Interlocked Molecules

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Formation of Self-Templated 2,6-Bis(1,2,3-triazol-4-yl)pyridine [2]Catenanes by Triazolyl Hydrogen Bonding: Selective Anion Hosts for Phosphate

Joseph P. Byrne, Salvador Blasco, Anna B. Aletti, Gary Hessman, and Thorfinnur Gunnlaugsson**

Dedicated to Professor David Parker FRS on the occasion of his 60th birthday

Abstract: *We report the remarkable ability of 2,6-bis(1,2,3-triazol-4-yl)pyridine (**btp**) compounds **2** with appended olefin amide arms to self-template the formation of interlocked [2]catenane structures **3** in up to 50 % yield when subjected to olefin ring-closing metathesis in CH_2Cl_2. X-ray diffraction crystallography enabled the structural characterization of both the [2]catenane **3a** and the non-interlocked macrocycle **4a**. These [2]catenanes showed selective triazolyl hydrogen-bonding interactions with the tetrahedral phosphate anion when screened against a range of ions; **3a**,**b** are the first examples of selective [2]catenane hosts for phosphate.*

The 2,6-bis(1,2,3-triazol-4-yl)pyridine motif (**btp**) is a versatile building block that has been explored for use in supramolecular d- and f-metal coordination chemistry.[1,2] Synthetically readily accessible **btp** ligands have found application in anion recognition,[3] molecular logic,[4] and the generation of supramolecular polymers and functional metallogels,[5] as well as in medicinal chemistry.[6,7] [*n*]Catenanes and [*n*]rotaxanes are supramolecular mechanically interlocked structures.[8] They are commonly formed by templating synthetic methods involving metal ions, "active metal" sites, and other supramolecular interactions,[9,10] often in combination with modular reactions,[11] such as olefin ring-closing metathesis (RCM).[12] Examples of diverse templates include d-metal ions, as used by Leigh an co-workers,[10d,13] and anion and halogen bonding, as reported by Beer and co-workers.[14] Recently, our research group[15] as well as Leigh and co-workers[16] reported the use of f-metal ions to template the formation of interlocked systems; olefin RCM reactions were used in both cases to "clip" three ligands together around the templating ion. These examples demonstrate the value of assisted templation and the importance of preorganization; however, examples of "self-templated" mechanically interlocked molecules formed solely through the use of hydrogen-bonding interactions are relatively scarce. Notable examples of such "self-templated" structures are the [2]catenanes developed by the research groups of Hunter,[17] Vögtle,[18] Leigh,[19] and Evans.[20] All of these systems relied on hydrogen-bonding amide interactions. Inspired by these examples, we set out to explore and develop the formation of novel alternative "self-templated" interlocked molecules by the use of nonclassical hydrogen-bonding motifs. Having recently observed that the **btp** motif can form hydrogen-bonding dimers through its triazolyl and pyridyl functionalities,[21] we chose to investigate the use of **btp** in the formation of functional interlocked molecules. Herein we present **btp** as a new type of system for the synthesis of interlocked molecules, and the **btp**-based [2]catenane structures **3** (Scheme 1). Furthermore, we describe the use of [2]catenanes **3** as novel anion receptors for the selective recognition of phosphate.

We previously reported the synthesis of the **btp** ligand **1** and its methyl ester derivative, as well as the coordination chemistry of these compounds with the d-metal ions Ru^{II}, Ir^{III}, Ni^{II}, and Pt^{II}.[1a] The derivatization of **1** through amide-bond formation presented itself as a facile and modular route to extended functionality, and a range of novel ligands were developed for Ln^{III} sensitization.[2a] To form precursors to the desired interlocked systems, we introduced terminal olefin groups through the reaction of **1** with alkenyl amines of various lengths (Scheme 1) to yield **2a**–**e** as white solids in good purity (see the Supporting Information for full characterization details for **2a**–**e**). ^{1}H NMR analysis of compound **2a** (600 MHz, [D$_6$]DMSO; Figure 1 a), which was formed in 61 % yield, showed characteristic proton shifts for the allyl moiety, including an apparent triplet at 3.90 ppm (labeled *q*) arising from the CH_2 group adjacent to the amide bond, and distinctive multiplets at 5.05–5.19 and 5.84–5.93 ppm, which were assigned to the terminal olefin hydrogen atoms (*s*) and the nonterminal olefin CH groups (*r*), respectively. Moreover, an NH COSY experiment facilitated the assignment of the broad triplet resonance at 8.66 ppm to the amide hydrogen atoms (*p*). The ^{1}H NMR spectra of **2b**–**e**, were similar, differing only in the number of resonances arising from the

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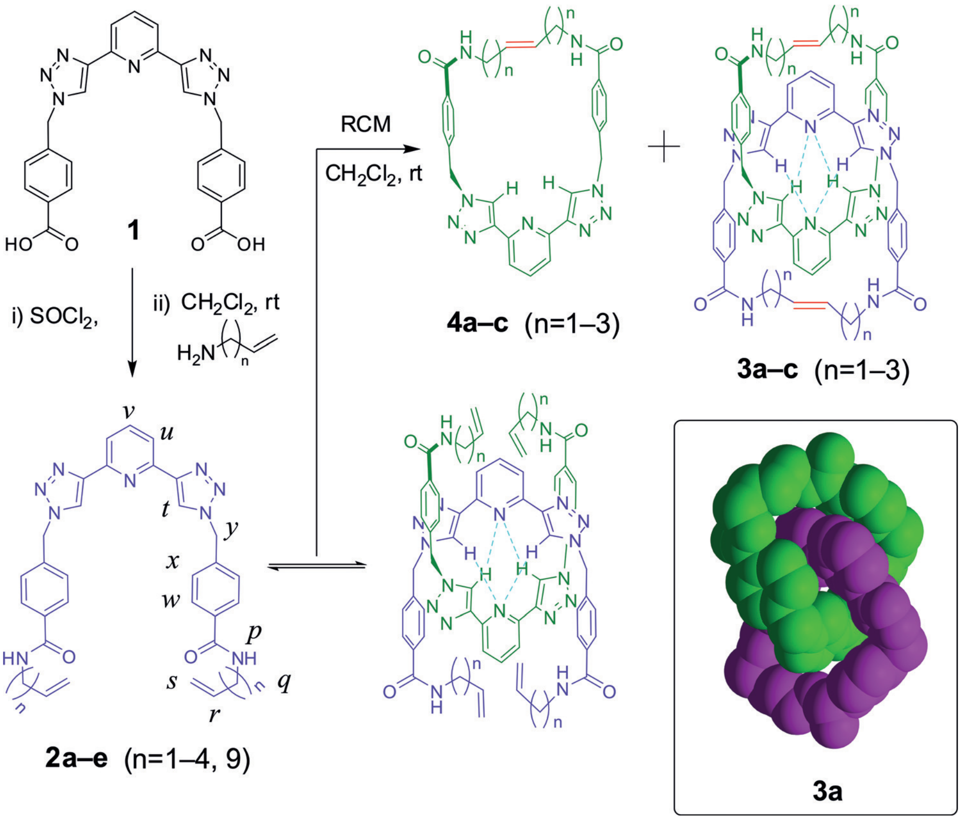

Scheme 1. Synthesis of olefin-appended **btp** compounds **2** and RCM to yield [2]catenane structures **3** and macrocycles **4**. The molecular structure of **3a** is shown (with hydrogen atoms omitted) to illustrate the interlocked nature of these systems.

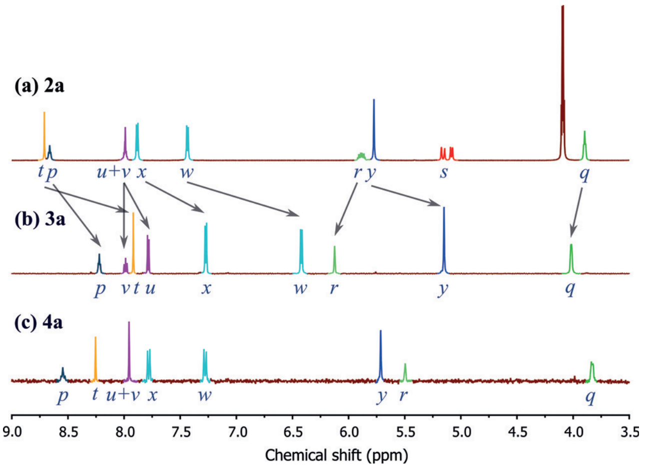

Figure 1. ^{1}H NMR spectra in [D$_6$]DMSO of a) RCM precursor **2a**, b) [2]catenane **3a**, c) macrocycle **4a**.

alkenyl chains. Compound **2a** gave a characteristic HRMS (ESI+) signal at *m*/*z* 560.2547 corresponding to the $[M+H]^+$ ion as well as signals at *m*/*z* 582.2375 and 1141.4424 corresponding to $[M+Na]^+$ and $[2M+Na]^+$, respectively.

With the view of forming **3**, the olefin precursors **2** (ca. 1 mM) were suspended in dry CH_2Cl_2 and subjected to RCM by treatment with the Hoveyda–Grubbs second-generation catalyst (10 mol%). The reaction mixture was stirred for 4–7 days. In the case of **2a**, the filtrate was concentrated, and compound **3a** was collected upon trituration with CH_3OH and isolated as an off-white solid in 50% yield. This yield is one of the highest reported to date for a hydrogen-bond-templated interlocked system.[22] The ^{1}H NMR spectrum of **3a** (600 MHz, [D$_6$]DMSO, Figure 1b) demonstrates significant changes from **2a**. The absence of the characteristic terminal olefin hydrogen atoms was most notable, and the apparent singlet observed at 6.08 ppm, which was assigned to the remaining olefin hydrogen atoms (*r*), was indicative of successful RCM. Moreover, the triazolyl CH resonance (*t*) was dramatically shielded, thus suggesting significant changes in its chemical environment relative to that in **2a**. The amide resonance (*p*, assigned by NH COSY) was also shifted upfield. Most remarkably, however, the proton resonances assigned to the phenyl rings were heavily shielded, so that the two signals were shifted upfield from 7.43 and 7.88 ppm to 6.42 and 7.27 ppm (*x* and *w*), whereas the methylene resonance (*y*) was shifted to 5.15 ppm. These NMR spectroscopic changes suggested a more dramatic change than would be expected from macrocyclization alone, and as such supported the successful formation of the desired [2]catenane structure **3a**. Such upfield shifts have been noted previously for other interlocked species.[9a,20] The formation of **3a** was further confirmed by HRMS (MALDI+) analysis, with the appearance of characteristic peaks at *m*/*z* 1063.4346 and 1085.4147, assigned to the $[M+H]^+$ and $[M+Na]^+$ species. This conclusion was also supported by selective ROESY experiments (see the Supporting Information), which showed weak through-space interactions between the phenyl rings and the **btp** motif, a result consistent with the close proximity of aromatic moieties in the solid-state structure (see below).

For the reactions of **2b**,**c**, flash chromatography provided products **3b**,**c** in diminishing yields as the chains lengthened (35% and <1%, respectively). No evidence was obtained for the formation of the [2]catenane products from **2d**,**e**; instead, only starting material was recovered. This result clearly indicates that the alkene chain length has a major influence on the favorability of catenane formation. When the RCM reactions were carried out in more polar solvents, such as CH_3CN and CH_3OH, no discernible amount of **3** was formed, thus indicating the importance of hydrogen-bond formation in self-templating of the desired interlocked structures. The requirement of a nonpolar solvent was noted previously by Leigh and co-workers for amide-templated [2]catenane systems.[19b]

Long, thin, colorless prismatic crystals of **3a** were grown by the slow evaporation of a dilute solution in CH_3CN. These crystals were suitable for X-ray diffraction analysis and enabled structure determination.[23] The resulting structure (Figure 2) indeed confirmed the formation of a "Hopf link" self-templated [2]catenane, whereby **3a** crystallized in the monoclinic $P2_1/c$ space group (the space-filling structure is depicted as an inset in Scheme 1). The asymmetric unit contained two crystallographically distinct molecules, along with two water molecules (see animation in the Supporting Information). All olefin bonds displayed the *E* configuration. A range of noncovalent supramolecular interactions organized the constituent molecules in the observed conformation. The ability of the triazolyl C−H atom to act as a nonclassical hydrogen-bond donor (as we reported previously[21]) resulted in the formation of a **btp**–**btp** dimeric hydrogen-bonding arrangement, with each pair of triazoles binding the pyridine ring of the other catenane "thread". These hydrogen bonds all have donor–acceptor lengths ranging from 3.415(10) to 3.700(12) Å (see Table S1 in the Supporting Information). As can be seen from Figure 2a, a significant number of amide hydrogen-bonding interactions also exist between various triazole rings and hydrogen atoms attached to N(5), N(14), N(24), and N(32). Moreover, amides were also shown to form hydrogen bonds with H_2O molecules. There are also a number of weak interactions between various aromatic moieties; many (but not all) of these weak interactions are approximately parallel. This range of supramolecular interactions results in a well-ordered and tightly packed solid-state structure, as shown in the depiction of the unit cell, which contains 16 [2]catenane molecules, in Figure 2b.

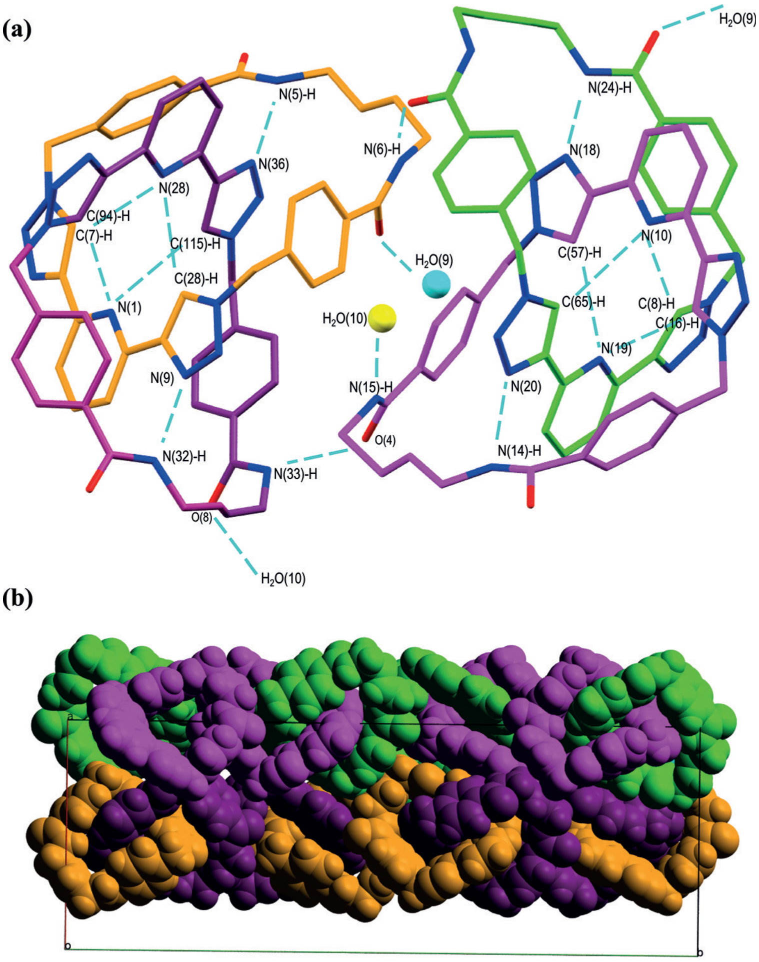

Figure 2. a) Capped stick model of the asymmetric unit of the X-ray crystal structure of [2]catenane **3a**, showing the various hydrogen-bonding and nonclassical hydrogen-bonding interactions present in the solid state, in particular those associated with the formation of the **btp**–**btp** dimer, as well as amide hydrogen bonds. The asymmetric unit contains two [2]catenanes and two H_2O molecules (shown as spheres). Hydrogen atoms are omitted. b) Space-filling packing structure of **3a**, showing the unit cell viewed along the *c*-axis (solvent molecules omitted).[23]

As stated above, **3a** was isolated as a solid upon trituration with CH_3OH. From the filtrate, colorless single block crystals were grown over a period of time. ^1H NMR analysis of these crystals (Figure 1c) showed a different spectrum to that observed for the [2]catenane **3a**. In particular, the resonances due to the flanking aryl groups were shifted significantly less upfield than for **3a** (Figure 1b). Indeed, the spectrum resembled that of **2a** more closely, and was assigned to the macrocycle **4a**. The molecular structure of the non-interlocked macrocycle was determined from the isolated single crystals (Figure 3). The molecular structure displays many hydrogen-bonding interactions, including amide hydrogen-bonding chains between adjacent molecules, π–π stacking between adjacent phenyl rings, and nonclassical triazolyl C−H···Cl interactions with CH_2Cl_2 solvent molecules; such behavior of triazoles has been reported previously (see the Supporting Information for further discussion).[1a,24] Macrocycles **4a**–**c** could also be isolated from the respective RCM reactions by flash chromatography, and all displayed similar properties to those described for **4a**. These results demonstrate that the formation of the desired **btp**–**btp** dimeric hydrogen-bond arrangement, and the chain lengths, are both critical for the catenation reaction to be successful. However, the RCM reaction also leads to the formation of non-interlocked macrocyles, which can be separated readily from the [2]catenane molecules.

We considered exploiting the unique **btp**–**btp** hydrogen-bonding features of **3** for anion recognition: an area that we have been actively exploring.[25] Although triazoles have not been widely exploited in catenane synthesis,[26d] they are often used in the synthesis of anion receptors owing to their hydrogen-bond-donor ability.[14a,24a,27] Similarly, whereas the anion-templated synthesis of interlocked structures has been elegantly demonstrated, most notably by Beer and co-workers,[26] the recognition and sensing of anions by the use of

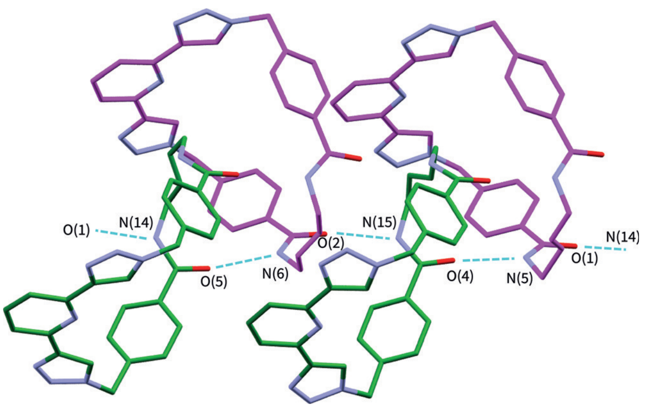

Figure 3. Molecular structure of macrocycle **4a**, showing amide hydrogen-bonding interactions between the crystallographically independent molecules in the asymmetric unit (carbon atoms are colored differently for each molecule). For clarity, hydrogen atoms, partial-occupancy solvent molecules, and disordered sites have been omitted.[23]

catenanes as "anion hosts" has been relatively unexplored. Most examples to date show selectivity for halide ions through halogen- or hydrogen-bonding interactions within the catenane cavity.[26e,f] From the crystal structure of **3** (Figure 2a), it can be seen that the **btp–btp** units are orientated in a manner that gives rise to a highly preorganized hydrogen-bonding environment, which can be described as being close to a "tetrahedral" arrangement.

We used solutions of **3a** in [D$_6$]DMSO for a series of NMR anion titrations. The titration with $H_2PO_4^-$ (as the tetrabutylammonium salt) gave rise to significant changes in the ^{1}H NMR spectrum. The spectra in Figure 4 show the changes after the addition of 10 equivalents of each anion. For $H_2PO_4^-$ in particular, downfield shifts and broadening were observed for both the triazolyl and the amide hydrogen atoms of **3a**. This result suggests that the anion interacted directly with these hydrogen atoms through hydrogen bonding upon binding to the [2]catenane. Importantly, such resonance changes were not observed upon the addition of Cl^-, SO_4^{2-}, or NO_3^-, thus suggesting that **3a** recognized $H_2PO_4^-$ specifically. We propose that this selective recognition is most likely due to the favorable preorganization of the anion-recognition site within **3a**. In contrast, effects of full amide deprotonation[29] were observed upon the addition of an excess of F^- (10 equiv) to **3a** (Figure 4). Unfortunately, we were unable to obtain crystals suitable for X-ray crystal-structure determination of the **3a**:$H_2PO_4^-$ host–guest complex. Nevertheless, the selective recognition of $H_2PO_4^-$ was further confirmed by MALDI HRMS experiments. The mass spectrum showed a characteristic signal at m/z 1159.3944, assigned to the desired **3a**:$H_2PO_4^-$ structure (i.e. $[M+H_2PO_4]^-$). Moreover, DOSY NMR analysis showed an increase in the diffusion rate of **3a** upon the binding of $H_2PO_4^-$, which further supports our overall observation that the tetrahedral $H_2PO_4^-$ anion is hosted within the cavity of the catenane **3a** (see the Supporting Information).[28] Similarly, we investigated the anion-recognition ability of **3b** (see the Supporting Information) and observed similar changes and selectivity to those seen in the NMR spectra above. The MALDI HRMS spectrum showed a clear signal for the desired **3b**:$H_2PO_4^-$ complex at m/z 1215.4523. RCM reactions in the presence of $H_2PO_4^-$ did not result in the formation of the [2]catenane product, thus further emphasizing the role of the **btp–btp** hydrogen-bonding dimer in the preorganization of the interlocking components. To the best of our knowledge, these examples are the only [2]catenanes which act as selective hosts for the tetrahedral $H_2PO_4^-$ anion and do not interact with halides.

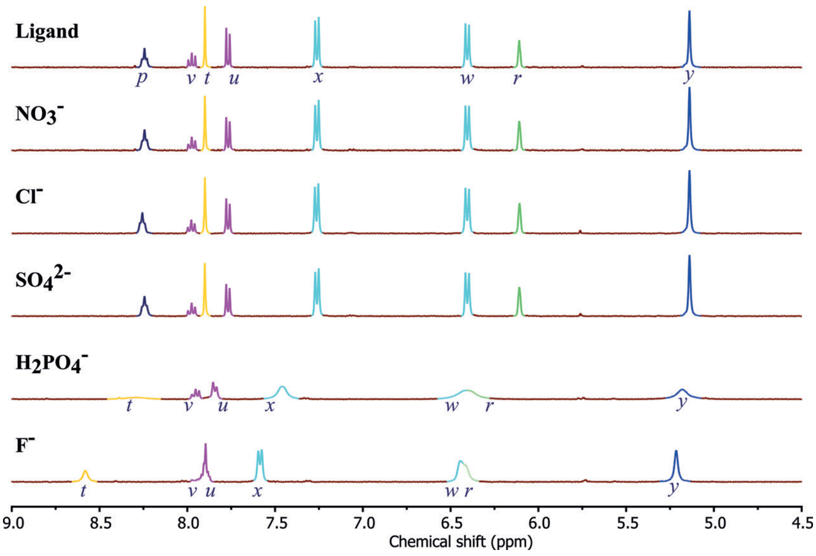

Figure 4. Effects of anions (10 equiv) on the ^{1}H NMR spectrum of catenane **3a** (400 MHz, [D$_6$]DMSO).

Having demonstrated that the [2]catenanes **3a** and **3b** could function as novel supramolecular anion hosts, we explored whether macrocycles **4** had the same properties. In contrast with the behavior described above, these compounds showed affinity towards both Cl^- and $H_2PO_4^-$. Although the binding of $H_2PO_4^-$ to **4a** resulted in a downfield shift of the amide proton resonances, only a very minor downfield shift was seen for the triazolyl proton resonance; this shift only occurred upon the addition of many equivalents of $H_2PO_4^-$. From these NMR titrations, the binding constants for $H_2PO_4^-$ were determined by nonlinear regression analysis as $\log\beta = 1.12(4)$, 0.87(6), and 0.83(9) for **4a–c**, respectively.[30] By comparison, the interlocked structures **3a** and **3b** display appreciably stronger and selective binding ability for $H_2PO_4^-$; $\log\beta$ values of 1.74(2) and 2.04(2) were determined for **3a** and **3b**, respectively. This result clearly demonstrates that the anion recognition is favored by preorganization and complementarity of the binding geometry within the internal cavity of the [2]catenane, and differs from the binding behavior of the non-interlocked macrocycle (see the Supporting Information for NMR titration data and Table S4 for binding constants).

Herein, we have demonstrated the formation of mechanically interlocked structures by use of the **btp** ligand motif. We have shown that these structures are formed by favorable self-templating hydrogen-bonding interactions that are non-amide-based. We further showed that these interactions can be employed for anion recognition, whereby a strong bias was observed for $H_2PO_4^-$. This selective recognition reflects the structural nature of the [2]catenane host. Further studies to fully understand the relationship between the [2]catenane structure and its anion-binding behavior and to extend the application of this molecular recognition in functional supramolecular chemistry are in progress in our laboratory.

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[22] The [2]catenane **3a** could also be separated from the macrocyclic side product **4a** by flash chromatography (ethyl acetate–methanol gradient), whereby the [2]catenane was the more polar product.

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