D_c = 1.135 g/cm^3, F_{000} = 960, CuKα radiation, λ = 1.54178 Å, T = 173(2)K, $2\theta_{max}$ = 133.2°, 20176 reflections collected, 8776 unique (R_{int} = 0.0418). Final *GooF* = 1.036, *R1* = 0.0525, *wR2* = 0.1415, *R* indices based on 6307 reflections with I >2sigma(I) (refinement on F^2), 586 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.583 mm^{-1}.

Crystal Data for ***6****.* $C_{56}H_{76}O_8$, M = 877.17, 0.37 × 0.32 × 0.23 mm^3, monoclinic, space group $C2/c$ (no. 15), a = 25.712(5), b = 23.741(5), c = 16.888(3) Å, $\alpha = \beta = \gamma$ = 90.00(3)°, V = 10309(4) Å^3, Z = 8, D_c = 1.130 g/cm^3, F_{000} = 3808, Cu Kα radiation, λ = 1.54178 Å, T = 173(2) K, $2\theta_{max}$ = 135.5°, 32 442 reflections collected, 8827 unique (R_{int} = 0.0334). Final GooF = 1.090, *R*1 = 0.1173, *wR*2 = 0.3285, *R* indices based on 7306 reflections with $I > 2\sigma(I)$ (refinement on F^2), 577 parameters, 19 restraints. Lp and absorption corrections applied, μ = 0.583 mm^{-1}.

Crystal Data for ***7****.* $C_{92.54}H_{120.54}Cl_{1.63}O_{16}$, M = 1546.63, 0.36 × 0.35 × 0.33 mm^3, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 15.0680(4), b = 23.3472(6), c = 24.7931(6), V = 8722.1(4) Å^3, Z = 4, D_c = 1.176 g/cm^3, F_{000} = 3317, Cu Kα radiation, λ = 1.54178 Å, T = 173(2) K, $2\theta_{max}$ = 131.9°, 44 842 reflections collected, 14 544 unique (R_{int} = 0.0340). Final GooF = 1.030, *R*1 = 0.1021, *wR*2 = 0.2677, *R* indices based on 12 528 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1082 parameters, 97 restraints. Lp and absorption corrections applied, μ = 1.070 mm^{-1}.

Crystal Data for ***8****.* $C_{72}H_{80}N_0O_{16}$, M = 1201.36, 0.25 × 0.25 × 0.07 mm^3, monoclinic, space group $P2_1/c$ (no. 14), a = 8.5228(2), b = 33.0695(8), c = 11.6141(3) Å, β = 108.023(3)°, V = 3112.76(13) Å^3, Z = 2, D_c = 1.282 g/cm^3, F_{000} = 1280, Cu Kα radiation, λ = 1.5418 Å, T = 100.01(10) K, $2\theta_{max}$ = 138.9°, 11 621 reflections collected, 5746 unique (R_{int} = 0.0368). Final GooF = 1.164, *R*1 = 0.0790, *wR*2 = 0.1994, *R* indices based on 5096 reflections with $I > 2\sigma(I)$ (refinement on F^2), 405 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.732 mm^{-1}.

Crystal Data for ***9****.* $C_{36}H_{40}O_8$, M = 600.68, 0.636 × 0.403 × 0.254 mm^3, monoclinic, space group $P2_1/n$ (no. 14), a = 8.72160(10), b = 22.4584(4), c = 15.5439(3) Å, β = 100.1410(10)°, V = 2997.07(9) Å^3, Z = 4, D_c = 1.331 g/cm^3, F_{000} = 1280, Cu Kα radiation, λ = 1.54178 Å, T = 100(2) K, $2\theta_{max}$ = 135.3°, 28 780 reflections collected, 5358 unique (R_{int} = 0.0289). Final GooF = 1.076, *R*1 = 0.0359, *wR*2 = 0.0873, *R* indices based on 5299 reflections with $I > 2\sigma(I)$ (refinement on F^2), 405 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.760 mm^{-1}.

Crystal Data for ***13****.* $C_{49}H_{57}NO_{12}$, M = 851.96, 0.12 × 0.12 × 0.07 mm^3, triclinic, space group P-1 (no. 2), a = 11.6028(2), b = 13.7155(2), c = 15.4868(3) Å, α = 74.8980(10), β = 72.6060(10), γ = 70.8830(10)°, V = 2185.69(7) Å^3, Z = 2, D_c = 1.295 g/cm^3, F_{000} = 908, Cu Kα radiation, λ = 1.54178 Å, T = 100(2) K, $2\theta_{max}$ = 133.2°, 25 445 reflections collected, 7606 unique (R_{int} = 0.0293). Final GooF = 1.016, *R*1 = 0.0385, *wR*2 = 0.0997, *R* indices based on 7429 reflections with $I > 2\sigma(I)$ (refinement on F^2), 572 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.756 mm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new macrocylic products (including two-dimensional spectra), ESI-MS spectra, details of the scrambling experiments, titration results, curve fitting with all parameters retrieved, and CIF files for the crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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