Template Synthesis

DOI: 10.1002/ange.201307640

Synthesis of a [2]Catenane from the Sodium Ion Templated Orthogonal Arrangement of Two Diethylene Glycol Chains**

*Shun-Te Tung, Chien-Chen Lai, Yi-Hung Liu, Shie-Ming Peng, and Sheng-Hsien Chiu**

An important feature for the efficient construction of a [2]catenane is the appropriate alignment of the individual precursor molecular components.[1] Although direct self-assembly of these components through intermolecular hydrogen bonding[2] and/or π-stacking interactions[3] is possible in some unique recognition systems, the use of an ionic template to bridge and preorganize them remains a commonly applied strategy. In addition to anions,[4] transition-metal cations[5] are the most frequently used ionic templates because their predictable chelation numbers and geometries allow precise arrangement of the precursor components of the [2]catenane. Pyridines, bipyridines, and their derivatives, which have strong binding affinities to transition-metal ions, have generally been used as recognition units in such systems (Figure 1 a), and have led to the construction of many elegant and functional [2]catenanes.[5] Although the binding of oligo(ethylene glycol) chains to alkali metal ions has long been applied in the synthesis of crown ethers,[6] we were unaware of any examples of the use of alkali metal ions to template the association of two oligo(ethylene glycol) chains in an orthogonal geometry (Figure 1 b) to facilitate the self-assembly of the corresponding catenanes or rotaxanes. We suspected, however, that if chemically relatively inert, readily accessible, and readily derivatized oligo(ethylene glycol) units could serve as primary recognition units for the construction of interlocked molecules, then facile new syntheses of structurally simple interlocked molecular switches capable of performing interesting functions might be possible. Herein, we report the orthogonal alignment of two diethylene glycol units templated by Na^+ ions and its application in the synthesis of a simple [2]catenane from five components (two diamines, two dialdehydes, one Na^+ ion).

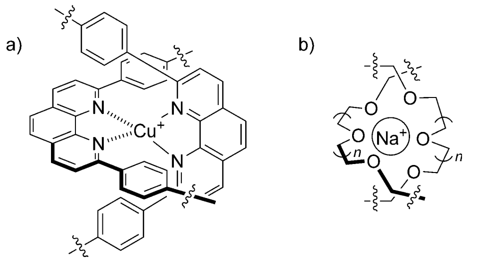


Figure 1. Conceptual representation of the orthogonal self-assembly of ligands through the interactions of a) two phenanthroline units with a Cu^+ ion and b) two oligo(ethylene glycol) strands with a Na^+ ion.

We anticipated that enhancing the binding affinity of an alkali metal ion to two linear oligo(ethylene glycol) chains would require weakening the interactions of the metal ion to its counteranion and to the surrounding solvent molecules. Moreover, the number of oxygen atoms present in the oligo(ethylene glycol) strands might also need to be minimized to ensure that the coordination number of the alkali metal ion would not be fulfilled merely by a single oligo(ethylene glycol) chain. Thus, we selected the diamine **1**,[7] which contains only three oxygen atoms in its diethylene glycol chain,[8] for the synthesis of [2]catenanes through imine formation with the dialdehyde **2** in a low-polarity solvent (e.g., $CHCl_3$, CH_2Cl_2) in the presence of sodium tetrakis(3,5-trifluoromethylphenyl)borate (NaTFPB)[9] as the templating salt (Scheme 1).[10]

^{1}H NMR spectroscopic analysis of an equimolar (20 mM) mixture of the diamine **1**, the dialdehyde **2**, and NaTFPB in $CDCl_3$ showed the signals corresponding to the imine and aldehyde units to increase and decrease, respectively, over time, thus indicating that the reaction equilibrium favored the formation of imine bonds (Figure 2). The reaction was accelerated by heating the mixture at 323 K for 20 min. This resulted in a simplified set of signals, which we rationalized as corresponding to the complexed macrocycle [$\mathbf{3}\cdot Na^+$] on the basis of the shapes, integration ratios, and chemical shifts of the signals in the ^{1}H NMR spectrum (Figure 2 b). Further heating of the solution at 323 K for 3 h led to only negligible changes in the ^{1}H NMR spectrum, thus suggesting that equilibrium was reached quickly under these conditions and that the complexed macrocycle [$\mathbf{3}\cdot Na^+$] was the thermodynamically preferred product. Electrospray ionization (ESI) mass spectrometric analysis of the solution revealed an intense signal at m/z 465.2, which corresponds to the ion [$\mathbf{3}\cdot Na^+$].

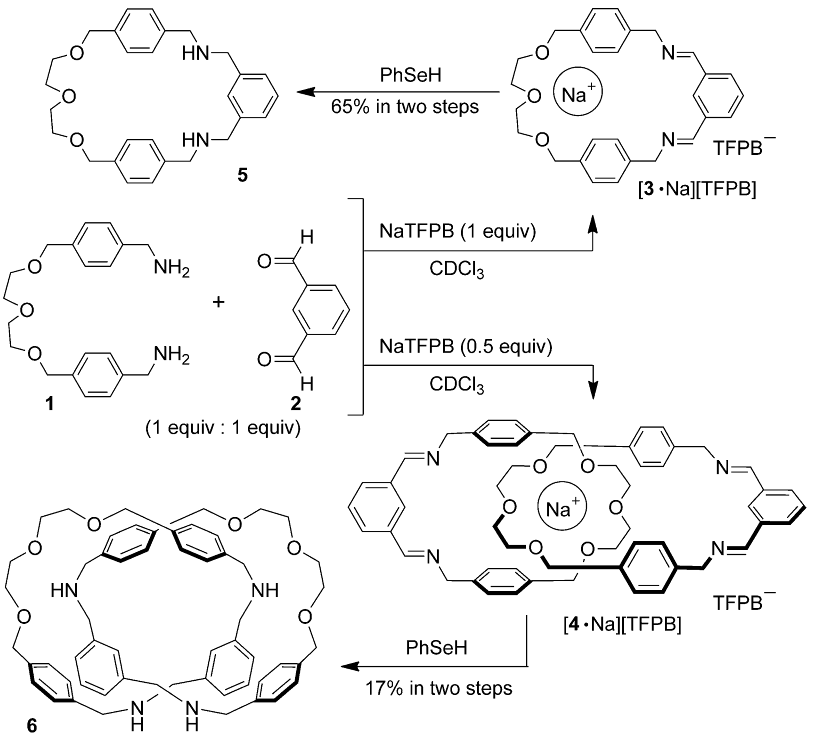
In contrast, the ^{1}H NMR spectrum of the corresponding solution containing only 0.5 equiv of NaTFPB displayed a completely different set of signals after heating it at 323 K for 3 h (Figure 2 f). The significant upfield shifts of the signals for the ethylene glycol units—from approximately $\delta = 3.50$–

---

[*] S.-T. Tung, Y.-H. Liu, Prof. S.-M. Peng, Prof. S.-H. Chiu
Department of Chemistry and Center for Emerging Material and Advanced Devices, National Taiwan University
No. 1, Sec. 4, Roosevelt Road, Taipei, Taiwan, 10617 (R.O.C.)
E-mail: shchiu@ntu.edu.tw
Prof. C.-C. Lai
Institute of Molecular Biology, National Chung Hsing University and Graduate Institute of Chinese Medical Science, China Medical University, Taichung, Taiwan (R.O.C.)

[**] We thank the National Science Council (Taiwan) (NSC-102-2119-M-002-007) and National Taiwan University (NTU-102-R890913) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307640.



Scheme 1. Template-directed synthesis of the [2]catenane **6**.

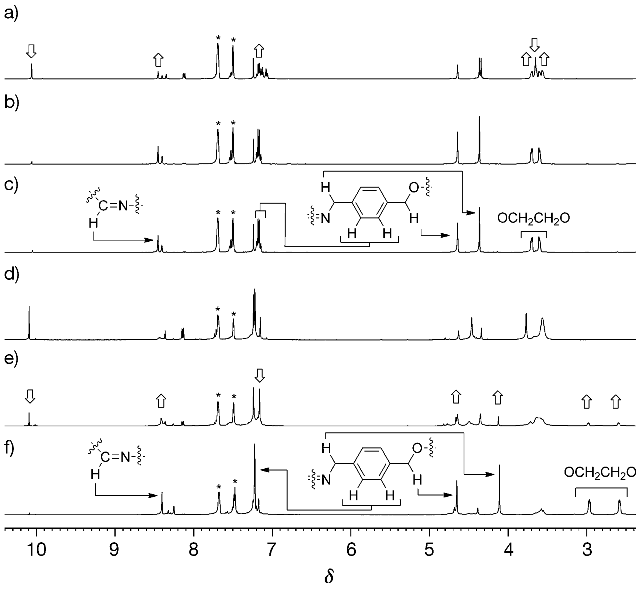


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of mixtures of the diamine **1**, the dialdehyde **2**, and NaTFPB: a)–c): 20, 20, and 20 mM, respectively; d)–f) 20, 20, and 10 mM, respectively, maintained at 323 K for a,d) 0 h, b,e) 0.33 h, and c,f) 3 h. Asterisks: signals from TFPB anions.

3.70 initially to $\delta = 2.59$ and 2.98 after 3 h—suggested that these protons were located within a shielding zone formed by the *p*-xylene units. The ^{1}H NMR spectrum of the reaction with only 0.5 equiv of Na^+ ions suggests that the structure formed was the [2]catenane [**4**·Na^+], with one Na^+ ion coordinating a diethylene glycol chain from each of two units of the macrocycle **3** in an orthogonal arrangement (Scheme 1). Nano-ESI-MS analysis of the solution revealed a signal at *m*/*z* 907.4, which corresponds to the singly charged Na^+-complexed dimer of **3**. The ^{1}H NMR spectrum of an equimolar mixture (20 mM) of only the diamine **1** and the dialdehyde **2** in $CDCl_3$, after it had been heated at 323 K for 3 h, featured no signals corresponding to either the macrocycle **3** or the [2]catenane **4** (see the Supporting Information). This finding suggests the important role played by the Na^+ ions as templates in the formation of the complexed macrocycle [**3**·Na^+] and the complexed [2]catenane [**4**·Na^+].[11]

To further support the formation of the macrocycle **3** and the [2]catenane **4**, we reduced their imino bonds to convert these molecules into thermodynamically stable amines. Thus, after heating an equimolar (20 mM) mixture of the diamine **1**, the dialdehyde **2**, and NaTFPB in $CHCl_3$ at 323 K for 16 h to generate predominantly the macrocycle [**3**·Na^+], we cooled the solution to ambient temperature, added PhSeH[12] (160 mM), and then stirred the mixture for 10 min. This resulted in the formation of the macrocycle **5**, which was isolated in 65 % yield after column chromatography. A similar procedure applied to a mixture of the diamine **1** (20 mM), the dialdehyde **2** (20 mM), and NaTFPB (10 mM) resulted in the isolation of the [2]catenane **6** in 17 % yield after column chromatography.[13] Nano-ESI-MS analysis of the [2]catenane **6** revealed an intense signal at *m*/*z* 893.5, which corresponds to the singly protonated dimer of the macrocycle **5**. Tandem mass spectrometric analysis (nano-ESI-MS/MS) of this signal provided two clear signals at *m*/*z* 893.5 and 447.3, which correspond to the ions [**6**·H]$^+$ and [**5**·H]$^+$, respectively, thus confirming that the [2]catenane comprised a pair of macrocycles **5**.

The absence of any of signals corresponding to the TFPB anion in the ^{1}H NMR spectrum of the [2]catenane **6** (Figure 3c) suggested that the templating Na^+ ions had been removed completely during the aqueous extraction and chromatography processes. It also suggested that the complexation of the Na^+ ion between the two diethylene glycol chains was not particularly strong under these conditions. The signal for the benzylic protons adjacent to the NH unit was shifted significantly upfield in the ^{1}H NMR spectrum of the [2]catenane **6** in $CDCl_3$, relative to that of the macrocycle **5**. This observation suggested that the two interlocked macrocycles preferred to interact mainly through [N-H⋯O] hydrogen bonding of one diethylene glycol loop of one component to the benzylamine unit(s) of the other (Scheme 1). The highly symmetric signals in the ^{1}H NMR spectrum of the [2]catenane **6** in $CDCl_3$ also suggested that such [N-H⋯O] hydrogen bonding was not sufficiently strong to slow the circumrotation of the components at room temperature to below the timescale of ^{1}H NMR spectroscopy at 400 MHz. Nevertheless, the interlocked nature of the components of the

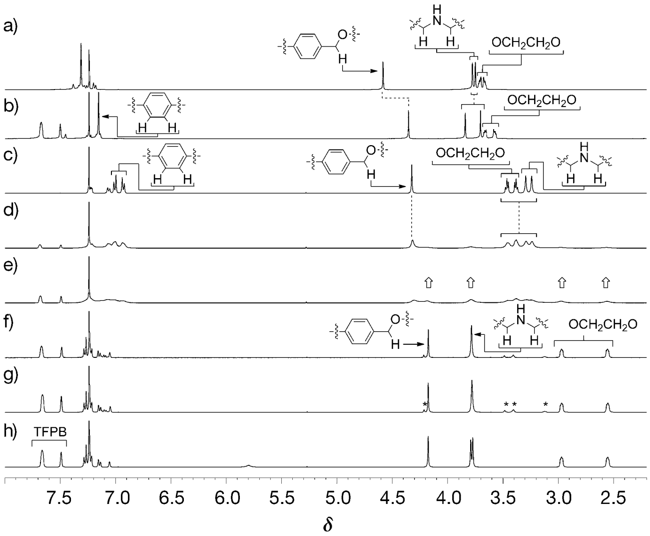


Figure 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) the macrocycle **5**; b) an equimolar mixture of **5** and NaTFPB (5 mM); c) the [2]catenane **6** (5 mM); d)–g) the solution in (c) after the addition of d) 0.3, e) 0.65, f) 1.0, and g) 1.5 equiv of NaTFPB; and h) the solution in (g) after the addition of NaOH (10 mg).

[2]catenane **6** is supported by the upfield shifts of most of the signals in its ^{1}H NMR spectrum relative to those in the spectrum of the macrocycle **5** under the same conditions.

We suspected that the complexation of a Na^+ ion to the [2]catenane **6** would occur with a binding stoichiometry similar to that of the imino [2]catenane [**4**·Na^+] and provide similar signals in the resulting ^{1}H NMR spectrum. Indeed, when we gradually titrated solutions of NaTFPB (0.30, 0.65, and 1.0 equiv) in small amounts of CD_3CN into a solution of the [2]catenane **6** in $CDCl_3$, we observed first broadened and then sharpened signals in the ^{1}H NMR spectra (Figure 3 d–f). The addition of even more NaTFPB (1.5 equiv in total) to the solution resulted in only a negligible change in the ^{1}H NMR spectrum, thus suggesting a 1:1 binding stoichiometry for the complexation of the [2]catenane **6** and the Na^+ ion. The signals at $\delta = 2.55/2.97$ and 4.17, which correspond to the ethylene glycol protons and benzylic protons adjacent to oxygen atoms, respectively, matched quite reasonably the signals of the corresponding protons in the [2]catenane [**4**·Na^+] in $CDCl_3$. This result confirmed the interlocked structure and thermodynamic predominance of the [2]catenane [**4**·Na^+] in the $CDCl_3$ solution of the diamine **1** (20 mM), the dialdehyde **2** (20 mM), and NaTFPB (10 mM). The significant upfield and downfield shifts of the signals of the diethylene glycol protons and the methylene protons adjacent to the NH units, respectively, in the ^{1}H NMR spectrum of the [2]catenane **6** after the addition of Na^+ ions confirmed that the two interlocked macrocyclic components of the [2]catenane **6** used their diethylene glycol loops cooperatively to complex the metal ion.[14]

Single crystals suitable for X-ray crystallography were grown by liquid diffusion of hexane into an equimolar solution of the [2]catenane **6** and NaTFPB in $CHCl_3$. Instead of trapping a Na^+ ion, the [2]catenane **6** was protonated under the crystallization conditions. The solid-state structure of [**6**-H_2]$^{2+}$ reveals[15,16] the [2]catenane geometry (Figure 4), in which one of the two amino units in each macrocycle was protonated, with this NH_2^+ center hydrogen bonded to the oxygen atoms of the diethylene glycol unit of the other interlocked macrocycle. We suspect that the interlocked nature of the [2]catenane **6** increased the basicity of one of the amino units in each interlocked macrocycle, thereby stabilizing the resulting NH_2^+ center through hydrogen bonding to the diethylene glycol chain of the other macrocyclic component.[17]

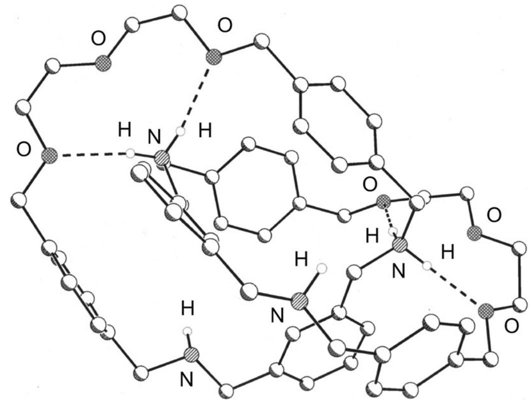


Figure 4. Ball-and-stick representation of the solid-state structure of the [2]catenane [**6**-H_2]$^{2+}$.

The ^{1}H NMR spectrum obtained after dissolving the crystals of the [2]catenane [**6**-H_2][2 TFPB] in $CDCl_3$ (see the Supporting Information) was similar to the minor signals observed in the equimolar mixture (Figure 3 f) and 1:1.5 mixture (Figure 3 g, indicated by an asterisk) of the [2]catenane **6** and NaTFPB in $CDCl_3$; thus, a small amount of the [2]catenane **6** was likely protonated under those experimental conditions. When solid NaOH (10 mg) was added to the 1:1.5 mixture of the [2]catenane **6** and NaTFPB in $CDCl_3$, these minor signals disappeared immediately, while the major ones remained unaffected (Figure 3 h).[18] We suspect that although we had treated the $CHCl_3$/$CDCl_3$ with $Na_2S_2O_3$ and K_2CO_3 and had freshly distilled it prior to use, it was difficult to completely avoid the presence of trace amounts of HCl/DCl generated through decomposition under the experimental conditions.

We have demonstrated that a Na^+ ion can be applied as a template for the alignment of two diethylene glycol chains in an orthogonal manner, thereby allowing the simple and efficient synthesis of a [2]catenane from five components (two dialdehydes, two diamines, one Na^+ ion). As readily accessible oligo(ethylene glycol)s are relatively chemically inert, their use as primary recognition units in the construction of interlocked molecules should provide additional structural flexibility for the design and development of functional materials and switches, which we are currently investigating.

Received: August 30, 2013

Keywords: catenanes · ethylene glycol · imines · molecular recognition · template synthesis

[1] For reviews, see a) K. Kim, *Chem. Soc. Rev.* **2002**, *31*, 96–107; b) K. E. Griffiths, J. F. Stoddart, *Pure Appl. Chem.* **2008**, *80*, 485–506; c) Z. Niu, H. W. Gibson, *Chem. Rev.* **2009**, *109*, 6024–6046; d) P. Gavina, S. Tatay, *Curr. Org. Synth.* **2010**, *7*, 24–43; e) N. H. Evans, P. D. Beer, Self-Assembled Links: Catenanes. *Supramolecular Chemistry: From Molecules to Nanomaterials*, Wiley, Chichester, UK, **2012**; f) V. N. Vukotic, S. J. Loeb, *Chem. Soc. Rev.* **2012**, *41*, 5896–5906; g) Y. Tachibana, K. Nakazono, T. Takata, Self-Assembly of Macromolecular Threaded Systems. *Supramolecular Chemistry: From Molecules to Nanomaterials*, Wiley, Chichester, UK, **2012**; h) J.-C. Chambron, J.-P. Sauvage, *New J. Chem.* **2013**, *37*, 49–57.

[2] For reviews, see a) R. Jäger, F. Vögtle, *Angew. Chem.* **1997**, *109*, 966–980; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930–944; b) G. A. Breault, C. A. Hunter, P. C. Mayers, *Tetrahedron* **1999**, *55*, 5265–5293; c) E. R. Kay, D. A. Leigh, *Top. Curr. Chem.* **2005**, *262*, 133–177.

[3] For reviews, see: a) M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 369–378; b) F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211–2221; c) G. Barin, A. Coskun, M. M. G. Fouda, J. F. Stoddart, *ChemPlusChem* **2012**, *77*, 159–185.

[4] a) A. Caballero, F. Zapata, N. G. White, P. J. Costa, V. Felix, P. D. Beer, *Angew. Chem.* **2012**, *124*, 1912–1916; *Angew. Chem. Int. Ed.* **2012**, *51*, 1876–1880; b) G. T. Spence, P. D. Beer, *Acc. Chem. Res.* **2013**, *46*, 571–586.

[5] For reviews, see a) B. Champin, P. Mobian, J.-P. Sauvage, *Chem. Soc. Rev.* **2007**, *36*, 358–366; b) J. E. Beves, B. A. Blight, C. J. Campbell, D. A. Leigh, R. T. McBurney, *Angew. Chem.* **2011**, *123*, 9428–9499; *Angew. Chem. Int. Ed.* **2011**, *50*, 9260–9327.

[6] a) G. W. Gokel, *Crown Ethers and Cryptands*, The Royal Society of Chemistry, Cambridge, **1991**; b) *Crown Ethers and Analogous Compounds* (Ed.: M. Hiraoka), Elsevier, Amsterdam, **1992**; c) M. C. T. Fyfe, J. F. Stoddart in *Advances in Supramolecular Chemistry, Vol. 5* (Ed.: G. W. Gokel), JAI, London, **1999**, pp. 1–53.

[7] Y.-L. Huang, W.-C. Hung, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Angew. Chem.* **2007**, *119*, 6749–6753; *Angew. Chem. Int. Ed.* **2007**, *46*, 6629–6633.

[8] In previous studies we combined one diethylene glycol chain with two aryl rings to develop a new class of "oxygen-deficient" hosts for the binding of dibenzylammonium ions; see a) P.-N. Cheng, P.-Y. Huang, W.-S. Li, S.-H. Ueng, W.-C. Hung, Y.-H. Liu, C.-C. Lai, S.-M. Peng, I. Chao, S.-H. Chiu, *J. Org. Chem.* **2006**, *71*, 2373–2383; b) N.-C. Chen, P.-Y. Huang, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Commun.* **2007**, 4122–4124; c) Y.-C. You, M.-C. Tzeng, C.-C. Lai, S.-H. Chiu, *Org. Lett.* **2012**, *14*, 1046–1049.

[9] a) S. H. Strauss, *Chem. Rev.* **1993**, *93*, 927–942; b) I. Krossing, I. Raabe, *Angew. Chem.* **2004**, *116*, 2116–2142; *Angew. Chem. Int. Ed.* **2004**, *43*, 2066–2090; c) J. Pérez, L. Riera, L. Ion, V. Riera, K. M. Anderson, J. W. Steed, D. Miguel, *Dalton Trans.* **2008**, 878–886; d) C. Gaeta, F. Troisi, P. Neri, *Org. Lett.* **2010**, *12*, 2092–2095; e) N.-C. Chen, C.-J. Chuang, L.-Y. Wang, C.-C. Lai, S.-H. Chiu, *Chem. Eur. J.* **2012**, *18*, 1896–1900; f) L.-Y. Wang, J.-L. Ko, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Eur. J.* **2013**, *19*, 8850–8860; g) Y.-H. Lin, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Angew. Chem.* **2013**, *125*, 10421–10426; *Angew. Chem. Int. Ed.* **2013**, *52*, 10231–10236.

[10] For examples of using imine formation to construct rotaxanes from dibenzylammonium or pyridinium ion containing dumbbell-shaped guests, see a) P. T. Glink, A. I. Oliva, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2001**, *113*, 1922–1927; *Angew. Chem. Int. Ed.* **2001**, *40*, 1870–1875; b) K. C.-F. Leung, F. Arico, S. J. Cantrill, J. F. Stoddart, *J. Am. Chem. Soc.* **2005**, *127*, 5808–5810; c) J. Wu, K. C.-F. Leung, J. F. Stoddart, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17266–17271; d) Z. Li, W. Liu, J. Wu, S. H. Liu, J. Yin, *J. Org. Chem.* **2012**, *77*, 7129–7135; e) A. Pun, D. A. Hanifi, G. Kiel, E. O'Brien, Y. Liu, *Angew. Chem.* **2012**, *124*, 13296–13299; *Angew. Chem. Int. Ed.* **2012**, *51*, 13119–13122; f) Y. Liu, Z.-T. Li, *Aust. J. Chem.* **2013**, *66*, 9–22.

[11] The exclusive formation of the complexed macrocycle [**3**·Na][TFPB] and the complexed [2]catenane [**4**·Na][TFPB] in solutions containing 1.0 and 0.5 equiv of Na^+ ions, respectively, suggested that the complexation of the free imino macrocycle **3** to a free Na^+ ion is energetically more favorable than its complexation to the bound Na^+ ion in [**3**·Na][TFPB], partly because of the higher entropic cost in forming the structurally more complicated and restricted [2]catenane.

[12] The same reagent has been used to "fix" an imine-based [2]rotaxane; see S. J. Cantrill, S. J. Rowan, J. F. Stoddart, *Org. Lett.* **1999**, *1*, 1363–1366.

[13] The relatively low yield of the isolated [2]catenane **6** was likely due to the lability of the imino bonds under the conditions for reduction; indeed, we isolated the macrocycle **5** as the major byproduct in 41 % yield.

[14] The use of the same solutions of NaTFPB in CD_3CN to titrate a solution of the macrocycle **5** in $CDCl_3$ did not lead to similar upfield shifts of the signals for the ethylene glycol loops in the ^{1}H NMR spectra, thereby eliminating the possibility that the upfield shifts were caused by intermolecular interactions.

[15] CCDC 952636 (excluding structure factors) for the [2]catenane [**6**-H_2][2TFPB] contains 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.

[16] Crystal data for [**6**-H_2][2TFPB]: $[C_{56}H_{70}O_6N_4][B_2C_{64}F_{48}H_{24}]$; $M_r = 2621.61$; triclinic; space group $P\bar{1}$; $a = 14.5245(4)$, $b = 20.1752(7)$, $c = 21.5392(8)$ Å; $V = 5997.0(4)$ Å^3; $\rho_{calcd} = 1.452\ g\,cm^{-3}$; $\mu(Cu_{K\alpha}) = 1.246\ mm^{-1}$; $T = 200(2)$ K; colorless plate; 21 825 independent measured reflections; F^2 refinement; $R_1 = 0.0571$; $wR_2 = 0.1700$.

[17] The phenanthroline motif of a [2]catenane exhibits enhanced basicity arising from its topology; see M. Cesario, C. O. Dietrich, A. Edel, J. Guilhem, J.-P. Kintzinger, C. Pascard, J.-P. Sauvage, *J. Am. Chem. Soc.* **1986**, *108*, 6250–6254.

[18] The addition of Na_2CO_3 to a solution containing a similar mixture did not eliminate these minor signals, possibly because of insufficient basicity.